

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

NCT Number: NCT02576795

Applicant/MAH: BioMarin Pharmaceutical Inc.

Version Date: 24 Aug 2021

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1/2, Dose-Escalation, Safety, Tolerability and Efficacy Study of BMN 270, an Adenovirus-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII in Patients with Severe Haemophilia A
Protocol Number:	270-201
Active Investigational Product:	AAV5-hFVIII-SQ
IND/European Union Drug Regulating Authorities Clinical Trials (EudraCT) Number:	2014-003880-38
Indication:	Haemophilia A
Sponsor:	BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949
Development Phase:	Phase 1/2
Sponsor's Responsible Medical Monitor:	PIMD, PhDPIBioMarin Pharmaceutical Inc.105 Digital Drive Novato, CA 94949
Duration of Subject Participation:	Approximately 368 weeks
Dose:	Varied
Study Population:	Males aged 18 or older
Date of Original Protocol:	10 February 2015
Date of Amendment 1:	06 March 2015
Date of Amendment 2:	26 May 2015
Date of Amendment 3:	06 November 2015
Date of Amendment 4:	02 September 2016
Date of Amendment 5:	14 February 2017
Date of Amendment 6:	21 December 2017
Date of Amendment 7:	10 October 2018
Date of Amendment 8:	31 January 2019
Date of Amendment 9:	19 June 2020
Date of Amendment 10:	24 August 2021

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May not be divulged, published, or otherwise disclosed to others without prior written approval from BioMarin. This study will be conducted according to the principles of Good Clinical Practice as described in the U.S. Code of Federal Regulations and the International Conference on Harmonisation Guidelines, including the archiving of essential documents



CLINICAL STUDY PROTOCOL AMENDMENT SUMMARY

Amendment: 10

Date: 24 August 2021

RATIONALE AND SUMMARY OF MAJOR CHANGES

A summary of major changes covered by Amendment 10 to the 270-201 protocol is provided below.

1. 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 after Year 4 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.

2. 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.

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

Rationale: Due to the current 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.

4. Guidance concerning the use of reactive corticosteroids for ALT elevations has been updated.

Rationale: The guidance suggests that subjects who are seeing ALT elevations more than 52 weeks after BMN 270 dosing should be started on reactive corticosteroids only after discussion between the Investigator and the Medical Monitor. Corticosteroids may be

270-201 Amendment 10

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

5. The definition of treatment failure has been changed.

Rationale: The previous definition required either a failure to achieve FVIII activity ≥ 5 IU/dL by Week 52 or an inability to maintain independence from prophylactic FVIII replacement therapy due to joint bleeding episodes; the revised definition requires both of these conditions to be present before a subject may be considered a treatment failure. The revision reflects the data seen as of the 52-week data cut for 270-301, where some subjects were still able to remain off of prophylactic FVIII replacement therapy (due to an absence of treated bleeding events) despite lower FVIII levels 1 or more years after BMN 270 infusion.

- 6. Frequency of several laboratory assessments after Year 1 has been decreased. These changes include:
 - Reducing FVIII Antigen BDD Assay to Q12W after Year 1 through Year 5, and Q26W in Years 6-7

Rationale: Robust characterization is already available from Year 1 data, and more frequent sampling is not needed to understand long-term protein to activity ratios

• Reducing AAV5 TAb to End of Year Visits only after Year 1

Rationale: Antibody response is high and does not change much over time. Yearly testing should be sufficient to understand longer term responses, as little change is expected.

• Reducing FVIII TAb to End of Year Visits only after Year 1

Rationale: FVIII Bethesda Inhibitor is the main safety assessment. After 3 years, if there is a need in specific instances for data more frequent than once a year, backup plasma from another assay may be used for testing.

- 7. The identity of the Medical Monitor has been updated.
- 8. The summary of risks and benefits (Section 7) has been updated.
- 9. Minor administrative changes have been made for consistency and clarity.

Specific changes included in this amendment, including the Synopsis, since Amendment 9 (approved 19 June 2020) are outlined in Section 24.



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2 SYNOPSIS

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BIMIN 270	Page:	
NAME OF ACTIVE INGREDIENT:	Reference:	
AAV5-hFVIII-SQ		
TITLE OF STUDY:	·	•
A Phase 1/2, Dose-Escalation, Safety, Tol	erability and Efficacy Study of	BMN 270, an
Adenovirus-Associated Virus Vector-Me		
with Severe Haemophilia A		
PROTOCOL NUMBER:		
270-201		
STUDY SITES:		
Approximately 6-10 sites worldwide.		
PHASE OF DEVELOPMENT:		
Phase 1/2		
STUDY RATIONALE:		
Haemophilia A (HA) is an X-linked reces	sive bleeding disorder that affect	ets approximately 1 in
5,000 males. It is caused by deficiency in		
essential cofactor in the intrinsic coagulati		,
a new mutation or an acquired immunolog		
dysfunctional FVIII, but all are characterit		
phenotype of HA patients is largely gover	-	
classified as FVIII activity less than 1% o 1-5% of wild type activity and the mild fo		
severe HA remain frequent spontaneous b		
tissues, with a substantially increased risk		
Treatment of severe HA presently consist:	e	

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 treatment (mean of 1 to 7 episodes/year with prophylaxis and up to 30 to 50 episodes/year for on demand treatment). The consequence of multiple bleeding events is the development of an underlying pathology that contributes to debilitating multiple-joint arthropathy and substantially increased risk of death. Chemical modification (eg, direct conjugation of polyethylene glycol (PEG) polymers) and bioengineering of FVIII (eg, FVIII-Fc fusion proteins) improve half-life by approximately 50%, and thus, show promise in reduced dosing and maintaining activity levels above 1% trough. However, these longer acting FVIIIs remain



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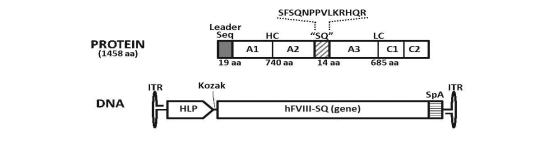
dependent on multiple infusions to maintain critical levels of FVIII activity in severe HA patients. There is therefore a strong unmet need for a fully preventive treatment of HA to give patients a FVIII level compatible with a normal and haemorrhage-free life.

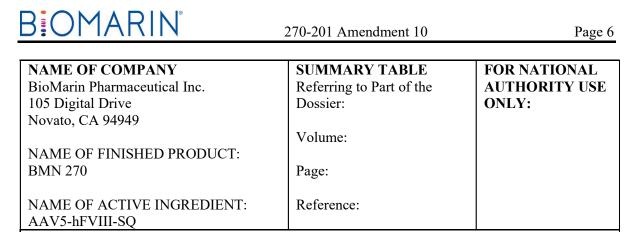
Gene therapy offers the potential of disease-modifying therapy by continuous endogenous production of active FVIII following a single intravenous administration of a vector with the appropriate gene sequence. Haemophilia A is well suited for a gene replacement approach because clinical manifestations 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 modest increases in the level of FVIII (any increase of the plasma level by 2 ng/ml induces an increase in activity of 1%) can ameliorate the severe form of the disease. Thus, relatively small changes in endogenous FVIII activity results in clinically relevant improvements in disease phenotype. Finally, the 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 for specific tissues such as the liver (for serotypes 2, 5 and 8 among others). Indeed, an on-going gene therapy clinical trial for a related disorder, haemophilia B, has established that stable (>36 months) expression of human factor IX at levels that are sufficient for conversion of their bleeding phenotype from severe to moderate or mild is achievable following a single peripheral vein administration of AAV-8 vector. Several participants in this trial have been able to discontinue factor prophylaxis without suffering spontaneous haemorrhages, 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 liver-selective promoter (Figure 1).







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 single intravenous dose and is designed to achieve stable, potentially life-long expression of active hFVIII in the plasma, synthesized from vector-transduced liver tissue. The clinical study 270-201 is a first-in-human study designed to assess the relationship of vector dose to the augmentation of residual FVIII activity, and whether these levels are sufficient to alter the clinical phenotype. The relationship of dose to safety will be correlated to the activity of hFVIII in patients with severe HA.

Liver Biopsy Substudy Rationale

The 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 in the second year of follow-up, with mean hFVIII activity levels remaining above the lower limit of normal (50 IU/dL). 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, and 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 270-201 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 some subjects, as well as inter-subject variability in post-therapy hFVIII levels. Neither the reasons for, nor the significance of, the ALT elevations or 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.

The purpose of this exploratory substudy is to provide a better understanding of the long-term gene expression related to circularized genomes, health of the liver, and variation in hFVIII levels observed after gene therapy with BMN 270. Whilst consenting subjects may not derive any direct benefit themselves by participating in the substudy, the overall findings could aid future patients by helping to characterize the means by which long-term efficacy is achieved and the safety of liver-directed gene therapy.

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NAME OF ACTIVE INGREDIENT: AAV5-hFVIII-SQ	Reference:	
OBJECTIVES:		
The primary objectives of the study are:		
• To assess the safety of a single in encoding human coagulation FV		ecombinant AAV5
• To determine the dose of AAV5- normal activity (≥5 IU/dL) at 16 magnitude of AAV-mediated FV determined and correlated to an a	weeks after infusion. The kinet III activity in individuals with h	ics, duration and
The secondary objectives of the study are	2.	
• To describe the immune response following systemic administratio		V capsid proteins
• To assess the impact of BMN 27 the study	0 on the frequency of FVIII repl	acement therapy during
• To assess the impact of BMN 27 during the study	0 on the number of bleeding epis	sodes requiring treatment
The exploratory objectives of the liver bi	opsy substudy are:	
• To examine the histopathology o assessing for possible safety find invasion)		
• To quantify FVIII DNA, RNA, a	nd protein expression within hep	patocytes
• To determine which forms of rA.	AV vector DNA are present at th	ne time of biopsy.
• To determine the transduction pa central vein hepatocytes)	ttern of BMN 270 in humans (ie	e, peri-portal hepatocytes,
STUDY DESIGN AND PLAN: This is a first-in-man, phase 1/2 open-lab haemophilia A. Eligible patients will enter 16-week Post-Infusion Follow-Up period taken. After the primary endpoint analysi	er the dose escalation part of the l during which safety and efficac	study followed by a ey assessments will be

for approximately 7 years.



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AAV5-hFVIII-SQ		

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

Cohort 1: 6E12 vector genomes [vg] per kilogram of body weight, given as a single intravenous dose (iv)

Cohort 2: 2E13 vg per kilogram, iv

Cohort 3: 6E13 vg per kilogram, iv

Cohort 4: 4E13 vg per kilogram, iv

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

Cohorts 1-3

The first 3 cohorts will be enrolled sequentially, allowing a period of 3 weeks or more between cohorts. Dose escalation may occur after a single subject has been safely dosed if the resulting FVIII activity at the Week 3 visit is < 5 IU/dL in both the one-stage clotting and chromogenic substrate assays. Three weeks is expected to be the time the expression will be close to the maximum. This escalation paradigm is intended to minimize the subject numbers exposed to subtherapeutic doses.

Approximately three weeks after an injection, the decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and a panel of investigators participating in the study, the Data Review Board (DRB).

If the FVIII activity reaches \geq 5 IU/dL at the Week 3 visit, then the remaining subjects in the cohort will be enrolled without the need to wait for 3 weeks between subjects.

Subject 1 will be dosed by intravenous infusion with 6E12 vector genomes [vg] per kilogram of body weight. If the FVIII activity level does not reach ≥ 5 IU/dL at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 1 and enrollment into Cohort 2 will initiate with Subject 2 at the next dose (2E13 vg/kg).

If the FVIII activity level in the first subject treated in Cohort 2 does not reach ≥ 5 IU/dL at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 2 and enrollment into Cohort 3 (6E13) will initiate with the next subject. If the FVIII activity level in the first subject treated in Cohort 3 does not reach ≥ 5 IU/dL at the Week 3 visit in both assays, then the Data Review Board (DRB) will recommend whether to continue to add subjects to the cohort and/or whether to continue the study.



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For the first subject treated in each of the first 3 cohorts, if the activity level reaches ≥ 5 IU/dL and no safety issue is found, then up to four subjects will be enrolled in the Cohort, though, the adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

Cohort 4

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

There will be an ongoing review of individual patient safety and efficacy data by the medical monitor and the DRB. The adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

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

In subjects who experience recurrent bleeding episodes, the Investigator and Medical Monitor will discuss whether to resume prior FVIII prophylaxis. Subjects who do not respond to BMN 270 treatment (ie, treatment failure, manifesting as failure to achieve FVIII activity \geq 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, follow an abbreviated visit schedule after Week 52, as applicable and at the discretion of the Investigator. Because subjects develop neutralizing immunity upon exposure to the capsid, re-challenge of vector is not a likely treatment option and these subjects have effectively a single opportunity for therapy using this AAV capsid. Efficacy will be determined by FVIII activity at 16 weeks post dose. Safety will be evaluated for approximately 7 years after dosing. Any safety signal may trigger a review of the data and possible additional immunogenicity studies that include an assessment of cellular immune responses using collected peripheral blood mononuclear cells (PBMC).



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At applicable sites, certain study assessments designated in the Schedule of Events may be performed by a mobile nursing (MN) professional at the subject's home or another suitable location, such as their school or office, to improve access and convenience for subjects 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 subject and the subject gives written informed consent to participate in MN visits, the MN network will communicate with the subject and the subject's site.

Liver Biopsy Substudy Design

All subjects enrolled in 270-201 and who are at least one year post-BMN 270 infusion are eligible for the optional liver biopsy substudy. Subjects who consent to participate in the substudy will have a liver biopsy via either the transjugular or percutaneous (ultrasound-guided) route, according to the standard procedures of the institution. Participation in the substudy may include liver biopsies at one or more time points. To enhance safety, all subjects will have an ultrasound examination of the liver within 3 months prior to the procedure (to ensure there are no pathological findings such as bile duct obstruction that might interfere with the safe performance of the liver biopsy) and a FibroScan of the liver within one week before the liver biopsy (to correlate with any potential histopathologic findings of fibrosis on the biopsy).

Subjects who consent should have their FVIII levels monitored/adjusted by the Investigator to enable the procedure to be performed safely. This may require the administration of exogenous FVIII replacement products in order to achieve the desired FVIII activity. The target FVIII activity level within 24 hours prior to the liver biopsy is at the discretion of the Investigator and/or according to local guidelines, but at a minimum should be at the lower limit of the normal range (ie, at least 50 IU/dL).

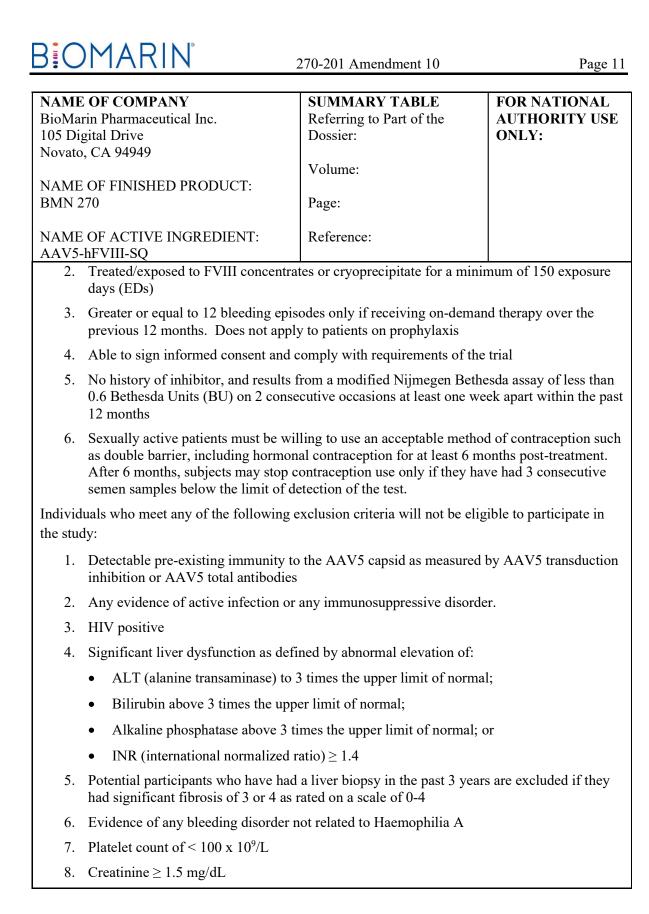
NUMBER OF SUBJECTS PLANNED:

Up to 15 subjects may enroll into the study; the actual number of subjects will depend on the FVIII activity levels seen in each Cohort.

DIAGNOSIS AND ALL CRITERIA FOR INCLUSION AND EXCLUSION:

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

1. Males that are 18 years or older with established severe haemophilia A as evidenced by their medical history. Patients will be considered as severe if their base FVIII level is 1 IU/dL or less



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	eirrhosis of any etiology as a	ussessed by liver ultrasound	1
10. Hepati	tis B if surface antigen is po	sitive	
11. Hepati	tis C if RNA is positive		
12. Treatm	ent with any IP within 30 d	ays prior to the end of the screen	ing period
fully contreatment	omplying with the requirem ent outlined in the protocol.	ysician's discretion that would pr ents of the study including possib The physician may exclude pation ol for the 16-week period followi	ole corticosteroid ents unwilling or
14. Prior ta	reatment with any vector or	gene transfer agent	
15. Major	surgery planned in the 16-w	eek period following the viral inf	fusion
16. Use of infusio		ve agents or live vaccines within	30 days before the vira
Individuals elig criteria:	gible to participate in the liv	er biopsy substudy must meet all	of the following
1. Curren	tly enrolled in 270-201		
2. Receiv	ed BMN 270 infusion at lea	st 1 year prior to enrollment in th	e substudy
3. Able to	sign informed consent and	comply with requirements of the	substudy
Investi levels exoger	gator discretion) within 24 l should be assessed at the loc lous FVIII replacement proc	or higher, depending on local guid hours prior to the liver biopsy bei cal laboratory.) Subjects may be flucts in order to increase their FV rision/instruction of the Investigat	ng performed. (FVIII treated with additiona 'III levels to an
Individuals wh	o meet any of the following	exclusion criteria will not be elig	gible to participate in
the liver biopsy	v substudy:		
underg		epatologist as having a medical c e contraindicated. These conditio	
• Sig	gnificant thrombocytopenia	(platelet count < $100 \times 10^9/L$)	
• Ev	idence of significant ascites		

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• Abnormalities detected on liv that would preclude safe perf	ver ultrasound (performed withir ormance of the biopsy.	90 days of procedure)
INVESTIGATIONAL PRODUCT(S) , Each subject will receive a single injectio infusion will depend on the dose level.	-	
REFERENCE THERAPY(IES), DOSE The study is open label with comparison of will be evaluated in this study.	-	ies. No reference therapy
DURATION OF TREATMENT: BMN 270 is given as a single dose by intr	ravenous infusion.	
CRITERIA FOR EVALUATION:		
Safety:		
The following safety outcome measureme		
• Incidence of adverse events (AEs		
• Change in clinical laboratory test	s (serum chemistry and haemato	ology)
• Change in vital signs		
• Change in physical examination		
Vector shedding		
• Liver tests (LTs, including ALT,	AST, GGT, LDH, total bilirubir	n, alkaline phosphatase)
• Immune response to FVIII transg	ene and AAV capsid proteins	
No major toxicity is expected based on pr have comprehensive surveillance monitor then once every 2 weeks from Week 37-5 during Year 2, every 6 weeks for Years 3 safety extension; the frequency and durati between the Medical Monitor and the Inv There will be a detailed assessment of cell protein. <u>Efficacy:</u>	ring of LTs (at local labs, once p 52) during Year 1. LTs will be m -5, and every 26 weeks for Year ion of LT testing may be change restigator and review of subject of	er week for Weeks 1-36 onitored every 4 weeks s 6-7 post-dose in the d based on discussion lata.
The primary efficacy measure will be to a study is to establish the dose relationship administration.	· · ·	
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Secondary efficacy measures include assessing the impact of BMN 270 on the frequency of FVIII replacement therapy and on the number of bleeding episodes during the study. Subjects will be asked to keep a subject diary to record the details in these areas.

Pharmacodynamics:

The FVIII antigen and activity level as measured by an ELISA (antigen level) and by one-stage clotting and/or chromogenic substrate assay (activity level), will be used for plasma profiles; FVIII activity will be used to determine PD parameters. Traditional PK analysis is not applicable.

If supported by the FVIII activity data, non-compartmental analysis and observation will be used to estimate individual values of Cb (baseline concentration), Css (steady state concentration), Tss (time to steady state), C(t) and AUC(0-t) where t is 16 weeks.

Liver Biopsy Substudy:

The following exploratory assessments will be performed as part of the optional liver biopsy substudy:

- Morphologic/pathogenic changes after FVIII gene transduction or any change that may be associated with sustained ALT rise
- Determine quantities of liver FVIII-SQ DNA/RNA
- Determine forms of vector DNA in liver at the time of biopsy
- Determine percentage of hepatocytes expressing FVIII protein
- Determine percentage of hepatocytes staining positive for vector DNA
- Determine hepatic liver transcriptome at single nuclei level if sufficient material is obtained
- Identify the forms of vector DNA in the liver
- Examination of potential stress inducing cellular pathways
- Other exploratory assessment to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to hemophilia A, coagulation, and/or AAV gene transfer

STATISTICAL METHODS:

The sample size is based upon clinical considerations and could detect a strong clinical efficacy signal. Up to 15 subjects may be dosed in the study. The subjects will be followed in a longitudinal manner and all the relevant information will be collected. The analysis of the data will be descriptive in nature but data collected in a longitudinal manner may be analyzed using longitudinal methods such as mixed effect model which takes into account the correlation among the observation taken at various time points within a participant. Efficacy is a secondary endpoint, defined as biologically active FVIII at ≥ 5 IU/dL by chromogenic substrate assay and/or one-stage clotting assay at 16 weeks following study treatment. We can only assess the true steady state of

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FVIII protein produced from BMN 270 af infusion of FVIII protein concentrates.	ter a minimum of 72 hours has	elapsed since the last

comparisons across doses.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

AAV	adeno-associated virus
ADL	activities of daily living
ADR	adverse drug reaction
AE	adverse event
ALT	alanine transaminase
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BPV	BioMarin Pharmacovigilance
BU	Bethesda Unit
CFR	Code of Federal Regulations
CRA	clinical research associate
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DRB	Data Review Board
eCRF	electronic case report form
ED	exposure days
EOSI	events of special interest
ETV	early termination visit
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
FIH	first-in-human
FVIII	coagulation factor VIII
FXa	coagulation factor Xa
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
НА	Haemophilia A
hFVIII	human coagulation factor VIII
HIPAA	Health Insurance Portability and Accountability Act
IB	investigator brochure
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

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ICH E6	ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E	6
IEC	independent ethics committee	
IND	Investigational New Drug (application)	
INR	international normalized ratio	
IP	investigational product	
IV	intravenous	
LT	liver test	
MedDRA	Medical Dictionary for Regulatory Activities	
NOAEL	no-observed-adverse-effect level	
PBMC	peripheral blood mononuclear cells	
PD	pharmacodynamics	
PEG	polyethylene glycol	
РК	Pharmacokinetics	
PRO	patient-reported outcome	
rhFVIII	recombinant human FVIII protein	
SAE	serious adverse event	
SAP	statistical analysis plan	
SDV	source data verification	
ULN	upper limit of normal	
vg	vector genomes	
VWF:Ag	von Willebrand factor Antigen	

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]).

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 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 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 IEC will be provided to BioMarin or its designee. The Investigator will provide the 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 to a language other than the native language of 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 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 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 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)

Specifically, this study is based on adequately performed laboratory and animal experimentation. The study will be conducted under a protocol reviewed and approved by an IEC and will be conducted by scientifically and medically qualified persons. The benefits of the study are in proportion to the 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, as well as when updates to the ICF are made. Where it is not feasible for the Investigator to receive the signed, written ICF from the subject prior to beginning new or changed study-related procedures contained in such an ICF update (for example, due to COVID-19-related restrictions), the Investigator will ask the subject to verbally confirm during an informed consent interview that the subject has signed and dated the ICF. The Investigator should document this verbal confirmation on the Investigator's copy of the ICF and, when it is possible to do so, receive the informed consent signed by the subject and archive the original(s) in the record file of the subject.

5.3 Subject Information and Informed Consent

A properly written and executed ICF, in compliance with ICH E6 (Section 4.8), United States Code of Federal Regulations (CFR) 21 CFR §50, European Clinical Trial Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC, and other applicable local regulations, will be obtained for each subject prior to entering the subject into the study. The Investigator will prepare the ICF and provide the documents to BioMarin for approval prior to submission to the IEC approval. BioMarin and the IEC must approve the documents before they are implemented. A copy of the approved ICF, and if applicable, a copy of the Proprietary and Confidential 24 August 2021

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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.

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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 US Food and Drug Administration (FDA) Form FDA 1572 and a Financial Disclosure Form. All sub-Investigators must be listed on Form FDA 1572. Financial Disclosure Forms must also be completed for all sub-Investigators listed on the Form FDA 1572 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.

Liver tests (LTs) will be performed at the local laboratories associated with the study sites. Local laboratory results of LTs will be used to trigger corticosteroid treatment as needed (refer to Section 9.4.8.2). In case of discrepant results between local and central laboratories, the Investigator and Medical Monitor will decide further action. Safety labs evaluations (including LTs) will be performed at the central lab, while bioanalytical samples will be performed at the appropriate specialty lab. Refer to the Laboratory Manual for more details.

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7 INTRODUCTION

Haemophilia 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 cascade. 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 haemorrhage. Treatment in Western (Berntorp 2012) countries consists of intravenous injection of plasma derived or recombinant FVIII protein concentrates at the time of a bleed, 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 haemophilia A patients. These individuals develop debilitating arthropathy and have a substantially increased risk of death from haemorrhage in life (Stonebraker 2010). Chemical modification or bioengineering of FVIII may improve half-life to 18-19 hours (Kaufman 2013). However, these long acting 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 following a single administration of vector. Haemophilia 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 liver-specific HLP transcription promoter. The expression cassette is inserted between AAV2 ITRs and this genome is packaged in the AAV5 capsid. A comprehensive review of BMN 270 is contained in the IB supplied by BioMarin. Investigators are to review this document prior to initiating this study.

7.1 Nonclinical Studies

The nonclinical program supports a single IV administration of BMN 270, the planned clinical route of administration, for the treatment of Haemophilia A in male patients. This nonclinical program took into account the guidelines and reflection papers for gene therapy medicinal products under EMA Advanced Therapies. The primary pharmacodynamics (PD), Proprietary and Confidential 24 August 2021

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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 (normal CD-1 mouse, B and T cell deficient mouse model of haemophilia 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.

The primary PD of BMN 270 was assessed in a series of non-GLP single dose studies in a FVIII KO x Rag2 mouse model of severe Haemophilia A that recapitulates the change in coagulation observed in the human severe disease population without interfering cross species immunogenicity. PD activity and expression of hFVIII was assessed for durations up to 13-weeks in the FVIII KO x Rag2 mouse given dose range of 2E11 through 2E14 vector genomes (vg)/kg. Low levels of plasma hFVIII were observed in mice given 2E12 vg/kg after eight-weeks, post dose. Plasma hFVIII activity using bleeding time as an endpoint was evaluated in the FVIII KO x Rag2 mouse given up to 2E13 and 1E14 vg/kg BMN 270 at 8 weeks, post dose. BMN 270 related correction of bleeding times showed a dose relationship that was similar to that observed in FVIII KO x Rag2 mice given matched IU levels of Refacto[®].

All cynomolgus monkeys used in this program were screened for neutralizing anti-AAV5 activity prior to study enrollment. PD activity and plasma hFVIII concentrations were evaluated in the cynomolgus monkey given up to 6E13 vg/kg BMN 270 for eight weeks. Peak expression of hFVIII was observed three to six weeks post administration with a subsequent decrease in expression presumably due to immunogenicity though not necessarily correlated to antibody titer.

The normal mouse was utilized in the GLP toxicology study to assess the safety profile of BMN 270 without the background of disease progression and in sufficient number per parameter. The GLP single dose toxicity study in normal CD-1 mice given 6E12 and 6E13 vg/kg with a 4 and 13-week follow up period monitored clinical pathology, defined potential target organs, immunogenicity, gene expression and activity. No changes in liver function were observed. In a single dose PD study in monkey given BMN 270, formation of anti-AAV5 total antibodies was observed at Week 8 with relatively low formation of anti-hFVIII total antibodies. No changes in liver function was observed.

The overall nonclinical safety profile includes formation of anti-AAV5 total antibodies with relatively lower formation of anti-hFVIII total antibodies. Immunogenicity against the AAV capsid and hFVIII is an anticipated finding for BMN 270 treatment and will be monitored in the nonclinical and clinical programs. Though not observed in the nonclinical species, liver

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toxicity utilizing clinical pathology parameters will be monitored in the clinical program based on previous literature. Cellular immune response will also be monitored.

Additionally, the BMN 270 transgene product has a final sequence closely matching that of the protein replacement treatment, Refacto[®] and therefore the safety profile of the BMN 270 transgene product is anticipated to be similar to Refacto® and have no unique FVIII-specific target organs of toxicity. The AAV5 capsid has not been modified and therefore no unique capsid-specific safety findings are anticipated. Because the biodistribution pattern of AAV5 after IV administration is consistent across species, BioMarin will confirm the nonclinical distribution pattern of BMN 270 during clinical development. Biodistribution of the AAV5 capsid has been documented to predominately target the liver with relatively lower levels of transduction observed in the lung, kidney, spleen, testes and blood compartment depending on the species and timing of administration. Liver targeted distribution of a similar AAV5 Factor IX gene therapy product was observed in the rhesus macaque monkey with low levels of vector genomes detected in spleen, kidney and testis (Nathwani 2006). Despite distribution to non-liver organs, no expression of Factor IX was detected in these tissues. Additionally, distribution to the testis was observed in another study in monkeys given an AAV5-codon-optimized human porphobilinogen deaminase; however, vector genomes in the semen were only transiently observed within one week but not thereafter (Paneda 2013).

Both normal and disease model mice and a limited number of monkeys were utilized to establish proof of concept, species scaling and dose response in order to select the first-in-human (FIH) dose of 6E12 vg/kg. This dose represents 10-fold safety factor from the no observed adverse effect level (NOAEL) in the GLP enabling nonclinical toxicology study in mice.

7.2 Previous and Ongoing Clinical Studies

This is the first clinical study for BMN 270.

BioMarin's program for haemophilia A builds on previous clinical trials of AAV-mediated gene transfer for a related condition, haemophilia B, that were conducted with an AAV2 vector (Manno 2003) and an AAV8 vector (Nathwani 2011; Nathwani 2014). The large size of the FVIII cDNA was shortened and a preclinical validation of this approach was performed with an AAV8 vector (McIntosh 2013).

AAV serotype 5 is being tested in other clinical trials and was reportedly well tolerated without treatment-related serious adverse events in a recent phase 1 study for treatment of Acute Intermittent Porphyria (D'Avola 2014). In addition, AAV using other serotypes have been used in 105 clinical studies to date and no safety issue specific to the vector was ever reported.

Ongoing clinical studies for BMN 270 include:

- 270-203, a phase 2 study in patients with severe HA who have anti-AAV5 antibody titers
- 270-205, a phase 1/2 study in patients with severe HA who have active or prior FVIII inhibitors
- 270-301, the pivotal phase 3 study in patients with severe HA who receive BMN 270 at the 6E13 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
- 270-303, a phase 3 study in patients with severe HA who received BMN 270 at the 6E13 vg/kg dose level along with prophylactic corticosteroids

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

7.3 Study Rationale

Haemophilia A (HA) is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males (Iorio 2019). It is caused by deficiency in the activity of coagulation factor VIII (FVIII), an essential cofactor in the intrinsic coagulation cascade. This disorder can be either inherited, due to a new mutation 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 is largely governed by the level of residual expression. Severe HA is classified as FVIII activity less than 1% of wild type (< 1 IU/dL), moderate disease comprises 1-5% of wild type activity and the mild form is 5-40% activity. The clinical manifestations of severe HA remain frequent spontaneous bleeding episodes, predominantly in joints and soft tissues, with a substantially increased risk of death from haemorrhage when the brain is involved.

Treatment of severe HA presently consists of intravenous injection of plasma derived or recombinant human FVIII protein (rhFVIII) concentrates both as prophylaxis 2-4 times per week, and at the time of a bleed, to prevent or control bleeding episodes, respectively. The half-life for FVIII (12-18 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 treatment (mean of 1 to 7 episodes/year with prophylaxis and up to 30 to 50 episodes/year for on demand treatment) (Nagel 2011). The consequence of multiple bleeding events is the development of an underlying pathology that contributes to debilitating multiple-joint arthropathy and

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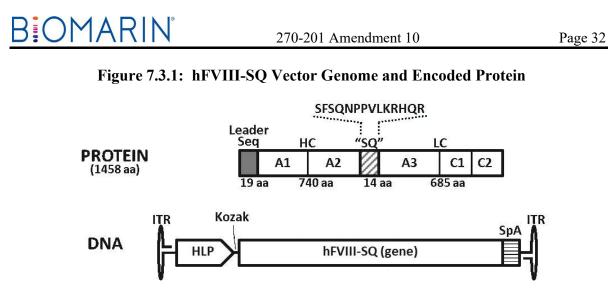
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substantially increased risk of death (Nagel, 2011, Haemophilia). Chemical modification (eg, direct conjugation of polyethylene glycol (PEG) polymers) and bioengineering of FVIII (eg, FVIII-Fc fusion proteins) improve half-life by approximately 50%, and thus, show promise in reduced dosing and maintaining activity levels above 1% trough (Stonebraker 2010; Mahlangu 2014). However, these longer acting FVIIIs remain dependent on multiple infusions to maintain critical levels of FVIII activity in severe HA patients. There is therefore a strong unmet need for a fully preventive treatment of HA to give patients a FVIII level compatible with a normal and haemorrhage-free life.

Gene therapy offers the potential of disease-modifying therapy by continuous endogenous production of active FVIII following a single intravenous administration of a vector with the appropriate gene sequence. Haemophilia 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 modest increases in the level of FVIII (any increase of the plasma level by 2 ng/ml induces an increase in activity of 1%) can ameliorate the severe form of the disease. Thus, relatively small changes in endogenous FVIII activity results in clinically relevant improvements in disease phenotype. Finally, the 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 (Mannucci 2001). They have an excellent and well defined safety profile, and can direct long term transgene expression with tropism for specific tissues such as the liver (Nathwani 2005) for serotypes 2, 5 and 8 among others. Indeed, an on-going gene therapy clinical trial for a related disorder, haemophilia B, has established that stable (>36 months) expression of human factor IX at levels that are sufficient for conversion of their bleeding phenotype from severe to moderate or mild is achievable following a single peripheral vein administration of AAV-8 vector (Nathwani 2014). Several participants in this trial have been able to discontinue factor prophylaxis without suffering spontaneous haemorrhages, 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 liver-selective promoter (Figure 7.3.1).



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 single intravenous dose and is designed to achieve stable, potentially life-long expression of active FVIII in the plasma, synthesized from vector-transduced liver tissue. The clinical study 270-201 is a first-in-human study designed to assess the relationship of vector dose to the augmentation of residual FVIII activity, and whether these levels are sufficient to alter the clinical phenotype. The relationship of dose to safety will be correlated to the activity of FVIII in patients with severe HA.

7.3.1 Liver Biopsy Substudy Rationale

The 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 in the second year of follow-up, with mean hFVIII activity levels remaining above the lower limit of normal (50 IU/dL). 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 270-201 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 some subjects, as well as Proprietary and Confidential 24 August 2021

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inter-subject variability in post-therapy hFVIII 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 substudies 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 substudy is to provide a better understanding of the long-term gene expression related to genome circularization, health of the liver, and variation in hFVIII levels observed after gene therapy with BMN 270. Whilst consenting subjects may not derive any direct benefit themselves by participating in the substudy, the overall findings could aid future patients by helping to characterize the means by which long-term efficacy is achieved and the safety of liver-directed gene therapy.

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. 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,

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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).

At the highest dose tested in 270-201 (6E13 vg/kg), the majority of subjects achieved FVIII levels above 50 IU/dL at 52 weeks post-infusion. 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 were included in the 1-year 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. 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 270-301 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 safety findings from clinical studies, refer to current version of the Investigator's Brochure.

Dose selection: The benefit of this study can only be enhanced by selecting a starting dose that maximizes the opportunity of observing a therapeutic effect, and therefore, reducing the possibility of a sub-therapeutic effect. With this consideration in mind, the starting dose 6E12 vg/kg was selected using overall data from the pre-clinical studies conducted in mice (normal and disease model, Rag2 -/- x FVIII -/-) and monkey. A detectable pharmacological response based on activity was observed at 6E12 vg/kg. A 10-fold safety margin based upon

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the NOAEL was observed in the GLP 13-week study in normal mouse at the highest dose administered. A 30-fold safety margin in an 8-week dose response study in disease model mice based on histology was observed at the highest dose administered. No BMN 270-related changes in clinical observations or chemistry was observed in the monkey at doses up to 6E13 vg/kg, a 10-fold safety margin after 8-weeks. Overall, no BMN 270-related findings, except expected formation of anti-AAV5 antibodies, were observed at the highest administered doses of 6E13, 2E14 and 6E13 vg/kg in the normal mouse, disease model mouse and monkey, respectively.

Based on these key pre-clinical findings it can be suggested that the proposed starting dose of 6E12 vg/kg should not pose any risk or safety concerns to subjects with the best chance of benefiting the subject therapeutically.

7.4.1 Optional Liver Biopsy Substudy 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 substudy will have a comprehensive pre-/post-biopsy surveillance plan according to the standard procedures at the institution. 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 substudy is optional and will not have any effect on the subject's continued participation in 270-201.

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8 STUDY OBJECTIVES

The primary objectives of the study are:

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

The secondary objectives of the study are:

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

The exploratory objectives of the liver biopsy substudy are:

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

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9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a first-in-man, phase 1/2 open-label, dose escalation study in patients with severe haemophilia A. Eligible patients will enter the dose escalation part of the study followed by a 16-week Post-Infusion Follow-Up period during which safety and efficacy assessments will be taken. After the primary endpoint analysis at 16 weeks, safety and efficacy will then be assessed for approximately 7 years.

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

- Cohort 1: 6E12 vector genomes [vg] per kilogram of body weight, given as a single intravenous dose (iv)
- Cohort 2: 2E13 vg per kilogram, iv
- Cohort 3: 6E13 vg per kilogram, iv
- Cohort 4: 4E13 vg per kilogram, iv

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

Cohorts 1-3

The first three cohorts will be enrolled sequentially, allowing a period of 3 weeks or more between cohorts. Dose escalation may occur after a single subject in a cohort has been safely dosed if the resulting FVIII activity at the Week 3 visit is < 5 IU/dL in both assays. Three weeks is expected to be the time the expression will be close to the maximum. This escalation paradigm is intended to minimize the subject numbers exposed to subtherapeutic doses. The decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and a panel of investigators participating in the study.

If the FVIII activity reaches ≥ 5 IU/dL at the Week 3 visit, then the remaining subjects in the cohort will be enrolled without the need to wait for 3 weeks between subjects.



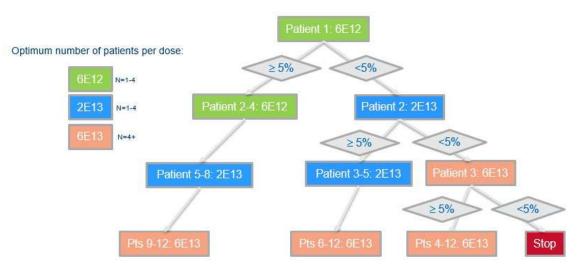


Figure 9.1.1: Flow Chart of Dose Escalation Scheme for Cohorts 1 to 3

Subject 1 (Cohort 1) will be dosed by intravenous infusion with 6E12 vg/kg of body weight. If the FVIII activity level does not reach 5 IU/dL or greater (expressed as % in Figure 9.1.1) at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 1 and enrollment into Cohort 2 will initiate with Subject 2 at the next dose (2E13 vg/kg).

If the FVIII activity level in the first subject treated in Cohort 2 does not reach \geq 5 IU/dL at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 2 and enrollment into Cohort 3 (6E13) will initiate with the next subject.

If the FVIII activity level in the first subject treated in Cohort 3 does not reach \geq 5 IU/dL at the Week 3 visit in both assays, then the DRB will recommend whether to continue to add subjects to the cohort and/or whether to continue the study.

For the first subject treated in each of the first 3 cohorts, if the activity level reaches ≥ 5 IU/dL and no safety issue is found, then up to four subjects will be enrolled in the Cohort, though the adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

<u>Cohort 4</u>

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

There will be an ongoing review of individual patient safety and efficacy data by the medical monitor and the Data Review Board (DRB). The adaptive nature of this trial allows the DRB

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to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

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

In subjects who experience recurrent bleeding episodes, the Investigator and Medical Monitor will discuss whether to resume prior FVIII prophylaxis. Subjects who do not respond to BMN 270 treatment (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, follow an abbreviated visit schedule after Week 52, as applicable and at the discretion of the Investigator.

At applicable sites, certain study assessments designated in the Schedule of Events may be performed by a mobile nursing (MN) professional at the subject's home or another suitable location, such as their school or office, to improve access and convenience for subjects 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 subject and the subject gives written informed consent to participate in MN visits, the MN network will communicate with the subject and the subject's site.

Because subjects develop neutralizing immunity upon exposure to the capsid, re-challenge of vector is not a likely treatment option and these subjects have effectively a single opportunity for therapy using this AAV capsid. Efficacy will be determined by FVIII activity at 16 weeks post dose. Safety will be evaluated for approximately 7 years after dosing. Any safety signal may trigger a review of the data and possible additional immunogenicity studies that include an assessment of cellular immune responses using collected PBMC. Additionally, if any of the events listed in Section 9.3.4.1 occur, enrollment into the trial will be halted to complete an extensive safety analysis. Notification of the study enrollment halt will be sent by the Sponsor to the participating sites via telephone and email immediately after becoming aware of a safety concern. This will ensure no additional subjects are dosed until the signal has been completely evaluated. If, following safety review by the DRB and the Sponsor, it is deemed

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appropriate to restart dosing, a request to restart dosing with pertinent data will be submitted to the health authority.

A summary of events and assessments are provided by visit in Table 9.1.1 for Screening, Baseline and BMN 270 Infusion, in Table 9.1.2 for Post-Infusion Follow-up, and in Table 9.1.3, Table 9.1.4, and Table 9.1.5 for Safety Follow-up.

Table 9.1.6, dealing with reactive corticosteroid use in the event of elevated LTs, is discussed in Section 9.4.8.2.

Liver Biopsy Substudy Design

All subjects enrolled in 270-201 and who are at least one year post-BMN 270 infusion are eligible for the optional liver biopsy substudy. Subjects who consent to participate in the substudy will have a liver biopsy via either the transjugular or percutaneous (ultrasound-guided) route, according to the standard procedures of the institution. To enhance safety, all subjects will have an ultrasound examination of the liver within 3 months prior to the procedure (to ensure there are no pathological findings such as bile duct obstruction that might interfere with the safe performance of the liver biopsy) and a FibroScan of the liver within one week before the liver biopsy (to correlate with any potential histopathologic findings of fibrosis on the biopsy).

Subjects who consent should have their FVIII levels monitored/adjusted by the Investigator to enable the procedure to be performed safely. This may require the administration of exogenous FVIII replacement products in order to achieve the desired FVIII activity. The target FVIII activity level within 24 hours prior to the liver biopsy is at the discretion of the Investigator and/or according to local guidelines, but at a minimum should be at the lower limit of the normal range (ie, at least 50 IU/dL).

Table 9.1.7 presents the schedule of assessments for participation in the liver biopsy substudy.

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Table 9.1.1: Schedule of Events – Screening and Infusion

	Pri	or to BMN 270 Infusion		BMN 270
Assessment	Screening ⁱ (Day -28 to Day -1)	Smart Rescreening ⁱ (Day -28 to Day -1)	Baseline (Day -7 to Day -1) ^h	Infusion Visit (Day 1) ^k
Informed consent	X			
Medical History	Х			
Physical Examination ^a	Х		X	Х
Height and Weight ^a	Х			
Vital Signs	Х	X		X
Assessment of Adverse Events and Concomitant Medications	Х	X	X	X
Documentation of bleeding episodes and FVIII usage (by either subject or clinical information)	X	X	Х	
Distribution of subject diaries and training in their use			X	
Electrocardiogram	X			
Chest X-ray	Х			
Liver Ultrasound	Х			
hFVIII Assays ^b	Х	Xj		
AAV5 Assays ^c	Х	Х		Х
Screen for Hepatitis B, Hepatitis C, HIV ^d	Х			
Blood chemistry, haematology, coagulation screen, and CRPe	Х	Х	Х	
Urine Tests ^e	Х	Х	X	
Liver Tests ^e	Х	Х	X	
PBMC collection for CTL baseline			Х	
Von Willebrand Factor Antigen (VWF:Ag)	Х			
Direct Thrombin Test			Х	
PCR of vector DNA in blood, saliva, urine, semen, and stools			Х	
Biomarker testing ^f	Х			
Exploratory biomarker assessments ^g			Х	
Haemo-QoL-A Quality of Life (QoL) assessment			X	
BMN 270 Infusion				Х

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- ^a Complete physical examination should be done at Screening. Brief physical examination may be done at Baseline and at the BMN 270 Infusion Visit. Height will be recorded at Screening only. Weight will be recorded at Screening and then every 6 months thereafter.
- ^b Includes baseline hFVIII activity (chromogenic substrate assay and one-stage clotting assay), hFVIII coagulation activity exploratory assay, hFVIII inhibitor level (Bethesda assay with Nijmegen modification), hFVIII total antibody titer, and hFVIII antigen (ELISA).
- ^c Screening (done during Screening) and testing (at Infusion Visit) of AAV5 pre-existing immunity may include plasma samples for 3 assays (in vivo transduction inhibition, in vitro transduction inhibition and AAV5 total antibody assays). Sample collection on the day of the infusion visit must be performed before the BMN 270 infusion is given.
- ^d Patients with documented negative results within the last 30 days do not need to be retested.
- ^e Refer to Table 9.7.9.2.1 for laboratory assessments to be included, and to Table 9.7.9.3.1 for liver tests.
- ^f Includes HLA genotyping, FVIII genotyping, TNFα and IL10a single nucleotide polymorphisms.
- ^g 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 Direct Thrombin Activity test and any other exploratory assessments) will be performed only as deemed necessary by the Sponsor.
- ^h Should the screening visit occur within 7 days of the drug infusion, physical examination, blood chemistry, LTs, haematology, urine tests, coagulation screen, and CRP do not need to be repeated at Baseline.
- ⁱ Smart rescreening should only be performed if a patient has been determined to be eligible for the study and is unable to complete the Baseline assessments and Infusion prior to the closing of the original Screening window. Subjects who undergo smart rescreening must complete the rescreening assessments and receive the infusion within 90 days of signing the original consent. Subjects who do not complete dosing within 90 days will be required to re-consent and undergo all screening procedures. Subjects may not undergo smart rescreening more than once.
- ^j Only the hFVIII inhibitor level (Bethesda assay with Nijmegen modification) assay must be done at smart rescreening.
- ^k Assessments on the day of infusion must be performed prior to the infusion. 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), following the infusion hourly (± 5 minutes) for 6 hours and then every 2 hours (± 15 minutes) for 6 hours and then at 4 hour intervals (± 15 minutes).

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

					F	'ollow-	Up Af	ter BN	/IN 27	0 Adm	inistra	tion –	Week	s*				
	,	Week	1															
Assessment	D2	D4	D8	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Physical examination ^a			X	X	X	X	X	X	X	X	X	X	X	X	X	X	Х	X
Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)			X	X	X	X	X	X	Х	X	Х	Х	X	X	X	X	Х	X
Vital Signs			X	X	X	Х	X	X	Х	X	X	X	X	Х	X	X	Х	X
Blood chemistry, haematology, coagulation screen, and CRP ^b				X		X		X		X		Х		X				X
Urine Tests ^b						Х				X				Х				X
Liver Tests (local) ^b		X	X	X	X	Х	X	X	X	X	X	X	X	Х	X	X	X	X
FVIII assays (local) ^c		X	X	Х	X	Х	X	X	Х	X	X	X	X	Х	X	X	Х	X
Liver Tests (central) ^b		X	X	Х	X	Х	Х	X	Х	X	X	X	X	Х	X	X	Х	X
FVIII assays (central) ^d		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Х	X
FVIII antibody titer						Х				X				X				X
PCR of vector DNA in blood, saliva, urine, semen, and stools ^e	X	X	X			X		X		X		X		X		X		X
Exploratory biomarker assessments ^f						Х				X				Х				X
Haemo-QoL-A QoL assessment			X	X	X	Х												X
AAV5 antibody titer										X								X
Testing for reactivation of hepatitis B and hepatitis C																		Xg
PBMC collection			X	Х	X	Х	Х	X	Х	X	Х	Х	X	Х	X	X	Х	X
Von Willebrand Factor Antigen (VWF:Ag)						Х				X				Х				X
Direct Thrombin test			Х												Х			

* Visit windows are \pm 48 hours (and include the Day 4 visit)

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^a Brief physical examination should be done at all weekly visits except Week 16, where a complete physical examination should be performed. Refer to Section 9.7.9.5. ^bRefer to Table 9.7.9.2.1 for laboratory assessments to be included, and to Table 9.7.9.3.1 for liver tests. LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) 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 \geq 3x ULN. Patients with ALT > 1.5 ULN during the study may undergo additional evaluations (eg, imaging studies including MRI or ultrasound, additional blood tests, and/or liver biopsy) at the discretion of the investigator. Additional testing of FVIII and LTs during any study week may be performed if: (1) the ALT has increased to above ULN; (2) Increases in ALT values from prior assessment are accompanied by declines in FVIII activity level; or after a discussion between the Medical Monitor and the Investigator based on a review of subject data. If FVIII levels and/or ALT values are stable over the course of several weeks, assessment of FVIII activity and ALT levels may be adjusted based on discussion between the Medical Monitor and the Investigator. ^c Includes hFVIII activity level (one-stage clotting assay and chromogenic substrate 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 \geq 5 IU/dL at 16 weeks after BMN 270 infusion and who have not resumed standard of care 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 Includes hFVIII activity level (one-stage clotting assay and chromogenic substrate assay), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, hFVIII coagulation activity exploratory assay, and hFVIII antigen (ELISA). If a subject has used FVIII within 72 hours of a measurement day, all efforts should be made to obtain FVIII activity measurements when a 72-hour interval without FVIII use is achieved; the 72-hour wash-out period is only intended for subjects who have achieved FVIII \geq 5 IU/dL at 16 weeks after BMN 270 infusion and who have not resumed standard of care 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 Collection to occur on Day 2 and 4 following BMN 270 infusion, and then until at least 3 consecutive negative results are obtained. Collection and testing of semen samples must continue through Week 12, even if 3 consecutive negative samples in that compartment have already been recorded.

- ^f 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 Direct Thrombin Activity test and any other exploratory assessments) will be performed only as deemed necessary by the Sponsor.
- ^g Testing for reactivation of hepatitis B and hepatitis C at Week 16, for subjects with a past medical history of Hepatitis B or Hepatitis C prior to study entry, should be performed only in subjects who have not received reactive corticosteroids prior to Week 16; subjects who have received reactive corticosteroids will have hepatitis B and hepatitis C testing at the time points indicated in Table 9.1.6.

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

	Follow-Up After BMN 270 Administration – Weeks*															
Assessment	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
Physical examination ^a	X	X	X	X	X	Х	X	X	X	X	X	X	X	X	X	X
Weight										X						
Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)	X	X	X	X	X	Х	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	Х	X	X	X	X	X	X	X	X	X	X
Blood chemistry, haematology, coagulation screen, and CRP ^b				X				X				X				X
Urine Tests ^b				X				X				X				X
Liver Tests (local) ^b	X	X	X	X	X	Х	X	X	X	X	X	X	X	X	X	X
FVIII assays (local) ^c	X	X	X	X	X	Х	X	X	X	X	X	X	X	X	X	X
Liver Tests (central) ^b	X	X	X	X	X	Х	X	X	X	X	X	X	X	X	X	X
FVIII assays (central) ^d	X	X	X	X	X	Х	X	X	X	X	X	X	X	X	X	X
FVIII antibody titer				X								X				
PCR of vector DNA in blood, saliva, urine, semen, and stools ^e				X				X				X				X
Exploratory biomarker assessments ^f				X				X				X				X
Haemo-QoL-A QoL assessment												X				
AAV5 antibody titer				X				X				X				X
PBMC collection	X	Х	X	X		Х		X		X		Х		X		X
Von Willebrand Factor Antigen (VWF:Ag)				X				X				Х				X
Direct Thrombin test										Х						

* Visit windows are \pm 48 hours

^a Brief physical examination should be done at all weekly visits. Refer to Section 9.7.9.5.

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^b Refer to Table 9.7.9.2.1 for laboratory assessments to be included, and to Table 9.7.9.3.1 for liver tests. LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) 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 \geq 3x ULN. Patients with ALT > 1.5 ULN during the study may undergo additional evaluations (eg, imaging studies including MRI or ultrasound, additional blood tests, and/or liver biopsy) at the discretion of the investigator. Additional testing of FVIII and LTs during any study week may be performed if: (1) the ALT has increased to above ULN; (2) Increases in ALT values from prior assessment are accompanied by declines in FVIII activity level; or after a discussion between the Medical Monitor and the Investigator based on a review of subject data. If FVIII levels and/or ALT values are stable over the course of several weeks, assessment of FVIII activity and ALT levels may be adjusted based on discussion between the Medical Monitor and the Investigator.

^c Includes hFVIII activity level (one-stage clotting and chromogenic substrate 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 standard of care 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 Includes hFVIII activity level (one-stage clotting and chromogenic substrate assay), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, hFVIII coagulation activity exploratory assay, and hFVIII antigen (ELISA). If a subject has used FVIII within 72 hours of a measurement day, all efforts should be made to obtain FVIII activity measurements when a 72-hour interval without FVIII use is achieved; the 72-hour wash-out period is only intended for subjects who have achieved FVIII \geq 5 IU/dL at 16 weeks after BMN 270 infusion and who have not resumed standard of care 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 Collection for each matrix to occur until at least 3 consecutive negative results are obtained.

^f 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 Direct Thrombin Activity test and any other exploratory assessments) will be performed only as deemed necessary by the Sponsor.

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

					1	Year 1 -	- Weeks	*				
Assessment	33	34	35	36	38	40	42	44	46	48	50	52
Physical examination ^a	Х	X	X	X	X	X	X	Х	X	X	X	X
Weight ^a												Х
Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)	Х	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	Х	X	X	X	X	X	X	X	X	X	X	Х
Blood chemistry, haematology, coagulation screen, and CRP ^b				X		X		Х		X		X
Urine Tests ^b				X		X		X		X		X
Liver Tests (local) ^b	Х	X	X	X	X	X	X	Х	X	X	X	X
FVIII assays (local) ^c	Х	X	X	X	X	X	X	Х	X	X	X	X
Liver Tests (central) ^b	Х	X	X	X	X	X	X	Х	X	X	X	X
FVIII assays (central) ^d	Х	X	X	X	X	X	X	X	X	X	X	X
AAV5 antibody titer				X		X		Х		X		X
FVIII antibody titer				X				X				X
PBMC Collection (for determination of FVIII and Capsid specific CTL activity)		X		X				X				X
Von Willebrand Factor Antigen (VWF:Ag)				X		X		X		X		X
Direct Thrombin Test					X							Х
PCR of vector DNA in blood, saliva, urine, semen, and stools ^e				X		X		X		X		X
Exploratory biomarker assessments ^f				X		X		X		X		X
Haemo-QoL-A QoL assessment												Х

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

^a Complete physical examination should be performed at Week 52; brief physical examination may be performed at other study visits. Refer to Section 9.7.9.5.

^b Refer to Table 9.7.9.2.1 for laboratory assessments to be included, and to Table 9.7.9.3.1 for liver tests. LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data, but LTs will be monitored at least

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twice weekly during periods when a subject's ALT is \geq 3x ULN. Patients with ALT > 1.5 ULN during the study may undergo additional evaluations (eg, imaging studies including MRI or ultrasound, additional blood tests, and/or liver biopsy) at the discretion of the investigator. Additional testing of FVIII and LTs during any study week may be performed if: (1) the ALT has increased to above ULN or increased by > 10 U/L from prior assessment; (2) Increases in ALT values from prior assessment are accompanied by declines in FVIII activity level; or after a discussion between the Medical Monitor and the Investigator based on a review of subject data. If FVIII levels and/or ALT values are stable over the course of several weeks, assessment of FVIII activity and ALT levels may be adjusted based on discussion

between the Medical Monitor and the Investigator.

^c Includes hFVIII activity level (one-stage clotting and chromogenic substrate 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 \geq 5 IU/dL at 16 weeks after BMN 270 infusion and who have not resumed standard of care 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 Includes hFVIII activity level (one-stage clotting and chromogenic substrate assay), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, hFVIII coagulation activity exploratory assay, and hFVIII antigen (ELISA). 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 standard of care 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 Sample testing during Safety Follow-Up is not required if at least 3 consecutive samples are cleared during the Post-Infusion Follow-Up period.
- ^f 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 Direct Thrombin Activity test and any other exploratory assessments) will be performed only as deemed necessary by the Sponsor.

Table 9.1.5: Schedule of Events – Safety Follow-Up (Years 2-7)

	Years 2-5*	Year 2*	Years 3-5*	Years	6-7]	End of Y	ear Visit	s		
				Q13W		Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	
Assessment	Q12W	Q4W ^h	Q6W ^{h,j}	(Remote) ⁱ	Q26W	W104	W156		W260	W312	W364	ETV
Physical examination ^a	Xa							Ka		X	X	X
Weight ^a	Xa						У	Ka		X	X	X
Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)	X	Х	Х	Х	Х		Σ	X		Х	Х	Х
Vital Signs	X						2	X		X	X	X
Blood chemistry, haematology, coagulation screen, and CRP ^b	X				X		2	K		Х	X	X
Urine Tests ^b	X						2	X				X
Liver Tests (local) ^b	X	Х	X				2	X				Х
FVIII assays (local) ^c	X	X	X				2	X				X
Liver Tests (central) ^b	X	X	X		X		2	X		Х	Х	X
FVIII assays (central) ^d	X	X	X		X		2	X		X	X	Х
FVIII Antigen assay	X				X		Σ	K		X	Х	Х
AAV5 antibody titer							2	K		Х	Х	Х
FVIII antibody titer							2	K		X	X	X
PBMC Collection (for determination of FVIII and Capsid specific CTL activity)	X						Σ	K				X
Von Willebrand Factor Antigen (VWF:Ag)	Х						Σ	K				Х
PCR of vector DNA in semen ^e	Xe	Xe	Xe		Xe		У	Ke		Xe	Xe	Х
PRC of vector DNA in blood, saliva, urine, stools ^e	Xe				Xe		У	Ke		Xe	Xe	Х
Exploratory biomarker assessments ^g	Х						2	X		Х	Х	Х

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	Years 2-5*	Year 2*	Years 3-5*	Years	6-7		1	End of Y	ear Visit	5	-	
				Q13W		Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	
Assessment	Q12W	Q4W ^h	Q6W ^{h,j}	(Remote) ⁱ	Q26W	W104	W156	W208	W260	W312	W364	ETV
Haemo-QoL-A QoL assessment	Xf				\mathbf{X}^{f}		Х	Kf		\mathbf{X}^{f}	Xf	X
Liver ultrasound ^k							X ^k (Yea	r 5 only)		X^k	X^k	Х

ETV: Early Termination Visit

* Visit windows are ± 2 weeks for visits in Years 2-5 and ± 4 weeks for visits in Years 6-7. The Q6W visits during Years 3-5 should restart after each End of Year visit (eg, the first Q6W visit during Year 3 should be ~6 weeks after the End of Year 2 visit).

^a Complete physical examination should be performed at the End of Year visits (genitourinary examination may be deferred unless the subject has genitourinary-related complaints); brief physical examination may be performed at other study visits. Weight should be recorded at the second Q12W visit each year during Years 2-5, and at every End of Year visit during Years 2-7.

- ^b Refer to Table 9.7.9.2.1 for laboratory assessments to be included, and to Table 9.7.9.3.1 for liver tests. LTs may be assessed more frequently when ALT values are $\geq 1.5x$ ULN or based upon discussion between the Medical Monitor and the Investigator. Subjects with ALT $\geq 1.5x$ ULN during the study may undergo additional evaluations (eg, imaging studies including MRI or ultrasound, additional blood tests, and/or liver biopsy) at the discretion of the investigator. Additional testing of FVIII and LTs during any study week may be performed if: (1) the ALT has increased to above ULN or increased by ≥ 10 U/L from prior assessment;; or (2) 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. 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. During Years 6-7, these tests should be performed at the Q26W and End of Year visits.
- ^c Includes hFVIII activity level (one-stage clotting and chromogenic substrate 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 \geq 5 IU/dL at 16 weeks after BMN 270 infusion and who have not resumed standard of care FVIII replacement therapy. If FVIII levels are elevated or stable over the course of several weeks, assessment of FVIII activity may be adjusted based on discussion between the Medical Monitor and the Investigator. A d-dimer may be considered under circumstances in which FVIII activity levels are above the normal physiological range and/or if there is a concern for a venous thromboembolism. If a subject tests positive in the Bethesda assay (with Nijmegen modification) during Years 3-5, a fresh sample should be collected within 4 weeks of the initial visit that had a positive result.

^d Includes hFVIII activity level (one-stage clotting and chromogenic substrate assay), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, and hFVIII coagulation activity exploratory assay. If a subject has used FVIII within 72 hours of a measurement day, all efforts should be made to obtain FVIII activity

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measurements when a 72 hour interval without FVIII use is achieved; the 72-hour wash-out period is only intended for subjects who have achieved FVIII \geq 5 IU/dL at 16 weeks after BMN 270 infusion and who have not resumed standard of care 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) in 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 Safety Follow-Up is not required if at least 3 consecutive samples are cleared during the Post-Infusion Follow-Up period. Subjects who have not had 3 consecutive negative semen samples by Week 52 should continue to have PCR testing every 4 weeks (during Year 2), every 6 weeks (during Years 3-5), and/or every 26 weeks (during Years 6-7) until 3 consecutive samples below the limit of detection are documented (or upon consultation between the Investigator and Medical Monitor).
- ^fHaemo-QoL-A QoL assessment during Years 2-5 of Safety Follow-up should be performed at the second Q12W visit each year and at every End of Year visit. During Years 6-7, the Haemo-QoL-A assessment should be performed at the Q26W visits and the End of Year visits.
- ^g 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 any other exploratory assessments) will be performed only as deemed necessary by the Sponsor.
- ^h 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), Q6W (during Years 3-5), or Q26W (during Years 6-7), until vector shedding has been cleared (but do not need to do other scheduled assessments at those visit dates), either by reporting to the site to provide samples or by providing those samples to an MN professional.
- ¹ For every 13 week remote visits during Years 6-7, the site should contact the subject to collect data on adverse events, new or changed concomitant medications, and diary entries (FVIII usage and bleeding events).
- ^j At applicable sites, certain study assessments designated in the Schedule of Events may be performed by a mobile nursing (MN) professional at the subject's home or another suitable location, such as their school or office. Refer to Section 9.7.9.2 for details.
- ^k Additional liver ultrasounds may be performed at interim timepoints (ie, between the End of Year visits) at the discretion of the Investigator.

Table 9.1.6: Schedule of Events – Reactive Corticosteroids for LT Elevations

	Steroid Treatment Period ^d									Post-Steroid Period ^c						
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11 ^b	Week 1	Week 2	Week 3	Week 4	Week 13
Reactive corticosteroids (dose in mg/day) ^a	60 mg	60 mg	40 mg	40 mg	30 mg	30 mg	20 mg	20 mg	15 mg	10 mg	5 mg					
FVIII activity testing												Х	X	Х	Х	
Liver testing												Х	X	X	Х	
Hepatitis B testing ^e						Х						Х				X
HCV Viral Load ^e						Х						Х				Х

^a Reactive corticosteroids may be initiated when a subject's ALT value is \geq 1.5x ULN or based on review of FVIII and liver enzyme data after consultation between the Investigator and the Medical Monitor.

^b Following initiation or completion of steroid regimen, if ALT elevation $\geq 1.5x$ ULN is reported, steroid management decisions will based on discussions between the Investigator and Medical Monitor. Modification of the steroid regimen may take into consideration timing of the ALT elevation (after Week 52), as well as possible confounders for the ALT elevation and adverse events related to corticosteroid dosing. Guidance for tapering oral corticosteroids can be found in Section 9.4.8.2.

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

^d Regardless of the assessments listed in the Schedule of Assessments (Table 9.1.2, Table 9.1.3, or Table 9.1.4), subjects initiated on corticosteroids will only be required to have laboratory evaluations on a weekly basis.

^e Should only be performed in subjects with a history of hepatitis B or hepatitis C prior to study entry.

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Table 9.1.7: Schedule of Events – Liver Biopsy Substudy

	Within 28 Days Before Biopsy Day	Within 7 Days Before Biopsy Day	1 Day Before Biopsy Day ^d	Biopsy Day (BD)
Informed Consent	X			
Liver Ultrasound ^a	X			
Brief Physical Examination	X		X	Х
Hematology, Coagulation, Chemistry Assessments ^b	X		X	
Liver Tests ^b	X		X	Х
FibroScan		Х		
Local FVIII Activity Level Assessment		Х	X	Х
Pre-Biopsy Consultation ^c		Х		
Liver Biopsy ^e				Х

^a Liver ultrasound must be performed within 28 days prior to the scheduled biopsy, unless an ultrasound result from the prior 3 months is already available.

^b Refer to Table 9.7.9.2.1 for laboratory assessments to be included, and to Table 9.7.9.3.1 for liver tests.

^c Subjects will undergo a pre-biopsy consultation with the investigator (treating hematologist).

^d Subjects may need to repeat/extend this visit if their FVIII activity levels need adjustment before the biopsy, at the discretion of the investigator (treating hematologist).

^e 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.

9.2 Discussion of Study Design, Including Choice of Control Group

Study 270-201 is designed to be a first-in-man, phase 1/2 open-label, dose escalation study in patients with severe haemophilia A. Four doses of BMN 270 will be evaluated and the dose escalation decision tree for Cohorts 1-3 is summarized in Figure 9.1.1.

The decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and the DRB.

There will be no control group. Parameters for each subject will be compared to a pre-treatment assessment of safety (liver function) and efficacy (number of bleeds, use of replacement therapy).

As AAV based treatment always leads to anti-capsid immune response, no true control group (for example with an empty AAV) is possible.

9.3 Selection of Study Population

Up to 15 severe haemophilia A patients may enroll into the study; the actual number of patients will depend on the criteria for dose escalation.

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 criteria:

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

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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 immunity to the AAV5 capsid as measured by AAV5 transduction inhibition or AAV5 total antibodies
- 2. Any evidence of active infection or any immunosuppressive disorder.
- 3. HIV positive
- 4. Significant liver dysfunction as defined by abnormal elevation of:
 - ALT (alanine transaminase) to 3 times the upper limit of normal;
 - Bilirubin above 3 times the upper limit of normal;
 - Alkaline phosphatase above 3 times the upper limit of normal; or
 - INR (international normalized ratio) \geq 1.4.
- 5. Potential participants who have had a liver biopsy in the past 3 years are excluded if they had significant fibrosis of 3 or 4 as rated on a scale of 0-4
- 6. Evidence of any bleeding disorder not related to Haemophilia A
- 7. Platelet count of $< 100 \text{ x } 10^9/\text{L}$
- 8. Creatinine $\geq 1.5 \text{ mg/dL}$
- 9. Liver cirrhosis of any etiology as assessed by liver ultrasound
- 10. Hepatitis B if surface antigen is positive
- 11. Hepatitis C if RNA is positive
- 12. Treatment with any IP within 30 days prior to the end of the screening period
- 13. Any disease or condition at the physician's discretion that would prevent the patient from fully complying with the requirements of the study including possible corticosteroid treatment outlined in the protocol. The physician may exclude patients unwilling or unable to agree on not using alcohol for the 16-week period following the viral infusion.
- 14. Prior treatment with any gene transfer agent
- 15. Major surgery planned in the 16-week period following the viral infusion
- 16. Use of immunosuppressive agents or live vaccines within 30 days before the viral infusion

9.3.3 Liver Biopsy Substudy Inclusion and Exclusion Criteria

Individuals eligible to participate in the liver biopsy substudy must meet all of the following criteria:

- 1. Currently enrolled in 270-201
- 2. Received BMN 270 infusion at least 1 year prior to enrollment in the substudy
- 3. Able to sign informed consent and comply with requirements of the substudy
- 4. FVIII activity at least >50 IU/dL (or higher, depending on local guidelines and/or Investigator discretion) within 24 hours prior to the liver biopsy being performed. (FVIII 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 to an appropriate level, under the supervision/instruction of the Investigator.

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

- 1. Assessed by the investigator or a hepatologist as having a medical condition such that undergoing a liver biopsy would be contraindicated. These conditions could include (but are not limited to):
 - Significant thrombocytopenia (platelet count $< 100 \text{ x } 10^{9}/\text{L}$)
 - Evidence of significant ascites
 - Abnormalities detected on liver ultrasound (performed within 90 days of procedure) that would preclude safe performance of the biopsy.

9.3.4 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. A subject's participation in the study may be discontinued at any time at the discretion 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.

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 admitted into the study or does not meet entry criteria
- 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 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 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.

9.3.4.1 Study Safety Evaluation Criteria

If any of the following events occur in a subject in the study who has received BMN 270 infusion, enrollment into the trial will be put on halt to complete an extensive safety analysis per Section 9.1.

• Any ALT elevation > 5x ULN for at least 2 consecutive weeks after administration of BMN 270, in the absence of a definitive alternate etiology for the increase

- The occurrence of Grade 3 or higher adverse events (excluding ALT elevation) assessed as related to study drug, including liver failure and clinical hepatitis
- The detection of neutralizing antibodies to hFVIII following BMN 270 infusion
- The detection of AAV vector DNA in the semen of a participant in 3 consecutive samples (which are at least 2 weeks apart) more than 52 weeks after BMN 270 infusion, as discussed in Section 9.7.9.7
- The occurrence of a malignancy excluding skin cancers at any point after BMN 270 infusion

If the following event occurs in a subject in the study who has received BMN 270 infusion, a DRB review and analysis of safety data will be undertaken to determine whether the enrollment into the trial will be put on halt:

• Grade 2 adverse event assessed as related to study drug that persists for at least 7 days

9.3.5 Subject Identification and Replacement of Subjects

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

Subjects who withdraw from the study will not be replaced.

9.3.6 Duration of Subject Participation

The duration of this study will be approximately 368 weeks. This includes 4 weeks of screening, 1 day of BMN 270 infusion, 16 weeks of Post-Infusion Follow-Up, and 348 weeks of Safety Follow-Up. A primary endpoint analysis on safety and efficacy will be performed at 16 weeks.

9.4 Treatments

BioMarin or its designee will provide the study site with study drug sufficient for study completion. BioMarin is responsible for shipping study drug to clinical sites.

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.

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 2 mL polypropylene cryovial. Each vial contains 1.1 mL of AAV5-hFVIII-SQ at a concentration of 2E13 vector genomes per mL in a pH 7.4 phosphate buffer.

The study drug label includes the following information: lot number, required storage conditions, a precautionary statement, expiry date, study number, and BioMarin name and address. Labelling will be done according to country specific requirements.

9.4.3 Storage

At the study site, all IP must be stored under the conditions specified in the IB 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

After a physical examination performed by the PI or designee, participants will be admitted on the day of BMN 270 infusion. 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. An electric syringe pump will be used to infuse through an in-line, low protein binding 0.22 micron filter. BMN 270 will be infused through the catheter using an appropriate infusion pump at a constant rate of 4 ml/min while monitoring the vital signs (pulse, blood pressure, respiration rate and temperature) at 15 minute (\pm 5 minutes) intervals. The anticipated maximum interval from initiation of thawing of BMN 270 to completion of the infusion is 4 hours, although the IP has been shown to be stable at room temperature for 6 hours.

Following completion of the infusion, vital signs will be monitored hourly (\pm 5 minutes) for 6 hours and then every 2 hours (\pm 15 minutes) for 6 hours and then at 4 hour intervals. If the vital signs are stable the catheter will be removed 20-24 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 24 hours to observe for any immediate toxicity of the procedure. After 24 hours, participants will be discharged from the clinic unless toxicity has been observed in which case the stay in the clinic may be Proprietary and Confidential 24 August 2021

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.

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 Sponsor will be required prior to enrollment of each study subject. Upon their enrollment into the study, subjects will be assigned a unique subject number and dose level by the Sponsor.

Cohorts 1 to 3 are enrolled serially and their dose is defined in Section 9.4.6.2 below. Escalation is based on FVIII activity 3 weeks after injection. Cohorts may receive the next higher dose if subjects in the previous cohort does not meet the activity criteria, or the same dose if subjects in the previous cohort meets the activity criteria. Subjects in Cohort 4 will all be enrolled at a single dose.

9.4.6 Selection of Doses Used in the Study

The starting dose was based on the expression of hFVIII observed in nonclinical studies of mice and monkeys. The starting dose has a significant safety margin (10-fold) from NOAEL in mice. The dose escalation is half-logs based.

9.4.6.1 Selection of Timing of Dose for Each Subject

A minimum of three weeks are required between subjects, to allow for evaluation of safety and expression of hFVIII. After three weeks, depending on the activity level, the choice of the dose for the next subject will be made as described below.

9.4.6.2 Selection of Dose for Each Subject

The starting dose was determined by expression of hFVIII observed in mice and monkeys and a scale up factor based on previous experience, an improved purification process over previous trials (thus potentially decreasing the risk of immune response), and a new evaluation of the titer (PCR performed after hairpin removal).

For Cohorts 1 to 3, approximately three weeks after an injection, the decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and the DRB.

Subject 1 (Cohort 1) will be dosed by intravenous infusion with 6E12 vg/kg of body weight. If the FVIII activity level does not reach 5 IU/dL or greater (expressed as % in Figure 9.1.1) at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 1 and enrollment into Cohort 2 will initiate with Subject 2 at the next dose (2E13 vg/kg).

If the FVIII activity level in the first subject treated in Cohort 2 does not reach \geq 5 IU/dL at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 2 and enrollment into Cohort 3 (6E13) will initiate with the next subject.

If the FVIII activity level in the first subject treated in Cohort 3 does not reach \geq 5 IU/dL at the Week 3 visit in both assays, then the DRB will recommend whether to continue to add subjects to the cohort and/or whether to continue the study.

For the first subject treated in each of the first 3 cohorts, if the activity level reaches ≥ 5 IU/dL and no safety issue is found, then up to four subjects will be enrolled in that cohort, though the adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

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

There will be an ongoing review of individual patient safety and efficacy data by the medical monitor and the DRB. The adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

Refer to Figure 9.1.1 for a visual representation of the study design for Cohorts 1-3

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 CRF. The Investigator may prescribe additional medications 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 CRF.

The following medications are prohibited starting 30 days before Screening:

- Live vaccines
- Systemic immunosuppressive agents
- Emicizumab

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- Fitusiran
- Concizumab
- Efavirenz

Subjects who begin antiretroviral therapy following BMN 270 infusion and during their participation in 270-201 must have their antiretroviral medication regimen approved by the Investigator and Medical Monitor prior to starting antiretroviral treatment.

Medications which are predominately metabolized by the liver (eg, acetaminophen) and alcohol should, whenever possible, be avoided for the first 52 weeks of the study, and particularly within 48 hours prior to lab work.

Administration of SARS-CoV-2 vaccine after BMN 270 infusion may occur after consultation between Investigator and Medical Monitor. Investigators should use clinical judgment, taking into consideration local factors, individual risk factors, and the benefit/risk related to timing of vaccine administration.

9.4.8.1 Concomitant Haemophilia Treatments

Subjects on "episodic" therapy for FVIII will continue their treatment at will. Subjects on prophylactic FVIII therapy will discontinue their treatment starting the day of infusion and switch to an "episodic" schedule. FVIII can always be taken as needed by the subject, who will carefully record his treatment and bleeding episodes in his diary. In addition, information on FVIII usage by medical history will be collected (if available) from subjects for the 6 month period immediately preceding study enrollment.

9.4.8.2 Glucocorticoid Treatment of Elevated Hepatic Transaminases

During the Post-Infusion Follow-up Period and the Safety Follow-Up Period, each subject will have comprehensive surveillance plan monitoring of LTs (at local labs, once per week for Weeks 1-36, then once every 2 weeks from Week 37-52). LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.

9.4.8.2.1 Reactive Corticosteroids

In general, reactive corticosteroids may be initiated when a subject's ALT value is $\geq 1.5x$ ULN, or based on review of FVIII and liver enzyme data after consultation between the Medical Monitor and the Investigator. Corticosteroids may be delayed, upon discussion with the Medical Monitor, if elevations in ALT are clearly not related to BMN 270 (eg, elevated ALT with concurrent increase in CPK due to intensive exercise) and in particular for elevations occurring more than 52 weeks after BMN 270 dosing.

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Reports of raised LTs (defined as $ALT \ge 1.5x$ ULN) should be made to the BioMarin medical monitor within 30 minutes of the lab value being available. Local laboratory results of LTs will be used to trigger corticosteroid treatment as needed. In case of discrepant results between local and central laboratories, the Investigator and Medical Monitor will decide further action.

Following initiation or completion of reactive corticosteroids, if ALT elevation \geq 1.5x ULN is reported, steroid management decisions will based on discussions between the Investigator and Medical Monitor. Modification of the steroid regimen may take into consideration possible confounders for the ALT elevation and impact on FVIII expression.

Unless otherwise indicated, treatment with reactive corticosteroids should be initiated at a dose of 60 mg per day and then gradually tapered if the ALT level remains stable or declines after 2 weeks (60 mg daily for the first 2 weeks, then 40 mg the next 2 weeks, then 30 mg the next two weeks, then 20 mg the next two weeks, then 15 mg for the next week, then 10 mg for the next week, then 5 mg for the next week, then stop, for a total treatment of 11 weeks) (refer to Table 9.1.6).

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 9.4.8.2.1.1):

Table 9.4.8.2.1.1: Management of ALT Elevations with Reactive Corticosteroids

r	
	• 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, contact the Medical Monitor to discuss the initiation of 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
$ALT \ge 1.5x$	• Consider evaluation with additional liver tests (including but not limited to ALT, AST, bilirubin, and alkaline phosphatase)
Baseline or > ULN	• 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
	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
Warraning ALT	 Increase corticosteroid dose up to a maximum of 1.2 mg/kg for no more than 2 weeks
Worsening ALT	• 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 ($\geq 1.5x$ 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 9.4.8.2.1.2): Proprietary and Confidential 24 August 2021

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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	

Table 9.4.8.2.1.2: Viral and Autoimmune Hepatitis Testing

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

Management and monitoring of reactions to corticosteroids should be determined by the Investigator's clinical judgment in consultation with the Sponsor's Medical Monitor. This includes the contraindicated use of NSAIDs during corticosteroid treatment, and specific monitoring not already covered by the schedule of events. The use of COX-2 inhibitors, while not contraindicated during corticosteroid treatment, should be limited, if possible. Practical management to prevent complications related to oral corticosteroid therapy may be undertaken at the discretion of the Investigator (eg, evaluation of glucose intolerance, hyperlipidemia etc.). For the subjects with a past medical history of hepatitis B or hepatitis C prior to study entry, Hepatitis B status and HCV viral load will be rechecked 6 weeks after the start of corticosteroid treatment, and then 1 week and 13 weeks after the completion of corticosteroid treatment. All adverse events 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.

9.4.9 Treatment Compliance

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

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9.5 Investigational Product Accountability

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

9.5.1 Return and Disposition of Clinical Supplies

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

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

All study drug and related materials should be stored, inventoried, reconciled, and destroyed or returned according to applicable state and federal regulations and study procedures.

9.6 Dietary or Other Protocol Restrictions

There are no dietary or other protocol restrictions for this 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 samples.

9.7 Safety and Efficacy Variables

As this is a first-in-man study, the primary endpoint of safety will be assessed as explained in Section 9.7.9.

The primary efficacy measure will be to assess plasma FVIII activity. The efficacy goal of the study is to establish the dose relationship to FVIII activity \geq 5 IU/dL at 16 weeks post BMN 270 administration.

9.7.1 Safety and Efficacy Measurements Assessed

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

9.7.2 Primary Efficacy Variables

The primary efficacy measure will be the plasma FVIII activity monitored on a regular basis after BMN 270 dose. The efficacy goal of the protocol is to ascertain the dose range of BMN 270 required to convert severe HA patients to expression of FVIII at 5 IU/dL or above, (ie, a mild severity). This is associated in natural history studies with clinically superior long term outcomes (Den Ujil 2011).

The following assays (assessed by the central laboratory) will be used to measure the primary efficacy variable:

- FVIII activity (chromogenic substrate assay)
- FVIII activity by one-stage clotting 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 standard of care FVIII replacement therapy.

The FVIII activity level in both assays and the number of subjects with FVIII activity ≥ 5 IU/dL in at least one of the two assays will be summarized.

FVIII activity assays will also be performed at the local laboratory at the time points indicated in Table 9.1.2, Table 9.1.3, Table 9.1.4, and Table 9.1.5 but will be used in conjunction with local lab LT assessments to monitor subject safety and need for initiation of reactive corticosteroid dosing; local laboratory FVIII activity assessments will not be used to assess efficacy or to measure the primary efficacy outcome of the study.

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, follow an abbreviated visit schedule after Week 52, as applicable and at the discretion of the Investigator.

Timing of assessment by these assays is provided in Table 9.1.2, Table 9.1.3, Table 9.1.4, and Table 9.1.5. Details on performing the assays are included in the Laboratory Manual.



9.7.3 Secondary Efficacy Variables

Secondary efficacy measures will be the reduction in the frequency of factor replacement therapy, and reduction in the number of bleeding episodes. 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.

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

9.7.4 Immunogenicity

Immunogenicity assays will be performed on plasma. The assays will include detection of anti-capsid, and anti-FVIII total antibody, and determination of neutralizing antibodies against FVIII. Any increase in total antibody level, especially during the time period of 5-12 weeks, will be compared with FVIII activity measurements. Any abnormality of the liver parameters will lead to a retrospective immunogenicity assessment to determine anti-FVIII and capsid specific CTL. Anti-FVIII and capsid specific CTL assays will be performed on collected PBMCs.

Timing of assessment by these assays is provided in Table 9.1.2, Table 9.1.3, and Table 9.1.4.

9.7.5 Pharmacodynamics

The hFVIII antigen and activity level will be measured by an ELISA (antigen) and by one-stage clotting and/or chromogenic substrate assay (activity). Individual antigen and activity plasma plots will be prepared to assess changes over 16 weeks. FVIII activity measurements will be used to determine PD parameters.

If supported by FVIII activity data, non-compartmental analysis and observation will be used to estimate individual values of C_b (baseline concentration), C_{ss} (steady state concentration), T_{ss} (time to steady state), C(t) and AUC(0-t) where t is 16 weeks. Other parameters that may be used to describe individual FVIII protein and activity plasma profiles are C_{max} (maximum concentration) and C_{avg} (average concentration, AUC(0-t)/t). The PD parameters and dose will be used to assess clinical pharmacology.

Sample collection times are indicated in Table 9.1.2, Table 9.1.3, Table 9.1.4, and Table 9.1.5.

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9.7.6 Exploratory Assessments

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

Liver biopsy samples collected as part of the exploratory substudy may also be tested to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to hemophilia A, coagulation, and/or AAV gene transfer. Subjects participating in the substudy 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 may be used for exploratory use once the primary use has been completed.

On an exploratory basis, samples may be fractionated prior to shedding analysis in order to better characterize the presence and location of vector DNA and/or vector capsid within each matrix. The fractionation may be performed with samples collected specifically for shedding analysis (saliva, blood, semen, urine, faeces), or by using exploratory samples, such as plasma, PBMCs, and red blood cells, collected under the study protocol.

9.7.7 Haemo-QoL-A Quality of Life Assessment

The Haemo-QoL-A is a patient-reported outcome (PRO) questionnaire which will be used to assess subject quality of life (QoL) during the study. Assessments will occur at the time points listed in the Schedules of Assessments.

Details regarding the QoL assessment will be included in the Study Reference Manual.

9.7.8 Liver Biopsy Substudy

The objectives of the liver biopsy substudy are considered exploratory.

Subjects who consent to the procedure will have a liver biopsy via either the transjugular or percutaneous (ultrasound-guided) route, according to the standard procedures of the institution. To enhance safety, all subjects will have an ultrasound exam of the liver within 28 days prior to the procedure (to ensure there is no obstruction to the liver that would interfere with the liver biopsy) and a FibroScan of the liver within one week before the liver

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biopsy (to correlate any histopathologic findings on the biopsy). Subjects will also undergo a pre-biopsy consultation with the investigator (treating hematologist).

Within 24 hours prior to the biopsy being performed, subjects must have a FVIII activity level of at least 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 the day before the biopsy. 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".

The liver biopsy should be performed in the morning, 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 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 and/or according to local guidelines.

Participation in the substudy may include liver biopsies at one or more time points.

Safety findings arising from the histopathological analysis of the biopsy sample are subject to Adverse Event reporting (Section 10), and such findings should be further assessed and followed-up as clinically appropriate and in order to safeguard the subject's ongoing medical care (this should be done in consultation with a hepatologist and/or other specialist clinicians if required). In the event fibrotic changes being observed on the biopsy sample, additional follow-up Fibroscans may be considered (with the frequency of subsequent scans at the discretion of the Investigator and/or hepatologist).

Where a biopsy has been taken for safety-related reasons (rather than as part of the liver biopsy substudy) 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 not performed as part of the substudy be made available for additional histopathological review.

9.7.9 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.

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9.7.9.1 Adverse Events

The occurrence of AEs will be assessed continuously from the time the subject signs the ICF. The determination, evaluation and reporting of AEs will be performed as outlined in Section 10. Assessments of AEs will occur at the time points shown in Table 9.1.1, Table 9.1.2, Table 9.1.3, Table 9.1.4, and Table 9.1.5.

9.7.9.2 Clinical Laboratory Assessments

Specific visits for obtaining clinical laboratory assessment samples are provided in Table 9.1.1, Table 9.1.2, Table 9.1.3, Table 9.1.4, and Table 9.1.5. The scheduled clinical laboratory tests are listed in Table 9.7.9.2.1. Refer to the Study Reference Manual 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 the cause of the abnormality is determined, the value returns to baseline or to within normal limits, or 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 CRF.

Blood Chemistry	Haematology	Urine Tests	Other
Albumin	Haemoglobin	Appearance	CRP
BUN	Haematocrit	Color	
Calcium	WBC count	pН	Coagulation Screen
Chloride	RBC count	Specific gravity	including:
Total cholesterol	Platelet count	Ketones	APTT
CO ₂	Differential cell count	Protein	PT/INR
СРК		Glucose	TT
Creatinine		Bilirubin	
Glucose		Nitrite	Other Tests:
Phosphorus		Urobilinogen	ABO blood typing*
Potassium		Haemoglobin	
Total protein			
Sodium			
Uric Acid			

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BUN, blood urea nitrogen; CO₂, carbon dioxide; 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.

* ABO blood typing assessment should be completed at the next regularly scheduled study visit (or at least prior to the end of the subject's participation in the study).

At applicable sites, certain study assessments designated in the Schedule of Events may be performed by a mobile nursing (MN) professional at the subject's home or another suitable location, such as their school or office, to improve access and convenience for subjects 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 subject and the subject gives written informed consent to participate in MN visits, the MN network will communicate with the subject and the subject's site.

9.7.9.3 Malignancies

Liver ultrasounds will be performed annually at each End of Year visit starting at Year 5 (Week 260) through the end of the study to screen for HCC. Additional liver ultrasounds may be performed between the End of Year visits at the discretion of the Investigator.

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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.

9.7.9.4 Liver and Hepatitis Testing

Subjects will be screened for evidence of previous hepatitis B or hepatitis C infection at Screening. Subjects with documented results showing an absence of active hepatitis B or hepatitis C infection (as measured by positive surface antigen for hepatitis B or positive RNA testing for hepatitis C) 30 days prior to providing signed informed consent do not need to be screened again.

Evidence of ongoing hepatitis B or hepatitis C infection is exclusionary. Subjects with a history of hepatitis B or hepatitis C will be asked for information about the treatments received as part of their medical history assessment at Screening.

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

A liver ultrasound and LTs at Screening will identify any significant hepatic dysfunction, which is defined as:

- More than 3x the normal ALT level
- More than 3x the normal bilirubin level
- More than 3x the normal Alkaline phosphatase level.
- INR \geq 1.4.
- Thrombocytopenia under $100 \ge 10^9/L$
- Liver ultrasound results indicative of a liver cirrhosis

Liver tests will be monitored on a regular basis, at the time points indicated in Table 9.1.1, Table 9.1.2, Table 9.1.3, Table 9.1.4, and Table 9.1.5. At each time point, the following LTs should be assessed:

Table 9.7.9.3.1: 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

Patients with ALT > 1.5 ULN during the study may undergo additional evaluations (eg, imaging studies including MRI or ultrasound, additional blood tests, and/or liver biopsy) at the discretion of the investigator.

9.7.9.5 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.

9.7.9.6 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 Screening, Baseline, and at the beginning of each visit during the Post-Infusion Follow-Up and Safety Follow-Up periods. On the day of the BMN 270 Infusion, vital signs will be monitored prior to infusion, during the infusion every 15 minutes (\pm 5 minutes), following the infusion hourly (\pm 5 minutes) for 6 hours and then at 4 hour intervals (\pm 15 minutes).

A complete physical examination is necessary during Screening/Baseline, at Week 16 and 52 and at the End of Years visits thereafter. 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.

At other visits, brief physical examinations may be performed at the discretion of the investigator based on the subject's clinical condition. A brief physical examination will include general appearance, cardiovascular, respiratory, neurologic, dermatologic,

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musculoskeletal, and gastrointestinal assessments. Particular attention should be given to signs of bleeding, as well as assessing possible hemarthroses.

Height will be recorded at Screening only. Weight will be recorded at Screening, at Weeks 26 and 52 during Year 1, and then at the second Q12W visit each year during Years 2-5 and at every End of Year visit during Years 2-7.

9.7.9.7 Vector Shedding

Vector shedding has been extensively studied in all similar clinical trials performed to date. (Nathwani 2014; Manno 2006; Schenk-Braat 2007; Croteau 2004). In the literature referenced above, including Haemophilia B clinical studies utilizing AAV2 and AAV8, vector was no longer detectable after 40 days in blood, saliva, urine or stool, but in one study was detected in the seminal fluid but not in motile sperm (Manno 2006). In these studies, the amount of vector present in these bodily fluids involved an extremely small fraction of the infused dose. More recent data from an ongoing AAV-FIX study demonstrates persistence of the vector in both the blood and the semen for at least 39 weeks (Miesbach 2016).

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 PCR at the time points indicated in Table 9.1.2, Table 9.1.3, Table 9.1.4, and Table 9.1.5. Fluids tested will include:

- Blood
- Saliva
- Semen
- Urine
- Stool

Vector shedding will also be extensively studied in the present clinical trial, every other week between Weeks 4-16, then every 4 weeks to Week 52 until at least 3 consecutive negative results are obtained. Testing of semen will continue through Week 12, even if 3 consecutive negative results have been recorded in that compartment prior to that timepoint. Subjects who have not had 3 consecutive negative semen samples by Week 52 should continue to have PCR testing every 4 weeks (during Year 2), every 6 weeks (during Years 3-5), and every 26 weeks (during Years 6-7) until 3 consecutive semen samples below the limit of detection of the test are documented (or upon consultation between the Investigator and Medical Monitor). Subjects who meet the definition of treatment failure and wish to follow an abbreviated schedule (refer to Section 12.5.3 but who have not cleared vector shedding from semen must still provide samples for assessment until vector shedding has cleared: Proprietary and Confidential 24 August 2021

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every 4 weeks (during Year 2), every 6 weeks (during Years 3-5), or every 26 weeks (during Years 6-7), either by reporting to the site to provide samples or by providing those samples to an MN professional.

Contraception use may need to be extended beyond 26 weeks in individual subjects based on observed vector shedding in semen. After 6 months, 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 haematology, 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, a reportable adverse event (AE) is any untoward medical occurrence (eg, sign, symptom, illness, disease or injury) in a subject administered the study-drug or other protocol-imposed intervention, regardless of attribution. This includes the following:

- AEs not previously observed in the subject that emerge during the course of the study.
- Pre-existing medical conditions judged by the Investigator to have worsened in severity or frequency or changed in character during the study.
- Complications that occur as a result of non-drug protocol-imposed interventions (eg, AEs related to screening procedures).

An adverse drug reaction is any AE for which there is a reasonable possibility that the study-drug caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the study-drug and the AE.

Whenever possible, it is preferable to record a diagnosis as the AE term rather than a series of terms relating to a diagnosis.

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 meets 1 or more of the following criteria:

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- Is fatal
- Is life threatening
- Note: Life-threatening refers to an event that places the subject at immediate risk of death. This definition does not include a reaction that, had it occurred in a more severe form, might have caused death.
- Requires or prolongs inpatient hospitalization.
- 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 intervention to prevent one of the above consequences (eg, anaphylaxis)

All adverse events that do not meet any of the criteria for SAEs should be regarded as non-serious AEs.

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 $ALT \ge 1.5x$ ULN, regardless of whether that triggers an initiation or modification of corticosteroid treatment
- Events meeting the criteria for Hy's law (ALT or AST elevation \ge 3x ULN plus total bilirubin \ge 2x ULN)
- Thromboembolic event
- 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 treatment, only SAEs associated with any protocol-imposed interventions will be reported. After informed consent is obtained and the first administration of study drug, the reporting period for all non-serious AEs and SAEs begins and continues for approximately 7 years or until study discontinuation/termination, whichever is longer. The criteria for determining, and the reporting of SAEs is provided in Section 10.1.1.1.

10.3.2 Eliciting Adverse Events

Investigators will seek information on AEs, SAEs, and EOSI at each subject contact by specific questioning and, as appropriate, by examination. Information on all AEs and SAEs and EOSI, should be recorded in the subject's medical record and on the 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 10.1.1.1 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 10.1.1.1. 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 severity of each will be assessed using the defined categories in Table 10.3.3.2.1.

The Investigator will determine the severity of each AE and SAE and EOSI using the NCI CTCAE v4. 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 as stated below.

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Table 10.3.3.2.1: Adverse Event Grading (Severity) Scale

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

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

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

10.3.3.3 Causality

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

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

Table 10.3.3.3.1: Causality Attribution Guidance

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

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

The investigator's assessment of causality for individual AE reports is part of the study documentation process. Regardless of the Investigator's assessment of causality for individual AE reports, the Sponsor will promptly evaluate all reported SAEs against

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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 an 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

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 haemorrhage 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.

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10.4.1.4 Abnormal Laboratory Values

Laboratory test results will be recorded on the laboratory results pages of the AE 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 hFVIII 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.

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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 document 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 10.1.1.1).

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 procedure or assessment
- Undergo a diagnostic or elective surgical procedure for a pre-existing medical condition that has not changed
- Insert an in-dwelling IV catheter (such as a Port-a-Cath or other brand) 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 Proprietary and Confidential 24 August 2021

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Sponsor. Pregnancy in partner should be reported during the period up to 5 years after viral infusion.

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

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

10.5 Reporting Requirements

10.5.1 Expedited Reporting Requirements

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

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

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

10.5.2 Ethics Committee Reporting Requirements

Reporting of SAEs to the Independent Ethics Committee (IEC) will be done in compliance with the standard operating procedures and policies of the IEC and with applicable regulatory requirements. Adequate documentation must be obtained by BioMarin showing that the IEC was properly and promptly notified as required. Proprietary and Confidential 24 August 2021

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10.6 Follow-up of Subjects after Adverse Events

The Investigator should follow all unresolved AEs and SAEs until the events are resolved or have stabilized, the subject is lost to follow-up, or it has been determined that the study treatment or participation is not the cause of the AE/SAE. Resolution of AEs and SAEs (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, 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 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 treatment.

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 treatment. 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 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

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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:

- Immediate need to revise the IP administration (eg, modified dose amount or frequency not defined in protocol)
- 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, PhD	
Address:	105 Digit	Biomarin Pharmaceutical Inc 105 Digital Drive Novato, CA 94949	
Phone	PI	CA 94949	
E-mail:	PI		

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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 assay and the one-stage clotting 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 will be performed within 28 days (+ 14 days) of BMN 270 infusion while baseline assessments will take place within 7 days of BMN 270 infusion (Day 1). Should the screening visit occur within 7 days of the drug infusion, physical examination, vital signs, blood chemistry, LTs, haematology, urine tests, coagulation screen, and CRP do not need to be repeated at Baseline.

The following procedures will be performed during the Screening Period:

- Full medical history, including haemophilia A history, hepatitis B, hepatitis C, and HIV.
 - Subjects with a history of hepatitis B or hepatitis C will be asked for information about the treatments received. Any prior pharmacokinetics information obtained while the subject was receiving prophylactic or on-demand FVIII therapy prior to the study should also be collected. For subjects who have already enrolled in 270-201, this information should be collected at the next regularly scheduled study visit (or at least prior to the subject's completion of study participation).
- 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)
- Electrocardiogram
- Chest X-ray
- Liver Ultrasound
- Samples for hFVIII Assays
 - Baseline hFVIII activity chromogenic substrate (plasma)
 - Baseline hFVIII activity level one-stage clotting assay

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- hFVIII coagulation activity exploratory assay
- hFVIII inhibitor level (Bethesda assay with Nijmegen modification)
- hFVIII total antibody assay
- hFVIII antigen (ELISA)
- Blood sample for AAV5 Assays
 - o AAV5 antibody titer
 - o AAV5 transduction inhibition assay
- Screen for hepatitis B, hepatitis C, and HIV if required (subjects with documented negative results 30 days prior to informed consent being obtained do not need to be retested)
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.9.2.1)
- Urine Tests (refer to Table 9.7.9.2.1)
- Liver Tests (refer to Table 9.7.9.3.1)
- Von Willebrand Factor Antigen (VWF:Ag)
- Blood samples for Biomarker testing (including HLA genotyping, FVIII genotyping status, TNFα and IL10a single nucleotide polymorphisms)

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 sample for AAV5 Assays

- o AAV5 antibody titer
- $\circ \quad AAV5 \ transduction \ inhibition \ assay$
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.9.2.1)
- Urine Tests (refer to Table 9.7.9.2.1)
- Liver Tests (refer to Table 9.7.9.3.1)

12.3 Baseline Visit

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

- Physical examination
- Assessment of Adverse Events and Concomitant Medications
- Documentation of bleeding episodes and FVIII usage (by either subject or clinical information)
- Distribution of subject diaries and training in diary completion
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.9.2.1)
- Urine Tests (refer to Table 9.7.9.2.1)
- Liver Tests (refer to Table 9.7.9.3.1)
- PBMC collection for CTL baseline
- Direct Thrombin test
- PCR of vector DNA in blood, saliva, urine, semen, and stools
- Exploratory biomarker assessments
- Haemo-QoL-A QoL assessment

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 24 hours for the BMN 270 Infusion Visit. The following procedures will be performed during the BMN 270 Infusion Visit:

- Physical examination
- Assessment of Adverse Events and Concomitant Medications
- Blood sample for AAV5 Assays (must be performed before the BMN 270 infusion)
 - o AAV5 antibody titer
 - AAV5 transduction inhibition assay

- BMN 270 Infusion
- Vital Signs
 - Vital signs will be recorded prior to BMN 270 infusion and then every 15 minutes (± 5 minutes) during BMN 270 infusion. Following infusion, vital signs will be monitored every 1 hour (± 5 minutes) for the first 6 hours, every 2 hours (± 15 minutes) for the next 6 hours, and then at 4 hour (± 15 minutes) intervals for the remainder of the subject's stay in the clinic.

12.5 BMN 270 Infusion Follow-Up Visits

After BMN 270 has been infused, subjects will return to the study site every week $(\pm 48 \text{ hours})$ for 16 weeks, when the following procedures will be completed:

12.5.1 Once per week (Weeks 1 through 16)

The following procedures will be performed at one visit per week from Weeks 1 through 16:

- Physical examination
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Vital Signs
- Liver Tests (refer to Table 9.7.9.3.1) central laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- Samples for FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
 - o FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level
 - o FVIII antigen (ELISA)

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

- Central assessment of FVIII activity level should be performed 1x/week from Week 1 through Week 16
- Liver Tests (refer to Table 9.7.9.3.1) local laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
- PBMC collection

12.5.2 Week 1 – Day 2 and Day 4

On Day 2 and Day 4 of Week 1, the following procedures will be performed:

- PCR of vector DNA in blood, saliva, urine, semen, and stools (Day 2 and Day 4)
- Samples for FVIII Assays (Day 4 only) central laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
 - o FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level
 - FVIII antigen (ELISA)

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

- Liver Tests (refer to Table 9.7.9.3.1) (Day 4 only) central laboratory assessment
- Liver Tests (refer to Table 9.7.9.3.1) (Day 4 only) local laboratory assessment
- FVIII activity level (Day 4 only) local laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)

12.5.3 Week 1 – Day 8

On Day 8, the following procedures will be performed:

- PCR of vector DNA in blood, saliva, urine, semen, and stools
- Direct Thrombin test
- Haemo-QoL-A QoL assessment

12.5.4 Every 2 Weeks

Every 2 weeks (Weeks 2, 4, 6, 8, 10, 12, 14 and 16), the following procedures will be performed:

- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.9.2.1) (not assessed at Week 14)
- PCR of vector DNA in blood, saliva, urine, semen, and stools (not collected at Week 2)
 - Collection to occur until at least 3 consecutive negative results are obtained. Semen samples should continue to be collected and tested through Week 12, even if 3 consecutive negative results in that compartment have been recorded prior to that timepoint.

12.5.5 Weeks 4, 8, 12, and 16

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

- Urine Tests (refer to Table 9.7.9.2.1)
- VWF:Ag
- FVIII antibody titer
- Exploratory biomarker assessments

12.5.6 Week 16

At Week 16, the following procedures will be performed:

- Test for hepatitis B and hepatitis C reactivation (in subjects with a history of hepatitis B or hepatitis C infection prior to study entry)
 - Subjects who receive reactive corticosteroids prior to Week 16 do not need to complete the Week 16 reactivation assessment; instead, they will be tested for hepatitis B and hepatitis C reactivation at the time points listed in Table 9.1.6.

12.5.7 Weeks 8 and 16

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

• AAV5 antibody titer

12.5.8 Weeks 2, 3, 4, and 16

At Weeks 2, 3, 4, and 16, the following procedure will be performed:

• Haemo-QoL-A QoL assessment

12.5.9 Week 13

At Week 13, the following procedure will be performed:

• Direct Thrombin test

12.6 Safety Follow-Up – Weeks 17-36

After the Post-Infusion Follow-Up visits are complete, subjects will return to the study site for Safety Follow-Up visits from Weeks 17 through Week 36 (\pm 48 hours), when the following procedures will be completed:

12.6.1 Once per week (Weeks 17 through 36)

Once per week from Week 17 through Week 36, the following procedures will be performed:

- Physical examination
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Vital Signs
- Liver Tests (refer to Table 9.7.9.3.1) central laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
 - o FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - o FVIII antigen (ELISA)

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

- Liver Tests (refer to Table 9.7.9.3.1) local laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)

12.6.2 Once per week (Weeks 17 through 20)

Once per week from Week 17 through Week 20, the following procedures will be performed:

• PBMC collection

12.6.3 Every 2 weeks (Weeks 21 through 36)

Every 2 weeks (Weeks 22, 24, 26, 28, 30, 32, 34, and 36), the following procedures will be performed:

• PBMC collection

12.6.4 Every 4 Weeks

Every 4 weeks (Weeks 20, 24, 28, 32, and 36), the following procedures will be performed:

- Exploratory biomarker assessments
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.9.2.1)
- Urine Tests (refer to Table 9.7.9.2.1)
- VWF:Ag
- AAV5 antibody titer
- PCR of vector DNA in blood, saliva, urine, semen, and stools
 - Sample testing during Safety Follow-Up is not required if at least
 3 consecutive samples are clear during the Post-Infusion Follow-Up period.

12.6.5 Every 8 Weeks

Every 8 weeks (Weeks 20, 28, and 36), the following procedure will be performed:

• FVIII antibody titer

12.6.6 Week 26

At Week 26, the following procedure will be performed:

• Direct Thrombin test

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• Weight

12.6.7 Week 28

At Week 28, the following procedure will be performed:

• Haemo-QoL-A QoL assessment

12.7 Safety Follow-Up – Weeks 37-52

Subjects will return every 2 weeks (Week 38, 40, 42, 44, 46, 48, 50, and 52) from Week 37-52 (± 1 week), when the following procedures will be completed:

12.7.1 Once per visit

At Weeks 38, 40, 42, 44, 46, 48, 50, and 52, the following procedures will be performed:

- Physical examination
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Vital Signs
- Liver Tests (refer to Table 9.7.9.3.1) local laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
- Liver Tests (refer to Table 9.7.9.3.1) central laboratory assessment
 - LTs may be monitored more or less frequently based (and in particular when ALT values are >1.5x ULN) on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
 - FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for FVIII inhibitor level

• FVIII antigen (ELISA)

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

12.7.2 Every 4 Weeks

Every 4 weeks (Weeks 40, 44, 48, and 52), the following procedures will be performed:

- Exploratory biomarker assessments
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.9.2.1)
- Urine Tests (refer to Table 9.7.9.2.1)
- AAV5 antibody titer
- VWF:Ag
- PCR of vector DNA in blood, saliva, urine, semen, and stools
 - Sample testing during Safety Follow-Up is not required if at least 3 consecutive samples are clear during the Post-Infusion Follow-Up period. Subjects who have not had 3 consecutive negative samples by Week 52 should continue to have PCR testing every 4 weeks until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor).

12.7.3 Every 8 Weeks

Every 8 weeks (Weeks 44 and 52), the following procedure will be performed:

- PBMC collection
- FVIII antibody titer

12.7.4 Week 38 and 52

At Week 38 and Week 52, the following procedure will be performed:

• Direct Thrombin test

12.7.5 Week 52

At Week 52, the following procedure will be performed:

- Haemo-QoL-A QoL assessment
- Weight

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12.8 Safety Follow-Up – Years 2-5

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, follow an abbreviated visit schedule after Week 52 of the study by attending only the Q12W and End of Year visits during Years 2-5.

Subjects who meet the definition of treatment failure and wish to follow an abbreviated schedule but who have not cleared vector shedding from semen must still provide samples for assessment every 4 weeks (during Year 2) or every 6 weeks (during Years 3-5) until vector shedding has cleared (but do not have to perform other scheduled assessments at those study visits).

At applicable sites, certain study assessments designated in the Schedule of Events may be performed by a mobile nursing (MN) professional at the subject's home or another suitable location, such as their school or office, to improve access and convenience for subjects participating in the study.

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

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

During Year 2, every 4 weeks (\pm 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 9.7.9.3.1) local laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
- Liver Tests (refer to Table 9.7.9.3.1) central laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.

- FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
 - o FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - FVIII antigen (ELISA)

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

- PCR of vector DNA in blood, saliva, urine, semen, and stools (if required)
 - Sample testing during Year 2 is not required if at least 3 consecutive samples are negative during the Post-Infusion Follow-Up period in Weeks 1-52.
 Subjects who have not had 3 consecutive negative semen samples by Week 52 should continue to have PCR testing of semen every 4 weeks during Year 2 until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor).
 - Subjects who meet the definition of treatment failure and wish to follow an abbreviated schedule but who have not cleared vector shedding from all fluids must still provide samples for assessment every 4 weeks during Year 2 until vector shedding has cleared (in such a case, these subjects do not need to perform other assessments except for PCR sample delivery scheduled at these timepoints).

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

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

- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Liver Tests (refer to Table 9.7.9.3.1) local laboratory assessment
 - LTs may be assessed more frequently when ALT values are >1.5x ULN or based upon discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)

- Liver Tests (refer to Table 9.7.9.3.1) central laboratory assessment
 - LTs may be assessed more frequently when ALT values are >1.5x ULN or based upon discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
 - o FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for FVIII inhibitor level

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

- PCR of vector DNA in blood, saliva, urine, semen, and stools (if required)
 - Sample testing during Years 3-5 is not required if at least 3 consecutive samples are negative during the Post-Infusion Follow-Up period in Weeks 1-52 and/or Year 2. Subjects who have not had 3 consecutive negative semen samples by the end of Year 2 should continue to have PCR testing of semen every 6 weeks during Years 3-5 until 3 consecutive 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 samples for assessment 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).

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

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

- Year 2 Week 64, Week 76, Week 88, Week 100, Week 104
- Year 3 Week 116, Week 128, Week 140, Week 152, Week 156
- Year 4 Week 168, Week 180, Week 192, Week 204, Week 208
- Year 5 Week 220, Week 232, Week 244, Week 256, Week 260

For each of these years, the last study visit listed (Week 104, Week 156, Week 208, and Week 260) will serve as an End of Year visit.

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

- Brief physical examination (at every 12 week visits) or complete physical examination (at End of Year visits) (genitourinary examination may be deferred unless the subject has genitourinary-related complaints)
- Weight (at Week 76, Week 128, Week 180, Week 232, and End of Year visits only)
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Liver Tests (refer to Table 9.7.9.3.1) local laboratory assessment
 - LTs may be assessed more frequently when ALT values are >1.5x ULN or based upon discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
- Liver Tests (refer to Table 9.7.9.3.1) central laboratory assessment
 - LTs may be assessed more frequently when ALT values are >1.5x ULN or based upon discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
 - FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for FVIII inhibitor level

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

• Vital Signs

- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.9.2.1)
 - ABO blood typing assessment should be performed at the next regularly scheduled study visit (or at least prior to the end of the subject's participation in the study)
- Urine Tests (refer to Table 9.7.9.2.1)
- FVIII antigen (ELISA)
- AAV5 antibody titer (at End of Year visits only)
- FVIII antibody titer (at End of Year visits only)
- PBMC collection
- VWF:Ag
- Exploratory biomarker assessments
- Haemo-QoL-A QOL assessment (at Week 76, Week 128, Week 180, Week 232, and End of Year visits only)
- Liver ultrasound (at End of Year 5 visit only)
 - Additional liver ultrasounds may be performed at interim time points (ie, between the End of Year visits) at the discretion of the Investigator.
- PCR of vector DNA in blood, saliva, urine, semen, and stools (if required)
 - Sample testing during Years 2-5 is not required if at least 3 consecutive samples are negative during the Post-Infusion Follow-Up period in Weeks 1-52. Subjects who have not had 3 consecutive negative semen samples by Week 52 should continue to have PCR testing of semen every 4 weeks (during Year 2) or every 6 weeks (during Years 3-5) until 3 consecutive samples below the limit of detection are documented (or upon consultation between the Investigator and Medical Monitor).

12.9 Safety Follow-Up – Years 6-7

If the investigator at a participating site determines that MN services are appropriate for a subject and the subject gives written informed consent to participate in MN visits, the MN network will communicate with the subject and the subject's site.

During Years 6-7 of Safety Follow-up, the following procedures will be completed:

12.9.1 Years 6-7 – Every 13 Weeks

Every 13 weeks (± 4 weeks) during Years 6-7, the site should contact the subject remotely to collect the following data:

• Adverse events

- New or changed concomitant medications
- Diary entries (FVIII usage and bleeding events)

12.9.2 Years 6-7 – Every 26 Weeks and End of Year Visits

During Years 6-7, the following assessments will be performed at a site visit every 26 weeks $(\pm 4 \text{ weeks})$ (Week 286 and Week 338) and at the End of Year Visits $(\pm 4 \text{ weeks})$ (Week 312 and Week 364):

- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Complete Physical Examination (genitourinary examination may be deferred unless the subject has genitourinary-related complaints) (Week 312 and Week 364 only)
- Weight (Week 312 and Week 364 only)
- Vital signs (Week 312 and Week 364 only)
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.9.2.1)
- Liver Tests (refer to Table 9.7.9.3.1) central laboratory assessment
 - LTs may be assessed more frequently when ALT values are >1.5x ULN or based upon discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
 - FVIII coagulation activity exploratory assay
 - Bethesda assay (with Nijmegen modification) for FVIII inhibitor level

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

- FVIII antigen (ELISA)
- AAV5 antibody titer (Week 312 and Week 364 only)
- FVIII antibody titer (Week 312 and Week 364 only)
- Exploratory biomarker assessments (Week 312 and Week 364 only)
- Haemo-QoL-A QOL assessment

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- Liver ultrasound (Week 312 and Week 364 only)
 - Additional liver ultrasounds may be performed at interim time points at the discretion of the Investigator.
- PCR of vector DNA in blood, saliva, urine, semen, and stools (if required)
 - Sample testing during Years 6-7 is not required if at least 3 consecutive samples are below the limit of detection as of the end of Year 5.

12.10 Liver Biopsy Substudy - Years 1-7

For the optional liver biopsy substudy (refer to Table 9.1.7), the following procedures will be performed at the following times:

- Within 28 days before Biopsy Day
 - o Informed consent
 - Liver ultrasound
 - Liver ultrasound does not need to be performed if an ultrasound result from the prior 3 months is already available
 - Brief physical examination
 - Hematology, Coagulation, and Chemistry Assessments (refer to Table 9.7.9.2.1)
 - Liver Tests (refer to Table 9.7.9.3.1)
- Within 7 Days before Biopsy Day
 - o FibroScan
 - Local laboratory FVIII activity level assessment
 - Pre-biopsy consultation with investigator (treating hematologist). This may need to be repeated/extended if the subject's FVIII activity levels need adjustment before the biopsy, at the discretion of the investigator (treating hematologist).
- 1 Day before Biopsy Day
 - Hematology, Coagulation, and Chemistry Assessments (refer to Table 9.7.9.2.1)
 - Liver Tests (refer to Table 9.7.9.3.1) local laboratory assessment
 - Brief physical examination

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- o Local laboratory FVIII activity level assessment
 - Subjects must have a FVIII activity level of at least 50 IU/dL (or higher, depending on local guidelines and/or investigator discretion). 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".
- Biopsy Day
 - Brief physical examination
 - Local laboratory FVIII activity level assessment (performed pre-biopsy)
 - Subjects must have a FVIII activity level of at least 50 IU/dL (or higher, depending on local guidelines and/or investigator discretion). 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".
 - Liver Tests (refer to Table 9.7.9.3.1) local laboratory assessment (pre-biopsy)
 - Liver Biopsy (refer to Laboratory Manual for guidelines for biopsy procedure and handling of biopsy samples)
 - If only a small amount of tissue is obtained at the time of the biopsy, the subject may be asked to consent for a second pass.

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.

Participation in the substudy may include liver biopsies at one or more time points.

12.11 Early Termination Visit

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

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If a subject leaves the study prior to the Week 364 visit, the subject will be asked to return to the study site and complete an Early Termination visit. At the Early Termination visit, as many of the following assessments as possible should be done:

- Physical examination
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Vital Signs
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.9.2.1)
- Urine Tests (refer to Table 9.7.9.2.1)
- Liver Tests (refer to Table 9.7.9.3.1) local laboratory assessment
- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
- Liver Tests (refer to Table 9.7.9.3.1) central laboratory assessment
- FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
 - o FVIII coagulation activity exploratory assay
 - Bethesda assay (with Nijmegen modification) for FVIII inhibitor level

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

- FVIII antigen (ELISA)
- AAV5 antibody titer
- FVIII antibody titer
- PBMC collection
- VWF:Ag

- Liver ultrasound
- PCR of vector DNA in blood, saliva, urine, semen, and stools
 - Sample testing at the ETV is not required if at least 3 consecutive samples are below the limit of detection prior to the ETV.
- Exploratory biomarker assessment
- Haemo-QoL-A QOL assessment

12.12 End of Study

The study will end after the last subject completes the last Safety Follow-Up visit (Week 364). 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.

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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, any applicable randomization procedures, source document requirements, eCRFs, monitoring requirements, and procedures for reporting AEs, including SAEs.

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

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

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14 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

14.1 Statistical and Analytical Plans

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

14.1.1 Interim Analyses

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

14.1.2 Procedures for Accounting for Missing, Unused and Spurious Data

Missing data will not be imputed.

14.2 Primary and Secondary Efficacy Analysis

The subjects will be followed in a longitudinal manner and all the relevant information will be collected. The analysis of the data will be descriptive in nature. Descriptive statistics include the number of subjects, mean, median, standard deviation, minimum, and maximum for continuous variables and count and percent for categorical variables. Efficacy variables will be summarized by dose cohort at each time point. Relationship between dose and efficacy results will be examined.

Data collected in a longitudinal manner may be analyzed using longitudinal methods such as mixed effect model which takes into account the correlation among the observation taken at various time points within a participant. Efficacy is a secondary endpoint, defined as biologically active hFVIII at ≥ 5 IU/dL by chromogenic substrate assay and/or one-stage clotting assay as measured by the central laboratory at 16 weeks following study treatment. We can only assess the true steady state of hFVIII protein produced from BMN 270 after a minimum of 72 hours has elapsed since the last infusion of FVIII protein concentrates.

14.3 Liver Biopsy Substudy Analysis

A separate report presenting and discussing analyses of the exploratory objectives for the optional liver biopsy substudy will be prepared.

14.4 Immunogenicity

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



14.5 Pharmacodynamic Analyses

The FVIII antigen and activity level as measured by an ELISA (antigen level) and by a one-stage clotting assay and/or chromogenic substrate assay (activity level), will be used for plasma profiles; FVIII activity will be used to determine PD parameters. Traditional PK analysis is not applicable.

If supported by FVIII activity data, non-compartmental analysis and observation will be used to estimate individual PD parameter values of C_b (baseline), C_{ss} (steady state), T_{ss} (time to steady state), C(t) and AUC(0-t) where t is 16 weeks. Other parameters that may be used to describe individual FVIII protein and activity plasma profiles are C_{max} (maximum concentration) and C_{avg} (average concentration, AUC(0-t)/t). The parameters will be summarized using descriptive statistics.

14.6 Safety Analysis

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

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

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

Detailed statistical methods will be provided in the SAP.

14.7 Determination of Sample Size

No formal sample size calculations based on statistical power were performed.

The sample size is determined based upon clinical consideration and could detect a strong clinical efficacy signal. Up to 15 subjects may be dosed in the study; the actual number of subjects will depend on the criteria for dose escalation.

14.8 Analysis Populations

The Safety analysis population is defined as all enrolled subjects who receive any study drug.The analysis of safety data will be performed on Safety Set.Proprietary and Confidential24 August 2021

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The Full Analysis Set (FAS) is defined as all enrolled subjects who receive study drug and have at least one Baseline and post-Baseline assessment. The FAS will be used for efficacy analysis.

14.9 Changes in the Conduct of the Study or Planned Analyses

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

With the exception of minor administrative or typographical changes, the 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 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 IEC, and all active subjects must again provide informed consent.

Note: If discrepancies exist between the text of the statistical analysis as planned in the protocol, and the final SAP, a protocol amendment will not be issued and the SAP will prevail.



15 DATA REVIEW BOARD

There will be no formal DMC for this study, however a safety and efficacy evaluation board (the Data Review Board [DRB]) composed of the investigator representatives and the Sponsor will be established.

The DRB will review safety and efficacy on an ongoing basis. The DRB will meet prior to dose escalation or dose expansion to assess available subject safety and efficacy data and make recommendations with regards to the conduct of study. Should a safety signal arise, including one which may warrant a halt of study enrollment, the DRB will promptly convene for further assessment of subject safety. Notification of all DRB meetings and meeting outcomes will be sent to participating sites.

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16 COSTS, COMPENSATION, AND SUBJECT INJURY

BioMarin will pay the full costs of the study-related tests, procedures, and treatments set forth in this protocol. In addition, after 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 IP 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 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 IP 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 and that are unrelated to this study.

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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 CRF casebook to verify its accuracy.

CRFs 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 CRF instructions, blank data fields are not acceptable.

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

BioMarin's policy is that study data on the CRFs 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 an Investigator or institution refuses to allow access to subject records because of confidentiality, arrangements must be made to allow an "interview" style of data verification.

A CRA designated by BioMarin will compare the CRFs 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 CRA, 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 CRA 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 CRF 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 CRFs is accurate and complete. The Data Manager, or designee, will then set the status of the forms, visits, and the entire casebook to Locked.

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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 IECs.

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.

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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.

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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 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).

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21 REFERENCES

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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 R2 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 patients.
- He or she will personally conduct or supervise the study.
- He or she will inform any potential patients, 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 R2 Sections 2.9 and 4.8 are met. As well, he or she will ensure that IEC review and approval in 21 CFR Part 56 and/or ICH E6 R2 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 R2 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 R2 Section 4.9 are kept, and those records are available for inspection in accordance with 21 CFR 312.68 and/or ICH E6 R2 Section 4.9.7.
- The IEC complies with the requirements of 21 CFR Part 56, ICH E6 R2 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 patients or others are reported to the IEC. Additionally, he or she will not make any changes in the research without IEC approval, except where necessary to eliminate apparent immediate hazards to human patients.
- 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 R2.

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

Protocol Number: 270-201 Amendment 10

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 R2, as stated in the protocol, and other information supplied to me.

Investigator Signature		Date
Printed name		
Accepted for the Sponsor:	PI DocuSigned by:	
recepted for the Sponsor.	Signer Name: PI Signing Reason: I approve this document Signing Time PI 934DEBF504AB4E6A83363FE5BE4B8D5F	
Medical Monitor Signature	Date	
Printed name: Pl	MD, PhD, Pl	, Clinical Sciences

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24 PROTOCOL AMENDMENT TEXT REVISIONS

The following table summarizes the revisions made to the protocol and relates the changes to the appropriate rationale (See page 2-3). Text that has been added or inserted is indicated by <u>underlined</u> font, and deleted text is indicated by <u>strikethrough</u> font.

Section No./Title	Revision	Rationale
2/Synopsis (Study Design and Plan)	In subjects who experience recurrent bleeding episodes, the Investigator and Medical Monitor will discuss whether to resume prior FVIII prophylaxis. Subjects who do not respond to BMN 270 treatment (ie, treatment failure, manifesting as either failure to achieve FVIII activity ≥ 5 IU/dL by Week 52 orand 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, follow an abbreviated visit schedule after Week 52, as applicable and at the discretion of the Investigator.	1, 5, 9
	Liver Biopsy Substudy Design	
	Participation in the sub-study may include liver biopsies at one or more time points.	
5.1/ Institutional Review Board or Independent Ethics Committee	Prior to initiating the study, the Investigator will obtain written confirmation that the institutional review board (IRB) or independent ethics committee (IEC)-[for Canadian protocols, Research Ethics Board (REB)] is properly constituted and compliant with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and Good Clinical Practice (GCP) requirements, applicable laws and local regulations. A copy of the confirmation from the IRB/IEC/REB will be provided to BioMarin or its designee. The Investigator will provide the IRB/IEC/REB with all appropriate material, including the protocol, Investigator's Brochure (IB), the Informed Consent Form (ICF) including compensation procedures, and any other written information provided to the subjects, including all ICFs translated to a language other than the native language of the clinical site. The study will not be initiated and Investigatoral Product (IP) supplies will not be shipped to the site until appropriate documents from the IRB/IEC/REB confirming unconditional approval of the protocol, the ICF and all subject recruitment materials are obtained in writing by the Investigator and copies are received at BioMarin or its designee. The approval document should refer to the study by protocol title and BioMarin protocol number (if possible), identify the documents reviewed, and include the date of the review and approval.	9
5.2/Ethical Conduct of Study	the Investigator in accordance with applicable guidance documents and governmental regulations. Specifically, this study is based on adequately performed laboratory and animal experimentation. The study will be conducted under a protocol reviewed and approved by an IRB/IEC/REB and will be conducted by scientifically and medically qualified persons.	9

Section No./Title	Revision	Rationale
5.3/Subject Information and Informed Consent	A properly written and executed ICF, in compliance with ICH E6 (Section 4.8), United States Code of Federal Regulations (CFR) 21 CFR §50, European Clinical Trial Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC, and other applicable local regulations, will be obtained for each subject prior to entering the subject into the study. The Investigator will prepare the ICF and provide the documents to BioMarin for approval prior to submission to the IRB/IEC/REB approval. BioMarin and the IRB/IEC/REB must approve the documents before they are implemented.	9
7/Introduction	 Haemophilia A (HA) is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males (Nathwani, 1992[Jorio 2019). 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 2020); thus the therapeutic goal for gene therapy is a modest increase in hFVIII. 	9
7.2/Previous <u>and</u> <u>Ongoing</u> Clinical Studies	 Ongoing clinical studies for BMN 270 include: 270-203, a phase 2 study in patients with severe HA who have anti-AAV5 antibody titers 270-205, a phase 1/2 study in patients with severe HA who have active or prior FVIII inhibitors 270-301, the pivotal phase 3 study in patients with severe HA who receive BMN 270 at the 6E13 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 270-303, a phase 3 study in patients with severe HA who receive BMN 270 at the 6E13 vg/kg dose level 270-303, a phase 3 study in patients with severe HA who received BMN 270 at the 6E13 vg/kg dose level along with prophylactic corticosteroids 	9
7.3/Study Rationale	Haemophilia A (HA) is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males (Mannucci, 2001 <u>Iorio 2019</u>).	9
7.4/Summary of Risks and Benefits	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 inAcross the use6E13 vg/kg cohort of corticosteroids across studies. Subjects in 270-201, who received corticosteroids an average of 8 weeks earlier following BMN 270 infusion than the mITT population and 270-301, subjects enrolled in 270-301, were more likely to avoid a significant decline in FVIII activity concurrently with an201 developed ALT elevation, and saw a more robust recovery of FVIII activity upon about 5.5 weeks later than subjects in 270-301, generally once the first usecourse of	8,9

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Section No./Title	Revision	Rationale
	corticosteroids, was being tapered, and experienced lower peak elevations in ALT (75.7 U/L) than did the subjects in 270-301 (112.5 U/L). The difference in the mITT population in 270-301. Despite the clinical response to steroids, no associationsALT profile seen between safety parameters (transient ALT rises), or efficacy as measured 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 FVIII activity levels were foundWeek 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 be temporally associated with anti-AAV5 antibodymanaging 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 cellular immune responses, 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).	
9.1/Overall Study Design and Plan	In subjects who experience recurrent bleeding episodes, the Investigator and Medical Monitor will discuss whether to resume prior FVIII prophylaxis. Subjects who do not respond to BMN 270 treatment (ie, treatment failure, manifesting as either failure to achieve FVIII activity \geq 5 IU/dL by Week 52 orand 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, follow an abbreviated visit schedule after Week 52, as applicable and at the discretion of the Investigator.	5
Table 9.1.5/Schedule of Events Years 2-7	Table 9.1.5 has been updated consistent with changes made in the footnotes and elsewhere in the protocol.	1, 6, 9
Table 9.1.5 footnotes	 <u>ETV: Early Termination Visit</u> ^a Complete physical examination should be performed at the End of Year visits; (genitourinary examination may be deferred unless the subject has genitourinary-related complaints); brief physical examination may be performed at other study visits. Weight should be recorded at the second Q12W visit each year during Years 2-5, and at every End of Year visit during Years 2-7. ^b Refer to Table 9.7.9.2.1 for laboratory assessments to be included, and to Table 9.7.9.3.1 for liver tests. LTs may be monitoredassessed more or less-frequently (and in particular when ALT values are ≥ 1.5x ULN) 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. Patients. Subjects with ALT ≥ 1.5x ULN during the study may 	1, 6, 9

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Section No./Title	Revision	Rationale
	undergo additional evaluations (eg, imaging studies including MRI or ultrasound, additional blood tests, and/or liver biopsy)	
	at the discretion of the investigator. Additional testing of FVIII and LTs during any study week may be performed if: (1) the	
	ALT has increased to above ULN or increased by > 10 U/L from prior assessment; (2) Increases in ALT values from prior	
	assessment are accompanied by declines in FVIII activity level; or;; or (2) after a discussion between the Medical Monitor	
	and the Investigator based on a review of subject data. If FVIII levels and/orIf 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. During Years 6-7,	
	these tests should be performed at the Q26W and End of Year visits.	
	^d Includes hFVIII activity level (one-stage clotting and chromogenic substrate assay), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, and hFVIII coagulation activity exploratory assay and hFVIII antigen (ELISA).	
	^e Sample testing during Safety Follow-Up is not required if at least 3 consecutive samples are cleared during the Post-Infusion	
	Follow-Up period. Subjects who have not had 3 consecutive negative semen samples by Week 52 should continue to have	
	PCR testing every 4 weeks (during Year 2), every 6 weeks (during Years 3-5), and/or every 26 weeks (during Years 6-7)	
	until 3 consecutive samples below the limit of detection are documented (or upon consultation between the Investigator and Medical Monitor).	
	^h 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 a fluidsemen must still provide samples Q4W (during Year 2), Q6W (during Years 3-5), or Q26W (during Years 6-7), until vector shedding has been cleared (but do not need to do other scheduled assessments at those visit dates), either by reporting to the site to provide samples or by providing those samples to an MN	
	professional.	
	<u>k</u> Additional liver ultrasounds may be performed at interim timepoints (ie, between the End of Year visits) at the discretion of the Investigator.	
Table 9.1.6/ Therapeutic <u>Reactive</u> Corticosteroids	Table 9.1.6 has been update consistent with changes made elsewhere in the protocol and in the footnotes.	4, 9
Table 9.1.6 footnotes	^a Therapeutic <u>Reactive</u> corticosteroids may be initiated when a subject's ALT value is $\geq 1.5x$ ULN or based on review of FVIII and liver enzyme data after consultation between the Investigator and the Medical Monitor.	4, 9
	^b Following initiation or completion of steroid regimen, if ALT elevation ≥ 1.5x ULN is reported, steroid management decisions will based on discussions between the Investigator and Medical Monitor. Modification of the steroid regimen may	

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Section No./Title	Revision		Rationale

Section No./Title	Revision	Rationale
	take into consideration timing of the ALT elevation (after Week 52), as well as possible confounders for the ALT elevation	
	and adverse events related to corticosteroid dosing impact on FVIII expression. Guidance for tapering oral corticosteroids	
	can be found in Section 9.4.8.2.	
9.4.8/Prior and	Administration of SARS-CoV-2 vaccine after BMN 270 infusion may occur after consultation between Investigator and	3
Concomitant	Medical Monitor. Investigators should use clinical judgment, taking into consideration local factors, individual risk factors,	
Medications	and the benefit/risk related to timing of vaccine administration.	
9.4.8.1/Concomitant Hemophilia Treatments	Subjects on "on demandepisodic" therapy for FVIII will continue their treatment at will. Subjects on prophylactic FVIII therapy will discontinue their treatment starting the day of infusion and switch to an "on demandepisodic" schedule.	9
9.4.8.2.1/Therapeutic	In general, therapeuticreactive corticosteroids may be initiated when a subject's ALT value is $\geq 1.5x$ ULN, or based on review	4,9
Reactive Corticosteroids	of FVIII and liver enzyme data after consultation between the Medical Monitor and the Investigator. <u>Corticosteroids may be</u>	4, 9
	delayed, upon discussion with the Medical Monitor, if elevations in ALT are clearly not related to BMN 270 (eg, elevated	
	ALT with concurrent increase in CPK due to intensive exercise) and in particular for elevations occurring more than 52 weeks	
	after BMN 270 dosing.	
	Following initiation or completion of therapeuticreactive corticosteroids, if ALT elevation $\geq 1.5x$ ULN is reported, steroid	
	management decisions will based on discussions between the Investigator and Medical Monitor. Modification of the steroid	
	regimen may take into consideration possible confounders for the ALT elevation and impact on FVIII expression.	
	<u>Unless otherwise indicated</u> , treatment with prednisolone willreactive corticosteroids should be initiated at a dose of 60 mg per	
	day and then gradually tapered if the ALT level remains stable or declines after 2 weeks (60 mg daily for the first 2 weeks,	
	then 40 mg the next 2 weeks, then 30 mg the next two weeks, then 20 mg the next two weeks, then 15 mg for the next week,	
	then 10 mg for the next week, then 5 mg for the next week, then stop, for a total treatment of 11 weeks) (refer to Table 9.1.6).	
	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 9.4.8.2.1.1):	
Table 9.4.8.2.1.1/Management of ALTElevations withCorticosteroids	Table 9.4.8.2.1.1 and its footnotes have been added.	4
Corricosteroids		

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Section No./Title	Revision	Rationale
9.4.8.2.1/ Therapeutic <u>Reactive</u> Corticosteroids (cont.)	When ruling out alternative viral or autoimmune hepatitis as part of the elevated ALT workup, the following tests should be performed (Table 9.4.8.2.1.2):	4
Table 9.4.8.2.1.2/Viral and Autoimmune Hepatitis Testing	Table 9.4.8.2.1.2 has been added	4
9.4.8.2.1/Therapeutic <u>Reactive</u> Corticosteroids (cont.)	After discontinuation of <u>reactive</u> corticosteroids, weekly labs for ALT and FVIII levels will be measured once a week for 4 weeks to ensure stability in values. Management and monitoring of reactions to corticosteroids should be determined by the Investigator's clinical judgment in consultation with the Sponsor's Medical Monitor. This includes the contraindicated use of NSAIDs during corticosteroid treatment, and specific monitoring not already covered by the schedule of events. <u>The use of COX-2 inhibitors, while not</u> <u>contraindicated during corticosteroid treatment, should be limited, if possible</u> . Practical management to prevent complications <u>related to oral corticosteroid therapy may be undertaken at the discretion of the Investigator (eg, evaluation of glucose intolerance, hyperlipidemia etc.).</u> For the subjects with a past medical history of hepatitis B or hepatitis C prior to study entry, Hepatitis B status and HCV viral load will be rechecked 6 weeks after the start of corticosteroid treatment, and then 1 week and 13 weeks after the completion of corticosteroid treatment. All adverse events should be reported as outlined in Section 10 of the protocol. <u>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.</u>	4,9
9.7.2/Primary Efficacy Variables	FVIII activity assays will also be performed at the local laboratory at the time points indicated in Table 9.1.2, Table 9.1.3, Table 9.1.4, and Table 9.1.5 but will be used in conjunction with local lab LT assessments to monitor subject safety and need for initiation of therapeuticreactive corticosteroid dosing; local laboratory FVIII activity assessments will not be used to assess efficacy or to measure the primary efficacy outcome of the study. Subjects who do not respond to BMN 270 treatment (ie, treatment failure, manifesting as either failure to achieve FVIII activity $\geq 5 \text{ IU/dL}$ by Week 52 orand inability to maintain independence from prophylactic FVIII replacement therapy due to	4, 5

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Section No./Title	Revision	Rationale
	joint bleeding episodes, in the judgment of the Investigator) may, at the Investigator's discretion and after discussion with the Medical Monitor, follow an abbreviated visit schedule after Week 52, as applicable and at the discretion of the Investigator.	
9.7.8/Liver Biopsy Substudy	Participation in the substudy may include liver biopsies at one or more time points.	1,9
<u>9.7.9.3/Malignancies</u>	 Liver ultrasounds will be performed annually at each End of Year visit starting at Year 5 (Week 260) through the end of the study to screen for HCC. Additional liver ultrasounds may be performed between the End of Year visits 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
9.7.8.6/Vital Signs and Physical Exams	A complete physical examination is necessary during Screening/Baseline, at Week 16 and 52 and at the End of Years visits thereafter. 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.	9
9.7.9.7/Vector Shedding	Vector shedding will also be extensively studied in the present clinical trial, every other week between Weeks 4-16, then every 4 weeks to Week 52 until at least 3 consecutive negative results are obtained. Testing of semen will continue through Week 12, even if 3 consecutive negative results have been recorded in that compartment prior to that timepoint. Subjects who have not had 3 consecutive negative semen samples by Week 52 should continue to have PCR testing every 4 weeks (during Year 2), every 6 weeks (during Years 3-5), and every 26 weeks (during Years 6-7) until 3 consecutive semen samples below the limit of detection of the test are documented (or upon consultation between the Investigator and Medical Monitor). Subjects who meet the definition of treatment failure and wish to follow an abbreviated schedule (refer to Section 12.5.3 but who have not cleared vector shedding from all fluidssemen must still provide samples for assessment until vector shedding has cleared: every 4 weeks (during Year 2), every 6 weeks (during Years 3-5), or every 26 weeks (during Years 6-7), either by reporting to the site to provide samples or by providing those samples to an MN professional.	9
10.2.1/EOSI	The following EOSI need to be reported to the Sponsor within 24 hours of site awareness, irrespective of seriousness, severity or causality:	2

Section No./Title	Revision	Rationale
	<u>Any new diagnosis of malignancy (except non-melanoma skin cancer)</u>	
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.	9
10.9/Contact Information	The medical monitor contact information has been updated	7
12.8/Safety Follow-Up Years 2-5	Subjects who do not respond to BMN 270 treatment (ie, treatment failure, manifesting as either failure to achieve FVIII activity ≥ 5 IU/dL by Week 52 orand 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, 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.	5,9
	Subjects who meet the definition of treatment failure and wish to follow an abbreviated schedule but who have not cleared vector shedding from a fluidsemen must still provide samples for assessment every 4 weeks (during Year 2) or every 6 weeks (during Years 3-5) until vector shedding has cleared (but do not have to perform other scheduled assessments at those study visits).	
12.8.2/Years 3-5 Every 6 Weeks	 During Years 3-5, every 6 weeks (± 2 weeks), the following procedures will be performed: Liver Tests (refer to Table 9.7.9.3.1) – local laboratory assessment 	4, 6, 9
	 LTs may be monitoredassessed more or less-frequently (and in particular-when ALT values are >1.5x ULN) or based on upon discussion between the Medical Monitor and the Investigator and review of subject data. 	
	• Liver Tests (refer to Table 9.7.9.3.1) – central laboratory assessment	
	 LTs may be monitoredassessed more or less-frequently (and in particular when ALT values are >1.5x ULN) or based onupon discussion between the Medical Monitor and the Investigator and review of subject data. 	
	• FVIII Assays – central laboratory assessment	
	○ FVIII antigen (ELISA)	

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Section No./Title	Revision	Rationale
	PCR of vector DNA in blood, saliva, urine, semen, and stools (if required)	
	 Subjects who meet the definition of treatment failure and wish to follow an abbreviated schedule but who have not cleared vector shedding from fluidsemen, must still provide samples of that fluid for assessment 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). 	
12.8.3/Years 3-5 Every	At the every 12 week and End of Year visits, the following procedures will be performed:	1, 4, 6, 9
12 Weeks and End of Year Visits	• Brief physical examination (at every 12 week visits) or complete physical examination (at End of Year visits) (genitourinary examination may be deferred unless the subject has genitourinary-related complaints)	
	• Liver Tests (refer to Table 9.7.9.3.1) – local laboratory assessment	
	 LTs may be monitoredassessed more or less frequently (and in particular when ALT values are >1.5x ULN) or based onupon discussion between the Medical Monitor and the Investigator and review of subject data. 	
	• Liver Tests (refer to Table 9.7.9.3.1) – central laboratory assessment	
	 LTs may be monitoredassessed more or less frequently (and in particular when ALT values are >1.5x ULN) or based onupon discussion between the Medical Monitor and the Investigator and review of subject data. 	
	• FVIII Assays – central laboratory assessment	
	○ FVIII antigen (ELISA)	
	• FVIII antigen (ELISA)	
	• AAV5 antibody titer (at End of Year visits only)	
	• FVIII antibody titer (at End of Year visits only)	
	• Liver ultrasound (at End of Year 5 visit only)	
	• Additional liver ultrasounds may be performed at interim time points (ie, between the End of Year visits) at the discretion of the Investigator.	
12.9.2/Years 6-7 Every 26 Weeks and End of Year	During Years 6-7, the following assessments will be performed at a site visit every 26 weeks (±4 weeks) (Week 286 and Week 338) and at the End of Year Visits (±4 weeks) (Week 312 and Week 364):	1, 4, 6, 9

Section No./Title	Revision	Rationale
	Complete Physical Examination (genitourinary examination may be deferred unless the subject has genitourinary-related complaints) (Week 312 and Week 364 only)	
	• Liver Tests (refer to Table 9.7.9.3.1) – central laboratory assessment	
	 LTs may be monitoredassessed more or less frequently (and in particular when ALT values are >1.5x ULN) or based onupon discussion between the Medical Monitor and the Investigator and review of subject data. 	
	• FVIII Assays – central laboratory assessment	
	○ FVIII antigen (ELISA)	
	• <u>FVIII antigen (ELISA)</u>	
	• Liver ultrasound (Week 312 and Week 364 only)	
	• Additional liver ultrasounds may be performed at interim time points at the discretion of the Investigator.	
12.10/Liver Biopsy Substudy	Participation in the substudy may include liver biopsies at one or more time points.	1,9
12.11/ETV	At the Early Termination visit, as many of the following assessments as possible should be done:	1,6
	FVIII Assays – central laboratory assessment	
	↔ FVIII antigen (ELISA)	
	• <u>FVIII antigen (ELISA)</u>	
	• <u>Liver ultrasound</u>	
14.9/Changes in Study Conduct	Only BioMarin may modify the protocol. Any change in study conduct considered necessary by the Investigator will be made only after consultation with BioMarin, who will then issue a formal protocol amendment to implement the change. The only exception is when an Investigator considers that a subject's safety is compromised without immediate action. In these circumstances, immediate approval of the chairman of the IRB/IEC/REB must be sought, and the Investigator should inform BioMarin and the full IRB/IEC/REB within 2 working days after the emergency occurs.	
	With the exception of minor administrative or typographical changes, the IRB/IEC/REB must review and approve all protocol amendments. Protocol amendments that have an impact on subject risk or the study objectives, or require revision of the ICF, must receive approval from the IRB/IEC/REB prior to their implementation.	

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Section No./Title	Revision	Rationale
	When a protocol amendment substantially alters the study design or the potential risks or burden to subjects, the ICF will be amended and approved by BioMarin and the IRB/IEC/REB, and all active subjects must again provide informed consent.	
16/Costs, Compensation, and Injury	BioMarin will pay the full costs of the study-related tests, procedures, and treatments set forth in this protocol. In addition, after IRB/IEC/REB approval, BioMarin may reimburse the reasonable cost of travel for study-related visits in accordance with BioMarin's travel and reimbursement policy.	9
18/Study Monitoring	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 IECs.	
21/References	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(S4):151-152.	9
	Heller CG & Clermont Y. Kinetics of the germinal epithelium in man. Recent Prog Horm Res. 1964;20:545-571.	
	Heller CG, Heller GV, Rowley MJ. Human spermatogenesis: an estimate of the duration of each cell association and each cell type. Excerpta Med Int Congr Ser. 1969;184:1012-1018.	
	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.	
	Monahan, P, Walsh CE, Powell JS, Konkle BA et al. Update on a phase 1/2 open-label trial of BAX335, an adeno-associated virus 8 (AAV8) vector based gene therapy program for hemophilia B. J Thromb Haemostasis 13[Suppl 2], 1-997. 2015.	
	Nathwani, AC, Tuddenham, EG. Epidemiology of coagulation disorders. Baillieres Clin Haematol 5[2], 383-439. 1992.	
	National Hemophilia Foundation. MASAC recommendation for liver biopsies in gene therapy trials for hemophilia. Available at https://hemophilia.org/sites/default/files/ document/files/256.pdf. 2019. MASAC Recommendation #256. Last accessed 5-June 202020 July 2021.	
	Pasi KJ, Rangarajan S, Walsh LMitchell N, Lester W et al. Multiyear Follow-up of AAV5-Factor_hFVIII-SQ Gene Transfer in Severe Therapy for Hemophilia A. NEJM. 2017;377(26):2519-2530N Engl J Med. 2020;382(1):29-40.	
	Srivastava, A, Brewer, AK, Mauser Bunschoten, EP, Key, NSSantagostino E, Dougall A, Kitchen S et. al. WFH guidelines	

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Section No./Title	Revision	Rationale
	Watkins, PB, Kaplowitz, N, Slattery, JT, Colonese, CR et al. Aminotransferase Elevations in Healthy Adults Receiving 4 Grams of Acetaminophen Daily: A Randomized Controlled Trial. JAMA 296[1], 87-93. 2006.	
	White, GC, Rosendaal, F, Aledort, FM, Lusher, JM et al. Definitions in hemophilia. Recommendation of the scientific subcommittee on factor VIII and factor IX of the scientific and standardization committee of the International society on Thrombosis and Haemostasis. Thromb Haemost. 85[3], 560. 2001.	
22.1/Conduct of Study	 In accordance with FDA Form 1572 and/or principles of ICH E6 R2 GCP, the Investigator will ensure that: He or she will inform any potential patients, 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 R2 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 R2 Section 2.6 are met. 	
	• The IRB/IEC/REB complies with the requirements of 21 CFR Part 56, ICH E6 R2 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 patients or others are reported to the IRB/IEC/REB. Additionally, he or she will not make any changes in the research without IRB/IEC/REB approval, except where necessary to eliminate apparent immediate hazards to human patients.	
23/Signature Page	Printed name: Nina Mitchell, MA MB BChir MSc, Tara Robinson, MD, PhD, Associate Medical Director, Clinical ScienceSciences ScienceSciences	7

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1/2, Dose-Escalation, Safety, Tolerability and Efficacy Study of BMN 270, an Adenovirus-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII in Patients with Severe Haemophilia A
Protocol Number:	270-201
Active Investigational Product:	AAV5-hFVIII-SQ
IND/European Union Drug Regulating Authorities Clinical Trials (EudraCT) Number:	2014-003880-38
Indication:	Haemophilia A
Sponsor:	BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949
Development Phase:	Phase 1/2
Sponsor's Responsible Medical Monitor:	Pl , MA MB BChir MSc BioMarin (UK) Ltd. 10 Bloomsbury Way London, WC1A 2SL
Duration of Subject Participation:	Approximately 368 weeks
Dose:	Varied
Study Population:	Males aged 18 or older
Date of Original Protocol:	10 February 2015
Date of Amendment 1:	06 March 2015
Date of Amendment 2:	26 May 2015
Date of Amendment 3:	06 November 2015
Date of Amendment 4:	02 September 2016
Date of Amendment 5:	14 February 2017
Date of Amendment 6:	21 December 2017
Date of Amendment 7:	10 October 2018
Date of Amendment 8:	31 January 2019
Date of Amendment 9:	19 June 2020

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May not be divulged, published, or otherwise disclosed to others without prior written approval from BioMarin.

This study will be conducted according to the principles of Good Clinical Practice as described in the U.S. Code of Federal Regulations and the International Conference on Harmonisation Guidelines, including the archiving of essential documents

CLINICAL STUDY PROTOCOL AMENDMENT SUMMARY

Amendment: 9

Date: 19 June 2020

RATIONALE AND SUMMARY OF MAJOR CHANGES

A summary of major changes covered by Amendment 9 to the 270-201 protocol is provided below.

1. The duration of the study has been extended from 5 years to 7 years post-infusion.

Rationale: Additional monitored follow-up will permit long-term analysis for key study objectives and increased long-term safety monitoring. The schedule of assessments for the additional 2 years has been reduced compared with Years 2-5, in order to minimize subject burden (only 2 clinic visits per year will be required).

2. Language has been added to permit the use of mobile nursing (MN) services, provided that the subject consents and that the site can implement the use of such services.

Rationale: Allowing for the use of MN services at study timepoints with a limited number of assessments will help alleviate subject travel burden and will allow for the collection of key data points where COVID-related travel and site visit restrictions exist. At applicable sites, certain study assessments designated in the Schedule of Events may be performed by a mobile nursing (MN) professional at the subject's home or another suitable location, such as their school or office.

3. 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.

4. The occurrence of events of Hy's law has been added as an event of special interest (EOSI) for purposes of expedited safety reporting.

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.

5. The development of anti-FVIII inhibitory antibodies (inhibitors) has been added as an EOSI for purposes of expedited safety reporting.

Rationale: To date, no subjects receiving BMN 270 have developed FVIII inhibitors in any BMN 270 study. While monitoring for the development of inhibitors 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.

6. Language has been added concerning the use of liver biopsy sample information from samples collected outside of the liver biopsy substudy.

Rationale: Where a biopsy has been taken for safety-related reasons (rather than as part of the liver biopsy substudy) 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 not performed as part of the substudy be made available for additional histopathological review.

7. Vector shedding and contraception use language has been updated to change the determination of a "clear" result from negative to below the limit of detection.

Rationale: The change in language better reflects regulatory guidance documents and aligns 270-201 with other clinical studies in the BMN 270 program.

8. Provision has been included to allow an investigator to document verbal confirmation by a subject that has signed and dated the written informed consent when the investigator cannot obtain a copy of the signed informed consent prior to initiating study procedures.

Rationale: Travel and site restrictions related to COVID-19 may make it impossible for a subject to go to the site to provide written informed consent. In such a case, the Investigator should have the subject verbally confirm during an informed consent interview that the subject has signed and dated the informed consent form (ICF). The Investigator should document this verbal confirmation on the Investigator's copy of the ICF and, when it is possible to do so, receive the informed consent signed by the subject and archive the original(s) in the record file of the subject. Since the study has already fully recruited, this process will only be used in currently enrolled subjects providing consent to updated versions of the ICF, and there is no intention that this will be used for the initial consenting process.

- 9. Guidance concerning how to determine whether a subject has been lost to follow-up has been added.
- 10. The vector genome schematic has been updated.
- 11. The costs and compensation language has been updated to clarify which study-related costs will be covered by the Sponsor.

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- 12. The summary of risks and benefits (Section 7) has been updated.
- 13. Minor administrative changes have been made for consistency and clarity.

Specific changes included in this amendment, including the Synopsis, since Amendment 8 (approved 31 January 2019) are outlined in Section 24.

2 SYNOPSIS

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

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

PROTOCOL NUMBER:

270-201

STUDY SITES:

Approximately 6-10 sites worldwide.

PHASE OF DEVELOPMENT:

Phase 1/2

STUDY RATIONALE:

Haemophilia 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 cascade. This disorder can be either inherited, due to a new mutation 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 is largely governed by the level of residual expression. Severe HA is classified as FVIII activity less than 1% of wild type (< 1 IU/dL), moderate disease comprises 1-5% of wild type activity and the mild form is 5-40% activity. The clinical manifestations of severe HA remain frequent spontaneous bleeding episodes, predominantly in joints and soft tissues, with a substantially increased risk of death from haemorrhage when the brain is involved. 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 treatment (mean of 1 to 7 episodes/year with prophylaxis and up to 30 to 50 episodes/year for on demand treatment). The consequence of multiple bleeding events is the development of an underlying pathology that contributes to debilitating multiple-joint arthropathy and substantially increased risk of death. Chemical modification (eg, direct conjugation of polyethylene glycol (PEG) polymers) and bioengineering of FVIII (eg, FVIII-Fc fusion proteins) improve half-life by approximately 50%, and thus, show promise in reduced dosing and maintaining activity levels above 1% trough. However, these longer acting FVIIIs remain dependent on multiple infusions to maintain critical levels of FVIII activity in severe HA patients.

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

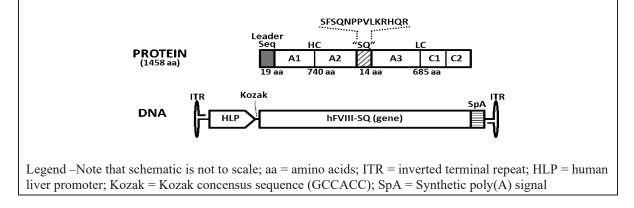
There is therefore a strong unmet need for a fully preventive treatment of HA to give patients a FVIII level compatible with a normal and haemorrhage-free life.

Gene therapy offers the potential of disease-modifying therapy by continuous endogenous production of active FVIII following a single intravenous administration of a vector with the appropriate gene sequence. Haemophilia 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 modest increases in the level of FVIII (any increase of the plasma level by 2 ng/ml induces an increase in activity of 1%) can ameliorate the severe form of the disease. Thus, relatively small changes in endogenous FVIII activity results in clinically relevant improvements in disease phenotype. Finally, the 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 for specific tissues such as the liver (for serotypes 2, 5 and 8 among others). Indeed, an on-going gene therapy clinical trial for a related disorder, haemophilia B, has established that stable (>36 months) expression of human factor IX at levels that are sufficient for conversion of their bleeding phenotype from severe to moderate or mild is achievable following a single peripheral vein administration of AAV-8 vector. Several participants in this trial have been able to discontinue factor prophylaxis without suffering spontaneous haemorrhages, 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 liver-selective promoter (Figure 1).





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

BMN 270 will be delivered by single intravenous dose and is designed to achieve stable, potentially life-long expression of active hFVIII in the plasma, synthesized from vector-transduced liver tissue. The clinical study 270-201 is a first-in-human study designed to assess the relationship of vector dose to the augmentation of residual FVIII activity, and whether these levels are sufficient to alter the clinical phenotype. The relationship of dose to safety will be correlated to the activity of hFVIII in patients with severe HA.

Liver Biopsy Substudy Rationale

The 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 in the second year of follow-up, with mean hFVIII activity levels remaining above the lower limit of normal (50 IU/dL). 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, and 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 270-201 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 some subjects, as well as inter-subject variability in post-therapy hFVIII levels. Neither the reasons for, nor the significance of, the ALT elevations or 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.

The purpose of this exploratory substudy is to provide a better understanding of the long-term gene expression related to circularized genomes, health of the liver, and variation in hFVIII levels observed after gene therapy with BMN 270. Whilst consenting subjects may not derive any direct benefit themselves by participating in the substudy, the overall findings could aid future patients by helping to characterize the means by which long-term efficacy is achieved and the safety of liver-directed gene therapy.



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OBJECTIVES:

The primary objectives of the study are:

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

The secondary objectives of the study are:

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

The exploratory objectives of the liver biopsy substudy are:

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

STUDY DESIGN AND PLAN:

This is a first-in-man, phase 1/2 open-label, dose escalation study in patients with severe haemophilia A. Eligible patients will enter the dose escalation part of the study followed by a 16-week Post-Infusion Follow-Up period during which safety and efficacy assessments will be taken. After the primary endpoint analysis at 16 weeks, safety and efficacy will then be assessed for approximately 7 years.

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

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AAV5-hFVIII-SQ		

Cohort 1: 6E12 vector genomes [vg] per kilogram of body weight, given as a single intravenous dose (iv)

Cohort 2: 2E13 vg per kilogram, iv

Cohort 3: 6E13 vg per kilogram, iv

Cohort 4: 4E13 vg per kilogram, iv

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

Cohorts 1-3

The first 3 cohorts will be enrolled sequentially, allowing a period of 3 weeks or more between cohorts. Dose escalation may occur after a single subject has been safely dosed if the resulting FVIII activity at the Week 3 visit is < 5 IU/dL in both the one-stage clotting and chromogenic substrate assays. Three weeks is expected to be the time the expression will be close to the maximum. This escalation paradigm is intended to minimize the subject numbers exposed to subtherapeutic doses.

Approximately three weeks after an injection, the decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and a panel of investigators participating in the study, the Data Review Board (DRB).

If the FVIII activity reaches ≥ 5 IU/dL at the Week 3 visit, then the remaining subjects in the cohort will be enrolled without the need to wait for 3 weeks between subjects.

Subject 1 will be dosed by intravenous infusion with 6E12 vector genomes [vg] per kilogram of body weight. If the FVIII activity level does not reach ≥ 5 IU/dL at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 1 and enrollment into Cohort 2 will initiate with Subject 2 at the next dose (2E13 vg/kg).

If the FVIII activity level in the first subject treated in Cohort 2 does not reach ≥ 5 IU/dL at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 2 and enrollment into Cohort 3 (6E13) will initiate with the next subject. If the FVIII activity level in the first subject treated in Cohort 3 does not reach ≥ 5 IU/dL at the Week 3 visit in both assays, then the Data Review Board (DRB) will recommend whether to continue to add subjects to the cohort and/or whether to continue the study.

For the first subject treated in each of the first 3 cohorts, if the activity level reaches ≥ 5 IU/dL and no safety issue is found, then up to four subjects will be enrolled in the Cohort, though, the adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

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Cohort 4

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

There will be an ongoing review of individual patient safety and efficacy data by the medical monitor and the DRB. The adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

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

In subjects who experience recurrent bleeding episodes, the Investigator and Medical Monitor will discuss whether to resume prior FVIII prophylaxis. Subjects who do not respond to BMN 270 treatment (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, follow an abbreviated visit schedule after Week 52, as applicable and at the discretion of the Investigator. Because subjects develop neutralizing immunity upon exposure to the capsid, re-challenge of vector is not a likely treatment option and these subjects have effectively a single opportunity for therapy using this AAV capsid. Efficacy will be determined by FVIII activity at 16 weeks post dose. Safety will be evaluated for approximately 7 years after dosing. Any safety signal may trigger a review of the data and possible additional immunogenicity studies that include an assessment of cellular immune responses using collected peripheral blood mononuclear cells (PBMC).

At applicable sites, certain study assessments designated in the Schedule of Events may be performed by a mobile nursing (MN) professional at the subject's home or another suitable location, such as their school or office, to improve access and convenience for subjects 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 subject and the subject gives written informed consent to participate in MN visits, the MN network will communicate with the subject and the subject's site.

Liver Biopsy Substudy Design

All subjects enrolled in 270-201 and who are at least one year post-BMN 270 infusion are eligible for the optional liver biopsy substudy. Subjects who consent to participate in the substudy will have a liver biopsy via either the transjugular or percutaneous (ultrasound-guided) route, according to the standard procedures of the institution. To enhance safety, all subjects will have an ultrasound examination of the liver within 3 months prior to the procedure (to ensure there are no pathological findings such as bile duct obstruction that might interfere with the safe performance of the liver biopsy) and a FibroScan of the liver within one week before the liver biopsy (to correlate with any potential histopathologic findings of fibrosis on the biopsy).

Subjects who consent should have their FVIII levels monitored/adjusted by the Investigator to enable the procedure to be performed safely. This may require the administration of exogenous FVIII replacement products in order to achieve the desired FVIII activity. The target FVIII activity level within 24 hours prior to the liver biopsy is at the discretion of the Investigator and/or according to local guidelines, but at a minimum should be at the lower limit of the normal range (ie, at least 50 IU/dL).



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NUMBER OF SUBJECTS PLANNED:

Up to 15 subjects may enroll into the study; the actual number of subjects will depend on the FVIII activity levels seen in each Cohort.

DIAGNOSIS AND ALL CRITERIA FOR INCLUSION AND EXCLUSION:

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

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

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

- 1. Detectable pre-existing immunity to the AAV5 capsid as measured by AAV5 transduction inhibition or AAV5 total antibodies
- 2. Any evidence of active infection or any immunosuppressive disorder.
- 3. HIV positive
- 4. Significant liver dysfunction as defined by abnormal elevation of:
 - ALT (alanine transaminase) to 3 times the upper limit of normal;
 - Bilirubin above 3 times the upper limit of normal;
 - Alkaline phosphatase above 3 times the upper limit of normal; or
 - INR (international normalized ratio) ≥ 1.4

BioMa 105 Di	C OF COMPANY rin Pharmaceutical Inc. gital Drive o, CA 94949	SUMMARY TABLE Referring to Part of the Dossier:	FOR NATIONAL AUTHORITY USE ONLY:
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5.	Potential participants who have had had significant fibrosis of 3 or 4 as r		are excluded if they
6.	Evidence of any bleeding disorder n	ot related to Haemophilia A	
7.	Platelet count of $< 100 \text{ x } 10^9/\text{L}$		
8.	$Creatinine \geq 1.5 \text{ mg/dL}$		
9.	Liver cirrhosis of any etiology as as	sessed by liver ultrasound	
10.	Hepatitis B if surface antigen is posi-	tive	
11.	Hepatitis C if RNA is positive		
12.	Treatment with any IP within 30 day	ys prior to the end of the screening	ng period
13.	Any disease or condition at the phys fully complying with the requirement treatment outlined in the protocol. The unable to agree on not using alcohol	nts of the study including possibl The physician may exclude patient	e corticosteroid nts unwilling or
14.	Prior treatment with any vector or ge	ene transfer agent	
15.	Major surgery planned in the 16-we	ek period following the viral infu	ision
16	. Use of systemic immunosuppressive infusion	e agents or live vaccines within 3	0 days before the viral
Individ criteria	uals eligible to participate in the liver	biopsy substudy must meet all o	of the following
1.	Currently enrolled in 270-201		
2.	Received BMN 270 infusion at least	1 year prior to enrollment in the	e substudy
3.	Able to sign informed consent and c	omply with requirements of the	substudy
4.	FVIII activity at least >50 IU/dL (or Investigator discretion) within 24 ho levels should be assessed at the loca exogenous FVIII replacement produ appropriate level, under the supervise	burs prior to the liver biopsy bein l laboratory.) Subjects may be the cts in order to increase their FVI	g performed. (FVIII reated with additional II levels to an
	luals who meet any of the following e er biopsy substudy:	xclusion criteria will not be eligi	ble to participate in



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1. Assessed by the investigator or a he undergoing a liver biopsy would be are not limited to):		
• Significant thrombocytopenia (p	platelet count < $100 \times 10^9/L$)	
• Evidence of significant ascites		
• Abnormalities detected on liver that would preclude safe perform	<u>a</u>	0 days of procedure)
INVESTIGATIONAL PRODUCT(S), DO	DSE, ROUTE AND REGIMEN	N:
Each subject will receive a single injection of		
infusion will depend on the dose level.		
REFERENCE THERAPY(IES), DOSE, I		
The study is open label with comparison of will be evaluated in this study.	FVIII activity to baseline values	. No reference therapy
DURATION OF TREATMENT:		
BMN 270 is given as a single dose by intrav	venous infusion.	
CRITERIA FOR EVALUATION:		
<u>Safety:</u>		
The following safety outcome measurement	s will be assessed:	
• Incidence of adverse events (AEs),	including serious AEs (SAEs)	
• Change in clinical laboratory tests (serum chemistry and haematolog	gy)
• Change in vital signs		
• Change in physical examination		
• Vector shedding		
• Liver tests (LTs, including ALT, AS	ST, GGT, LDH, total bilirubin, a	lkaline phosphatase)
• Immune response to FVIII transgen	e and AAV capsid proteins	/
No major toxicity is expected based on prec have comprehensive surveillance monitoring	linical studies in mice and monk	week for Weeks 1-36,

have comprehensive surveillance monitoring of LTs (at local labs, once per week for Weeks 1-36, then once every 2 weeks from Week 37-52) during Year 1. LTs will be monitored every 4 weeks during Year 2, every 6 weeks for Years 3-5, and every 26 weeks for Years 6-7 post-dose in the safety extension; the frequency and duration of LT testing may be changed based on discussion between the Medical Monitor and the Investigator and review of subject data.

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



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ie:	
nce:	
re	rence:

Efficacy:

The primary efficacy measure will be to assess plasma FVIII activity. The efficacy goal of the study is to establish the dose relationship to FVIII activity \geq 5 IU/dL at 16 weeks post BMN 270 administration.

Secondary efficacy measures include assessing the impact of BMN 270 on the frequency of FVIII replacement therapy and on the number of bleeding episodes during the study. Subjects will be asked to keep a subject diary to record the details in these areas.

Pharmacodynamics:

The FVIII antigen and activity level as measured by an ELISA (antigen level) and by one-stage clotting and/or chromogenic substrate assay (activity level), will be used for plasma profiles; FVIII activity will be used to determine PD parameters. Traditional PK analysis is not applicable.

If supported by the FVIII activity data, non-compartmental analysis and observation will be used to estimate individual values of Cb (baseline concentration), Css (steady state concentration), Tss (time to steady state), C(t) and AUC(0-t) where t is 16 weeks.

Liver Biopsy Substudy:

The following exploratory assessments will be performed as part of the optional liver biopsy substudy:

- Morphologic/pathogenic changes after FVIII gene transduction or any change that may be associated with sustained ALT rise
- Determine quantities of liver FVIII-SQ DNA/RNA
- Determine forms of vector DNA in liver at the time of biopsy
- Determine percentage of hepatocytes expressing FVIII protein
- Determine percentage of hepatocytes staining positive for vector DNA
- Determine hepatic liver transcriptome at single nuclei level if sufficient material is obtained
- Identify the forms of vector DNA in the liver
- Examination of potential stress inducing cellular pathways
- Other exploratory assessment to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to hemophilia A, coagulation, and/or AAV gene transfer

STATISTICAL METHODS:

The sample size is based upon clinical considerations and could detect a strong clinical efficacy signal. Up to 15 subjects may be dosed in the study. The subjects will be followed in a longitudinal manner and all the relevant information will be collected. The analysis of the data will be descriptive in nature but data collected in a longitudinal manner may be analyzed using longitudinal methods such as mixed effect model which takes into account the correlation among the observation taken at various time points within a participant. Efficacy is a secondary endpoint,

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AAV5-hFVIII-SQ			
defined as biologically active FVIII at ≥ 5 II	J/dL by chromogenic substrate a	assay and/or one-stage	
clotting assay at 16 weeks following study t	reatment. We can only assess the	e true steady state of	
FVIII protein produced from BMN 270 after a minimum of 72 hours has elapsed since the last			
infusion of FVIII protein concentrates.			
Analysis of neutralizing antibody response a	und other immunological parame	eters as well as vector	

Analysis of neutralizing antibody response and other immunological parameters as well as vector shedding will be primarily descriptive and involve both inter-participant and intra-participant comparisons across doses.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

AAV	adeno-associated virus
ADL	activities of daily living
ADR	adverse drug reaction
AE	adverse event
ALT	alanine transaminase
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BPV	BioMarin Pharmacovigilance
BU	Bethesda Unit
CFR	Code of Federal Regulations
CRA	clinical research associate
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DRB	Data Review Board
eCRF	electronic case report form
ED	exposure days
EOSI	events of special interest
ETV	early termination visit
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
FIH	first-in-human
FVIII	coagulation factor VIII
FXa	coagulation factor Xa
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
НА	Haemophilia A
hFVIII	human coagulation factor VIII
HIPAA	Health Insurance Portability and Accountability Act
IB	investigator brochure
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICH E6	ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6
IEC	independent ethics committee

INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IV	intravenous
LT	liver test
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	no-observed-adverse-effect level
PBMC	peripheral blood mononuclear cells
PD	pharmacodynamics
PEG	polyethylene glycol
РК	Pharmacokinetics
PRO	patient-reported outcome
rhFVIII	recombinant human FVIII protein
REB	research ethics board
SAE	serious adverse event
SAP	statistical analysis plan
SDV	source data verification
ULN	upper limit of normal
vg	vector genomes
VWF:Ag	von Willebrand factor Antigen

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]).

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

5 ETHICS

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

5.1 Institutional Review Board or Independent Ethics Committee

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

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

5.2 Ethical Conduct of Study

It is expected that Investigators understand and comply with the protocol. This includes, but is not limited to: establishing and meeting enrollment commitments, including providing eligible subjects for study enrollment; adhering to 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)

Specifically, this study is based on adequately performed laboratory and animal experimentation. The study will be conducted under a protocol reviewed and approved by an IRB/IEC/REB and will be conducted by scientifically and medically qualified persons. The benefits of the study are in proportion to the 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, as well as when updates to the ICF are made. Where it is not feasible for the Investigator to receive the signed, written ICF from the subject prior to beginning new or changed study-related procedures contained in such an ICF update (for example, due to COVID-19-related restrictions), the Investigator will ask the subject to verbally confirm during an informed consent interview that the subject has signed and dated the ICF. The Investigator should document this verbal confirmation on the Investigator's copy of the ICF and, when it is possible to do so, receive the informed consent signed by the subject and archive the original(s) in the record file of the subject.

5.3 Subject Information and Informed Consent

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

than the native language of the clinical site must also be received by BioMarin or designee prior to any study-specific procedures being performed.

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

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

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

Prior to beginning the study, the Investigator at each site must provide to BioMarin or designee, a fully executed and signed US Food and Drug Administration (FDA) Form FDA 1572 and a Financial Disclosure Form. All sub-Investigators must be listed on Form FDA 1572. Financial Disclosure Forms must also be completed for all sub-Investigators listed on the Form FDA 1572 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.

Liver tests (LTs) will be performed at the local laboratories associated with the study sites. Local laboratory results of LTs will be used to trigger corticosteroid treatment as needed (refer to Section 9.4.8.2). In case of discrepant results between local and central laboratories, the Investigator and Medical Monitor will decide further action. Safety labs evaluations (including LTs) will be performed at the central lab, while bioanalytical samples will be performed at the appropriate specialty lab. Refer to the Laboratory Manual for more details.

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7 INTRODUCTION

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Haemophilia A (HA) is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males (Nathwani, 1992). It is caused by mutations in the factor VIII (FVIII) gene that codes for FVIII protein, an essential cofactor in the coagulation cascade. 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 haemorrhage. Treatment in Western (Berntorp, 2012) countries consists of intravenous injection of plasma derived or recombinant FVIII protein concentrates at the time of a bleed, 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 haemophilia A patients. These individuals develop debilitating arthropathy and have a substantially increased risk of death from haemorrhage in life (Stonebraker, 2010). Chemical modification or bioengineering of FVIII may improve half-life to 18-19 hours (Kaufman, 2013). However, these long acting 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 following a single administration of vector. Haemophilia A is well suited for this approach because its clinical manifestations are attributable to the lack of a single gene product (FVIII) that circulates in low amounts (100-200 ng/ml) in the plasma. Tightly regulated control of gene expression is not essential and a modest increase in the level of FVIII (a plasma level of 2 ng/ml protein leads to a 1% expression) can ameliorate the severe phenotype (Srivastava, 2013); thus the therapeutic goal for gene therapy is a modest increase in hFVIII. Finally, the consequences of gene transfer can be assessed using simple quantitative rather than qualitative endpoints that can be easily assayed in most clinical laboratories.

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

7.1 Nonclinical Studies

The nonclinical program supports a single IV administration of BMN 270, the planned clinical route of administration, for the treatment of Haemophilia A in male patients. This nonclinical program took into account the guidelines and reflection papers for gene therapy medicinal products under EMA Advanced Therapies. The primary pharmacodynamics (PD), pharmacokinetics (PK), and toxicity of IV BMN 270 were characterized in a series of single

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dose studies in species that were vector permissive and responsive to the transgene (normal CD-1 mouse, B and T cell deficient mouse model of haemophilia 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.

The primary PD of BMN 270 was assessed in a series of non-GLP single dose studies in a FVIII KO x Rag2 mouse model of severe Haemophilia A that recapitulates the change in coagulation observed in the human severe disease population without interfering cross species immunogenicity. PD activity and expression of hFVIII was assessed for durations up to 13-weeks in the FVIII KO x Rag2 mouse given dose range of 2E11 through 2E14 vector genomes (vg)/kg. Low levels of plasma hFVIII were observed in mice given 2E12 vg/kg after eight-weeks, post dose. Plasma hFVIII activity using bleeding time as an endpoint was evaluated in the FVIII KO x Rag2 mouse given up to 2E13 and 1E14 vg/kg BMN 270 at 8 weeks, post dose. BMN 270 related correction of bleeding times showed a dose relationship that was similar to that observed in FVIII KO x Rag2 mice given matched IU levels of Refacto[®].

All cynomolgus monkeys used in this program were screened for neutralizing anti-AAV5 activity prior to study enrollment. PD activity and plasma hFVIII concentrations were evaluated in the cynomolgus monkey given up to 6E13 vg/kg BMN 270 for eight weeks. Peak expression of hFVIII was observed three to six weeks post administration with a subsequent decrease in expression presumably due to immunogenicity though not necessarily correlated to antibody titer.

The normal mouse was utilized in the GLP toxicology study to assess the safety profile of BMN 270 without the background of disease progression and in sufficient number per parameter. The GLP single dose toxicity study in normal CD-1 mice given 6E12 and 6E13 vg/kg with a 4 and 13-week follow up period monitored clinical pathology, defined potential target organs, immunogenicity, gene expression and activity. No changes in liver function were observed. In a single dose PD study in monkey given BMN 270, formation of anti-AAV5 total antibodies was observed at Week 8 with relatively low formation of anti-hFVIII total antibodies. No changes in liver function was observed.

The overall nonclinical safety profile includes formation of anti-AAV5 total antibodies with relatively lower formation of anti-hFVIII total antibodies. Immunogenicity against the AAV capsid and hFVIII is an anticipated finding for BMN 270 treatment and will be monitored in the nonclinical and clinical programs. Though not observed in the nonclinical species, liver toxicity utilizing clinical pathology parameters will be monitored in the clinical program based on previous literature. Cellular immune response will also be monitored.

Additionally, the BMN 270 transgene product has a final sequence closely matching that of the protein replacement treatment, Refacto® and therefore the safety profile of the BMN 270

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transgene product is anticipated to be similar to Refacto® and have no unique FVIII-specific target organs of toxicity. The AAV5 capsid has not been modified and therefore no unique capsid-specific safety findings are anticipated. Because the biodistribution pattern of AAV5 after IV administration is consistent across species, BioMarin will confirm the nonclinical distribution pattern of BMN 270 during clinical development. Biodistribution of the AAV5 capsid has been documented to predominately target the liver with relatively lower levels of transduction observed in the lung, kidney, spleen, testes and blood compartment depending on the species and timing of administration. Liver targeted distribution of a similar AAV5 Factor IX gene therapy product was observed in the rhesus macaque monkey with low levels of vector genomes detected in spleen, kidney and testis (Nathwani, 2006). Despite distribution to non-liver organs, no expression of Factor IX was detected in these tissues. Additionally, distribution to the testis was observed in another study in monkeys given an AAV5-codon-optimized human porphobilinogen deaminase; however, vector genomes in the semen were only transiently observed within one week but not thereafter (Paneda, 2013).

Both normal and disease model mice and a limited number of monkeys were utilized to establish proof of concept, species scaling and dose response in order to select the first-in-human (FIH) dose of 6E12 vg/kg. This dose represents 10-fold safety factor from the no observed adverse effect level (NOAEL) in the GLP enabling nonclinical toxicology study in mice.

7.2 Previous Clinical Studies

This is the first clinical study for BMN 270.

BioMarin's program for haemophilia A builds on previous clinical trials of AAV-mediated gene transfer for a related condition, haemophilia B, that were conducted with an AAV2 vector (Manno, 2003) and an AAV8 vector (Nathwani, 2011), (Nathwani, 2014). The large size of the FVIII cDNA was shortened and a preclinical validation of this approach was performed with an AAV8 vector (McIntosh, 2013).

AAV serotype 5 is being tested in other clinical trials and was reportedly well tolerated without treatment-related serious adverse events in a recent phase 1 study for treatment of Acute Intermittent Porphyria (D'Avola, 2014). In addition, AAV using other serotypes have been used in 105 clinical studies to date and no safety issue specific to the vector was ever reported.

7.3 Study Rationale

Haemophilia A (HA) is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males (Mannucci, 2001). It is caused by deficiency in the activity of coagulation factor VIII (FVIII), an essential cofactor in the intrinsic coagulation cascade. This disorder can be either inherited, due to a new mutation or an acquired immunologic process, leading

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to insufficient quantities of FVIII or a dysfunctional FVIII, but all are characterized by a defective coagulation process. The clinical phenotype of HA patients is largely governed by the level of residual expression. Severe HA is classified as FVIII activity less than 1% of wild type (< 1 IU/dL), moderate disease comprises 1-5% of wild type activity and the mild form is 5-40% activity. The clinical manifestations of severe HA remain frequent spontaneous bleeding episodes, predominantly in joints and soft tissues, with a substantially increased risk of death from haemorrhage when the brain is involved.

Treatment of severe HA presently consists of intravenous injection of plasma derived or recombinant human FVIII protein (rhFVIII) concentrates both as prophylaxis 2-4 times per week, and at the time of a bleed, to prevent or control bleeding episodes, respectively. The half-life for FVIII (12-18 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 treatment (mean of 1 to 7 episodes/year with prophylaxis and up to 30 to 50 episodes/year for on demand treatment) (Nagel, 2011). The consequence of multiple bleeding events is the development of an underlying pathology that contributes to debilitating multiple-joint arthropathy and substantially increased risk of death (Nagel, 2011, Haemophilia). Chemical modification (eg, direct conjugation of polyethylene glycol (PEG) polymers) and bioengineering of FVIII (eg, FVIII-Fc fusion proteins) improve half-life by approximately 50%, and thus, show promise in reduced dosing and maintaining activity levels above 1% trough (Stonebraker, 2010), (Mahlangu, 2014). However, these longer acting FVIIIs remain dependent on multiple infusions to maintain critical levels of FVIII activity in severe HA patients. There is therefore a strong unmet need for a fully preventive treatment of HA to give patients a FVIII level compatible with a normal and haemorrhage-free life.

Gene therapy offers the potential of disease-modifying therapy by continuous endogenous production of active FVIII following a single intravenous administration of a vector with the appropriate gene sequence. Haemophilia 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 modest increases in the level of FVIII (any increase of the plasma level by 2 ng/ml induces an increase in activity of 1%) can ameliorate the severe form of the disease. Thus, relatively small changes in endogenous FVIII activity results in clinically relevant improvements in disease phenotype. Finally, the 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 (Mannucci, 2001).

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They have an excellent and well defined safety profile, and can direct long term transgene expression with tropism for specific tissues such as the liver (Nathwani, 2005) for serotypes 2, 5 and 8 among others. Indeed, an on-going gene therapy clinical trial for a related disorder, haemophilia B, has established that stable (>36 months) expression of human factor IX at levels that are sufficient for conversion of their bleeding phenotype from severe to moderate or mild is achievable following a single peripheral vein administration of AAV-8 vector (Nathwani, 2014). Several participants in this trial have been able to discontinue factor prophylaxis without suffering spontaneous haemorrhages, 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, 2011), (Bainbridge, 2008), (Maguire, 2009); (Simonelli, 2010).

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

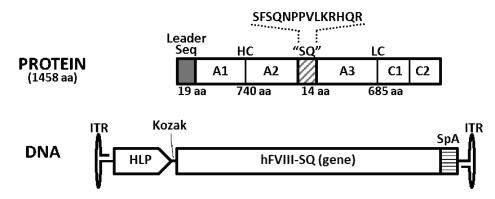


Figure 7.3.1: hFVIII-SQ Vector Genome and Encoded Protein

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 single intravenous dose and is designed to achieve stable, potentially life-long expression of active FVIII in the plasma, synthesized from vector-transduced liver tissue. The clinical study 270-201 is a first-in-human study designed to assess the relationship of vector dose to the augmentation of residual FVIII activity, and whether these levels are sufficient to alter the clinical phenotype. The relationship of dose to safety will be correlated to the activity of FVIII in patients with severe HA.

7.3.1 Liver Biopsy Substudy Rationale

The 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 in the second year of follow-up, with mean

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hFVIII activity levels remaining above the lower limit of normal (50 IU/dL). 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 270-201 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 some subjects, as well as inter-subject variability in post-therapy hFVIII 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 substudy is to provide a better understanding of the long-term gene expression related to genome circularization, health of the liver, and variation in hFVIII levels observed after gene therapy with BMN 270. Whilst consenting subjects may not derive any direct benefit themselves by participating in the substudy, the overall findings could aid future patients by helping to characterize the means by which long-term efficacy is achieved and the safety of liver-directed gene therapy.

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

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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, who 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 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.

At the highest dose tested in 270-201 (6E13 vg/kg), the majority of subjects achieved FVIII levels above 50 IU/dL at 52 weeks post-infusion. 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. 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 270-301 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 safety findings in 270-201, refer to current version of the Investigator's Brochure.

Dose selection: The benefit of this study can only be enhanced by selecting a starting dose that maximizes the opportunity of observing a therapeutic effect, and therefore, reducing the possibility of a sub-therapeutic effect. With this consideration in mind, the starting dose

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6E12 vg/kg was selected using overall data from the pre-clinical studies conducted in mice (normal and disease model, Rag2 -/- x FVIII -/-) and monkey. A detectable pharmacological response based on activity was observed at 6E12 vg/kg. A 10-fold safety margin based upon the NOAEL was observed in the GLP 13-week study in normal mouse at the highest dose administered. A 30-fold safety margin in an 8-week dose response study in disease model mice based on histology was observed at the highest dose administered. No BMN 270-related changes in clinical observations or chemistry was observed in the monkey at doses up to 6E13 vg/kg, a 10-fold safety margin after 8-weeks. Overall, no BMN 270-related findings, except expected formation of anti-AAV5 antibodies, were observed at the highest administered doses of 6E13, 2E14 and 6E13 vg/kg in the normal mouse, disease model mouse and monkey, respectively.

Based on these key pre-clinical findings it can be suggested that the proposed starting dose of 6E12 vg/kg should not pose any risk or safety concerns to subjects with the best chance of benefiting the subject therapeutically.

7.4.1 Optional Liver Biopsy Substudy 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 substudy will have a comprehensive pre-/post-biopsy surveillance plan according to the standard procedures at the institution. 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 substudy is optional and will not have any effect on the subject's continued participation in 270-201.

8 STUDY OBJECTIVES

The primary objectives of the study are:

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

The secondary objectives of the study are:

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

The exploratory objectives of the liver biopsy substudy are:

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

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a first-in-man, phase 1/2 open-label, dose escalation study in patients with severe haemophilia A. Eligible patients will enter the dose escalation part of the study followed by a 16-week Post-Infusion Follow-Up period during which safety and efficacy assessments will be taken. After the primary endpoint analysis at 16 weeks, safety and efficacy will then be assessed for approximately 7 years.

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

- Cohort 1: 6E12 vector genomes [vg] per kilogram of body weight, given as a single intravenous dose (iv)
- Cohort 2: 2E13 vg per kilogram, iv
- Cohort 3: 6E13 vg per kilogram, iv
- Cohort 4: 4E13 vg per kilogram, iv

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

Cohorts 1-3

The first three cohorts will be enrolled sequentially, allowing a period of 3 weeks or more between cohorts. Dose escalation may occur after a single subject in a cohort has been safely dosed if the resulting FVIII activity at the Week 3 visit is < 5 IU/dL in both assays. Three weeks is expected to be the time the expression will be close to the maximum. This escalation paradigm is intended to minimize the subject numbers exposed to subtherapeutic doses. The decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and a panel of investigators participating in the study.

If the FVIII activity reaches ≥ 5 IU/dL at the Week 3 visit, then the remaining subjects in the cohort will be enrolled without the need to wait for 3 weeks between subjects.

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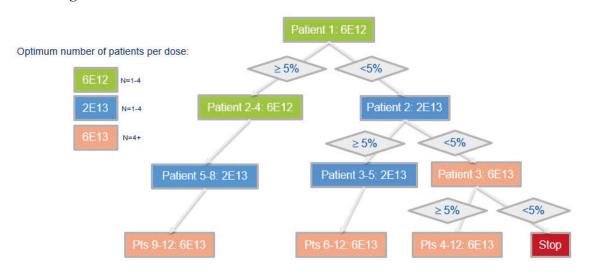


Figure 9.1.1: Flow Chart of Dose Escalation Scheme for Cohorts 1 to 3

Subject 1 (Cohort 1) will be dosed by intravenous infusion with 6E12 vg/kg of body weight. If the FVIII activity level does not reach 5 IU/dL or greater (expressed as % in Figure 9.1.1) at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 1 and enrollment into Cohort 2 will initiate with Subject 2 at the next dose (2E13 vg/kg).

If the FVIII activity level in the first subject treated in Cohort 2 does not reach \geq 5 IU/dL at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 2 and enrollment into Cohort 3 (6E13) will initiate with the next subject.

If the FVIII activity level in the first subject treated in Cohort 3 does not reach \geq 5 IU/dL at the Week 3 visit in both assays, then the DRB will recommend whether to continue to add subjects to the cohort and/or whether to continue the study.

For the first subject treated in each of the first 3 cohorts, if the activity level reaches \geq 5 IU/dL and no safety issue is found, then up to four subjects will be enrolled in the Cohort, though the adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

Cohort 4

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

There will be an ongoing review of individual patient safety and efficacy data by the medical monitor and the Data Review Board (DRB). The adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

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

In subjects who experience recurrent bleeding episodes, the Investigator and Medical Monitor will discuss whether to resume prior FVIII prophylaxis. Subjects who do not respond to BMN 270 treatment (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, follow an abbreviated visit schedule after Week 52, as applicable and at the discretion of the Investigator.

At applicable sites, certain study assessments designated in the Schedule of Events may be performed by a mobile nursing (MN) professional at the subject's home or another suitable location, such as their school or office, to improve access and convenience for subjects 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 subject and the subject gives written informed consent to participate in MN visits, the MN network will communicate with the subject and the subject's site.

Because subjects develop neutralizing immunity upon exposure to the capsid, re-challenge of vector is not a likely treatment option and these subjects have effectively a single opportunity for therapy using this AAV capsid. Efficacy will be determined by FVIII activity at 16 weeks post dose. Safety will be evaluated for approximately 7 years after dosing. Any safety signal may trigger a review of the data and possible additional immunogenicity studies that include an assessment of cellular immune responses using collected PBMC. Additionally, if any of the events listed in Section 9.3.4.1 occur, enrollment into the trial will be halted to complete an extensive safety analysis. Notification of the study enrollment halt will be sent by the Sponsor to the participating sites via telephone and email immediately after becoming aware of a safety concern. This will ensure no additional subjects are dosed until the signal has been completely evaluated. If, following safety review by the DRB and the Sponsor, it is deemed appropriate to restart dosing, a request to restart dosing with pertinent data will be submitted to the health authority.

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A summary of events and assessments are provided by visit in Table 9.1.1 for Screening, Baseline and BMN 270 Infusion, in Table 9.1.2 for Post-Infusion Follow-up, and in Table 9.1.3, Table 9.1.4, and Table 9.1.5 for Safety Follow-up.

Table 9.1.6, dealing with the apeutic corticosteroid use in the event of elevated LTs, is discussed in Section 9.4.8.2.

Liver Biopsy Substudy Design

All subjects enrolled in 270-201 and who are at least one year post-BMN 270 infusion are eligible for the optional liver biopsy substudy. Subjects who consent to participate in the substudy will have a liver biopsy via either the transjugular or percutaneous (ultrasound-guided) route, according to the standard procedures of the institution. To enhance safety, all subjects will have an ultrasound examination of the liver within 3 months prior to the procedure (to ensure there are no pathological findings such as bile duct obstruction that might interfere with the safe performance of the liver biopsy) and a FibroScan of the liver within one week before the liver biopsy (to correlate with any potential histopathologic findings of fibrosis on the biopsy).

Subjects who consent should have their FVIII levels monitored/adjusted by the Investigator to enable the procedure to be performed safely. This may require the administration of exogenous FVIII replacement products in order to achieve the desired FVIII activity. The target FVIII activity level within 24 hours prior to the liver biopsy is at the discretion of the Investigator and/or according to local guidelines, but at a minimum should be at the lower limit of the normal range (ie, at least 50 IU/dL).

Table 9.1.7 presents the schedule of assessments for participation in the liver biopsy substudy.

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Table 9.1.1: Schedule of Events – Screening and Infusion

Assessment (Day Informed consent Assessment (Day Medical History Height and Veight ^a Physical Examination ^a Physical Examination ^a Vital Signs Physical Examination ^a Vital Signs Sessment of Adverse Events and Concomitant Medications Physical information Documentation of bleeding episodes and FVIII usage (by either subject or clinical information) Distribution of subject diaries and training in their use	Screening ⁱ (Day -28 to Day -1) X X X X X X X X X	Smart Rescreening ⁱ (Day -28 to Day -1) X X X	Baseline (Day -7 to Day -1) ^h X X X X X X X	Visit (Day 1) ^k X X
	(1- Yeu ou oz- yeu) X X X X X X X X X X X X		X X X X X X X X X	
Medical HistoryMedical HistoryPhysical Examination ^a Physical Examination ^a Height and Weight ^a Vital SignsVital SignsAssessment of Adverse Events and Concomitant MedicationsAssessment of bleeding episodes and FVIII usage (by either subject or clinical information)Documentation of subject diaries and training in their use	X X X X X ;	XXX	X X X	XXX
Physical Examination ^a Physical Examination ^a Height and Weight ^a Vital SignsVital SignsAssessment of Adverse Events and Concomitant MedicationsDocumentation of bleeding episodes and FVIII usage (by either subject or clinical information)Distribution of subject diaries and training in their use	X X X X ;	X X	x x x x	XXXX
Height and WeightaVital SignsVital SignsAssessment of Adverse Events and Concomitant MedicationsAssessment of bleeding episodes and FVIII usage (by either subject or clinical information)Documentation of subject diaries and training in their use	X X X X	X X X	X X X	X
Vital SignsVital SignsAssessment of Adverse Events and Concomitant MedicationsDocumentation of bleeding episodes and FVIII usage (by either subject or clinical information)Distribution of subject diaries and training in their use	X X ;	XXX	x x x	XX
Assessment of Adverse Events and Concomitant Medications Documentation of bleeding episodes and FVIII usage (by either subject or clinical information) Distribution of subject diaries and training in their use	X X ;	X	x x x	X
Documentation of bleeding episodes and FVIII usage (by either subject or clinical information) Distribution of subject diaries and training in their use	X	Х	x x	V
Distribution of subject diaries and training in their use	,,,		X	
Electrocardiogram	×			
Chest X-ray	Х			
Liver Ultrasound	X			
hFVIII Assays ^b	Х	Xj		
AAV5 Assays ^c	Х	Х		Х
Screen for Hepatitis B, Hepatitis C, HIV ^d	Х			
Blood chemistry, haematology, coagulation screen, and CRP ^e	Х	Х	Х	
Urine Tests ^e	Х	Х	Х	
Liver Tests ^e	Х	Х	X	
PBMC collection for CTL baseline			X	
Von Willebrand Factor Antigen (VWF:Ag)	Х			
Direct Thrombin Test			X	
PCR of vector DNA in blood, saliva, urine, semen, and stools			Х	
Biomarker testing ^f	Х			
Exploratory biomarker assessments ^g			X	
Haemo-QoL-A Quality of Life (QoL) assessment			Х	
BMN 270 Infusion				Х

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^a Complete physical examination should be done at Screening. Brief physical examination Screening only. Weight will be recorded at Screening and then every 6 months thereafter. ^b Includes baseline hFVIII activity (chromogenic substrate assay and one-stage clotting asse Niimeeen modification) hFVIII total antibody titer and hFVIII antioned (FITSA)	^a Complete physical examination should be done at Screening. Brief physical examination may be done at Baseline and at the BMN 270 Infusion Visit. Height will be recorded at Screening only. Weight will be recorded at Screening and then every 6 months thereafter. ^b Includes baseline hFVIII activity (chromogenic substrate assay and one-stage clotting assay), hFVIII coagulation activity exploratory assay, hFVIII inhibitor level (Bethesda assay with Niimeen modification), hFVIII total antibody titer and hEVIII articen (FI ISA).
^c Screening (done during Screening) and testing (at Infusion Visit) of AAV5 pre-existing immunity may include plasma samples for 3 assays (in vivo transduction inhibition and AAV5 total antibody assays). Sample collection on the day of the infusion visit must be performed before the BMN 270 infusion is given. ^d Patients with documented negative results within the last 30 days do not need to be retested. ^e Refer to Table 9.7.9.2.1 for laboratory assessments to be included, and to Table 9.7.9.3.1 for liver tests.	 ^c Screening (done during Screening) and testing (at Infusion Visit) of AAV5 pre-existing immunity may include plasma samples for 3 assays (in vivo transduction inhibition, in vitro transduction inhibition, in vitro transduction inhibition and AAV5 total antibody assays). Sample collection on the day of the infusion visit must be performed before the BMN 270 infusion is given. ^d Patients with documented negative results within the last 30 days do not need to be retested. ^e Refer to Table 9.7.9.2.1 for laboratory assessments to be included, and to Table 9.7.9.3.1 for liver tests.
$^{\rm f}$ Includes HLA genotyping, FVIII genotyping, TNF α and IL 10a single nucleotide polymorphisms.	/morphisms.
^g Blood samples will be collected to evaluate biochemical, molecular, cellular, and genetic/genomic as assays used for these evaluations. Subjects may choose to opt out of the exploratory genetic/genomi associated with hemophilia A. While exploratory samples will be collected at the time points indicat and any other exploratory assessments) will be performed only as deemed necessary by the Sponsor.	^g 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 Direct Thrombin Activity test and any other exploratory assessments) will be performed only as deemed necessary by the Sponsor.
^h Should the screening visit occur within 7 days of the drug infusion, physical examinate repeated at Baseline.	physical examination, blood chemistry, LTs, haematology, urine tests, coagulation screen, and CRP do not need to be
¹ Smart rescreening should only be performed if a patient has been determined to be el of the original Screening window. Subjects who undergo smart rescreening must co consent. Subjects who do not complete dosing within 90 days will be required to re- once.	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.	ust be done at smart rescreening.
k Assessments on the day of infusion must be performed prior to the infusion. On the every 15 minutes (± 5 minutes), following the infusion hourly (± 5 minutes) for 6 ho	^k Assessments on the day of infusion must be performed prior to the infusion. On the day of the BMN 270 Infusion, vital signs will be monitored prior to the infusion, during the infusion every 15 minutes (\pm 5 minutes (\pm 5 minutes) for 6 hours and then every 2 hours (\pm 15 minutes) for 6 hours and then at 4 hour intervals (\pm 15 minutes).

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Assessment						1-woll	Jp Afte	Follow-Up After BMN	N 270	Administration	istrati	I.	Weeks*					
Assessment	M	Week 1																
	D2	D4	D8	7	e	4	S	9	7	8	6	10	11	12	13	14	15	16
Physical examination ^a			Х	X	x	×	X	X	x	X	X	X	X	X	X	X	X	Х
Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)			Х	Х	Х	Х	X	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Vital Signs			x	X	×	×	X	x	x	X	X	X	Х	Х	×	×	X	Х
Blood chemistry, haematology, coagulation screen, and CRP ^b				x		x		×		×		×		×				X
Urine Tests ^b						Х				Х				Х				Х
Liver Tests (local) ^b		x	Х	X	X	×	X	x	x	X	x	X	X	X	X	x	X	Х
FVIII assays (local) ^c		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	X	Х	Х
Liver Tests (central) ^b		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
FVIII assays (central) ^d		Х	Х	Х	Х	Х	Х	X	Χ	Χ	Х	Х	Х	X	Х	X	Х	Х
FVIII antibody titer						Х				Χ				X				Х
PCR of vector DNA in blood, saliva, urine, semen, and stools ^e	Х	Х	Х			Х		Х		Х		Х		Х		Х		Х
Exploratory biomarker assessments ^f						Х				Χ				X				Х
Haemo-QoL-A QoL assessment			Х	Х	Х	Х												Х
AAV5 antibody titer										Х								Х
Testing for reactivation of hepatitis B and hepatitis C																		X ^g
PBMC collection			Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Von Willebrand Factor Antigen (VWF:Ag)						Х				Х				Х				Х
Direct Thrombin test			X												X			

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- Refer to Table 9.7.9.2.1 for laboratory assessments to be included, and to Table 9.7.9.3.1 for liver tests. LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) 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 \geq 3x ULN. Patients with ALT > 1.5 ULN during the study may undergo additional evaluations (eg, imaging studies including MRI or ultrasound, additional blood tests, 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 and/or liver biopsy) at the discretion of the investigator. Additional testing of FVIII and LTs during any study week may be performed if: (1) the ALT has increased to above ULN; (2) Increases in ALT values from prior assessment are accompanied by declines in FVIII activity level; or after a discussion between the Medical Monitor and the Investigator based on a Brief physical examination should be done at all weekly visits except Week 16, where a complete physical examination should be performed. Refer to Section 9.7.9.5. between the Medical Monitor and the Investigator.
- obtain FVIII activity measurements when a 72-hour interval without FVIII as is achieved; the 72-hour wash-out period is only intended for subjects who have achieved FVIII \geq 5 IU/dL at Includes hFVIII activity level (one-stage clotting assay and chromogenic substrate assay). If a subject has used FVIII within 72 hours of a measurement day, all efforts should be made to 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 16 weeks after BMN 270 infusion and who have not resumed standard of care FVIII replacement therapy. If FVIII levels are elevated or stable over the course of several weeks, activity levels are above the normal physiological range and/or if there is a concern for a venous thromboenbolism.
- BMN 270 infusion and who have not resumed standard of care FVIII replacement therapy. If FVIII levels are elevated or stable over the course of several weeks, assessment of FVIII Includes hFVIII activity level (one-stage clotting assay and chromogenic substrate assay), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, hFVIII coagulation 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 \ge 5 IU/dL at 16 weeks after 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 activity exploratory assay, and hFVIII antigen (ELISA). If a subject has used FVIII within 72 hours of a measurement day, all efforts should be made to obtain FVIII activity above the normal physiological range and/or if there is a concern for a venous thromboembolism.
- Collection to occur on Day 2 and 4 following BMN 270 infusion, and then until at least 3 consecutive negative results are obtained. Collection and testing of semen samples must continue through Week 12, even if 3 consecutive negative samples in that compartment have already been recorded.
- 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 associated with hemophilia A. While exploratory samples will be collected at the time points indicated above, testing of these samples (including those for Direct Thrombin Activity test 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 and any other exploratory assessments) will be performed only as deemed necessary by the Sponsor.
- subjects who have not received therapeutic corticosteroids prior to Week 16; subjects who have received therapeutic corticosteroids will have hepatitis B and hepatitis C testing at the time Testing for reactivation of hepatitis B and hepatitis C at Week 16, for subjects with a past medical history of Hepatitis B or Hepatitis C prior to study entry, should be performed only in points indicated in Table 9.1.6.

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

					Follow-Up		ter BM	After BMN 270		Administration –		Weeks*				
Assessment	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
Physical examination ^a	Х	Х	Х	Х	Х	х	x	х	Х	Х	Х	Х	Х	Х	Х	Х
Weight										Х						
Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)	Х	Х	×	×	×	×	X	Х	Х	×	Х	Х	Х	X	Х	Х
Vital Signs	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Blood chemistry, haematology, coagulation screen, and CRP ^b				x				Х				Х				Х
Urine Tests ^b				Х				x				Х				Х
Liver Tests (local) ^b	Х	х	х	х	Х	x	x	x	х	Х	Х	Х	Х	Х	Х	Х
FVIII assays (local) ^c	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Liver Tests (central) ^b	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
FVIII assays (central) ^d	Х	Х	Х	Х	Х	Х	Χ	Х	Х	Х	Х	Х	Х	Х	Х	Х
FVIII antibody titer				х								Х				
PCR of vector DNA in blood, saliva, urine, semen, and stools ^e				Х				Х				Х				Х
Exploratory biomarker assessments ^f				Х				Х				Х				Х
Haemo-QoL-A QoL assessment												Х				
AAV5 antibody titer				Х				Х				Х				Х
PBMC collection	Х	Х	Х	Х		Х		Х		Х		Х		Х		Х
Von Willebrand Factor Antigen (VWF:Ag)				Х				Х				Х				Х
Direct Thrombin test										Х						
* Visit windows are ± 48 hours																

^a Brief physical examination should be done at all weekly visits. Refer to Section 9.7.9.5.

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Refer to Table 9.7.9.2.1 for laboratory assessments to be included, and to Table 9.7.9.3.1 for liver tests. LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) 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 $\ge 3x$ ULN. Patients with ALT > 1.5 ULN during the study may undergo additional evaluations (eg, imaging studies including MRI or ultrasound, additional blood tests, 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 and/or liver biopsy) at the discretion of the investigator. Additional testing of FVIII and LTs during any study week may be performed if; (1) the ALT has increased to above ULN; (2) Increases in ALT values from prior assessment are accompanied by declines in FVIII activity level; or after a discussion between the Medical Monitor and the Investigator based on a between the Medical Monitor and the Investigator.

Includes hFVIII activity level (one-stage clotting and chromogenic substrate assay). If a subject has used FVIII within 72 hours of a measurement day, all efforts should be made to obtain 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 FVIII activity measurements when a 72-hour interval without FVIII use is achieved; the 72-hour wash-out period is only intended for subjects who have achieved FVIII \geq 5 IU/dL at 16 weeks after BMN 270 infusion and who have not resumed standard of care FVIII replacement therapy. If FVIII levels are elevated or stable over the course of several weeks. activity levels are above the normal physiological range and/or if there is a concern for a venous thromboembolism.

exploratory assay, and hFVIII antigen (ELISA). If a subject has used FVIII within 72 hours of a measurement day, all efforts should be made to obtain FVIII activity measurements when a 72-hour interval without FVIII use is achieved; the 72-hour wash-out period is only intended for subjects who have achieved FVIII \geq 5 IU/dL at 16 weeks after BMN 270 infusion and Includes hFVIII activity level (one-stage clotting and chromogenic substrate assay), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, hFVIII coagulation activity who have not resumed standard of care 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 Collection for each matrix to occur until at least 3 consecutive negative results are obtained.

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 associated with hemophilia A. While exploratory samples will be collected at the time points indicated above, testing of these samples (including those for Direct Thrombin Activity test 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 and any other exploratory assessments) will be performed only as deemed necessary by the Sponsor.

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Schedule
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Tab

						Year 1 -	- Weeks*	*				
Assessment	33	34	35	36	38	40	42	44	46	48	50	52
Physical examination ^a	Х	Х	Х	Х	х	Х	Х	Х	х	Х	Х	X
Weight ^a												Х
Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Vital Signs	Х	Х	Х	Х	х	Х	Х	Х	х	Х	Х	X
Blood chemistry, haematology, coagulation screen, and CRP ^b				Х		Х		Х		Х		Х
Urine Tests ^b				Х		Х		Х		Х		X
Liver Tests (local) ^b	Х	Х	Х	Х	x	Х	Х	Х	Х	Х	х	Х
FVIII assays (local) ^c	х	Х	Х	Х	x	Х	Х	Х	Х	Х	х	Х
Liver Tests (central) ^b	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
FVIII assays (central) ^d	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
AAV5 antibody titer				Х		Х		Х		Х		Х
FVIII antibody titer				Х				Х				Χ
PBMC Collection (for determination of FVIII and Capsid specific CTL activity)		Х		Х				Х				Х
Von Willebrand Factor Antigen (VWF:Ag)				Х		Х		Х		Х		Х
Direct Thrombin Test					Х							Χ
PCR of vector DNA in blood, saliva, urine, semen, and stools $^{\ensuremath{\varepsilon}}$				Х		Х		Х		Х		Х
Exploratory biomarker assessments ^f				Х		Х		Х		Х		Х
Haemo-QoL-A QoL assessment												Χ
* Visit windows are \pm 48 hours through Week 36, then \pm 1 week until Week 52.		-	c	•				•				

^a Complete physical examination should be performed at Week 52; brief physical examination may be performed at other study visits. Refer to Section 9.7.9.5.

^b Refer to Table 9.7.9.2.1 for laboratory assessments to be included, and to Table 9.7.9.3.1 for liver tests. LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) 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 $\ge 3x$ ULN. Patients with ALT > 1.5 ULN during the study may undergo additional evaluations (eg, imaging studies including MRI or ultrasound, additional blood tests,

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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 increased by > 10 U/L from prior assessment; (2) Increases in ALT values from prior assessment are accompanied by declines in FVIII activity level; or after a discussion between the and/or liver biopsy) at the discretion of the investigator. Additional testing of FVIII and LTs during any study week may be performed if: (1) the ALT has increased to above ULN or ALT levels may be adjusted based on discussion between the Medical Monitor and the Investigator.

- Includes hFVIII activity level (one-stage clotting and chromogenic substrate assay). If a subject has used FVIII within 72 hours of a measurement day, all efforts should be made to obtain 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 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 $FVIII \ge 5$ IU/dL at 16 weeks after BMN 270 infusion and who have not resumed standard of care FVIII replacement therapy. If FVIII levels are elevated or stable over the course of several weeks activity levels are above the normal physiological range and/or if there is a concern for a venous thromboembolism.
- exploratory assay, and hFVIII antigen (ELISA). If a subject has used FVIII within 72 hours of a measurement day, all efforts should be made to obtain FVIII activity measurements when a 72 hour interval without FVIII use is achieved; the 72-hour wash-out period is only intended for subjects who have achieved FVIII \geq 5 IU/dL at 16 weeks after BMN 270 infusion and ¹ Includes hFVIII activity level (one-stage clotting and chromogenic substrate assay), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, hFVIII coagulation activity who have not resumed standard of care 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.

Sample testing during Safety Follow-Up is not required if at least 3 consecutive samples are cleared during the Post-Infusion Follow-Up period.

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 associated with hemophilia A. While exploratory samples will be collected at the time points indicated above, testing of these samples (including those for Direct Thrombin Activity test 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 and any other exploratory assessments) will be performed only as deemed necessary by the Sponsor.

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coagulation screen,XXXXXXXYYYXXXXYYXXXXYYXXXXYYXXXXYYXXXYYYXXXYYYXYYYYYXYYYYYXYYYYYXYYYYYIva, urine, semen,YYYYXfYYYYY Xf^{s} YYYY Xf^{s} YYYY	Vital Signs	Х						X			Х	Х	Х
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X X	Urine Tests ^b	Х						X					Х
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ation of FVIII and X X X X X (VWF:Ag) X X Y Y (VWF:Ag) X X Y Y liva, urine, semen, x^{e} X^{e} X^{e} X^{e} ints ^g X Y Y Y^{e} ints ^g X Y Y Y^{f}	FVIII antibody titer	Х						Х			Х	Х	Х
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liva, urine, semen, Xe Xe Xe Xe Xe ints ^g Xe Xe	Von Willebrand Factor Antigen (VWF:Ag)	Х						Х					Х
ints ^g X ^f X ^f X ^f	PCR of vector DNA in blood, saliva, urine, semen, and stools $^{\rm c}$	Xe	Xe	Xe		Xe		Х	o		Xe	Xe	Х
X ^f X ^f	Exploratory biomarker assessments ^g	Х						Х			Х	Х	Х
	Haemo-QoL-A QoL assessment	\mathbf{X}^{f}				\mathbf{X}^{f}		Х	f		\mathbf{X}^{f}	\mathbf{X}^{f}	Х

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- $^{\circ}$ Visit windows are ± 2 weeks for visits in Years 2-5 and ± 4 weeks for visits in Years 6-7. The Q6W visits during Years 3-5 should restart after each End of Year visit (eg. the first Q6W) visit during Year 3 should be ~ 6 weeks after the End of Year 2 visit).
 - ^o Complete physical examination should be performed at the End of Year visits; brief physical examination may be performed at other study visits. Weight should be recorded at the second Q12W visit each year during Years 2-5, and at every End of Year visit during Years 2-7.
- Refer to Table 9.7.9.2.1 for laboratory assessments to be included, and to Table 9.7.9.3.1 for liver tests. LTs may be monitored more or less frequently (and in particular when ALT values subject's ALT is $\ge 3x$ ULN. Patients with ALT $\ge 1.5x$ ULN during the study may undergo additional evaluations (e.g., imaging studies including MRI or ultrasound, additional blood tests, are \geq 1.5x ULN) 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 chemistry, and coagulation tests should be performed at the second Q12W visit each year and at every End of Year visit. During Years 6-7, these tests should be performed at the Q26W 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 increased by > 10 U/L from prior assessment; (2) Increases in ALT values from prior assessment are accompanied by declines in FVIII activity level; or after a discussion between the and/or liver biopsy) at the discretion of the investigator. Additional testing of FVIII and LTs during any study week may be performed if: (1) the ALT has increased to above ULN or 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, and End of Year visits.
 - Includes hFVIII activity level (one-stage clotting and chromogenic substrate assay). If a subject has used FVIII within 72 hours of a measurement day, all efforts should be made to obtain 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 FVIII activity measurements when a 72 hour interval without FVIII use is achieved; the 72-hour wash-out period is only intended for subjects who have achieved FVIII \geq 5 IU/dL at 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 16 weeks after BMN 270 infusion and who have not resumed standard of care FVIII replacement therapy. If FVIII levels are elevated or stable over the course of several weeks, modification) during Years 3-5, a fresh sample should be collected within 4 weeks of the initial visit that had a positive result.
- exploratory assay, and hFVIII antigen (ELISA). If a subject has used FVIII within 72 hours of a measurement day, all efforts should be made to obtain FVIII activity measurements when 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) in years 3-5, a fresh sample a 72 hour interval without FVIII use is achieved; the 72-hour wash-out period is only intended for subjects who have achieved FVIII \geq 5 IU/dL at 16 weeks after BMN 270 infusion and ^d Includes hFVIII activity level (one-stage clotting and chromogenic substrate assay), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, hFVIII coagulation activity who have not resumed standard of care 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 should be collected within 4 weeks of the initial visit that had a positive result.
- Sample testing during Safety Follow-Up is not required if at least 3 consecutive samples are cleared during the Post-Infusion Follow-Up period. Subjects who have not had 3 consecutive negative samples by Week 52 should continue to have PCR testing every 4 weeks (during Year 2), every 6 weeks (during Years 3-5), and/or every 26 weeks (during Years 6-7) until 3 consecutive samples below the limit of detection are documented (or upon consultation between the Investigator and Medical Monitor).
 - Haemo-QoL-A QoL assessment during Years 2-5 of Safety Follow-up should be performed at the second Q12W visit each year and at every End of Year visit. During Years 6-7, the Haemo-QoL-A assessment should be performed at the Q26W visits and the End of Year visits.

³ 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

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associated with hemophilia A. While exploratory samples will be collected at the time points indicated above, testing of these samples (including any other exploratory assessments) will be performed only as deemed necessary by the Sponsor.

- ^h 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 a fluid must still provide samples Q4W (during Year 2), Q6W (during Years 3-5), or Q26W (during Years 6-7), until vector shedding has been cleared (but do not need to do other scheduled assessments at those visit dates), either by reporting to the site to provide samples or by providing those samples to an MN professional.
 - For every 13 week remote visits during Years 6-7, the site should contact the subject to collect data on adverse events, new or changed concomitant medications, and diary entries (FVIII usage and bleeding events).
- At applicable sites, certain study assessments designated in the Schedule of Events may be performed by a mobile nursing (MN) professional at the subject's home or another suitable location, such as their school or office. Refer to Section 9.7.9.2 for details.

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				Steroid Treatment Period ^d	reatment	Period ^a						Post-S	Post-Steroid Period ^c	eriod ^c	
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Therapeutic 60 r corticosteroids (dose in mg/dav) ^a	60 mg 60 mg	g 40 mg	40 mg	30 mg	30 mg	20 mg	20 mg	15 mg	10 mg	5 mg					
FVIII activity testing											Х	X	X	X	
Liver testing											Х	X	Х	X	
Hepatitis B testing ^e					X						Х				Х
HCV Viral Load ^e					Х						Х				Х

the Medical Monitor.

^b Following initiation or completion of steroid regimen, if ALT elevation $\geq 1.5x$ ULN is reported, steroid management decisions will based on discussions between the Investigator and Medical Monitor. Modification of the steroid regimen may take into consideration possible confounders for the ALT elevation and impact on FVIII expression. ^c After discontinuation of corticosteroids, weekly labs for ALT and FVIII levels will be measured once a week for 4 weeks to ensure stability in values. If these assessments are already being done as part of normal study follow-up, they do not need to be duplicated.

Regardless of the assessments listed in the Schedule of Assessments (Table 9.1.2, Table 9.1.3, or Table 9.1.4), subjects initiated on corticosteroids will only be required to have laboratory evaluations on a weekly basis.

^e Should only be performed in subjects with a history of hepatitis B or hepatitis C prior to study entry.

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Table 9.1.7: Schedule of Events – Liver Biopsy Substudy

	Within 28 Days Before Biopsy Day	Within 7 Days Before Biopsy Day	1 Day Before Biopsy Day ^d	Biopsy Day (BD)
Informed Consent	X			
Liver Ultrasound ^a	X			
Brief Physical Examination	X		X	Х
Hematology, Coagulation, Chemistry Assessments ^b	X		X	
Liver Tests ^b	X		Х	Х
FibroScan		Х		
Local FVIII Activity Level Assessment		Х	Х	Х
Pre-Biopsy Consultation ^c		Х		
Liver Biopsy ^e				Х
^a Liver ultrasound must be performed within 28 days prior to the scheduled biopsy, unless an ultrasound result from the prior 3 months is already available.	sy, unless an ultrasound resul	t from the prior 3 months is	s already available.	

^b Refer to Table 9.7.9.2.1 for laboratory assessments to be included, and to Table 9.7.9.3.1 for liver tests.

^e Subjects will undergo a pre-biopsy consultation with the investigator (treating hematologist).

^d Subjects may need to repeat/extend this visit if their FVIII activity levels need adjustment before the biopsy, at the discretion of the investigator (treating hematologist).

^e 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.

9.2 Discussion of Study Design, Including Choice of Control Group

Study 270-201 is designed to be a first-in-man, phase 1/2 open-label, dose escalation study in patients with severe haemophilia A. Four doses of BMN 270 will be evaluated and the dose escalation decision tree for Cohorts 1-3 is summarized in Figure 9.1.1.

The decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and the DRB.

There will be no control group. Parameters for each subject will be compared to a pre-treatment assessment of safety (liver function) and efficacy (number of bleeds, use of replacement therapy).

As AAV based treatment always leads to anti-capsid immune response, no true control group (for example with an empty AAV) is possible.

9.3 Selection of Study Population

Up to 15 severe haemophilia A patients may enroll into the study; the actual number of patients will depend on the criteria for dose escalation.

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 criteria:

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

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 immunity to the AAV5 capsid as measured by AAV5 transduction inhibition or AAV5 total antibodies
- 2. Any evidence of active infection or any immunosuppressive disorder.
- 3. HIV positive
- 4. Significant liver dysfunction as defined by abnormal elevation of:
 - ALT (alanine transaminase) to 3 times the upper limit of normal;
 - Bilirubin above 3 times the upper limit of normal;
 - Alkaline phosphatase above 3 times the upper limit of normal; or
 - INR (international normalized ratio) \geq 1.4.
- 5. Potential participants who have had a liver biopsy in the past 3 years are excluded if they had significant fibrosis of 3 or 4 as rated on a scale of 0-4
- 6. Evidence of any bleeding disorder not related to Haemophilia A
- 7. Platelet count of $< 100 \text{ x } 10^9/\text{L}$
- 8. Creatinine $\geq 1.5 \text{ mg/dL}$
- 9. Liver cirrhosis of any etiology as assessed by liver ultrasound
- 10. Hepatitis B if surface antigen is positive
- 11. Hepatitis C if RNA is positive
- 12. Treatment with any IP within 30 days prior to the end of the screening period
- 13. Any disease or condition at the physician's discretion that would prevent the patient from fully complying with the requirements of the study including possible corticosteroid treatment outlined in the protocol. The physician may exclude patients unwilling or unable to agree on not using alcohol for the 16-week period following the viral infusion.
- 14. Prior treatment with any gene transfer agent
- 15. Major surgery planned in the 16-week period following the viral infusion
- 16. Use of immunosuppressive agents or live vaccines within 30 days before the viral infusion

9.3.3 Liver Biopsy Substudy Inclusion and Exclusion Criteria

Individuals eligible to participate in the liver biopsy substudy must meet all of the following criteria:

- 1. Currently enrolled in 270-201
- 2. Received BMN 270 infusion at least 1 year prior to enrollment in the substudy
- 3. Able to sign informed consent and comply with requirements of the substudy
- 4. FVIII activity at least >50 IU/dL (or higher, depending on local guidelines and/or Investigator discretion) within 24 hours prior to the liver biopsy being performed. (FVIII 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 to an appropriate level, under the supervision/instruction of the Investigator.

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

- 1. Assessed by the investigator or a hepatologist as having a medical condition such that undergoing a liver biopsy would be contraindicated. These conditions could include (but are not limited to):
 - Significant thrombocytopenia (platelet count $< 100 \text{ x } 10^{9}/\text{L}$)
 - Evidence of significant ascites
 - Abnormalities detected on liver ultrasound (performed within 90 days of procedure) that would preclude safe performance of the biopsy.

9.3.4 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. A subject's participation in the study may be discontinued at any time at the discretion 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.

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 admitted into the study or does not meet entry criteria
- 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 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/REB. It is the Investigator's (or designee's) responsibility to obtain written permission to use protected health information per country-specific regulations, such as the Health Insurance Portability and Accountability Act (HIPAA) in the US, from each subject. If permission to use protected health information is withdrawn, it is the Investigator's responsibility to obtain a written request, to ensure that no further data will be collected from the subject and the subject will be removed from the study.

9.3.4.1 Study Safety Evaluation Criteria

If any of the following events occur in a subject in the study who has received BMN 270 infusion, enrollment into the trial will be put on halt to complete an extensive safety analysis per Section 9.1.

- Any ALT elevation > 5x ULN for at least 2 consecutive weeks after administration of BMN 270, in the absence of a definitive alternate etiology for the increase
- The occurrence of Grade 3 or higher adverse events (excluding ALT elevation) assessed as related to study drug, including liver failure and clinical hepatitis
- The detection of neutralizing antibodies to hFVIII following BMN 270 infusion

- The detection of AAV vector DNA in the semen of a participant in 3 consecutive samples (which are at least 2 weeks apart) more than 52 weeks after BMN 270 infusion, as discussed in Section 9.7.9.6
- The occurrence of a malignancy excluding skin cancers at any point after BMN 270 infusion

If the following event occurs in a subject in the study who has received BMN 270 infusion, a DRB review and analysis of safety data will be undertaken to determine whether the enrollment into the trial will be put on halt:

• Grade 2 adverse event assessed as related to study drug that persists for at least 7 days

9.3.5 Subject Identification and Replacement of Subjects

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

Subjects who withdraw from the study will not be replaced.

9.3.6 Duration of Subject Participation

The duration of this study will be approximately 368 weeks. This includes 4 weeks of screening, 1 day of BMN 270 infusion, 16 weeks of Post-Infusion Follow-Up, and 348 weeks of Safety Follow-Up. A primary endpoint analysis on safety and efficacy will be performed at 16 weeks.

9.4 Treatments

BioMarin or its designee will provide the study site with study drug sufficient for study completion. BioMarin is responsible for shipping study drug to clinical sites.

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.

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 2 mL polypropylene cryovial. Each vial contains 1.1 mL of AAV5-hFVIII-SQ at a concentration of 2E13 vector genomes per mL in a pH 7.4 phosphate buffer.

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The study drug label includes the following information: lot number, required storage conditions, a precautionary statement, expiry date, study number, and BioMarin name and address. Labelling will be done according to country specific requirements.

9.4.3 Storage

At the study site, all IP must be stored under the conditions specified in the IB 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

After a physical examination performed by the PI or designee, participants will be admitted on the day of BMN 270 infusion. 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. An electric syringe pump will be used to infuse through an in-line, low protein binding 0.22 micron filter. BMN 270 will be infused through the catheter using an appropriate infusion pump at a constant rate of 4 ml/min while monitoring the vital signs (pulse, blood pressure, respiration rate and temperature) at 15 minute (\pm 5 minutes) intervals. The anticipated maximum interval from initiation of thawing of BMN 270 to completion of the infusion is 4 hours, although the IP has been shown to be stable at room temperature for 6 hours.

Following completion of the infusion, vital signs will be monitored hourly (\pm 5 minutes) for 6 hours and then every 2 hours (\pm 15 minutes) for 6 hours and then at 4 hour intervals. If the vital signs are stable the catheter will be removed 20-24 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 24 hours to observe for any immediate toxicity of the procedure. After 24 hours, participants 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.

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 Sponsor will be required prior to enrollment of each

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study subject. Upon their enrollment into the study, subjects will be assigned a unique subject number and dose level by the Sponsor.

Cohorts 1 to 3 are enrolled serially and their dose is defined in Section 9.4.6.2 below. Escalation is based on FVIII activity 3 weeks after injection. Cohorts may receive the next higher dose if subjects in the previous cohort does not meet the activity criteria, or the same dose if subjects in the previous cohort meets the activity criteria. Subjects in Cohort 4 will all be enrolled at a single dose.

9.4.6 Selection of Doses Used in the Study

The starting dose was based on the expression of hFVIII observed in nonclinical studies of mice and monkeys. The starting dose has a significant safety margin (10-fold) from NOAEL in mice. The dose escalation is half-logs based.

9.4.6.1 Selection of Timing of Dose for Each Subject

A minimum of three weeks are required between subjects, to allow for evaluation of safety and expression of hFVIII. After three weeks, depending on the activity level, the choice of the dose for the next subject will be made as described below.

9.4.6.2 Selection of Dose for Each Subject

The starting dose was determined by expression of hFVIII observed in mice and monkeys and a scale up factor based on previous experience, an improved purification process over previous trials (thus potentially decreasing the risk of immune response), and a new evaluation of the titer (PCR performed after hairpin removal).

For Cohorts 1 to 3, approximately three weeks after an injection, the decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and the DRB.

Subject 1 (Cohort 1) will be dosed by intravenous infusion with 6E12 vg/kg of body weight. If the FVIII activity level does not reach 5 IU/dL or greater (expressed as % in Figure 9.1.1) at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 1 and enrollment into Cohort 2 will initiate with Subject 2 at the next dose (2E13 vg/kg).

If the FVIII activity level in the first subject treated in Cohort 2 does not reach \geq 5 IU/dL at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 2 and enrollment into Cohort 3 (6E13) will initiate with the next subject.

If the FVIII activity level in the first subject treated in Cohort 3 does not reach \geq 5 IU/dL at the Week 3 visit in both assays, then the DRB will recommend whether to continue to add subjects to the cohort and/or whether to continue the study.

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For the first subject treated in each of the first 3 cohorts, if the activity level reaches \geq 5 IU/dL and no safety issue is found, then up to four subjects will be enrolled in that cohort, though the adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

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

There will be an ongoing review of individual patient safety and efficacy data by the medical monitor and the DRB. The adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

Refer to Figure 9.1.1 for a visual representation of the study design for Cohorts 1-3

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 CRF. The Investigator may prescribe additional medications 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 CRF.

The following medications are prohibited starting 30 days before Screening:

- Live vaccines
- Systemic immunosuppressive agents
- Emicizumab
- Fitusiran
- Concizumab
- Efavirenz

Subjects who begin antiretroviral therapy following BMN 270 infusion and during their participation in 270-201 must have their antiretroviral medication regimen approved by the Investigator and Medical Monitor prior to starting antiretroviral treatment.

Medications which are predominately metabolized by the liver (eg, acetaminophen) and alcohol should, whenever possible, be avoided for the first 52 weeks of the study, and particularly within 48 hours prior to lab work.

9.4.8.1 Concomitant Haemophilia Treatments

Subjects on "on demand" therapy for FVIII will continue their treatment at will. Subjects on prophylactic FVIII therapy will discontinue their treatment starting the day of infusion and switch to an "on demand" schedule. FVIII can always be taken as needed by the subject, who will carefully record his treatment and bleeding episodes in his diary. In addition, information on FVIII usage by medical history will be collected (if available) from subjects for the 6 month period immediately preceding study enrollment.

9.4.8.2 Glucocorticoid Treatment of Elevated Hepatic Transaminases

During the Post-Infusion Follow-up Period and the Safety Follow-Up Period, each subject will have comprehensive surveillance plan monitoring of LTs (at local labs, once per week for Weeks 1-36, then once every 2 weeks from Week 37-52). LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.

9.4.8.2.1 Therapeutic Corticosteroids

In general, therapeutic corticosteroids may be initiated when a subject's ALT value is $\geq 1.5x$ ULN, or based on review of FVIII and liver enzyme data after consultation between the Medical Monitor and the Investigator.

Reports of raised LTs (defined as $ALT \ge 1.5x$ ULN) should be made to the BioMarin medical monitor within 30 minutes of the lab value being available. Local laboratory results of LTs will be used to trigger corticosteroid treatment as needed. In case of discrepant results between local and central laboratories, the Investigator and Medical Monitor will decide further action.

Following initiation or completion of therapeutic corticosteroids, if ALT elevation $\geq 1.5x$ ULN is reported, steroid management decisions will based on discussions between the Investigator and Medical Monitor. Modification of the steroid regimen may take into consideration possible confounders for the ALT elevation and impact on FVIII expression.

Treatment with prednisolone will be initiated at a dose of 60 mg per day and then gradually tapered (60 mg daily for the first 2 weeks, then 40 mg the next 2 weeks, then 30 mg the next two weeks, then 20 mg the next two weeks, then 15 mg for the next week, then 10 mg for the next week, then 5 mg for the next week, then stop, for a total treatment of 11 weeks) (refer to Table 9.1.6).

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

Management and monitoring of reactions to corticosteroids should be determined by the Investigator's clinical judgment in consultation with the Sponsor's Medical Monitor. This includes the contraindicated use of NSAIDs during corticosteroid treatment, and specific monitoring not already covered by the schedule of events. For the subjects with a past medical history of hepatitis B or hepatitis C prior to study entry, Hepatitis B status and HCV viral load will be rechecked 6 weeks after the start of corticosteroid treatment, and then 1 week and 13 weeks after the completion of corticosteroid treatment. All adverse events should be reported as outlined in Section 10 of the protocol.

9.4.9 Treatment Compliance

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

9.5 Investigational Product Accountability

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

9.5.1 Return and Disposition of Clinical Supplies

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

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

All study drug and related materials should be stored, inventoried, reconciled, and destroyed or returned according to applicable state and federal regulations and study procedures.

9.6 Dietary or Other Protocol Restrictions

There are no dietary or other protocol restrictions for this 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 samples.

9.7 Safety and Efficacy Variables

As this is a first-in-man study, the primary endpoint of safety will be assessed as explained in Section 9.7.9.

The primary efficacy measure will be to assess plasma FVIII activity. The efficacy goal of the study is to establish the dose relationship to FVIII activity \geq 5 IU/dL at 16 weeks post BMN 270 administration.

9.7.1 Safety and Efficacy Measurements Assessed

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

9.7.2 Primary Efficacy Variables

The primary efficacy measure will be the plasma FVIII activity monitored on a regular basis after BMN 270 dose. The efficacy goal of the protocol is to ascertain the dose range of BMN 270 required to convert severe HA patients to expression of FVIII at 5 IU/dL or above, (ie, a mild severity). This is associated in natural history studies with clinically superior long term outcomes (Den Ujil, 2011).

The following assays (assessed by the central laboratory) will be used to measure the primary efficacy variable:

- FVIII activity (chromogenic substrate assay)
- FVIII activity by one-stage clotting 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 standard of care FVIII replacement therapy.

The FVIII activity level in both assays and the number of subjects with FVIII activity ≥ 5 IU/dL in at least one of the two assays will be summarized.

FVIII activity assays will also be performed at the local laboratory at the time points indicated in Table 9.1.2, Table 9.1.3, Table 9.1.4, and Table 9.1.5 but will be used in

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conjunction with local lab LT assessments to monitor subject safety and need for initiation of therapeutic corticosteroid dosing; local laboratory FVIII activity assessments will not be used to assess efficacy or to measure the primary efficacy outcome of the study.

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, follow an abbreviated visit schedule after Week 52, as applicable and at the discretion of the Investigator.

Timing of assessment by these assays is provided in Table 9.1.2, Table 9.1.3, Table 9.1.4, and Table 9.1.5. Details on performing the assays are included in the Laboratory Manual.

9.7.3 Secondary Efficacy Variables

Secondary efficacy measures will be the reduction in the frequency of factor replacement therapy, and reduction in the number of bleeding episodes. 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.

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

9.7.4 Immunogenicity

Immunogenicity assays will be performed on plasma. The assays will include detection of anti-capsid, and anti-FVIII total antibody, and determination of neutralizing antibodies against FVIII. Any increase in total antibody level, especially during the time period of 5-12 weeks, will be compared with FVIII activity measurements. Any abnormality of the liver parameters will lead to a retrospective immunogenicity assessment to determine anti-FVIII and capsid specific CTL. Anti-FVIII and capsid specific CTL assays will be performed on collected PBMCs.

Timing of assessment by these assays is provided in Table 9.1.2, Table 9.1.3, and Table 9.1.4.

9.7.5 Pharmacodynamics

The hFVIII antigen and activity level will be measured by an ELISA (antigen) and by one-stage clotting and/or chromogenic substrate assay (activity). Individual antigen and activity plasma plots will be prepared to assess changes over 16 weeks. FVIII activity measurements will be used to determine PD parameters.

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If supported by FVIII activity data, non-compartmental analysis and observation will be used to estimate individual values of C_b (baseline concentration), C_{ss} (steady state concentration), T_{ss} (time to steady state), C(t) and AUC(0-t) where t is 16 weeks. Other parameters that may be used to describe individual FVIII protein and activity plasma profiles are C_{max} (maximum concentration) and C_{avg} (average concentration, AUC(0-t)/t). The PD parameters and dose will be used to assess clinical pharmacology.

Sample collection times are indicated in Table 9.1.2, Table 9.1.3, Table 9.1.4, and Table 9.1.5.

9.7.6 Exploratory Assessments

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

Liver biopsy samples collected as part of the exploratory substudy may also be tested to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to hemophilia A, coagulation, and/or AAV gene transfer. Subjects participating in the substudy 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 may be used for exploratory use once the primary use has been completed.

On an exploratory basis, samples may be fractionated prior to shedding analysis in order to better characterize the presence and location of vector DNA and/or vector capsid within each matrix. The fractionation may be performed with samples collected specifically for shedding analysis (saliva, blood, semen, urine, faeces), or by using exploratory samples, such as plasma, PBMCs, and red blood cells, collected under the study protocol.

9.7.7 Haemo-QoL-A Quality of Life Assessment

The Haemo-QoL-A is a patient-reported outcome (PRO) questionnaire which will be used to assess subject quality of life (QoL) during the study. Assessments will occur at the time points listed in the Schedules of Assessments.

Details regarding the QoL assessment will be included in the Study Reference Manual.

9.7.8 Liver Biopsy Substudy

The objectives of the liver biopsy substudy are considered exploratory.

Subjects who consent to the procedure will have a liver biopsy via either the transjugular or percutaneous (ultrasound-guided) route, according to the standard procedures of the institution. To enhance safety, all subjects will have an ultrasound exam of the liver within 28 days prior to the procedure (to ensure there is no obstruction to the liver that would interfere with the liver biopsy) and a FibroScan of the liver within one week before the liver biopsy (to correlate any histopathologic findings on the biopsy). Subjects will also undergo a pre-biopsy consultation with the investigator (treating hematologist).

Within 24 hours prior to the biopsy being performed, subjects must have a FVIII activity level of at least 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 the day before the biopsy. 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".

The liver biopsy should be performed in the morning, 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 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 and/or according to local guidelines.

Safety findings arising from the histopathological analysis of the biopsy sample are subject to Adverse Event reporting (Section 10), and such findings should be further assessed and followed-up as clinically appropriate and in order to safeguard the subject's ongoing medical care (this should be done in consultation with a hepatologist and/or other specialist clinicians if required). In the event fibrotic changes being observed on the biopsy sample, additional follow-up Fibroscans may be considered (with the frequency of subsequent scans at the discretion of the Investigator and/or hepatologist).

Where a biopsy has been taken for safety-related reasons (rather than as part of the liver biopsy substudy) 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 not performed as part of the substudy be made available for additional histopathological review.

9.7.9 Safety Variables

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

9.7.9.1 Adverse Events

The occurrence of AEs will be assessed continuously from the time the subject signs the ICF. The determination, evaluation and reporting of AEs will be performed as outlined in Section 10. Assessments of AEs will occur at the time points shown in Table 9.1.1, Table 9.1.2, Table 9.1.3, Table 9.1.4, and Table 9.1.5.

9.7.9.2 Clinical Laboratory Assessments

Specific visits for obtaining clinical laboratory assessment samples are provided in Table 9.1.1, Table 9.1.2, Table 9.1.3, Table 9.1.4, and Table 9.1.5. The scheduled clinical laboratory tests are listed in Table 9.7.9.2.1. Refer to the Study Reference Manual 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 the cause of the abnormality is determined, the value returns to baseline or to within normal limits, or 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 CRF.

Blood Chemistry	Haematology	Urine Tests	Other
Albumin	Haemoglobin	Appearance	CRP
BUN	Haematocrit	Color	
Calcium	WBC count	pН	Coagulation Screen
Chloride	RBC count	Specific gravity	including:
Total cholesterol	Platelet count	Ketones	APTT
CO ₂	Differential cell count	Protein	PT/INR

Table 9.7.9.2.1: Clinical Laboratory Tests

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СРК	Glucose	TT
	Glueose	11
Creatinine	Bilirubin	
Glucose	Nitrite	Other Tests:
Phosphorus	Urobilinogen	ABO blood typing*
Potassium	Haemoglobin	
Total protein		
Sodium		
Uric Acid		

BUN, blood urea nitrogen; CO₂, carbon dioxide; 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.

* ABO blood typing assessment should be completed at the next regularly scheduled study visit (or at least prior to the end of the subject's participation in the study).

At applicable sites, certain study assessments designated in the Schedule of Events may be performed by a mobile nursing (MN) professional at the subject's home or another suitable location, such as their school or office, to improve access and convenience for subjects 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 subject and the subject gives written informed consent to participate in MN visits, the MN network will communicate with the subject and the subject's site.

9.7.9.3 Liver and Hepatitis Testing

Subjects will be screened for evidence of previous hepatitis B or hepatitis C infection at Screening. Subjects with documented results showing an absence of active hepatitis B or hepatitis C infection (as measured by positive surface antigen for hepatitis B or positive RNA testing for hepatitis C) 30 days prior to providing signed informed consent do not need to be screened again.

Evidence of ongoing hepatitis B or hepatitis C infection is exclusionary. Subjects with a history of hepatitis B or hepatitis C will be asked for information about the treatments received as part of their medical history assessment at Screening.

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

A liver ultrasound and LTs at Screening will identify any significant hepatic dysfunction, which is defined as:

- More than 3x the normal ALT level
- More than 3x the normal bilirubin level
- More than 3x the normal Alkaline phosphatase level.
- INR \geq 1.4.
- Thrombocytopenia under $100 \ge 10^9/L$
- Liver ultrasound results indicative of a liver cirrhosis

Liver tests will be monitored on a regular basis, at the time points indicated in Table 9.1.1, Table 9.1.2, Table 9.1.3, Table 9.1.4, and Table 9.1.5. At each time point, the following LTs should be assessed:

Table 9.7.9.3.1: 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

Patients with ALT > 1.5 ULN during the study may undergo additional evaluations (eg, imaging studies including MRI or ultrasound, additional blood tests, and/or liver biopsy) at the discretion of the investigator.

9.7.9.4 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.

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

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

Systolic blood pressure, diastolic blood pressure, heart rate, respiration rate, and temperature will be assessed at Screening, Baseline, and at the beginning of each visit during the Post-Infusion Follow-Up and Safety Follow-Up periods. On the day of the BMN 270 Infusion, vital signs will be monitored prior to infusion, during the infusion every 15 minutes

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(\pm 5 minutes), following the infusion hourly (\pm 5 minutes) for 6 hours and then every 2 hours (\pm 15 minutes) for 6 hours and then at 4 hour intervals (\pm 15 minutes).

A complete physical examination is necessary during Screening/Baseline, at Week 16 and 52 and at the End of Years visits thereafter. A complete physical examination will include general appearance (head, eyes, ears, nose, and throat), cardiovascular, dermatologic, lymphatic, respiratory, gastrointestinal, genitourinary, musculoskeletal, and neurologic systems.

At other visits, brief physical examinations may be performed at the discretion of the investigator based on the subject's clinical condition. A brief physical examination will include general appearance, cardiovascular, respiratory, neurologic, dermatologic, musculoskeletal, and gastrointestinal assessments. Particular attention should be given to signs of bleeding, as well as assessing possible hemarthroses.

Height will be recorded at Screening only. Weight will be recorded at Screening, at Weeks 26 and 52 during Year 1, and then at the second Q12W visit each year during Years 2-5 and at every End of Year visit during Years 2-7.

9.7.9.6 Vector Shedding

Vector shedding has been extensively studied in all similar clinical trials performed to date. (Nathwani, 2014); (Manno, 2006); (Schenk-Braat, 2007); (Croteau, 2004). In the literature referenced above, including Haemophilia B clinical studies utilizing AAV2 and AAV8, vector was no longer detectable after 40 days in blood, saliva, urine or stool, but in one study was detected in the seminal fluid but not in motile sperm (Manno, 2006). In these studies, the amount of vector present in these bodily fluids involved an extremely small fraction of the infused dose. More recent data from an ongoing AAV-FIX study demonstrates persistence of the vector in both the blood and the semen for at least 39 weeks (Miesbach, 2016).

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 PCR at the time points indicated in Table 9.1.2, Table 9.1.3, Table 9.1.4, and Table 9.1.5. Fluids tested will include:

- Blood
- Saliva
- Semen
- Urine
- Stool

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Vector shedding will also be extensively studied in the present clinical trial, every other week between Weeks 4-16, then every 4 weeks to Week 52 until at least 3 consecutive negative results are obtained. Testing of semen will continue through Week 12, even if 3 consecutive negative results have been recorded in that compartment prior to that timepoint. Subjects who have not had 3 consecutive negative samples by Week 52 should continue to have PCR testing every 4 weeks until 3 consecutive samples below the limit of detection of the test are documented (or upon consultation between the Investigator and Medical Monitor). Subjects who meet the definition of treatment failure and wish to follow an abbreviated schedule (refer to Section 12.5.3 but who have not cleared vector shedding from all fluids must still provide samples for assessment until vector shedding has cleared: every 4 weeks (during Year 2), every 6 weeks (during Years 3-5), or every 26 weeks (during Years 6-7), either by reporting to the site to provide samples or by providing those samples to an MN professional.

Contraception use may need to be extended beyond 26 weeks in individual subjects based on observed vector shedding in semen. After 6 months, 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 haematology, 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, a reportable adverse event (AE) is any untoward medical occurrence (eg, sign, symptom, illness, disease or injury) in a subject administered the study-drug or other protocol-imposed intervention, regardless of attribution. This includes the following:

- AEs not previously observed in the subject that emerge during the course of the study.
- Pre-existing medical conditions judged by the Investigator to have worsened in severity or frequency or changed in character during the study.
- Complications that occur as a result of non-drug protocol-imposed interventions (eg, AEs related to screening procedures).

An adverse drug reaction is any AE for which there is a reasonable possibility that the study-drug caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the study-drug and the AE.

Whenever possible, it is preferable to record a diagnosis as the AE term rather than a series of terms relating to a diagnosis.

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 meets 1 or more of the following criteria:

- Is fatal
- Is life threatening
- Note: Life-threatening refers to an event that places the subject at immediate risk of death. This definition does not include a reaction that, had it occurred in a more severe form, might have caused death.
- Requires or prolongs inpatient hospitalization.
- 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 intervention to prevent one of the above consequences (eg, anaphylaxis)

All adverse events that do not meet any of the criteria for SAEs should be regarded as non-serious AEs.

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 $ALT \ge 1.5x$ ULN, regardless of whether that triggers an initiation or modification of corticosteroid treatment
- Events meeting the criteria for Hy's law (ALT or AST elevation \ge 3x ULN plus total bilirubin \ge 2x ULN)
- Thromboembolic event
- 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 treatment, only SAEs associated with any protocol-imposed interventions will be reported. After informed consent is obtained and the first administration of study drug, the reporting period for all non-serious AEs and SAEs begins and continues for approximately 7 years or until study discontinuation/termination, whichever is longer. The criteria for determining, and the reporting of SAEs is provided in Section 10.1.1.1.

10.3.2 Eliciting Adverse Events

Investigators will seek information on AEs, SAEs, and EOSI at each subject contact by specific questioning and, as appropriate, by examination. Information on all AEs and SAEs and EOSI, should be recorded in the subject's medical record and on the 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 10.1.1.1 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 10.1.1.1. 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 severity of each will be assessed using the defined categories in Table 10.3.3.2.1.

The Investigator will determine the severity of each AE and SAE and EOSI using the NCI CTCAE v4. 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 as stated below.

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 or debilitating: consequences; urgent intervention indicated	Grade 4 and 5 AEs should always be	
5	Death related to AE	reported as SAEs	

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

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

10.3.3.3 Causality

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

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

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

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

The investigator's assessment of causality for individual AE reports is part of the study documentation process. Regardless of the Investigator's assessment of causality for individual AE reports, the Sponsor will promptly evaluate all reported SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators and applicable regulatory authorities.

10.4 Procedures for Recording Adverse Events

10.4.1 Recording Adverse Events on a eCRF

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

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

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

10.4.1.1 Diagnosis versus Signs and Symptoms

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 haemorrhage 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.

10.4.1.4 Abnormal Laboratory Values

Laboratory test results will be recorded on the laboratory results pages of the AE 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 hFVIII 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 document 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 10.1.1.1).

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 procedure or assessment
- Undergo a diagnostic or elective surgical procedure for a pre-existing medical condition that has not changed
- Insert an in-dwelling IV catheter (such as a Port-a-Cath or other brand) for administration of study drug or FVIII replacement therapy.
- Receive scheduled therapy (study drug or otherwise) for the study indication

10.4.1.8 Deaths

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

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

10.4.1.9 Pregnancy

Although not an AE per se, pregnancy in the partner of a subject taking trial medication should be reported expeditiously to the Sponsor to facilitate outcome monitoring by the

Sponsor. Pregnancy in partner should be reported during the period up to 5 years after viral infusion.

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

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

10.5 Reporting Requirements

10.5.1 Expedited Reporting Requirements

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

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

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

10.5.2 Ethics Committee Reporting Requirements

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

10.6 Follow-up of Subjects after Adverse Events

The Investigator should follow all unresolved AEs and SAEs until the events are resolved or have stabilized, the subject is lost to follow-up, or it has been determined that the study treatment or participation is not the cause of the AE/SAE. Resolution of AEs and SAEs (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, 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 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 treatment.

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 treatment. The Sponsor should also be notified if the Investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that participated in this study.

10.8 Urgent Safety Measures

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

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

events which may require the implementation of urgent safety measures to BioMarin within 24 hours.

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

- Immediate need to revise the IP administration (eg, modified dose amount or frequency not defined in protocol)
- 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

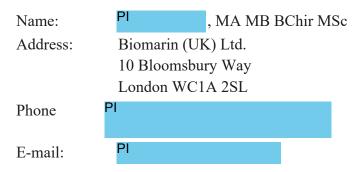
10.9 BioMarin Pharmacovigilance Contact Information

Contact information for BioMarin Pharmacovigilance is as follows:

BioMarin Pharmaceutical Inc.

Address	105 Digital Drive
	Novato, CA 94949
Phone:	PI
Fax:	
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:



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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 assay and the one-stage clotting 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 will be performed within 28 days (+ 14 days) of BMN 270 infusion while baseline assessments will take place within 7 days of BMN 270 infusion (Day 1). Should the screening visit occur within 7 days of the drug infusion, physical examination, vital signs, blood chemistry, LTs, haematology, urine tests, coagulation screen, and CRP do not need to be repeated at Baseline.

The following procedures will be performed during the Screening Period:

- Full medical history, including haemophilia A history, hepatitis B, hepatitis C, and HIV.
 - Subjects with a history of hepatitis B or hepatitis C will be asked for information about the treatments received. Any prior pharmacokinetics information obtained while the subject was receiving prophylactic or on-demand FVIII therapy prior to the study should also be collected. For subjects who have already enrolled in 270-201, this information should be collected at the next regularly scheduled study visit (or at least prior to the subject's completion of study participation).
- 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)
- Electrocardiogram
- Chest X-ray
- Liver Ultrasound
- Samples for hFVIII Assays
 - Baseline hFVIII activity chromogenic substrate (plasma)
 - Baseline hFVIII activity level one-stage clotting assay

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- hFVIII coagulation activity exploratory assay
- hFVIII inhibitor level (Bethesda assay with Nijmegen modification)
- o hFVIII total antibody assay
- hFVIII antigen (ELISA)
- Blood sample for AAV5 Assays
 - o AAV5 antibody titer
 - o AAV5 transduction inhibition assay
- Screen for hepatitis B, hepatitis C, and HIV if required (subjects with documented negative results 30 days prior to informed consent being obtained do not need to be retested)
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.9.2.1)
- Urine Tests (refer to Table 9.7.9.2.1)
- Liver Tests (refer to Table 9.7.9.3.1)
- Von Willebrand Factor Antigen (VWF:Ag)
- Blood samples for Biomarker testing (including HLA genotyping, FVIII genotyping status, TNFα and IL10a single nucleotide polymorphisms)

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 sample for AAV5 Assays
 - AAV5 antibody titer

- o AAV5 transduction inhibition assay
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.9.2.1)
- Urine Tests (refer to Table 9.7.9.2.1)
- Liver Tests (refer to Table 9.7.9.3.1)

12.3 Baseline Visit

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

- Physical examination
- Assessment of Adverse Events and Concomitant Medications
- Documentation of bleeding episodes and FVIII usage (by either subject or clinical information)
- Distribution of subject diaries and training in diary completion
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.9.2.1)
- Urine Tests (refer to Table 9.7.9.2.1)
- Liver Tests (refer to Table 9.7.9.3.1)
- PBMC collection for CTL baseline
- Direct Thrombin test
- PCR of vector DNA in blood, saliva, urine, semen, and stools
- Exploratory biomarker assessments
- Haemo-QoL-A QoL assessment

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 24 hours for the BMN 270 Infusion Visit. The following procedures will be performed during the BMN 270 Infusion Visit:

- Physical examination
- Assessment of Adverse Events and Concomitant Medications
- Blood sample for AAV5 Assays (must be performed before the BMN 270 infusion)
 - o AAV5 antibody titer
 - AAV5 transduction inhibition assay
- BMN 270 Infusion

- Vital Signs
 - Vital signs will be recorded prior to BMN 270 infusion and then every 15 minutes (± 5 minutes) during BMN 270 infusion. Following infusion, vital signs will be monitored every 1 hour (± 5 minutes) for the first 6 hours, every 2 hours (± 15 minutes) for the next 6 hours, and then at 4 hour (± 15 minutes) intervals for the remainder of the subject's stay in the clinic.

12.5 BMN 270 Infusion Follow-Up Visits

After BMN 270 has been infused, subjects will return to the study site every week $(\pm 48 \text{ hours})$ for 16 weeks, when the following procedures will be completed:

12.5.1 Once per week (Weeks 1 through 16)

The following procedures will be performed at one visit per week from Weeks 1 through 16:

- Physical examination
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Vital Signs
- Liver Tests (refer to Table 9.7.9.3.1) central laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- Samples for FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
 - FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level
 - FVIII antigen (ELISA)

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

• Central assessment of FVIII activity level should be performed 1x/week from Week 1 through Week 16

- Liver Tests (refer to Table 9.7.9.3.1) local laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
- PBMC collection

12.5.2 Week 1 – Day 2 and Day 4

On Day 2 and Day 4 of Week 1, the following procedures will be performed:

- PCR of vector DNA in blood, saliva, urine, semen, and stools (Day 2 and Day 4)
- Samples for FVIII Assays (Day 4 only) central laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
 - FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level
 - FVIII antigen (ELISA)

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

- Liver Tests (refer to Table 9.7.9.3.1) (Day 4 only) central laboratory assessment
- Liver Tests (refer to Table 9.7.9.3.1) (Day 4 only) local laboratory assessment
- FVIII activity level (Day 4 only) local laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)

12.5.3 Week 1 – Day 8

On Day 8, the following procedures will be performed:

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

• Haemo-QoL-A QoL assessment

12.5.4 Every 2 Weeks

Every 2 weeks (Weeks 2, 4, 6, 8, 10, 12, 14 and 16), the following procedures will be performed:

- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.9.2.1) (not assessed at Week 14)
- PCR of vector DNA in blood, saliva, urine, semen, and stools (not collected at Week 2)
 - Collection to occur until at least 3 consecutive negative results are obtained. Semen samples should continue to be collected and tested through Week 12, even if 3 consecutive negative results in that compartment have been recorded prior to that timepoint.

12.5.5 Weeks 4, 8, 12, and 16

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

- Urine Tests (refer to Table 9.7.9.2.1)
- VWF:Ag
- FVIII antibody titer
- Exploratory biomarker assessments

12.5.6 Week 16

At Week 16, the following procedures will be performed:

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

12.5.7 Weeks 8 and 16

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

• AAV5 antibody titer

12.5.8 Weeks 2, 3, 4, and 16

At Weeks 2, 3, 4, and 16, the following procedure will be performed:

• Haemo-QoL-A QoL assessment

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12.5.9 Week 13

At Week 13, the following procedure will be performed:

• Direct Thrombin test

12.6 Safety Follow-Up – Weeks 17-36

After the Post-Infusion Follow-Up visits are complete, subjects will return to the study site for Safety Follow-Up visits from Weeks 17 through Week 36 (\pm 48 hours), when the following procedures will be completed:

12.6.1 Once per week (Weeks 17 through 36)

Once per week from Week 17 through Week 36, the following procedures will be performed:

- Physical examination
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Vital Signs
- Liver Tests (refer to Table 9.7.9.3.1) central laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
 - FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - FVIII antigen (ELISA)

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

- Liver Tests (refer to Table 9.7.9.3.1) local laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.

- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)

12.6.2 Once per week (Weeks 17 through 20)

Once per week from Week 17 through Week 20, the following procedures will be performed:

• PBMC collection

12.6.3 Every 2 weeks (Weeks 21 through 36)

Every 2 weeks (Weeks 22, 24, 26, 28, 30, 32, 34, and 36), the following procedures will be performed:

• PBMC collection

12.6.4 Every 4 Weeks

Every 4 weeks (Weeks 20, 24, 28, 32, and 36), the following procedures will be performed:

- Exploratory biomarker assessments
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.9.2.1)
- Urine Tests (refer to Table 9.7.9.2.1)
- VWF:Ag
- AAV5 antibody titer
- PCR of vector DNA in blood, saliva, urine, semen, and stools
 - Sample testing during Safety Follow-Up is not required if at least
 3 consecutive samples are clear during the Post-Infusion Follow-Up period.

12.6.5 Every 8 Weeks

Every 8 weeks (Weeks 20, 28, and 36), the following procedure will be performed:

• FVIII antibody titer

12.6.6 Week 26

At Week 26, the following procedure will be performed:

- Direct Thrombin test
- Weight

12.6.7 Week 28

At Week 28, the following procedure will be performed:

• Haemo-QoL-A QoL assessment

12.7 Safety Follow-Up – Weeks 37-52

Subjects will return every 2 weeks (Week 38, 40, 42, 44, 46, 48, 50, and 52) from Week 37-52 (± 1 week), when the following procedures will be completed:

12.7.1 Once per visit

At Weeks 38, 40, 42, 44, 46, 48, 50, and 52, the following procedures will be performed:

- Physical examination
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Vital Signs
- Liver Tests (refer to Table 9.7.9.3.1) local laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
- Liver Tests (refer to Table 9.7.9.3.1) central laboratory assessment
 - LTs may be monitored more or less frequently based (and in particular when ALT values are >1.5x ULN) on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
 - o FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - FVIII antigen (ELISA)

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

12.7.2 Every 4 Weeks

Every 4 weeks (Weeks 40, 44, 48, and 52), the following procedures will be performed:

- Exploratory biomarker assessments
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.9.2.1)
- Urine Tests (refer to Table 9.7.9.2.1)
- AAV5 antibody titer
- VWF:Ag
- PCR of vector DNA in blood, saliva, urine, semen, and stools
 - Sample testing during Safety Follow-Up is not required if at least 3 consecutive samples are clear during the Post-Infusion Follow-Up period. Subjects who have not had 3 consecutive negative samples by Week 52 should continue to have PCR testing every 4 weeks until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor).

12.7.3 Every 8 Weeks

Every 8 weeks (Weeks 44 and 52), the following procedure will be performed:

- PBMC collection
- FVIII antibody titer

12.7.4 Week 38 and 52

At Week 38 and Week 52, the following procedure will be performed:

• Direct Thrombin test

12.7.5 Week 52

At Week 52, the following procedure will be performed:

- Haemo-QoL-A QoL assessment
- Weight

12.8 Safety Follow-Up – Years 2-5

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

Subjects who meet the definition of treatment failure and wish to follow an abbreviated schedule but who have not cleared vector shedding from a fluid must still provide samples for assessment every 4 weeks (during Year 2) or every 6 weeks (during Years 3-5) until vector shedding has cleared (but do not have to perform other scheduled assessments at those study visits).

At applicable sites, certain study assessments designated in the Schedule of Events may be performed by a mobile nursing (MN) professional at the subject's home or another suitable location, such as their school or office, to improve access and convenience for subjects participating in the study.

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

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

During Year 2, every 4 weeks (\pm 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 9.7.9.3.1) local laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
- Liver Tests (refer to Table 9.7.9.3.1) central laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
 - FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - FVIII antigen (ELISA)

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

- PCR of vector DNA in blood, saliva, urine, semen, and stools (if required)
 - Sample testing during Year 2 is not required if at least 3 consecutive samples are negative during the Post-Infusion Follow-Up period in Weeks 1-52.
 Subjects who have not had 3 consecutive negative semen samples by Week 52 should continue to have PCR testing of semen every 4 weeks during Year 2 until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor).
 - Subjects who meet the definition of treatment failure and wish to follow an abbreviated schedule but who have not cleared vector shedding from all fluids must still provide samples for assessment every 4 weeks during Year 2 until vector shedding has cleared (in such a case, these subjects do not need to perform other assessments except for PCR sample delivery scheduled at these timepoints).

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

During Years 3-5, every 6 weeks (\pm 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 9.7.9.3.1) local laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
- Liver Tests (refer to Table 9.7.9.3.1) central laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)

- FVIII coagulation activity exploratory assay
- o Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
- FVIII antigen (ELISA)

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

- PCR of vector DNA in blood, saliva, urine, semen, and stools (if required)
 - Sample testing during Years 3-5 is not required if at least 3 consecutive samples are negative during the Post-Infusion Follow-Up period in Weeks 1-52 and/or Year 2. Subjects who have not had 3 consecutive negative semen samples by the end of Year 2 should continue to have PCR testing of semen every 6 weeks during Years 3-5 until 3 consecutive 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 a fluid, must still provide samples of that fluid for assessment 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).

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

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

- Year 2 Week 64, Week 76, Week 88, Week 100, Week 104
- Year 3 Week 116, Week 128, Week 140, Week 152, Week 156
- Year 4 Week 168, Week 180, Week 192, Week 204, Week 208
- Year 5 Week 220, Week 232, Week 244, Week 256, Week 260

For each of these years, the last study visit listed (Week 104, Week 156, Week 208, and Week 260) will serve as an End of Year visit.

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

- Brief physical examination (at every 12 week visits) or complete physical examination (at End of Year visits)
- Weight (at Week 76, Week 128, Week 180, Week 232, and End of Year visits only)

- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Liver Tests (refer to Table 9.7.9.3.1) local laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
- Liver Tests (refer to Table 9.7.9.3.1) central laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
 - FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - FVIII antigen (ELISA)

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

- Vital Signs
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.9.2.1)
 - ABO blood typing assessment should be performed at the next regularly scheduled study visit (or at least prior to the end of the subject's participation in the study)
- Urine Tests (refer to Table 9.7.9.2.1)
- AAV5 antibody titer
- FVIII antibody titer
- PBMC collection

- VWF:Ag
- Exploratory biomarker assessments
- Haemo-QoL-A QOL assessment (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 negative during the Post-Infusion Follow-Up period in Weeks 1-52. Subjects who have not had 3 consecutive negative semen samples by Week 52 should continue to have PCR testing of semen every 4 weeks (during Year 2) or every 6 weeks (during Years 3-5) until 3 consecutive samples below the limit of detection are documented (or upon consultation between the Investigator and Medical Monitor).

12.9 Safety Follow-Up – Years 6-7

If the investigator at a participating site determines that MN services are appropriate for a subject and the subject gives written informed consent to participate in MN visits, the MN network will communicate with the subject and the subject's site.

During Years 6-7 of Safety Follow-up, the following procedures will be completed:

12.9.1 Years 6-7 – Every 13 Weeks

Every 13 weeks (± 4 weeks) during Years 6-7, the site should contact the subject remotely to collect the following data:

- Adverse events
- New or changed concomitant medications
- Diary entries (FVIII usage and bleeding events)

12.9.2 Years 6-7 – Every 26 Weeks and End of Year Visits

During Years 6-7, the following assessments will be performed at a site visit every 26 weeks (± 4 weeks) (Week 286 and Week 338) and at the End of Year Visits (± 4 weeks) (Week 312 and Week 364):

- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Complete Physical Examination (Week 312 and Week 364 only)
- Weight (Week 312 and Week 364 only)
- Vital signs (Week 312 and Week 364 only)

- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.9.2.1)
- Liver Tests (refer to Table 9.7.9.3.1) central laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
 - FVIII coagulation activity exploratory assay
 - Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - FVIII antigen (ELISA)

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

- AAV5 antibody titer (Week 312 and Week 364 only)
- FVIII antibody titer (Week 312 and Week 364 only)
- Exploratory biomarker assessments (Week 312 and Week 364 only)
- Haemo-QoL-A QOL assessment
- PCR of vector DNA in blood, saliva, urine, semen, and stools (if required)
 - Sample testing during Years 6-7 is not required if at least 3 consecutive samples are below the limit of detection as of the end of Year 5.

12.10 Liver Biopsy Substudy - Years 1-5

For the optional liver biopsy substudy (refer to Table 9.1.7), the following procedures will be performed at the following times:

- Within 28 days before Biopsy Day
 - o Informed consent
 - Liver ultrasound
 - Liver ultrasound does not need to be performed if an ultrasound result from the prior 3 months is already available
 - Brief physical examination

- Hematology, Coagulation, and Chemistry Assessments (refer to Table 9.7.9.2.1)
- Liver Tests (refer to Table 9.7.9.3.1)
- Within 7 Days before Biopsy Day
 - o FibroScan
 - Local laboratory FVIII activity level assessment
 - Pre-biopsy consultation with investigator (treating hematologist). This may need to be repeated/extended if the subject's FVIII activity levels need adjustment before the biopsy, at the discretion of the investigator (treating hematologist).
- 1 Day before Biopsy Day
 - Hematology, Coagulation, and Chemistry Assessments (refer to Table 9.7.9.2.1)
 - Liver Tests (refer to Table 9.7.9.3.1) local laboratory assessment
 - Brief physical examination
 - o Local laboratory FVIII activity level assessment
 - Subjects must have a FVIII activity level of at least 50 IU/dL (or higher, depending on local guidelines and/or investigator discretion). 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".
- Biopsy Day
 - Brief physical examination
 - Local laboratory FVIII activity level assessment (performed pre-biopsy)
 - Subjects must have a FVIII activity level of at least 50 IU/dL (or higher, depending on local guidelines and/or investigator discretion). 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".

- Liver Tests (refer to Table 9.7.9.3.1) local laboratory assessment (prebiopsy)
- Liver Biopsy (refer to Laboratory Manual for guidelines for biopsy procedure and handling of biopsy samples)
 - If only a small amount of tissue is obtained at the time of the biopsy, the subject may be asked to consent for a second pass.

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.

12.11 Early Termination Visit

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

If a subject leaves the study prior to the Week 364 visit, the subject will be asked to return to the study site and complete an Early Termination visit. At the Early Termination visit, as many of the following assessments as possible should be done:

- Physical examination
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Vital Signs
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.9.2.1)
- Urine Tests (refer to Table 9.7.9.2.1)
- Liver Tests (refer to Table 9.7.9.3.1) local laboratory assessment
- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
- Liver Tests (refer to Table 9.7.9.3.1) central laboratory assessment
- FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
 - FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - o FVIII antigen (ELISA)

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

- AAV5 antibody titer
- FVIII antibody titer
- PBMC collection
- VWF:Ag
- PCR of vector DNA in blood, saliva, urine, semen, and stools
 - Sample testing at the ETV is not required if at least 3 consecutive samples are below the limit of detection prior to the ETV.
- Exploratory biomarker assessment
- Haemo-QoL-A QOL assessment

12.12 End of Study

The study will end after the last subject completes the last Safety Follow-Up visit (Week 364). 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.

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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, any applicable randomization procedures, source document requirements, eCRFs, monitoring requirements, and procedures for reporting AEs, including SAEs.

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

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

14 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

14.1 Statistical and Analytical Plans

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

14.1.1 Interim Analyses

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

14.1.2 Procedures for Accounting for Missing, Unused and Spurious Data

Missing data will not be imputed.

14.2 Primary and Secondary Efficacy Analysis

The subjects will be followed in a longitudinal manner and all the relevant information will be collected. The analysis of the data will be descriptive in nature. Descriptive statistics include the number of subjects, mean, median, standard deviation, minimum, and maximum for continuous variables and count and percent for categorical variables. Efficacy variables will be summarized by dose cohort at each time point. Relationship between dose and efficacy results will be examined.

Data collected in a longitudinal manner may be analyzed using longitudinal methods such as mixed effect model which takes into account the correlation among the observation taken at various time points within a participant. Efficacy is a secondary endpoint, defined as biologically active hFVIII at \geq 5 IU/dL by chromogenic substrate assay and/or one-stage clotting assay as measured by the central laboratory at 16 weeks following study treatment. We can only assess the true steady state of hFVIII protein produced from BMN 270 after a minimum of 72 hours has elapsed since the last infusion of FVIII protein concentrates.

14.3 Liver Biopsy Substudy Analysis

A separate report presenting and discussing analyses of the exploratory objectives for the optional liver biopsy substudy will be prepared.

14.4 Immunogenicity

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

14.5 Pharmacodynamic Analyses

The FVIII antigen and activity level as measured by an ELISA (antigen level) and by a one-stage clotting assay and/or chromogenic substrate assay (activity level), will be used for plasma profiles; FVIII activity will be used to determine PD parameters. Traditional PK analysis is not applicable.

If supported by FVIII activity data, non-compartmental analysis and observation will be used to estimate individual PD parameter values of C_b (baseline), C_{ss} (steady state), T_{ss} (time to steady state), C(t) and AUC(0-t) where t is 16 weeks. Other parameters that may be used to describe individual FVIII protein and activity plasma profiles are C_{max} (maximum concentration) and C_{avg} (average concentration, AUC(0-t)/t). The parameters will be summarized using descriptive statistics.

14.6 Safety Analysis

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

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

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

Detailed statistical methods will be provided in the SAP.

14.7 Determination of Sample Size

No formal sample size calculations based on statistical power were performed.

The sample size is determined based upon clinical consideration and could detect a strong clinical efficacy signal. Up to 15 subjects may be dosed in the study; the actual number of subjects will depend on the criteria for dose escalation.

14.8 Analysis Populations

The Safety analysis population is defined as all enrolled subjects who receive any study drug. The analysis of safety data will be performed on Safety Set.

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The Full Analysis Set (FAS) is defined as all enrolled subjects who receive study drug and have at least one Baseline and post-Baseline assessment. The FAS will be used for efficacy analysis.

14.9 Changes in the Conduct of the Study or Planned Analyses

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

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

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

Note: If discrepancies exist between the text of the statistical analysis as planned in the protocol, and the final SAP, a protocol amendment will not be issued and the SAP will prevail.

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15 DATA REVIEW BOARD

There will be no formal DMC for this study, however a safety and efficacy evaluation board (the Data Review Board [DRB]) composed of the investigator representatives and the Sponsor will be established.

The DRB will review safety and efficacy on an ongoing basis. The DRB will meet prior to dose escalation or dose expansion to assess available subject safety and efficacy data and make recommendations with regards to the conduct of study. Should a safety signal arise, including one which may warrant a halt of study enrollment, the DRB will promptly convene for further assessment of subject safety. Notification of all DRB meetings and meeting outcomes will be sent to participating sites.

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16 COSTS, COMPENSATION, AND SUBJECT INJURY

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

The Investigator should contact BioMarin immediately upon notification that a study subject has been injured by the IP 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 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 IP 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 and that are unrelated to this study.

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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 CRF casebook to verify its accuracy.

CRFs 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 CRF instructions, blank data fields are not acceptable.

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

BioMarin's policy is that study data on the CRFs 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 an Investigator or institution refuses to allow access to subject records because of confidentiality, arrangements must be made to allow an "interview" style of data verification.

A CRA designated by BioMarin will compare the CRFs 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 CRA, 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 CRA 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 CRF 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 CRFs is accurate and complete. The Data Manager, or designee, will then set the status of the forms, visits, and the entire casebook to Locked.



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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.

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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 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).

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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 R2 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 patients.
- He or she will personally conduct or supervise the study.
- He or she will inform any potential patients, 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 R2 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 R2 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 R2 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 R2 Section 4.9 are kept, and those records are available for inspection in accordance with 21 CFR 312.68 and/or ICH E6 R2 Section 4.9.7.
- The IRB/IEC/REB complies with the requirements of 21 CFR Part 56, ICH E6 R2 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 patients or others are reported to the IRB/IEC/REB. Additionally, he or she will not make any changes in the research without IRB/IEC/REB approval, except where necessary to eliminate apparent immediate hazards to human patients.
- 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 R2.

270-201 Amendment 9

23 SIGNATURE PAGE

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

Protocol Number: 270-201 Amendment 9

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 R2, as stated in the protocol, and other information supplied to me.

Investigator Signature		Date
Printed name		
Accepted for the Sponsor:	DocuSigned by:	
	Signing Reason: I approve this document Signing Time: 22-Jun-2020 8:49 AM PDT	
	D81F76E32EA74F83864C63F8E75F1EBE	
Medical Monitor Signature	Date	
incurear inclinitor Signature	Duie	
Printed name: PI	, MA MB BChir MSc, ^{Pl}	Clinical Science

24 PROTOCOL AMENDMENT TEXT REVISIONS

The following table summarizes the revisions made to the protocol and relates the changes to the appropriate rationale (See page 2-4). Text that has been added or inserted is indicated by <u>underlined</u> font, and deleted text is indicated by <u>strikethrough</u> font.

Section No./Title	Revision	Rationale
2/Synopsis (Study Rationale)	The vector genome figure was updated.	10
2/Synopsis (Study Design and Plan)	At applicable sites, certain study assessments designated in the Schedule of Events may be performed by a mobile nursing (MN) professional at the subject's home or another suitable location, such as their school or office, to improve access and convenience for subjects 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 subject and the subject gives written informed consent to participate in MN visits, the MN network will communicate with the subject and the subject's site.	2
2/Synopsis (Inclusion Criteria)	 Individuals eligible to participate in this study must meet all of the following criteria: 6. Sexually active patients must be willing to use an acceptable method of contraception such as double barrier, including hormonal contraception for at least 6 months post-treatment. After 6 months, subjects may stop contraception use only if they have had 3 consecutive negative semen samples below the limit of detection of the test. 	7
2/Synopsis (Criteria for Evaluation)	No major toxicity is expected based on preclinical studies in mice and monkeys. Each subject will have comprehensive surveillance monitoring of LTs (at local labs, once per week for Weeks 1-36, then once every 2 weeks from Week 37-52) during Year 1. LTs will be monitored every 4 weeks during Year 2, and then every 6 weeks for Years 3-5, and every 26 weeks for Years 6-7 post-dose in the safety extension; the frequency and duration of LT testing may be changed based on discussion between the Medical Monitor and the Investigator and review of subject data.	1
2/Synopsis (Statistical Methods)	The sample size is based upon clinical considerations and could detect a strong clinical efficacy signal. Up to 15 subjects may be dosed in the study. The subjects will be followed in a longitudinal manner and all the relevant information will be collected. The analysis of the data will be descriptive in nature but data collected in a longitudinal manner may be analyzed using longitudinal methods such as mixed effect model which takes into account the correlation among the observation taken at various time points within a participant. Efficacy is a secondary endpoint, defined as biologically active FVIII at \geq 5 IU/dL by chromogenic substrate assay and/or one-stage clotting assay at 16 weeks following study treatment. FVIII activity will be assessed weekly during the study period.	13

Section No./Title	Revision	Rationale
5.2/Ethical Conduct of Study	Specifically, this study is based on adequately performed laboratory and animal experimentation. The study will be conducted under a protocol reviewed and approved by an IRB/IEC/REB and will be conducted by scientifically and medically qualified persons. The benefits of the study are in proportion to the 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. Each subject will provide written informed consent before any study-related tests or evaluations are performed, as well as when updates to the ICF are made. Where it is not feasible for the Investigator to receive the signed, written ICF from the subject prior to beginning new or changed study-related procedures contained in such an ICF update (for example, due to COVID-19-related restrictions), the Investigator will ask the subject to verbally confirm during an informed consent interview that the subject has signed and dated the ICF. The Investigator should document this verbal confirmation on the Investigator's copy of the ICF and, when it is possible to do so, receive the informed consent signed by the subject and archive the original(s) in the record file of the subject.	8
7.3/Study Rationale	The vector genome figure was updated.	10
7.3.1/Liver Biopsy Substudy Rationale	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 some subjects, as well as inter-subject variability in post-therapy hFVIII 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).	13
7.4/Summary of Overall Risks and Benefits	The majority of subjects in the ongoing 270-201 clinical study who have received 4E13 or 6E13 vg/kg doses of BMN 270 have had Grade 1 asymptomatic elevations in ALT. For most subjects, the elevations have reached only slightly above the upper limit of normal (ULN). Based on the effectiveness of transient oral corticosteroid used to suppress a presumed Class 1 (eytotoxic T-cell) response in prior studies with hepatic transduction with AAV vectors (Mingozzi, 2013), subjects were treated with 7-32 weeks of oral corticosteroids prophylactically or in response to the elevations in ALT to ensure preservation of the transduced hepatocytes. Using this approach, no sustained loss of FVIII activity has been observed in subjects with ALT elevations, consistent with maintaining a high level of hepatocyte function. Moreover, the rise in ALT levels were not accompanied by significant or lasting aberrations in other liver tests such as AST, bilirubin or albumin, indicating that extent of toxicity is limited. There has been one HIV-positive subject in the ongoing 270-302 elinical study who experienced Grade 3	12

Section No./Title	Revision	Rationale
	asymptomatic elevations in ALT and AST, which has been attributed to an interaction between one or more of his	
	antiretroviral therapy medications and/or unsuspected underlying hepatic disease with BMN 270. In addition, there has been	
	one subject with Gilbert's syndrome in the ongoing 270-301 clinical study who has experienced Grade 3 asymptomatic	
	elevations in ALT and AST. These cases have led to the exclusion of subsequent HIV-positive subjects and requirement of	
	liver tests at Screening that are <1.25 times the upper limit of the normal range in the ongoing 270-301 and 270-302 elinical	
	studies. Of note, two HIV positive subjects in 270 301 and one presumed Gilbert's syndrome subject in 270 201 have	
	received BMN 270 without experiencing any elevations in ALT to date. Overall, the literature and clinical 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, 2016).	
	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, who 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.	

Section No./Title	Revision	Rationale
	At the highest dose tested in 270-201 (6E13 vg/kg), the majority of subjects achieved FVIII levels above 50 IU/dL at 52 weeks post-infusion. 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 for BMN 270 does not yet permit comprehensive assessment of the has shown an established positive benefit:-risk profile of this investigational drug for BMN 270 at the 6E13 vg/kg dosing level. Given the monitoring measures in place in the clinical protocol(s) to minimize the risk to subjects. Each subject in 270-201301 will have a comprehensive surveillance plan that monitors LTs during the study, and elevations in LTLTs will be addressed according to the guidelines set forth in the protocol. Safety will be assessed by adverse event reporting and clinical laboratory assessments.	
9.1/Overall Study Design and Plan	At applicable sites, certain study assessments designated in the Schedule of Events may be performed by a mobile nursing (MN) professional at the subject's home or another suitable location, such as their school or office, to improve access and convenience for subjects 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 subject and the subject gives written informed consent to participate in MN visits, the MN network will communicate with the subject and the subject's site.	2
Table 9.1.5/SOE (Years 2-7)	Table 9.1.5 was updated to reflect changes made elsewhere in the protocol.	1, 2
Table 9.1.5 Notes	* Visit windows are ± 2 weeks for visits in Years 2-5 and ± 4 weeks for visits in Years 6-7. The Q6W visits during Years 3-5 should restart after each End of Year visit (eg, the first Q6W visit during Year 3 should be ~6 weeks after the End of Year 2 visit).	1, 2, 7, 13

Section No./Title	Revision	Rationale
	^a Complete physical examination should be performed at the End of Year visits; brief physical examination may be performed at other study visits. Weight should be recorded at the second Q12W visit each year <u>during Years 2-5</u> , and at every End of Year visit during Years 2-57.	
	 ^b Refer to Table 9.7.9.2.1 for laboratory assessments to be included, and to Table 9.7.9.3.1 for liver tests. LTs may be monitored more or less frequently (and in particular when ALT values are ≥ 1.5x ULN) 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. Patients with ALT ≥ 1.5x ULN during the study may undergo additional evaluations (eg, imaging studies including MRI or ultrasound, additional blood tests, and/or liver biopsy) at the discretion of the investigator. Additional testing of FVIII and LTs during any study week may be performed if: (1) the ALT has increased to above ULN or increased by > 10 U/L from prior assessment; (2) Increases in ALT values from prior assessment are accompanied by declines in FVIII activity level; or after a discussion between the Medical Monitor and the Investigator based on a review of subject data. If FVIII levels and/or ALT values are stable over the course of several weeks, assessment of FVIII activity and ALT levels may be adjusted based on discussion between the Medical Monitor and the Investigator. During Years 2-5 of the Post-Infusion Follow-Up period, urine tests and blood, chemistry, and coagulation tests should be performed at the second Q12W visit each year and at every End of Year visit. During Years 6-7, these tests should be performed at the Q26W and End of Year visits. 	
	 ^e Sample testing during Safety Follow-Up is not required if at least 3 consecutive samples are cleared during the Post-Infusion Follow-Up period. Subjects who have not had 3 consecutive negative samples by Week 52 should continue to have PCR testing every 4 weeks (during Year 2) or), every 6 weeks (during Years 3-5), and/or every 26 weeks (during Years 6-7) until 3 consecutive negative samples below the limit of detection are documented (or upon consultation between the Investigator and Medical Monitor). 	
	^f Haemo-QoL-A QoL assessment during Years 2-5 of Safety Follow-up should be performed at the second Q12W visit each year and at every End of Year visit. <u>During Years 6-7</u> , the Haemo-QoL-A assessment should be performed at the Q26W visits and the End of Year visits.	
	^h Subjects who meet the definition of treatment failure to BMN 270 therapy after Week 52 may omit the Q4W and Q6W visits during Years 2-5, and must attend only the Q12W and End of Year visits. Such subjects following the abbreviated schedule who have not yet cleared vector shedding in all fluidsa fluid must still provide samples Q4W (during Years 2) or), Q6W (during Years 3-5)), or Q26W (during Years 6-7), until vector shedding has been cleared (but do not need to do other scheduled assessments at those visit dates), either by reporting to the site to provide samples or by providing those samples to an MN professional.	

Section No./Title	Revision	Rationale
	ⁱ For every 13 week remote visits during Years 6-7, the site should contact the subject to collect data on adverse events, new	
	or changed concomitant medications, and diary entries (FVIII usage and bleeding events).	
	^j At applicable sites, certain study assessments designated in the Schedule of Events may be performed by a mobile nursing	
	(MN) professional at the subject's home or another suitable location, such as their school or office. Refer to Section 9.7.9.2). for details.	
9.3.1/Inclusion Criteria	Individuals eligible to participate in this study must meet all of the following criteria:	7
	6. Sexually active patients must be willing to use an acceptable method of contraception such as double barrier, including hormonal contraception for at least 6 months post-treatment. After 6 months, subjects may stop contraception use only if they have had 3 consecutive negative semen samples below the limit of detection of the test.	
9.3.4/Removal of	Subjects may be considered lost to follow-up if the site has documented at least 4 attempted contacts by key research	9
Subjects from	personnel to reach the subject without success in the following manner:	
Treatment or Assessment	• <u>2 attempts by telephone or email (if possible); then</u>	
Assessment	 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.	
9.3.6/Duration of	The duration of this study will be approximately 264368 weeks. This includes 4 weeks of screening, 1 day of BMN 270	1
Subject Participation	infusion, 16 weeks of Post-Infusion Follow-Up, and 244348 weeks of Safety Follow-Up.	
9.4.8/Prior and	The following medications are prohibited starting 30 days before Screening:	3
Concomitant Medications	• Lamivudine	
9.7.8/Liver Biopsy	Where a biopsy has been taken for safety-related reasons (rather than as part of the liver biopsy substudy) or was available	6
Substudy	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 not performed as part of the substudy be made available for	
	additional histopathological review.	
Table 9.7.9.2.1/Clinical Laboratory Tests	The ABO blood typing test has been listed as an "other test" rather than as part of the hematology panel.	13

Section No./Title	Revision	Rationale
Section 9.7.9.2/Clinical Laboratory Assessments	At applicable sites, certain study assessments designated in the Schedule of Events may be performed by a mobile nursing (MN) professional at the subject's home or another suitable location, such as their school or office, to improve access and convenience for subjects 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 subject and the subject gives written informed consent to participate in MN visits, the MN network will communicate with the subject and the subject's site.	2
9.7.9.5/Vital Signs, Physical Exams and Other Observations Related to Safety	Height will be recorded at Screening only. Weight will be recorded at Screening, at Weeks 26 and 52 during Year 1, and then at the second Q12W visit each year <u>during Years 2-5</u> and at every End of <u>Years Year</u> visit during Years 2- <u>57</u> .	1
9.7.9.6/Vector Shedding	Vector shedding will also be extensively studied in the present clinical trial, every other week between Weeks 4-16, then every 4 weeks to Week 52 until at least 3 consecutive negative results are obtained. Testing of semen will continue through Week 12, even if 3 consecutive negative results have been recorded in that compartment prior to that timepoint. Subjects who have not had 3 consecutive negative samples by Week 52 should continue to have PCR testing every 4 weeks until 3 consecutive negative samples below the limit of detection of the test are documented (or upon consultation between the Investigator and Medical Monitor). Subjects who meet the definition of treatment failure and wish to follow an abbreviated schedule (refer to Section 12.5.3 but who have not cleared vector shedding from all fluids must still provide samples for assessment until vector shedding has cleared: every 4 weeks (during Year 2), or every 6 weeks (during Years 3-5).every 6 weeks (during Years 3-5), or every 26 weeks (during Years 6-7), either by reporting to the site to provide samples or by providing those samples to an MN professional.	1, 7
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: Events meeting the criteria for Hy's law (ALT or AST elevation ≥ 3x ULN plus total bilirubin ≥ 2x ULN) 	4, 5

Section No./Title	Revision	Rationale
	Development of anti-FVIII inhibitory antibodies (inhibitors)	
10.4.1.4/Abnormal Laboratory Values	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, <u>unless the abnormal laboratory results has been reported or captured as part of an underlying diagnosis</u> .	13
	For purposes of this study, laboratory tests showing a decreased level of hFVIII activity should not be reported as adverse events unless signs of worsening are observed. there is an impact to clinical outcomes (eg, increased rate of bleeding, worsening of joint disease).	
12.8/Safety Follow-Up Years 2-5	At applicable sites, certain study assessments designated in the Schedule of Events may be performed by a mobile nursing (MN) professional at the subject's home or another suitable location, such as their school or office, to improve access and convenience for subjects participating in the study.	2
12.8.2/Years 3-5 – Every 6 Weeks	 During Years 3-5, every 6 weeks (± 2 weeks), the following procedures will be performed: PCR of vector DNA in blood, saliva, urine, semen, and stools (if required) Sample testing during Years 3-5 is not required if at least 3 consecutive samples are negative during the Post-Infusion Follow-Up period in Weeks 1-52 and/or Year 2. Subjects who have not had 3 consecutive negative semen samples by Week 52the end of Year 2 should continue to have PCR testing of semen every 6 weeks during Years 3-5 until 3 consecutive negative-samples below the limit of detection are documented (or upon consultation between the Investigator and Medical Monitor). 	7
12.8.3/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 100, Week 104 Year 3 – Week 116, Week 128, Week 140, Week 152, Week 156 Year 4 – Week 168, Week 180, Week 192, Week 204, Week 208 Year 5 – Week 220, Week 232, Week 244, Week 256, Week 260 At the every 12 week and End of Year visits, the following procedures will be performed: 	7, 13

Section No./Title	Revision	Rationale
	PCR of vector DNA in blood, saliva, urine, semen, and stools (if required)	
	 Sample testing during Years 2-5 is not required if at least 3 consecutive samples are negative during the Post-Infusion Follow-Up period in Weeks 1-52. Subjects who have not had 3 consecutive negative semen samples by Week 52 should continue to have PCR testing of semen every 4 weeks (during Year 2) or every 6 weeks (during Years 3-5) until 3 consecutive negative-samples below the limit of detection are documented (or upon consultation between the Investigator and Medical Monitor). 	
<u>12.9/Safety Follow-Up</u> Years 6-7	If the investigator at a participating site determines that MN services are appropriate for a subject and the subject gives written informed consent to participate in MN visits, the MN network will communicate with the subject and the subject's site.	1
	During Years 6-7 of Safety Follow-up, the following procedures will be completed:	
<u>12.9.1/Years 6-7 –</u> Every 13 Weeks	 Every 13 weeks (± 4 weeks) during Years 6-7, the site should contact the subject remotely to collect the following data: Adverse events 	1
	 New or changed concomitant medications Diary entries (FVIII usage and bleeding events) 	
<u>12.9.2/Years 6-7 –</u> Every 26 Weeks and End of Year Visits	 During Years 6-7, the following assessments will be performed at a site visit every 26 weeks (± 4 weeks) (Week 286 and Week 338) and at the End of Year Visits (± 4 weeks) (Week 312 and Week 364): Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use) 	1
	 <u>Complete Physical Examination (Week 312 and Week 364 only)</u> <u>Weight (Week 312 and Week 364 only)</u> <u>Vital signs (Week 312 and Week 364 only)</u> 	
	 <u>Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.9.2.1)</u> <u>Liver Tests (refer to Table 9.7.9.3.1) – central laboratory assessment</u> <u>LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.</u> 	
	<u>FVIII Assays – central laboratory assessment</u>	

Section No./Title	Revision	Rationale
	• FVIII activity level (one-stage clotting assay)	
	• FVIII activity level (chromogenic substrate assay)	
	• <u>FVIII coagulation activity exploratory assay</u>	
	o Bethesda assay (with Nijmegen modification) for FVIII inhibitor level	
	• <u>FVIII antigen (ELISA)</u>	
	Note: If a subject has used FVIII within 72 hours of a measurement day, all efforts should be made to obtain FVIII activity measurements when a 72-hour interval without FVIII use is achieved; the 72-hour wash-out period is only intended for subjects who have achieved FVIII \geq 5 IU/dL at 16 weeks after BMN 270 infusion and who have not resumed standard of care FVIII replacement therapy.	
	• AAV5 antibody titer (Week 312 and Week 364 only)	
	• FVIII antibody titer (Week 312 and Week 364 only)	
	• Exploratory biomarker assessments (Week 312 and Week 364 only)	
	• <u>Haemo-QoL-A QOL assessment</u>	
	• <u>PCR of vector DNA in blood, saliva, urine, semen, and stools (if required)</u>	
	• Sample testing during Years 6-7 is not required if at least 3 consecutive samples are below the limit of detection as of the end of Year 5.	
12.11/ETV	If a subject leaves the study prior to the Week 260364 visit, the subject will be asked to return to the study site and complete an Early Termination visit. At the Early Termination visit, as many of the following assessments as possible should be done:	1, 7
	• PCR of vector DNA in blood, saliva, urine, semen, and stools	
	 Sample testing at the ETV is not required if at least 3 consecutive samples are clear during the Post- Infusion Follow-Up period<u>below the limit of detection prior to the ETV</u>. 	
12.12/End of Study	The study will end after the last subject completes the last Safety Follow-Up visit (Week 260364).	1
14.2/Primary and Secondary Efficacy Analysis	Data collected in a longitudinal manner may be analyzed using longitudinal methods such as mixed effect model which takes into account the correlation among the observation taken at various time points within a participant. Efficacy is a secondary endpoint, defined as biologically active hFVIII at \geq 5 IU/dL by chromogenic substrate assay and/or one-stage clotting assay as	13

Section No./Title	Revision	Rationale
	measured by the central laboratory at 16 weeks following study treatment. hFVIII activity will be assessed weekly during the study period.	
16/Costs, Compensation and Subject Injury	There will be no charge to study subjects to be in this study. BioMarin will pay allthe full costs of the study-related tests, procedures, and treatments that are part ofset forth in this studyprotocol. In addition, after IRB/IEC/REB approval, BioMarin may reimburse the reasonable cost of travel for study-related visits. BioMarin will not pay for any hospitalizations, tests, or treatments for medical problems of any sort, whether or not related to the study subject's disease that are not part of this study. Costs associated in accordance with hospitalizations, tests, BioMarin's travel and treatments should be billed and collected in the way that such costs are usually billed and collectedreimbursement policy. The Investigator should contact BioMarin immediately upon notification that a study subject has been injured by the IP 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 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 subject has followed the Investigator's instructions, BioMarin will pay pay for reasonable and necessary medical services to treat the injuries caused by the IP or study procedures, if these costs are not covered by health insurance or another third party that usually pays these costs. In some jurisdictions, 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 related injuries set or any concurrent disease and that are unrelated to this study.	11
21/References	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. Mingozzi, F and High, KA. Immune responses to AAV vectors: overcoming barriers to successful gene therapy. Blood 122[1], 23-36. 2013. National Hemophilia Foundation. MASAC recommendation for liver biopsies in gene therapy trials for hemophilia. Available at https://hemophilia.org/sites/default/files/ document/files/256.pdf. 2019. MASAC Recommendation #256. Last accessed 5 June 2020.	13

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Section No./Title	Revision	Rationale
	Pasi, J, Wong, W, Rangarajan, S, Wilde, J et al. Interim results of an open label, phase 1/2 study of BMN 270, an AAV5-	
	FVIII gene transfer in severe hemophilia A. Haemophilia 22[Suppl. 4], 151-152. 2016.	

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1/2, Dose-Escalation, Safety, Tolerability and Efficacy Study of BMN 270, an Adenovirus-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII in Patients with Severe Haemophilia A
Protocol Number:	270-201
Active Investigational Product:	AAV5-hFVIII-SQ
IND/European Union Drug Regulating Authorities Clinical Trials (EudraCT) Number:	2014-003880-38
Indication:	Haemophilia A
Sponsor:	BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949
Development Phase:	Phase 1/2
Sponsor's Responsible Medical Monitor:	Plane, MA MB BChir MSc BioMarin (UK) Ltd. 10 Bloomsbury Way London, WC1A 2SL
Duration of Subject Participation:	Approximately 264 weeks
Dose:	Varied
Study Population:	Males aged 18 or older
Date of Original Protocol:	10 February 2015
Date of Amendment 1:	06 March 2015
Date of Amendment 2:	26 May 2015
Date of Amendment 3:	06 November 2015
Date of Amendment 4:	02 September 2016
Date of Amendment 5:	14 February 2017
Date of Amendment 6:	21 December 2017
Date of Amendment 7:	10 October 2018
Date of Amendment 8:	31 January 2019

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May not be divulged, published, or otherwise disclosed to others without prior written approval from BioMarin.

This study will be conducted according to the principles of Good Clinical Practice as described in the U.S. Code of Federal Regulations and the International Conference on Harmonisation Guidelines, including the archiving of essential documents

Proprietary and Confidential



CLINICAL STUDY PROTOCOL AMENDMENT SUMMARY

Amendment: 8

Date: 31 January 2019

RATIONALE AND SUMMARY OF MAJOR CHANGES

A summary of major changes covered by Amendment 8 to the 270-201 protocol is provided below.

1. An optional liver biopsy substudy has been added to the protocol.

Rationale: BMN 270 is an AAV5-based gene therapy vector that expresses the SQ form of hFVIII under the control of a liver-selective promoter. It was designed to direct long term FVIII transgene expression within the liver as measured by an increase in circulating levels of hFVIII and produce less frequent episodes of bleeding and the need for exogenous FVIII infusions. Health of the liver after gene transduction has been monitored indirectly by periodic assessments of hepatic enzymes released into the blood stream. Inter-subject variability in post-therapy hFVIII levels has been observed. Neither the reasons for the variations in response to FVIII gene therapy nor the effects on hepatic tissue structure and function are known. The purpose of this exploratory substudy is to provide a better understanding of the variation in hFVIII levels observed after gene therapy by direct examination of liver tissue for any pathologic alterations within the liver or alterations in hepatocyte structure and to characterize the transduced gene form and distribution.

2. Assessment of the Direct Thrombin Activity test has been removed from the Year 2-5 follow-up visits.

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

3. Minor administrative changes have been made for consistency and clarity.

Specific changes included in this amendment, including the Synopsis, since Amendment 7 (approved 10 October 2018) are outlined in Section 24.



2 SYNOPSIS

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AAV5-hFVIII-SQ		
TITLE OF STUDY:		
A Phase 1/2, Dose-Escalation, Safety, Tolerability and Efficacy Study of BMN 270, an		

Adenovirus-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII in Patients with Severe Haemophilia A

PROTOCOL NUMBER:

270-201

STUDY SITES:

Approximately 6-10 sites worldwide.

PHASE OF DEVELOPMENT:

Phase 1/2

STUDY RATIONALE:

Haemophilia 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 cascade. This disorder can be either inherited, due to a new mutation 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 is largely governed by the level of residual expression. Severe HA is classified as FVIII activity less than 1% of wild type (< 1 IU/dL), moderate disease comprises 1-5% of wild type activity and the mild form is 5-40% activity. The clinical manifestations of severe HA remain frequent spontaneous bleeding episodes, predominantly in joints and soft tissues, with a substantially increased risk of death from haemorrhage when the brain is involved. 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 treatment (mean of 1 to 7 episodes/year with prophylaxis and up to 30 to 50 episodes/year for on demand treatment). The consequence of multiple bleeding events is the development of an underlying pathology that contributes to 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

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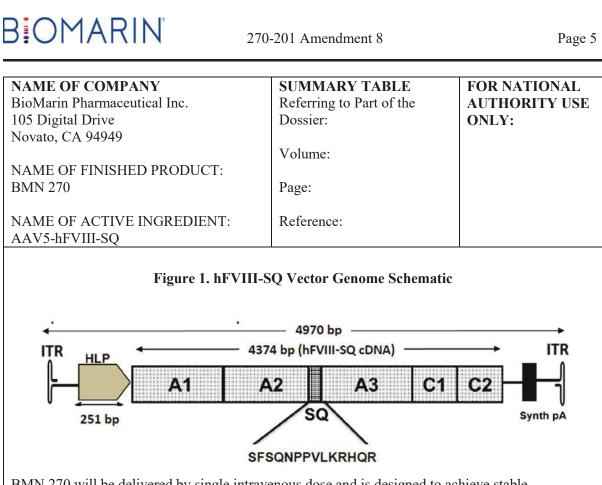
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maintaining activity levels above 1% trough. However, these longer acting FVIIIs remain dependent on multiple infusions to maintain critical levels of FVIII activity in severe HA patients. There is therefore a strong unmet need for a fully preventive treatment of HA to give patients a FVIII level compatible with a normal and haemorrhage-free life.

Gene therapy offers the potential of disease-modifying therapy by continuous endogenous production of active FVIII following a single intravenous administration of a vector with the appropriate gene sequence. Haemophilia 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 modest increases in the level of FVIII (any increase of the plasma level by 2 ng/ml induces an increase in activity of 1%) can ameliorate the severe form of the disease. Thus, relatively small changes in endogenous FVIII activity results in clinically relevant improvements in disease phenotype. Finally, the 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 for specific tissues such as the liver (for serotypes 2, 5 and 8 among others). Indeed, an on-going gene therapy clinical trial for a related disorder, haemophilia B, has established that stable (>36 months) expression of human factor IX at levels that are sufficient for conversion of their bleeding phenotype from severe to moderate or mild is achievable following a single peripheral vein administration of AAV-8 vector. Several participants in this trial have been able to discontinue factor prophylaxis without suffering spontaneous haemorrhages, 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 liver-selective promoter (Figure 1).



BMN 270 will be delivered by single intravenous dose and is designed to achieve stable, potentially life-long expression of active hFVIII in the plasma, synthesized from vector-transduced liver tissue. The clinical study 270-201 is a first-in-human study designed to assess the relationship of vector dose to the augmentation of residual FVIII activity, and whether these levels are sufficient to alter the clinical phenotype. The relationship of dose to safety will be correlated to the activity of hFVIII in patients with severe HA.

Liver Biopsy Substudy Rationale

The 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 in the second year of follow-up, with mean hFVIII activity levels remaining above the lower limit of normal (50 IU/dL). 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, and 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 270-201 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 some subjects, as well as inter-subject variability in post-therapy hFVIII levels. Neither the reasons for, nor the significance of, the ALT elevations

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or 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.

The purpose of this exploratory substudy is to provide a better understanding of the long-term gene expression related to circularized genomes, health of the liver, and variation in hFVIII levels observed after gene therapy with BMN 270. Whilst consenting subjects may not derive any direct benefit themselves by participating in the substudy, the overall findings could aid future patients by helping to characterize the means by which long-term efficacy is achieved and the safety of liver-directed gene therapy.

OBJECTIVES:

The primary objectives of the study are:

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

The secondary objectives of the study are:

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

The exploratory objectives of the liver biopsy substudy are:

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

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STUDY DESIGN AND PLAN:

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

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

Cohort 1: 6E12 vector genomes [vg] per kilogram of body weight, given as a single intravenous dose (iv)

Cohort 2: 2E13 vg per kilogram, iv

Cohort 3: 6E13 vg per kilogram, iv

Cohort 4: 4E13 vg per kilogram, iv

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

Cohorts 1-3

The first 3 cohorts will be enrolled sequentially, allowing a period of 3 weeks or more between cohorts. Dose escalation may occur after a single subject has been safely dosed if the resulting FVIII activity at the Week 3 visit is < 5 IU/dL in both the one-stage clotting and chromogenic substrate assays. Three weeks is expected to be the time the expression will be close to the maximum. This escalation paradigm is intended to minimize the subject numbers exposed to subtherapeutic doses.

Approximately three weeks after an injection, the decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and a panel of investigators participating in the study, the Data Review Board (DRB).

If the FVIII activity reaches ≥ 5 IU/dL at the Week 3 visit, then the remaining subjects in the cohort will be enrolled without the need to wait for 3 weeks between subjects.

Subject 1 will be dosed by intravenous infusion with 6E12 vector genomes [vg] per kilogram of body weight. If the FVIII activity level does not reach ≥ 5 IU/dL at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 1 and enrollment into Cohort 2 will initiate with Subject 2 at the next dose (2E13 vg/kg).

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If the FVIII activity level in the first subject treated in Cohort 2 does not reach ≥ 5 IU/dL at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 2 and enrollment into Cohort 3 (6E13) will initiate with the next subject. If the FVIII activity level in the first subject treated in Cohort 3 does not reach ≥ 5 IU/dL at the Week 3 visit in both assays, then the Data Review Board (DRB) will recommend whether to continue to add subjects to the cohort and/or whether to continue the study.

For the first subject treated in each of the first 3 cohorts, if the activity level reaches \geq 5 IU/dL and no safety issue is found, then up to four subjects will be enrolled in the Cohort, though, the adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

Cohort 4

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

There will be an ongoing review of individual patient safety and efficacy data by the medical monitor and the DRB. The adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

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

In subjects who experience recurrent bleeding episodes, the Investigator and Medical Monitor will discuss whether to resume prior FVIII prophylaxis. Subjects who do not respond to BMN 270 treatment (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, follow an abbreviated visit schedule after Week 52, as applicable and at the discretion of the Investigator. Because subjects develop neutralizing immunity upon exposure to the capsid, re-challenge of vector is not a likely treatment option and these subjects have effectively a single opportunity for therapy using this AAV capsid. Efficacy will be determined by FVIII activity at 16 weeks post dose. Safety will be evaluated for approximately 5 years after dosing. Any safety signal may trigger a review of the data and possible additional immunogenicity studies that include an assessment of cellular immune responses using collected peripheral blood mononuclear cells (PBMC).

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Liver Biopsy Substudy Design

All subjects enrolled in 270-201 and who are at least one year post-BMN 270 infusion are eligible for the optional liver biopsy substudy. Subjects who consent to participate in the substudy will have a liver biopsy via either the transjugular or percutaneous (ultrasound-guided) route, according to the standard procedures of the institution. To enhance safety, all subjects will have an ultrasound examination of the liver within 3 months prior to the procedure (to ensure there are no pathological findings such as bile duct obstruction that might interfere with the safe performance of the liver biopsy) and a FibroScan of the liver within one week before the liver biopsy (to correlate with any potential histopathologic findings of fibrosis on the biopsy).

Subjects who consent should have their FVIII levels monitored/adjusted by the Investigator to enable the procedure to be performed safely. This may require the administration of exogenous FVIII replacement products in order to achieve the desired FVIII activity. The target FVIII activity level within 24 hours prior to the liver biopsy is at the discretion of the Investigator and/or according to local guidelines, but at a minimum should be at the lower limit of the normal range (ie, at least 50 IU/dL).

NUMBER OF SUBJECTS PLANNED:

Up to 15 subjects may enroll into the study; the actual number of subjects will depend on the FVIII activity levels seen in each Cohort.

DIAGNOSIS AND ALL CRITERIA FOR INCLUSION AND EXCLUSION:

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

- 1. Males that are 18 years or older with established severe haemophilia A as evidenced by their medical history. Patients will be considered as severe if their base FVIII level is 1 IU/dL or less
- 2. Treated/exposed to FVIII concentrates or cryoprecipitate for a minimum of 150 exposure days (EDs)
- 3. Greater or equal to 12 bleeding episodes only if receiving on-demand therapy over the previous 12 months. Does not apply to patients on prophylaxis
- 4. Able to sign informed consent and comply with requirements of the trial
- 5. No history of inhibitor, and results from a modified Nijmegen Bethesda assay of less than 0.6 Bethesda Units (BU) on 2 consecutive occasions at least one week apart within the past 12 months



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	hFVIII-SQ		
6.	Sexually active patients must be will as double barrier, including hormona After 6 months, subjects may stop con negative semen samples.	al contraception for at least 6 mc	onths post-treatment.
Individ the stud	uals who meet any of the following e ly:	xclusion criteria will not be eligi	ble to participate in
1.	Detectable pre-existing immunity to inhibition or AAV5 total antibodies	the AAV5 capsid as measured b	by AAV5 transduction
2.	Any evidence of active infection or a	any immunosuppressive disorder	r.
3.	HIV positive		
4.	Significant liver dysfunction as defin	ned by abnormal elevation of:	
	• ALT (alanine transaminase) to 3	3 times the upper limit of normal	•
	• Bilirubin above 3 times the upper	er limit of normal;	
	• Alkaline phosphatase above 3 ti	mes the upper limit of normal; o	r
	• INR (international normalized ra	atio) ≥ 1.4	
5.	Potential participants who have had had significant fibrosis of 3 or 4 as r		are excluded if they
6.	Evidence of any bleeding disorder n	ot related to Haemophilia A	
7.	Platelet count of $< 100 \text{ x } 10^9/\text{L}$		
8.	$Creatinine \geq 1.5 \text{ mg/dL}$		
9.	Liver cirrhosis of any etiology as ass	sessed by liver ultrasound	
10.	Hepatitis B if surface antigen is posi	itive	
11.	Hepatitis C if RNA is positive		
12.	Treatment with any IP within 30 day	ys prior to the end of the screening	ng period

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NAME OF COMPANY BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949	SUMMARY TABLE Referring to Part of the Dossier:	FOR NATIONAL AUTHORITY USE ONLY:
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NAME OF ACTIVE INGREDIENT: AAV5-hFVIII-SQ	Reference:	
treatment outlined in the protoco	obysician's discretion that would pro- ments of the study including possibol. The physician may exclude patie obol for the 16-week period following	le corticosteroid ents unwilling or
14. Prior treatment with any vector	or gene transfer agent	
15. Major surgery planned in the 16	-week period following the viral inf	usion
16. Use of systemic immunosuppres infusion	sive agents or live vaccines within ?	30 days before the viral
Individuals eligible to participate in the criteria:	iver biopsy substudy must meet all	of the following
1. Currently enrolled in 270-201		
2. Received BMN 270 infusion at	least 1 year prior to enrollment in th	e substudy
3. Able to sign informed consent a	nd comply with requirements of the	substudy
levels should be assessed at the exogenous FVIII replacement pr	(or higher, depending on local guid 4 hours prior to the liver biopsy bein local laboratory.) Subjects may be t roducts in order to increase their FV ervision/instruction of the Investigat	ng performed. (FVIII reated with additional III levels to an
Individuals who meet any of the following the liver biopsy substudy:	ng exclusion criteria will not be elig	ible to participate in
 Assessed by the investigator or a undergoing a liver biopsy would are not limited to): 	a hepatologist as having a medical c be contraindicated. These condition	
• Significant thrombocytopen	ia (platelet count < $100 \times 10^9/L$)	
• Evidence of significant ascit	es	
• Abnormalities detected on li that would preclude safe per	ver ultrasound (performed within 9) formance of the biopsy.	0 days of procedure)
INVESTIGATIONAL PRODUCT(S) . Each subject will receive a single injecti infusion will depend on the dose level.	-	

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AAV5-hFVIII-SQ		

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

The study is open label with comparison of FVIII activity to baseline values. 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:

Safety:

The following safety outcome measurements will be assessed:

- Incidence of adverse events (AEs), including serious AEs (SAEs)
- Change in clinical laboratory tests (serum chemistry and haematology)
- Change in vital signs
- Change in physical examination
- Vector shedding
- Liver tests (LTs, including ALT, AST, GGT, LDH, bilirubin, alkaline phosphatase)
- Immune response to FVIII transgene and AAV capsid proteins

No major toxicity is expected based on preclinical studies in mice and monkeys. Each subject will have comprehensive surveillance monitoring of LTs (at local labs, once per week for Weeks 1-36, then once every 2 weeks from Week 37-52) during Year 1. LTs will be monitored every 4 weeks during Year 2, and then every 6 weeks for Years 3-5 post-dose in the safety extension; the frequency and duration of LT testing may be changed based on discussion between the Medical Monitor and the Investigator and review of subject data.

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

Efficacy:

The primary efficacy measure will be to assess plasma FVIII activity. The efficacy goal of the study is to establish the dose relationship to FVIII activity \geq 5 IU/dL at 16 weeks post BMN 270 administration.

Secondary efficacy measures include assessing the impact of BMN 270 on the frequency of FVIII replacement therapy and on the number of bleeding episodes during the study. Subjects will be asked to keep a subject diary to record the details in these areas.

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AAV5-hFVIII-SQ		

Pharmacodynamics:

The FVIII antigen and activity level as measured by an ELISA (antigen level) and by one-stage clotting and/or chromogenic substrate assay (activity level), will be used for plasma profiles; FVIII activity will be used to determine PD parameters. Traditional PK analysis is not applicable.

If supported by the FVIII activity data, non-compartmental analysis and observation will be used to estimate individual values of Cb (baseline concentration), Css (steady state concentration), Tss (time to steady state), C(t) and AUC(0-t) where t is 16 weeks.

Liver Biopsy Substudy:

The following exploratory assessments will be performed as part of the optional liver biopsy substudy:

- Morphologic/pathogenic changes after FVIII gene transduction or any change that may be associated with sustained ALT rise
- Determine quantities of liver FVIII-SQ DNA/RNA
- Determine forms of vector DNA in liver at the time of biopsy
- Determine percentage of hepatocytes expressing FVIII protein
- Determine percentage of hepatocytes staining positive for vector DNA
- Determine hepatic liver transcriptome at single nuclei level if sufficient material is obtained
- Identify the forms of vector DNA in the liver
- Examination of potential stress inducing cellular pathways
- Other exploratory assessment to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to hemophilia A, coagulation, and/or AAV gene transfer

STATISTICAL METHODS:

The sample size is based upon clinical considerations and could detect a strong clinical efficacy signal. Up to 15 subjects may be dosed in the study. The subjects will be followed in a longitudinal manner and all the relevant information will be collected. The analysis of the data will be descriptive in nature but data collected in a longitudinal manner may be analyzed using longitudinal methods such as mixed effect model which takes into account the correlation among the observation taken at various time points within a participant. Efficacy is a secondary endpoint, defined as biologically active FVIII at ≥ 5 IU/dL by chromogenic substrate assay and/or one-stage clotting assay at 16 weeks following study treatment. FVIII activity will be assessed weekly during the study period. We can only assess the true steady state of FVIII protein produced from

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elapsed since the last infusion of	of FVIII protein
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shedding will be primarily descriptive and involve both inter-participant and intra-participant comparisons across doses.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

AAV	adeno-associated virus
ADL	activities of daily living
ADR	adverse drug reaction
AE	adverse event
ALT	alanine transaminase
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BPV	BioMarin Pharmacovigilance
BU	Bethesda Unit
CFR	Code of Federal Regulations
CRA	clinical research associate
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DRB	Data Review Board
eCRF	electronic case report form
ED	exposure days
EOSI	events of special interest
ETV	early termination visit
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
FIH	first-in-human
FVIII	coagulation factor VIII
FXa	coagulation factor Xa
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
HA	Haemophilia A
hFVIII	human coagulation factor VIII
HIPAA	Health Insurance Portability and Accountability Act
IB	investigator brochure
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for
	Registration of Pharmaceuticals for Human Use
ICH E6	ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6
IEC	independent ethics committee

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IND	Investigational New Drug (application)
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IV	intravenous
LT	liver test
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	no-observed-adverse-effect level
PBMC	peripheral blood mononuclear cells
PD	pharmacodynamics
PEG	polyethylene glycol
PK	Pharmacokinetics
PRO	patient-reported outcome
rhFVIII	recombinant human FVIII protein
REB	research ethics board
SAE	serious adverse event
SAP	statistical analysis plan
SDV	source data verification
ULN	upper limit of normal
vg	vector genomes
VWF:Ag	von Willebrand factor Antigen

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]).

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

5 ETHICS

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

5.1 Institutional Review Board or Independent Ethics Committee

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

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

5.2 Ethical Conduct of Study

It is expected that Investigators understand and comply with the protocol. This includes, but is not limited to: establishing and meeting enrollment commitments, including providing eligible subjects for study enrollment; adhering to 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)

Specifically, this study is based on adequately performed laboratory and animal experimentation. The study will be conducted under a protocol reviewed and approved by an IRB/IEC/REB and will be conducted by scientifically and medically qualified persons. The benefits of the study are in proportion to the 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), United States Code of Federal Regulations (CFR) 21 CFR §50, European Clinical Trial Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC, and other applicable local regulations, will be obtained for each subject prior to entering the subject into the study. The Investigator will prepare the ICF and provide the documents to BioMarin for approval prior to submission to the IRB/IEC/REB approval. BioMarin and the IRB/IEC/REB must approve the documents before they are implemented. A copy of the approved ICF, and if applicable, a copy of the approved subject information sheet and all ICFs translated to a language other than the native language of the clinical site must also be received by BioMarin or designee prior to any study-specific procedures being performed.

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

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

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

Prior to beginning the study, the Investigator at each site must provide to BioMarin or designee, a fully executed and signed US Food and Drug Administration (FDA) Form FDA 1572 and a Financial Disclosure Form. All sub-Investigators must be listed on Form FDA 1572. Financial Disclosure Forms must also be completed for all sub-Investigators listed on the Form FDA 1572 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.

Liver tests (LTs) will be performed at the local laboratories associated with the study sites. Local laboratory results of LTs will be used to trigger corticosteroid treatment as needed (refer to Section 9.4.8.2). In case of discrepant results between local and central laboratories, the Investigator and Medical Monitor will decide further action. Safety labs evaluations (including LTs) will be performed at the central lab, while bioanalytical samples will be performed at the appropriate specialty lab. Refer to the Laboratory Manual for more details.

7 INTRODUCTION

Haemophilia A (HA) is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males (Nathwani, 1992, Baillieres Clin.Haematol.). It is caused by mutations in the factor VIII (FVIII) gene that codes for FVIII protein, an essential cofactor in the coagulation cascade. 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 haemorrhage. Treatment in Western (Berntorp, 2012, Haemophilia.) countries consists of intravenous injection of plasma derived or recombinant FVIII protein concentrates at the time of a bleed, 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 haemophilia A patients. These individuals develop debilitating arthropathy and have a substantially increased risk of death from haemorrhage in life (Stonebraker, 2010, Haemophilia.). Chemical modification or bioengineering of FVIII may improve half-life to 18-19 hours (Kaufman, 2013, Blood). However, these long acting FVIII variants do not eliminate the need for lifelong FVIII protein administration (Hay, 2012, Blood).

Gene therapy offers the potential of disease-modifying therapy by continuous endogenous production of human FVIII following a single administration of vector. Haemophilia 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, Haemophilia.); thus the therapeutic goal for gene therapy is a modest increase in hFVIII. Finally, the consequences of gene transfer can be assessed using simple quantitative rather than qualitative endpoints that can be easily assayed in most clinical laboratories.

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

7.1 Nonclinical Studies

The nonclinical program supports a single IV administration of BMN 270, the planned clinical route of administration, for the treatment of Haemophilia A in male patients. This

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nonclinical program took into account the guidelines and reflection papers for gene therapy medicinal products under EMA Advanced Therapies. 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 (normal CD-1 mouse, B and T cell deficient mouse model of haemophilia 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.

The primary PD of BMN 270 was assessed in a series of non-GLP single dose studies in a FVIII KO x Rag2 mouse model of severe Haemophilia A that recapitulates the change in coagulation observed in the human severe disease population without interfering cross species immunogenicity. PD activity and expression of hFVIII was assessed for durations up to 13-weeks in the FVIII KO x Rag2 mouse given dose range of 2E11 through 2E14 vector genomes (vg)/kg. Low levels of plasma hFVIII were observed in mice given 2E12 vg/kg after eight-weeks, post dose. Plasma hFVIII activity using bleeding time as an endpoint was evaluated in the FVIII KO x Rag2 mouse given up to 2E13 and 1E14 vg/kg BMN 270 at 8 weeks, post dose. BMN 270 related correction of bleeding times showed a dose relationship that was similar to that observed in FVIII KO x Rag2 mice given matched IU levels of Refacto[®].

All cynomolgus monkeys used in this program were screened for neutralizing anti-AAV5 activity prior to study enrollment. PD activity and plasma hFVIII concentrations were evaluated in the cynomolgus monkey given up to 6E13 vg/kg BMN 270 for eight weeks. Peak expression of hFVIII was observed three to six weeks post administration with a subsequent decrease in expression presumably due to immunogenicity though not necessarily correlated to antibody titer.

The normal mouse was utilized in the GLP toxicology study to assess the safety profile of BMN 270 without the background of disease progression and in sufficient number per parameter. The GLP single dose toxicity study in normal CD-1 mice given 6E12 and 6E13 vg/kg with a 4 and 13-week follow up period monitored clinical pathology, defined potential target organs, immunogenicity, gene expression and activity. No changes in liver function were observed. In a single dose PD study in monkey given BMN 270, formation of anti-AAV5 total antibodies was observed at Week 8 with relatively low formation of anti-hFVIII total antibodies. No changes in liver function was observed.

The overall nonclinical safety profile includes formation of anti-AAV5 total antibodies with relatively lower formation of anti-hFVIII total antibodies. Immunogenicity against the AAV capsid and hFVIII is an anticipated finding for BMN 270 treatment and will be monitored in

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the nonclinical and clinical programs. Though not observed in the nonclinical species, liver toxicity utilizing clinical pathology parameters will be monitored in the clinical program based on previous literature. Cellular immune response will also be monitored.

Additionally, the BMN 270 transgene product has a final sequence closely matching that of the protein replacement treatment, Refacto® and therefore the safety profile of the BMN 270 transgene product is anticipated to be similar to Refacto® and have no unique FVIII-specific target organs of toxicity. The AAV5 capsid has not been modified and therefore no unique capsid-specific safety findings are anticipated. Because the biodistribution pattern of AAV5 after IV administration is consistent across species, BioMarin will confirm the nonclinical distribution pattern of BMN 270 during clinical development. Biodistribution of the AAV5 capsid has been documented to predominately target the liver with relatively lower levels of transduction observed in the lung, kidney, spleen, testes and blood compartment depending on the species and timing of administration. Liver targeted distribution of a similar AAV5 Factor IX gene therapy product was observed in the rhesus macaque monkey with low levels of vector genomes detected in spleen, kidney and testis (Nathwani, 2006, Blood). Despite distribution to non-liver organs, no expression of Factor IX was detected in these tissues. Additionally, distribution to the testis was observed in another study in monkeys given an AAV5-codon-optimized human porphobilinogen deaminase; however, vector genomes in the semen were only transiently observed within one week but not thereafter (Paneda, 2013, Hum.Gene Ther.).

Both normal and disease model mice and a limited number of monkeys were utilized to establish proof of concept, species scaling and dose response in order to select the first-in-human (FIH) dose of 6E12 vg/kg. This dose represents 10-fold safety factor from the no observed adverse effect level (NOAEL) in the GLP enabling nonclinical toxicology study in mice.

7.2 Previous Clinical Studies

This is the first clinical study for BMN 270.

BioMarin's program for haemophilia A builds on previous clinical trials of AAV-mediated gene transfer for a related condition, haemophilia B, that were conducted with an AAV2 vector (Manno, 2003, Blood) and an AAV8 vector (Nathwani, 2011, N.Engl.J.Med.), (Nathwani, 2014, N.Engl.J.Med.). The large size of the FVIII cDNA was shortened and a preclinical validation of this approach was performed with an AAV8 vector (McIntosh, 2013, Blood).

AAV serotype 5 is being tested in other clinical trials and was reportedly well tolerated without treatment-related serious adverse events in a recent phase 1 study for treatment of Acute Intermittent Porphyria (D'Avola, 2014, J.Hepatol.). In addition, AAV using other serotypes have been used in 105 clinical studies to date and no safety issue specific to the vector was ever reported.

7.3 Study Rationale

Haemophilia A (HA) is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males (Mannucci, 2001, N.Engl.J.Med.). It is caused by deficiency in the activity of coagulation factor VIII (FVIII), an essential cofactor in the intrinsic coagulation cascade. This disorder can be either inherited, due to a new mutation 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 is largely governed by the level of residual expression. Severe HA is classified as FVIII activity less than 1% of wild type (< 1 IU/dL), moderate disease comprises 1-5% of wild type activity and the mild form is 5-40% activity. The clinical manifestations of severe HA remain frequent spontaneous bleeding episodes, predominantly in joints and soft tissues, with a substantially increased risk of death from haemorrhage when the brain is involved.

Treatment of severe HA presently consists of intravenous injection of plasma derived or recombinant human FVIII protein (rhFVIII) concentrates both as prophylaxis 2-4 times per week, and at the time of a bleed, to prevent or control bleeding episodes, respectively. The half-life for FVIII (12-18 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 treatment (mean of 1 to 7 episodes/year with prophylaxis and up to 30 to 50 episodes/year for on demand treatment) (Nagel, 2011, Haemophilia.). The consequence of multiple bleeding events is the development of an underlying pathology that contributes to debilitating multiple-joint arthropathy and substantially increased risk of death (Nagel, 2011, Haemophilia). Chemical modification (eg, direct conjugation of polyethylene glycol (PEG) polymers) and bioengineering of FVIII (eg, FVIII-Fc fusion proteins) improve half-life by approximately 50%, and thus, show promise in reduced dosing and maintaining activity levels above 1% trough (Stonebraker, 2010, Haemophilia.), (Mahlangu, 2014, Blood). However, these longer acting FVIIIs remain dependent on multiple infusions to maintain critical levels of FVIII activity in severe HA patients. There is therefore a strong unmet need for a fully preventive treatment of HA to give patients a FVIII level compatible with a normal and haemorrhage-free life.

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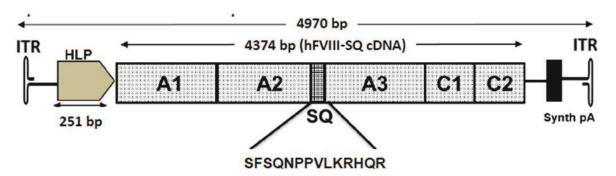
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Gene therapy offers the potential of disease-modifying therapy by continuous endogenous production of active FVIII following a single intravenous administration of a vector with the appropriate gene sequence. Haemophilia A is well suited for a gene 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 modest increases in the level of FVIII (any increase of the plasma level by 2 ng/ml induces an increase in activity of 1%) can ameliorate the severe form of the disease. Thus, relatively small changes in endogenous FVIII activity results in clinically relevant improvements in disease phenotype. Finally, the 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 (Mannucci, 2001, N.Engl.J.Med.). They have an excellent and well defined safety profile, and can direct long term transgene expression with tropism for specific tissues such as the liver (Nathwani, 2005, Curr.Hematol.Rep.) for serotypes 2, 5 and 8 among others. Indeed, an on-going gene therapy clinical trial for a related disorder, haemophilia B, has established that stable (>36 months) expression of human factor IX at levels that are sufficient for conversion of their bleeding phenotype from severe to moderate or mild is achievable following a single peripheral vein administration of AAV-8 vector (Nathwani, 2014, N.Engl.J.Med.). Several participants in this trial have been able to discontinue factor prophylaxis without suffering spontaneous haemorrhages, 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, 2011, Mol.Ther.), (Bainbridge, 2008, N.Engl.J.Med.), (Maguire, 2009, Lancet); (Simonelli, 2010, Mol.Ther.).

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





BMN 270 will be delivered by single intravenous dose and is designed to achieve stable, potentially life-long expression of active FVIII in the plasma, synthesized from vector-transduced liver tissue. The clinical study BMN 270-201 is a first-in-human study designed to assess the relationship of vector dose to the augmentation of residual FVIII activity, and whether these levels are sufficient to alter the clinical phenotype. The relationship of dose to safety will be correlated to the activity of FVIII in patients with severe HA.

7.3.1 Liver Biopsy Substudy Rationale

The 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 in the second year of follow-up, with mean hFVIII activity levels remaining above the lower limit of normal (50 IU/dL). 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 270-201 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 some subjects, as well as inter-subject variability in post-therapy hFVIII 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.

The purpose of this exploratory substudy is to provide a better understanding of the long-term gene expression related to genome circularization, health of the liver, and variation in hFVIII levels observed after gene therapy with BMN 270. Whilst consenting subjects may not derive any direct benefit themselves by participating in the substudy, the overall findings could aid future patients by helping to characterize the means by which long-term efficacy is achieved and the safety of liver-directed gene therapy.

7.4 Summary of Overall Risks and Benefits

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

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The current data available for BMN 270 does not yet permit comprehensive assessment of the benefit:risk profile of this investigational drug. Given the monitoring measures in place in the clinical protocol(s) to minimize the risk to subjects participating in the existing studies, the identified risks are justified by the anticipated benefits that may be afforded to subjects. Each subject in 270-201 will have a comprehensive surveillance plan that monitors LTs during the study, and elevations in LT will be addressed according to the guidelines set forth in the protocol. Safety will be assessed by adverse event reporting and clinical laboratory assessments.

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

Dose selection: The benefit of this study can only be enhanced by selecting a starting dose that maximizes the opportunity of observing a therapeutic effect, and therefore, reducing the possibility of a sub-therapeutic effect. With this consideration in mind, the starting dose 6E12 vg/kg was selected using overall data from the pre-clinical studies conducted in mice (normal and disease model, Rag2 -/- x FVIII -/-) and monkey. A detectable pharmacological response based on activity was observed at 6E12 vg/kg. A 10-fold safety margin based upon the NOAEL was observed in the GLP 13-week study in normal mouse at the highest dose administered. A 30-fold safety margin in an 8-week dose response study in disease model mice based on histology was observed at the highest dose administered. No BMN 270-related changes in clinical observations or chemistry was observed in the monkey at doses up to 6E13 vg/kg, a 10-fold safety margin after 8-weeks. Overall, no BMN 270-related findings, except expected formation of anti-AAV5 antibodies, were observed at the highest administered doses of 6E13, 2E14 and 6E13 vg/kg in the normal mouse, disease model mouse and monkey, respectively.

Based on these key pre-clinical findings it can be suggested that the proposed starting dose of 6E12 vg/kg should not pose any risk or safety concerns to subjects with the best chance of benefiting the subject therapeutically.

7.4.1 Liver Biopsy Substudy 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 substudy will have a comprehensive pre-/post-biopsy surveillance plan according to the standard procedures at the institution. 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 substudy is optional and will not have any effect on the subject's continued participation in 270-201.

8 STUDY OBJECTIVES

The primary objectives of the study are:

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

The secondary objectives of the study are:

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

The exploratory objectives of the liver biopsy substudy are:

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

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

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

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

- Cohort 1: 6E12 vector genomes [vg] per kilogram of body weight, given as a single intravenous dose (iv)
- Cohort 2: 2E13 vg per kilogram, iv
- Cohort 3: 6E13 vg per kilogram, iv
- Cohort 4: 4E13 vg per kilogram, iv

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

Cohorts 1-3

The first three cohorts will be enrolled sequentially, allowing a period of 3 weeks or more between cohorts. Dose escalation may occur after a single subject in a cohort has been safely dosed if the resulting FVIII activity at the Week 3 visit is < 5 IU/dL in both assays. Three weeks is expected to be the time the expression will be close to the maximum. This escalation paradigm is intended to minimize the subject numbers exposed to subtherapeutic doses. The decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and a panel of investigators participating in the study.

If the FVIII activity reaches ≥ 5 IU/dL at the Week 3 visit, then the remaining subjects in the cohort will be enrolled without the need to wait for 3 weeks between subjects.

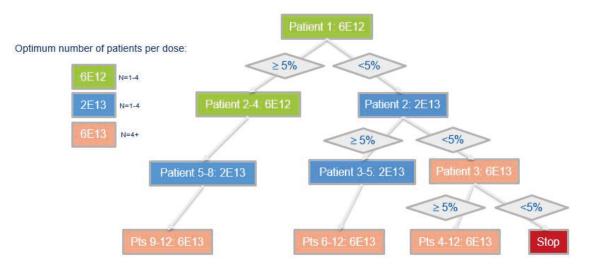


Figure 9.1.1: Flow Chart of Dose Escalation Scheme for Cohorts 1 to 3

Subject 1 (Cohort 1) will be dosed by intravenous infusion with 6E12 vg/kg of body weight. If the FVIII activity level does not reach 5 IU/dL or greater (expressed as % in Figure 9.1.1) at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 1 and enrollment into Cohort 2 will initiate with Subject 2 at the next dose (2E13 vg/kg).

If the FVIII activity level in the first subject treated in Cohort 2 does not reach \geq 5 IU/dL at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 2 and enrollment into Cohort 3 (6E13) will initiate with the next subject.

If the FVIII activity level in the first subject treated in Cohort 3 does not reach \geq 5 IU/dL at the Week 3 visit in both assays, then the DRB will recommend whether to continue to add subjects to the cohort and/or whether to continue the study.

For the first subject treated in each of the first 3 cohorts, if the activity level reaches \geq 5 IU/dL and no safety issue is found, then up to four subjects will be enrolled in the Cohort, though the adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

Cohort 4

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

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There will be an ongoing review of individual patient safety and efficacy data by the medical monitor and the Data Review Board (DRB). The adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

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

In subjects who experience recurrent bleeding episodes, the Investigator and Medical Monitor will discuss whether to resume prior FVIII prophylaxis. Subjects who do not respond to BMN 270 treatment (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, follow an abbreviated visit schedule after Week 52, as applicable and at the discretion of the Investigator.

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

A summary of events and assessments are provided by visit in Table 9.1.1 for Screening, Baseline and BMN 270 Infusion, in Table 9.1.2 for Post-Infusion Follow-up, and in Table 9.1.3, Table 9.1.4, and Table 9.1.5 for Safety Follow-up.

Table 9.1.6, dealing with the apeutic corticosteroid use in the event of elevated LTs, is discussed in Section 9.4.8.2.

Liver Biopsy Substudy Design

All subjects enrolled in 270-201 and who are at least one year post-BMN 270 infusion are eligible for the optional liver biopsy substudy. Subjects who consent to participate in the substudy will have a liver biopsy via either the transjugular or percutaneous (ultrasound-guided) route, according to the standard procedures of the institution. To enhance safety, all subjects will have an ultrasound examination of the liver within 3 months prior to the procedure (to ensure there are no pathological findings such as bile duct obstruction that might interfere with the safe performance of the liver biopsy) and a FibroScan of the liver within one week before the liver biopsy (to correlate with any potential histopathologic findings of fibrosis on the biopsy).

Subjects who consent should have their FVIII levels monitored/adjusted by the Investigator to enable the procedure to be performed safely. This may require the administration of exogenous FVIII replacement products in order to achieve the desired FVIII activity. The target FVIII activity level within 24 hours prior to the liver biopsy is at the discretion of the Investigator and/or according to local guidelines, but at a minimum should be at the lower limit of the normal range (ie, at least 50 IU/dL).

Table 9.1.7 presents the schedule of assessments for participation in the liver biopsy substudy.

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	Pri	BMN 270		
Assessment	Screening ⁱ (Day -28 to Day -1)	Smart Rescreening ⁱ (Day -28 to Day -1)	Baseline (Day -7 to Day -1) ^h	Infusion Visit (Day 1) ^k
Informed consent	X			, , ,
Medical History	Х			
Physical Examination ^a	Х		Х	Х
Height and Weight ^a	X			
Vital Signs	Х	Х		Х
Assessment of Adverse Events and Concomitant Medications	Х	X	Х	Х
Documentation of bleeding episodes and FVIII usage (by either subject or clinical information)	X	Х	Х	
Distribution of subject diaries and training in their use			Х	
Electrocardiogram	Х			
Chest X-ray	X			
Liver Ultrasound	X			
hFVIII Assays ^b	X	Xj		
AAV5 Assays ^c	Х	X		Х
Screen for Hepatitis B, Hepatitis C, HIV ^d	Х			
Blood chemistry, haematology, coagulation screen, and CRPe	Х	Х	Х	
Urine Tests ^e	Х	X	Х	
Liver Tests ^e	Х	Х	Х	
PBMC collection for CTL baseline			Х	
Von Willebrand Factor Antigen (VWF:Ag)	Х			
Direct Thrombin Test			Х	
PCR of vector DNA in blood, saliva, urine, semen, and stools			Х	
Biomarker testing ^f	Х			
Exploratory biomarker assessments ^g			Х	
Haemo-QoL-A Quality of Life (QoL) assessment			Х	
BMN 270 Infusion				Х

Table 9.1.1: Schedule of Events – Screening and Infusion

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- ^a Complete physical examination should be done at Screening. Brief physical examination may be done at Baseline and at the BMN 270 Infusion Visit. Height will be recorded at Screening only. Weight will be recorded at Screening and then every 6 months thereafter.
- ^b Includes baseline hFVIII activity (chromogenic substrate assay and one-stage clotting assay), hFVIII coagulation activity exploratory assay, hFVIII inhibitor level (Bethesda assay with Nijmegen modification), hFVIII total antibody titer, and hFVIII antigen (ELISA).
- ^c Screening (done during Screening) and testing (at Infusion Visit) of AAV5 pre-existing immunity may include plasma samples for 3 assays (in vivo transduction inhibition, in vitro transduction inhibition and AAV5 total antibody assays). Sample collection on the day of the infusion visit must be performed before the BMN 270 infusion is given.
- ^d Patients with documented negative results within the last 30 days do not need to be retested.
- ^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.
- $^{\rm f}$ Includes HLA genotyping, FVIII genotyping, TNF α and IL10a single nucleotide polymorphisms.
- ^g 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 Direct Thrombin Activity test and any other exploratory assessments) will be performed only as deemed necessary by the Sponsor.
- ^h Should the screening visit occur within 7 days of the drug infusion, physical examination, blood chemistry, LTs, haematology, urine tests, coagulation screen, and CRP do not need to be repeated at Baseline.
- ⁱ Smart rescreening should only be performed if a patient has been determined to be eligible for the study and is unable to complete the Baseline assessments and Infusion prior to the closing of the original Screening window. Subjects who undergo smart rescreening must complete the rescreening assessments and receive the infusion within 90 days of signing the original consent. Subjects who do not complete dosing within 90 days will be required to re-consent and undergo all screening procedures. Subjects may not undergo smart rescreening more than once.
- ^j Only the hFVIII inhibitor level (Bethesda assay with Nijmegen modification) assay must be done at smart rescreening.
- ^k Assessments on the day of infusion must be performed prior to the infusion. 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), following the infusion hourly (± 5 minutes) for 6 hours and then every 2 hours (± 15 minutes) for 6 hours and then at 4 hour intervals (± 15 minutes).

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					F	ollow-	Up Af	ter BN	1N 27	0 Adm	inistra	tion –	Week	s*				
	· ·	Week	1															
Assessment	D2	D4	D8	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Physical examination ^a			Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)			Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Vital Signs			Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Blood chemistry, haematology, coagulation screen, and $\mathrm{CRP}^{\mathrm{b}}$				Х		Х		Х		Х		Х		Х				Х
Urine Tests ^b						Х				Х				Х				Х
Liver Tests (local) ^b		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
FVIII assays (local) ^c		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Liver Tests (central) ^b		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
FVIII assays (central) ^d		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
FVIII antibody titer						Х				Х				Х				Х
PCR of vector DNA in blood, saliva, urine, semen, and stools ^e	X	Х	Х			Х		Х		Х		Х		Х		Х		Х
Exploratory biomarker assessments ^f						Х				Х				Х				Х
Haemo-QoL-A QoL assessment			Х	Х	Х	Х												Х
AAV5 antibody titer										Х								Х
Testing for reactivation of hepatitis B and hepatitis C																		Xg
PBMC collection			Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Von Willebrand Factor Antigen (VWF:Ag)						Х				Х				Х				Х

Х

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

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Direct Thrombin test

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* Visit windows are \pm 48 hours (and include the Day 4 visit)

^a Brief physical examination should be done at all weekly visits except Week 16, where a complete physical examination should be performed. Refer to Section 9.7.8.5.
^b Refer to Table 9.7.8.2.1 for laboratory assessments to be included, and to Table 9.7.8.3.1 for liver tests. LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) 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. Patients with ALT > 1.5 ULN during the study may undergo additional evaluations (eg, imaging studies including MRI or ultrasound, additional blood tests, and/or liver biopsy) at the discretion of the investigator. Additional testing of FVIII and LTs during any study week may be performed if: (1) the ALT has increased to above ULN; (2) Increases in ALT values from prior assessment are accompanied by declines in FVIII activity level; or after a discussion between the Medical Monitor and the Investigator based on a review of subject data. If FVIII levels and/or ALT values are stable over the course of several weeks, assessment of FVIII activity and ALT levels may be adjusted based on discussion between the Medical Monitor and the Investigator.

- ^c Includes hFVIII activity level (one-stage clotting assay and chromogenic substrate 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 standard of care 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 Includes hFVIII activity level (one-stage clotting assay and chromogenic substrate assay), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, hFVIII coagulation activity exploratory assay, and hFVIII antigen (ELISA). If a subject has used FVIII within 72 hours of a measurement day, all efforts should be made to obtain FVIII activity measurements when a 72-hour interval without FVIII use is achieved; the 72-hour wash-out period is only intended for subjects who have achieved FVIII \geq 5 IU/dL at 16 weeks after BMN 270 infusion and who have not resumed standard of care 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 Collection to occur on Day 2 and 4 following BMN 270 infusion, and then until at least 3 consecutive negative results are obtained. Collection and testing of semen samples must continue through Week 12, even if 3 consecutive negative samples in that compartment have already been recorded.

^f 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 Direct Thrombin Activity test and any other exploratory assessments) will be performed only as deemed necessary by the Sponsor.

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

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	Follow-Up After BMN 270 Administration – Weeks*															
Assessment	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
Physical examination ^a	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Weight										Х						
Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	X
Vital Signs	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	X
Blood chemistry, haematology, coagulation screen, and $\mathrm{CRP}^{\mathrm{b}}$				X				Х				Х				X
Urine Tests ^b				Х				Х				Х				Х
Liver Tests (local) ^b	Х	Х	X	Х	Х	Х	Х	Х	Х	X	Х	Х	X	Х	Х	Х
FVIII assays (local) ^c	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	X
Liver Tests (central) ^b	Х	X	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	X	Х	Х	X
FVIII assays (central) ^d	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
FVIII antibody titer				Х								Х				
PCR of vector DNA in blood, saliva, urine, semen, and stools ^e				X				Х				Х				X
Exploratory biomarker assessments ^f				Х				Х				Х				X
Haemo-QoL-A QoL assessment												Х				
AAV5 antibody titer				Х				Х				Х				X
PBMC collection	Х	Х	Х	Х		Х		Х		Х		Х		Х		Х
Von Willebrand Factor Antigen (VWF:Ag)				Х				Х				Х				Х
Direct Thrombin test										X						

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

* Visit windows are \pm 48 hours

^a Brief physical examination should be done at all weekly visits. Refer to Section 9.7.8.5.

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^b Refer to Table 9.7.8.2.1 for laboratory assessments to be included, and to Table 9.7.8.3.1 for liver tests. LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) 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 \geq 3x ULN. Patients with ALT > 1.5 ULN during the study may undergo additional evaluations (eg, imaging studies including MRI or ultrasound, additional blood tests, and/or liver biopsy) at the discretion of the investigator. Additional testing of FVIII and LTs during any study week may be performed if: (1) the ALT has increased to above ULN; (2) Increases in ALT values from prior assessment are accompanied by declines in FVIII activity level; or after a discussion between the Medical Monitor and the Investigator based on a review of subject data. If FVIII levels and/or ALT values are stable over the course of several weeks, assessment of FVIII activity and ALT levels may be adjusted based on discussion between the Medical Monitor and the Investigator.

- ^c Includes hFVIII activity level (one-stage clotting and chromogenic substrate 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 \geq 5 IU/dL at 16 weeks after BMN 270 infusion and who have not resumed standard of care 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 Includes hFVIII activity level (one-stage clotting and chromogenic substrate assay), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, hFVIII coagulation activity exploratory assay, and hFVIII antigen (ELISA). If a subject has used FVIII within 72 hours of a measurement day, all efforts should be made to obtain FVIII activity measurements when a 72-hour interval without FVIII use is achieved; the 72-hour wash-out period is only intended for subjects who have achieved FVIII \geq 5 IU/dL at 16 weeks after BMN 270 infusion and who have not resumed standard of care 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 Collection for each matrix to occur until at least 3 consecutive negative results are obtained.

^f 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 Direct Thrombin Activity test and any other exploratory assessments) will be performed only as deemed necessary by the Sponsor.

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					1	Year 1 –	Weeks	*				
Assessment	33	34	35	36	38	40	42	44	46	48	50	52
Physical examination ^a	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	X
Weight ^a												X
Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)	Х	X	Х	Х	Х	Х	Х	Х	Х	X	X	X
Vital Signs	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	X
Blood chemistry, haematology, coagulation screen, and CRP ^b				Х		Х		Х		Х		Х
Urine Tests ^b				Х		Х		Х		Х		Х
Liver Tests (local) ^b	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	X	Х
FVIII assays (local) ^c	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Liver Tests (central) ^b	Х	Х	Х	Х	Х	Х	Х	Х	Х	X	X	X
FVIII assays (central) ^d	Х	Х	Х	Х	Х	Х	Х	Х	Х	X	X	X
AAV5 antibody titer				Х		Х		Х		X		X
FVIII antibody titer				Х				Х				Х
PBMC Collection (for determination of FVIII and Capsid specific CTL activity)		X		Х				Х				X
Von Willebrand Factor Antigen (VWF:Ag)				Х		Х		Х		X		X
Direct Thrombin Test					Х							Х
PCR of vector DNA in blood, saliva, urine, semen, and stools ^e				Х		Х		Х		Х		Х
Exploratory biomarker assessments ^f				Х		Х		Х		Х		Х
Haemo-QoL-A QoL assessment												X

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

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

^a Complete physical examination should be performed at Week 52; brief physical examination may be performed at other study visits. Refer to Section 9.7.8.5.

^b Refer to Table 9.7.8.2.1 for laboratory assessments to be included, and to Table 9.7.8.3.1 for liver tests. LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) 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

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subject's ALT is \geq 3x ULN. Patients with ALT > 1.5 ULN during the study may undergo additional evaluations (eg, imaging studies including MRI or ultrasound, additional blood tests, and/or liver biopsy) at the discretion of the investigator. Additional testing of FVIII and LTs during any study week may be performed if: (1) the ALT has increased to above ULN or increased by > 10 U/L from prior assessment; (2) Increases in ALT values from prior assessment are accompanied by declines in FVIII activity level; or after a discussion between the Medical Monitor and the Investigator based on a review of subject data. If FVIII levels and/or ALT values are stable over the course of several weeks, assessment of FVIII activity and ALT levels may be adjusted based on discussion between the Medical Monitor and the Investigator.

- ^c Includes hFVIII activity level (one-stage clotting and chromogenic substrate 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 \geq 5 IU/dL at 16 weeks after BMN 270 infusion and who have not resumed standard of care 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 Includes hFVIII activity level (one-stage clotting and chromogenic substrate assay), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, hFVIII coagulation activity exploratory assay, and hFVIII antigen (ELISA). If a subject has used FVIII within 72 hours of a measurement day, all efforts should be made to obtain FVIII activity measurements when a 72 hour interval without FVIII use is achieved; the 72-hour wash-out period is only intended for subjects who have achieved FVIII \geq 5 IU/dL at 16 weeks after BMN 270 infusion and who have not resumed standard of care 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 Sample testing during Safety Follow-Up is not required if at least 3 consecutive samples are cleared during the Post-Infusion Follow-Up period.

^f 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 Direct Thrombin Activity test and any other exploratory assessments) will be performed only as deemed necessary by the Sponsor.

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	Years 2-5*	Year 2*	Years 3-5*						
	01000	O ATT	O(Wh	Year 2	Year 3	Year 4	Year 5	ETV	
Assessment	Q12W	Q4W ^h	Q6W ^h	W104	W156	W208	W260		
Physical examination ^a	Xa				Xa				
Weight ^a	Xa				У	K ^a		Х	
Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)	X	Х	X		Х				
Vital Signs	Х			Х				Х	
Blood chemistry, haematology, coagulation screen, and CRP ^b	Х			Х				Х	
Urine Tests ^b	Х			Х				Х	
Liver Tests (local) ^b	Х	Х	Х	Х				Х	
FVIII assays (local) ^c	Х	Х	Х	Х				Х	
Liver Tests (central) ^b	Х	Х	X	Х				Х	
FVIII assays (central) ^d	Х	Х	Х		2	X		Х	
AAV5 antibody titer	Х				2	X		Х	
FVIII antibody titer	Х				Х			Х	
PBMC Collection (for determination of FVIII and Capsid specific CTL activity)	X				Х			Х	
Von Willebrand Factor Antigen (VWF:Ag)	Х				2	X		Х	
PCR of vector DNA in blood, saliva, urine, semen, and stools ^e	Xe	Xe	Xe		Σ	Ke		Х	
Exploratory biomarker assessments ^g	Х				2	X		Х	
Haemo-QoL-A QoL assessment	Xf				Σ	ζf		Х	

Table 9.1.5: Schedule of Events – Safety Follow-Up (Years 2-5)

* Visit windows are ± 2 weeks for visits in Years 2-5. The Q6W visits during Years 3-5 should restart after each End of Year visit (eg, the first Q6W visit during Year 3 should be ~6 weeks after the End of Year 2 visit).

^a Complete physical examination should be performed at the End of Year visits; brief physical examination 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.

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

- ^c Includes hFVIII activity level (one-stage clotting and chromogenic substrate 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 \geq 5 IU/dL at 16 weeks after BMN 270 infusion and who have not resumed standard of care FVIII replacement therapy. If FVIII levels are elevated or stable over the course of several weeks, assessment of FVIII activity may be adjusted based on discussion between the Medical Monitor and the Investigator. A d-dimer may be considered under circumstances in which FVIII activity levels are above the normal physiological range and/or if there is a concern for a venous thromboembolism. If a subject tests positive in the Bethesda assay (with Nijmegen modification) during Years 3-5, a fresh sample should be collected within 4 weeks of the initial visit that had a positive result.
- ^d Includes hFVIII activity level (one-stage clotting and chromogenic substrate assay), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, hFVIII coagulation activity exploratory assay, and hFVIII antigen (ELISA). If a subject has used FVIII within 72 hours of a measurement day, all efforts should be made to obtain FVIII activity measurements when a 72 hour interval without FVIII use is achieved; the 72-hour wash-out period is only intended for subjects who have achieved FVIII \geq 5 IU/dL at 16 weeks after BMN 270 infusion and who have not resumed standard of care 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) in 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 Safety Follow-Up is not required if at least 3 consecutive samples are cleared during the Post-Infusion Follow-Up period. Subjects who have not had 3 consecutive negative samples by Week 52 should continue to have PCR testing every 4 weeks (during Year 2) or every 6 weeks (during Years 3-5) until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor).
- ^fHaemo-QoL-A QoL assessment during Years 2-5 of Safety Follow-up should be performed at the second Q12W visit each year and at every End of Year visit.
- ^g 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 any other exploratory assessments) will be performed only as deemed necessary by the Sponsor.
- ^h Subjects who meet the definition of treatment failure to BMN 270 therapy after Week 52 may omit the Q4W and Q6W visits during Years 2-5, and must attend only the Q12W and End of Year visits. Such subjects following the abbreviated schedule who have not yet cleared vector shedding in all fluids must still provide samples Q4W (during Year 2) or Q6W (during Years 3-5) until vector shedding has been cleared (but do not need to do other scheduled assessments at those visit dates).

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					Steroid T	reatment	Period ^d					Post-Steroid Period ^c					
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11 ^b	Week 1	Week 2	Week 3	Week 4	Week 13	
Therapeutic corticosteroids (dose in mg/day) ^a	60 mg	60 mg	40 mg	40 mg	30 mg	30 mg	20 mg	20 mg	15 mg	10 mg	5 mg						
FVIII activity testing												Х	Х	Х	Х		
Liver testing												Х	Х	Х	Х		
Hepatitis B testing ^e						Х						Х				Х	
HCV Viral Load ^e						Х						Х				Х	

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

^a Therapeutic corticosteroids may be initiated when a subject's ALT value is ≥ 1.5x ULN or based on review of FVIII and liver enzyme data after consultation between the Investigator and the Medical Monitor.

^b Following initiation or completion of steroid regimen, if ALT elevation ≥ 1.5x ULN is reported, steroid management decisions will based on discussions between the Investigator and Medical Monitor. Modification of the steroid regimen may take into consideration possible confounders for the ALT elevation and impact on FVIII expression.

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

^d Regardless of the assessments listed in the Schedule of Assessments (Table 9.1.2, Table 9.1.3, or Table 9.1.4), subjects initiated on corticosteroids will only be required to have laboratory evaluations on a weekly basis.

^e Should only be performed in subjects with a history of hepatitis B or hepatitis C prior to study entry.

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	Within 28 Days Before Biopsy Day	Within 7 Days Before Biopsy Day	1 Day Before Biopsy Day ^d	Biopsy Day (BD)
Informed Consent	Х			
Liver Ultrasound ^a	X			
Brief Physical Examination	X		X	Х
Hematology, Coagulation, Chemistry Assessments ^b	X		X	
Liver Tests ^b	X		X	Х
FibroScan		Х		
Local FVIII Activity Level Assessment		Х	X	Х
Pre-Biopsy Consultation ^c		Х		
Liver Biopsy ^e				Х

Table 9.1.7: Schedule of Events – Liver Biopsy Substudy

^a Liver ultrasound must be performed within 28 days prior to the scheduled biopsy, unless an ultrasound result from the prior 3 months is already available.

^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).

^d Subjects may need to repeat/extend this visit if their FVIII activity levels need adjustment before the biopsy, at the discretion of the investigator (treating hematologist).

^e 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.

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9.2 Discussion of Study Design, Including Choice of Control Group

Study 270-201 is designed to be a first-in-man, phase 1/2 open-label, dose escalation study in patients with severe haemophilia A. Four doses of BMN 270 will be evaluated and the dose escalation decision tree for Cohorts 1-3 is summarized in Figure 9.1.1.

The decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and the DRB.

There will be no control group. Parameters for each subject will be compared to a pre-treatment assessment of safety (liver function) and efficacy (number of bleeds, use of replacement therapy).

As AAV based treatment always leads to anti-capsid immune response, no true control group (for example with an empty AAV) is possible.

9.3 Selection of Study Population

Up to 15 severe haemophilia A patients may enroll into the study; the actual number of patients will depend on the criteria for dose escalation.

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 criteria:

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

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 immunity to the AAV5 capsid as measured by AAV5 transduction inhibition or AAV5 total antibodies
- 2. Any evidence of active infection or any immunosuppressive disorder.
- 3. HIV positive
- 4. Significant liver dysfunction as defined by abnormal elevation of:
 - ALT (alanine transaminase) to 3 times the upper limit of normal;
 - Bilirubin above 3 times the upper limit of normal;
 - Alkaline phosphatase above 3 times the upper limit of normal; or
 - INR (international normalized ratio) \geq 1.4.
- 5. Potential participants who have had a liver biopsy in the past 3 years are excluded if they had significant fibrosis of 3 or 4 as rated on a scale of 0-4
- 6. Evidence of any bleeding disorder not related to Haemophilia A
- 7. Platelet count of $< 100 \text{ x } 10^9/\text{L}$
- 8. Creatinine $\geq 1.5 \text{ mg/dL}$
- 9. Liver cirrhosis of any etiology as assessed by liver ultrasound
- 10. Hepatitis B if surface antigen is positive
- 11. Hepatitis C if RNA is positive
- 12. Treatment with any IP within 30 days prior to the end of the screening period
- 13. Any disease or condition at the physician's discretion that would prevent the patient from fully complying with the requirements of the study including possible corticosteroid treatment outlined in the protocol. The physician may exclude patients unwilling or unable to agree on not using alcohol for the 16-week period following the viral infusion.
- 14. Prior treatment with any gene transfer agent
- 15. Major surgery planned in the 16-week period following the viral infusion
- 16. Use of immunosuppressive agents or live vaccines within 30 days before the viral infusion

9.3.3 Liver Biopsy Substudy Inclusion and Exclusion Criteria

Individuals eligible to participate in the liver biopsy substudy must meet all of the following criteria:

- 1. Currently enrolled in 270-201
 - 2. Received BMN 270 infusion at least 1 year prior to enrollment in the substudy
 - 3. Able to sign informed consent and comply with requirements of the substudy
 - 4. FVIII activity at least >50 IU/dL (or higher, depending on local guidelines and/or Investigator discretion) within 24 hours prior to the liver biopsy being performed. (FVIII 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 to an appropriate level, under the supervision/instruction of the Investigator.

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

- 1. Assessed by the investigator or a hepatologist as having a medical condition such that undergoing a liver biopsy would be contraindicated. These conditions could include (but are not limited to):
 - Significant thrombocytopenia (platelet count $< 100 \text{ x } 10^{9}/\text{L}$)
 - Evidence of significant ascites
 - Abnormalities detected on liver ultrasound (performed within 90 days of procedure) that would preclude safe performance of the biopsy.

9.3.4 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. A subject's participation in the study may be discontinued at any time at the discretion 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.

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 admitted into the study or does not meet entry criteria
- Subject is lost to follow-up

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

The Investigator or designee must explain to each subject, before enrollment into the study, that for evaluation of study results, the subject's protected health information obtained during the study may be shared with the study Sponsor, regulatory agencies, and IRB/IEC/REB. It is the Investigator's (or designee's) responsibility to obtain written permission to use protected health information per country-specific regulations, such as the Health Insurance Portability and Accountability Act (HIPAA) in the US, from each subject. If permission to use protected health information is withdrawn, it is the Investigator's responsibility to obtain a written request, to ensure that no further data will be collected from the subject and the subject will be removed from the study.

9.3.4.1 Study Safety Evaluation Criteria

If any of the following events occur in a subject in the study who has received BMN 270 infusion, enrollment into the trial will be put on halt to complete an extensive safety analysis per Section 9.1.

- Any ALT elevation > 5x ULN for at least 2 consecutive weeks after administration of BMN 270, in the absence of a definitive alternate etiology for the increase
- The occurrence of Grade 3 or higher adverse events (excluding ALT elevation) assessed as related to study drug, including liver failure and clinical hepatitis
- The detection of neutralizing antibodies to hFVIII following BMN 270 infusion
- The detection of AAV vector DNA in the semen of a participant in 3 consecutive samples (which are at least 2 weeks apart) more than 52 weeks after BMN 270 infusion, as discussed in Section 9.7.8.6
- The occurrence of a malignancy excluding skin cancers at any point after BMN 270 infusion

If the following event occurs in a subject in the study who has received BMN 270 infusion, a DRB review and analysis of safety data will be undertaken to determine whether the enrollment into the trial will be put on halt:

• Grade 2 adverse event assessed as related to study drug that persists for at least 7 days

9.3.5 Subject Identification and Replacement of Subjects

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

Subjects who withdraw from the study will not be replaced.

9.3.6 Duration of Subject Participation

The duration of this study will be approximately 264 weeks. This includes 4 weeks of screening, 1 day of BMN 270 infusion, 16 weeks of Post-Infusion Follow-Up, and 244 weeks of Safety Follow-Up. A primary endpoint analysis on safety and efficacy will be performed at 16 weeks.

9.4 Treatments

BioMarin or its designee will provide the study site with study drug sufficient for study completion. BioMarin is responsible for shipping study drug to clinical sites.

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.

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 2 mL polypropylene cryovial. Each vial contains 1.1 mL of AAV5-hFVIII-SQ at a concentration of 2E13 vector genomes per mL in a pH 7.4 phosphate buffer.

The study drug label includes the following information: lot number, required storage conditions, a precautionary statement, expiry date, study number, and BioMarin name and address. Labelling will be done according to country specific requirements.

9.4.3 Storage

At the study site, all IP must be stored under the conditions specified in the IB 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

After a physical examination performed by the PI or designee, participants will be admitted on the day of BMN 270 infusion. 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. An electric syringe pump will be used to infuse through an in-line, low protein binding 0.22 micron filter. BMN 270 will be infused through the catheter using an appropriate infusion pump at a constant rate of 4 ml/min while monitoring the vital signs (pulse, blood pressure, respiration rate and temperature) at 15 minute (\pm 5 minutes) intervals. The anticipated maximum interval from initiation of thawing of BMN 270 to completion of the infusion is 4 hours, although the IP has been shown to be stable at room temperature for 6 hours.

Following completion of the infusion, vital signs will be monitored hourly (\pm 5 minutes) for 6 hours and then every 2 hours (\pm 15 minutes) for 6 hours and then at 4 hour intervals. If the vital signs are stable the catheter will be removed 20-24 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 24 hours to observe for any immediate toxicity of the procedure. After 24 hours, participants 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.

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 Sponsor will be required prior to enrollment of each study subject. Upon their enrollment into the study, subjects will be assigned a unique subject number and dose level by the Sponsor.

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Cohorts 1 to 3 are enrolled serially and their dose is defined in Section 9.4.6.2 below. Escalation is based on FVIII activity 3 weeks after injection. Cohorts may receive the next higher dose if subjects in the previous cohort does not meet the activity criteria, or the same dose if subjects in the previous cohort meets the activity criteria. Subjects in Cohort 4 will all be enrolled at a single dose.

9.4.6 Selection of Doses Used in the Study

The starting dose was based on the expression of hFVIII observed in nonclinical studies of mice and monkeys. The starting dose has a significant safety margin (10-fold) from NOAEL in mice. The dose escalation is half-logs based.

9.4.6.1 Selection of Timing of Dose for Each Subject

A minimum of three weeks are required between subjects, to allow for evaluation of safety and expression of hFVIII. After three weeks, depending on the activity level, the choice of the dose for the next subject will be made as described below.

9.4.6.2 Selection of Dose for Each Subject

The starting dose was determined by expression of hFVIII observed in mice and monkeys and a scale up factor based on previous experience, an improved purification process over previous trials (thus potentially decreasing the risk of immune response), and a new evaluation of the titer (PCR performed after hairpin removal).

For Cohorts 1 to 3, approximately three weeks after an injection, the decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and the DRB.

Subject 1 (Cohort 1) will be dosed by intravenous infusion with 6E12 vg/kg of body weight. If the FVIII activity level does not reach 5 IU/dL or greater (expressed as % in Figure 9.1.1) at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 1 and enrollment into Cohort 2 will initiate with Subject 2 at the next dose (2E13 vg/kg).

If the FVIII activity level in the first subject treated in Cohort 2 does not reach \geq 5 IU/dL at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 2 and enrollment into Cohort 3 (6E13) will initiate with the next subject.

If the FVIII activity level in the first subject treated in Cohort 3 does not reach \geq 5 IU/dL at the Week 3 visit in both assays, then the DRB will recommend whether to continue to add subjects to the cohort and/or whether to continue the study.

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For the first subject treated in each of the first 3 cohorts, if the activity level reaches \geq 5 IU/dL and no safety issue is found, then up to four subjects will be enrolled in that cohort, though the adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

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

There will be an ongoing review of individual patient safety and efficacy data by the medical monitor and the DRB. The adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

Refer to Figure 9.1.1 for a visual representation of the study design for Cohorts 1-3

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 CRF. The Investigator may prescribe additional medications 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 CRF.

The following medications are prohibited starting 30 days before Screening:

- Live vaccines
- Systemic immunosuppressive agents
- Emicizumab
- Fitusiran
- Concizumab
- Efavirenz
- Lamivudine

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Subjects who begin antiretroviral therapy following BMN 270 infusion and during their participation in 270-201 must have their antiretroviral medication regimen approved by the Investigator and Medical Monitor prior to starting antiretroviral treatment.

Medications which are predominately metabolized by the liver (eg, acetaminophen) and alcohol should, whenever possible, be avoided for the first 52 weeks of the study, and particularly within 48 hours prior to lab work.

9.4.8.1 Concomitant Haemophilia Treatments

Subjects on "on demand" therapy for FVIII will continue their treatment at will. Subjects on prophylactic FVIII therapy will discontinue their treatment starting the day of infusion and switch to an "on demand" schedule. FVIII can always be taken as needed by the subject, who will carefully record his treatment and bleeding episodes in his diary. In addition, information on FVIII usage by medical history will be collected (if available) from subjects for the 6 month period immediately preceding study enrollment.

9.4.8.2 Glucocorticoid Treatment of Elevated Hepatic Transaminases

During the Post-Infusion Follow-up Period and the Safety Follow-Up Period, each subject will have comprehensive surveillance plan monitoring of LTs (at local labs, once per week for Weeks 1-36, then once every 2 weeks from Week 37-52). LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.

9.4.8.2.1 Therapeutic Corticosteroids

In general, therapeutic corticosteroids may be initiated when a subject's ALT value is $\geq 1.5x$ ULN, or based on review of FVIII and liver enzyme data after consultation between the Medical Monitor and the Investigator.

Reports of raised LTs (defined as $ALT \ge 1.5x$ ULN) should be made to the BioMarin medical monitor within 30 minutes of the lab value being available. Local laboratory results of LTs will be used to trigger corticosteroid treatment as needed. In case of discrepant results between local and central laboratories, the Investigator and Medical Monitor will decide further action.

Following initiation or completion of therapeutic corticosteroids, if ALT elevation $\geq 1.5x$ ULN is reported, steroid management decisions will based on discussions between the Investigator and Medical Monitor. Modification of the steroid regimen may take into consideration possible confounders for the ALT elevation and impact on FVIII expression.

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Treatment with prednisolone will be initiated at a dose of 60 mg per day and then gradually tapered (60 mg daily for the first 2 weeks, then 40 mg the next 2 weeks, then 30 mg the next two weeks, then 20 mg the next two weeks, then 15 mg for the next week, then 10 mg for the next week, then 5 mg for the next week, then stop, for a total treatment of 11 weeks) (refer to Table 9.1.6).

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

Management and monitoring of reactions to corticosteroids should be determined by the Investigator's clinical judgment in consultation with the Sponsor's Medical Monitor. This includes the contraindicated use of NSAIDs during corticosteroid treatment, and specific monitoring not already covered by the schedule of events. For the subjects with a past medical history of hepatitis B or hepatitis C prior to study entry, Hepatitis B status and HCV viral load will be rechecked 6 weeks after the start of corticosteroid treatment, and then 1 week and 13 weeks after the completion of corticosteroid treatment. All adverse events should be reported as outlined in Section 10 of the protocol.

9.4.9 Treatment Compliance

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

9.5 Investigational Product Accountability

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

9.5.1 Return and Disposition of Clinical Supplies

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

Unused study drug may be destroyed on site, per the site's standard operating procedures, but only after BioMarin has granted approval for drug destruction. The monitor must account for all study drug in a formal reconciliation process prior to study drug destruction. All study drug destroyed on site must be documented. Documentation must be provided to BioMarin

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and retained in the Investigator study files. If a site is unable to destroy study drug appropriately, the site can return unused study drug to BioMarin upon request. The return of study drug or study drug materials must be accounted for on a study drug return form provided by BioMarin.

All study drug and related materials should be stored, inventoried, reconciled, and destroyed or returned according to applicable state and federal regulations and study procedures.

9.6 Dietary or Other Protocol Restrictions

There are no dietary or other protocol restrictions for this 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 samples.

9.7 Safety and Efficacy Variables

As this is a first-in-man study, the primary endpoint of safety will be assessed as explained in Section 9.7.7.1.

The primary efficacy measure will be to assess plasma FVIII activity. The efficacy goal of the study is to establish the dose relationship to FVIII activity \geq 5 IU/dL at 16 weeks post BMN 270 administration.

9.7.1 Safety and Efficacy Measurements Assessed

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

9.7.2 Primary Efficacy Variables

The primary efficacy measure will be the plasma FVIII activity monitored on a regular basis after BMN 270 dose. The efficacy goal of the protocol is to ascertain the dose range of BMN 270 required to convert severe HA patients to expression of FVIII at 5 IU/dL or above, (ie, a mild severity). This is associated in natural history studies with clinically superior long term outcomes (Den Ujil, 2011, Haemophilia).

The following assays (assessed by the central laboratory) will be used to measure the primary efficacy variable:

- FVIII activity (chromogenic substrate assay)
- FVIII activity by one-stage clotting 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.

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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 standard of care FVIII replacement therapy.

The FVIII activity level in both assays and the number of subjects with FVIII activity ≥ 5 IU/dL in at least one of the two assays will be summarized.

FVIII activity assays will also be performed at the local laboratory at the time points indicated in Table 9.1.2, Table 9.1.3, Table 9.1.4, and Table 9.1.5 but will be used in conjunction with local lab LT assessments to monitor subject safety and need for initiation of therapeutic corticosteroid dosing; local laboratory FVIII activity assessments will not be used to assess efficacy or to measure the primary efficacy outcome of the study.

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, follow an abbreviated visit schedule after Week 52, as applicable and at the discretion of the Investigator.

Timing of assessment by these assays is provided in Table 9.1.2, Table 9.1.3, Table 9.1.4, and Table 9.1.5. Details on performing the assays are included in the Laboratory Manual.

9.7.3 Secondary Efficacy Variables

Secondary efficacy measures will be the reduction in the frequency of factor replacement therapy, and reduction in the number of bleeding episodes. 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.

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

9.7.4 Immunogenicity

Immunogenicity assays will be performed on plasma. The assays will include detection of anti-capsid, and anti-FVIII total antibody, and determination of neutralizing antibodies against FVIII. Any increase in total antibody level, especially during the time period of 5-12 weeks, will be compared with FVIII activity measurements. Any abnormality of the liver parameters will lead to a retrospective immunogenicity assessment to determine

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anti-FVIII and capsid specific CTL. Anti-FVIII and capsid specific CTL assays will be performed on collected PBMCs.

Timing of assessment by these assays is provided in Table 9.1.2, Table 9.1.3, and Table 9.1.4.

9.7.5 Pharmacodynamics

The hFVIII antigen and activity level will be measured by an ELISA (antigen) and by one-stage clotting and/or chromogenic substrate assay (activity). Individual antigen and activity plasma plots will be prepared to assess changes over 16 weeks. FVIII activity measurements will be used to determine PD parameters.

If supported by FVIII activity data, non-compartmental analysis and observation will be used to estimate individual values of C_b (baseline concentration), C_{ss} (steady state concentration), T_{ss} (time to steady state), C(t) and AUC(0-t) where t is 16 weeks. Other parameters that may be used to describe individual FVIII protein and activity plasma profiles are C_{max} (maximum concentration) and C_{avg} (average concentration, AUC(0-t)/t). The PD parameters and dose will be used to assess clinical pharmacology.

Sample collection times are indicated in Table 9.1.2, Table 9.1.3, Table 9.1.4, and Table 9.1.5.

9.7.6 Exploratory Assessments

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

Liver biopsy samples collected as part of the exploratory substudy may also be tested to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to hemophilia A, coagulation, and/or AAV gene transfer. Subjects participating in the substudy 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 may be used for exploratory use once the primary use has been completed.

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On an exploratory basis, samples may be fractionated prior to shedding analysis in order to better characterize the presence and location of vector DNA and/or vector capsid within each matrix. The fractionation may be performed with samples collected specifically for shedding analysis (saliva, blood, semen, urine, faeces), or by using exploratory samples, such as plasma, PBMCs, and red blood cells, collected under the study protocol.

9.7.7 Haemo-QoL-A Quality of Life Assessment

The Haemo-QoL-A is a patient-reported outcome (PRO) questionnaire which will be used to assess subject quality of life (QoL) during the study. Assessments will occur at the time points listed in the Schedules of Assessments.

Details regarding the QoL assessment will be included in the Study Reference Manual.

9.7.7.1 Liver Biopsy Substudy

The objectives of the liver biopsy substudy are considered exploratory.

Subjects who consent to the procedure will have a liver biopsy via either the transjugular or percutaneous (ultrasound-guided) route, according to the standard procedures of the institution. To enhance safety, all subjects will have an ultrasound exam of the liver within 28 days prior to the procedure (to ensure there is no obstruction to the liver that would interfere with the liver biopsy) and a FibroScan of the liver within one week before the liver biopsy (to correlate any histopathologic findings on the biopsy). Subjects will also undergo a pre-biopsy consultation with the investigator (treating hematologist).

Within 24 hours prior to the biopsy being performed, subjects must have a FVIII activity level of at least 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 the day before the biopsy. 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".

The liver biopsy should be performed in the morning, 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 Laboratory Manual.

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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 and/or according to local guidelines.

Safety findings arising from the histopathological analysis of the biopsy sample are subject to Adverse Event reporting (Section 10), and such findings should be further assessed and followed-up as clinically appropriate and in order to safeguard the subject's ongoing medical care (this should be done in consultation with a hepatologist and/or other specialist clinicians if required). In the event fibrotic changes being observed on the biopsy sample, additional follow-up Fibroscans may be considered (with the frequency of subsequent scans 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.

9.7.8.1 Adverse Events

The occurrence of AEs will be assessed continuously from the time the subject signs the ICF. The determination, evaluation and reporting of AEs will be performed as outlined in Section 10. Assessments of AEs will occur at the time points shown in Table 9.1.1, Table 9.1.2, Table 9.1.3, Table 9.1.4, and Table 9.1.5.

9.7.8.2 Clinical Laboratory Assessments

Specific visits for obtaining clinical laboratory assessment samples are provided in Table 9.1.1, Table 9.1.2, Table 9.1.3, Table 9.1.4, and Table 9.1.5. The scheduled clinical laboratory tests are listed in Table 9.7.8.2.1. Refer to the Study Reference Manual 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 the cause of the abnormality is determined, the value returns to baseline or to within normal limits, or 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 CRF.

Blood Chemistry	Haematology	Urine Tests	Other
Albumin	Haemoglobin	Appearance	CRP
BUN	Haematocrit	Color	
Calcium	WBC count	рН	Coagulation Screen including:
Chloride	RBC count	Specific gravity	APTT
Total cholesterol	Platelet count	Ketones	PT/INR
CO_2	Differential cell count	Protein	TT
СРК	ABO blood typing*	Glucose	
Creatinine		Bilirubin	
Glucose		Nitrite	
Phosphorus		Urobilinogen	
Potassium		Haemoglobin	
Total protein			
Sodium			
Uric Acid			

Table 9.7.8.2.1: Clinical Laboratory Tests

BUN, blood urea nitrogen; CO₂, carbon dioxide; 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. * ABO blood typing assessment should be completed at the next regularly scheduled study visit (or at least prior to the end of the subject's participation in the study).

9.7.8.3 Liver and Hepatitis Testing

Subjects will be screened for evidence of previous hepatitis B or hepatitis C infection at Screening. Subjects with documented results showing an absence of active hepatitis B or hepatitis C infection (as measured by positive surface antigen for hepatitis B or positive RNA testing for hepatitis C) 30 days prior to providing signed informed consent do not need to be screened again.

Evidence of ongoing hepatitis B or hepatitis C infection is exclusionary. Subjects with a history of hepatitis B or hepatitis C will be asked for information about the treatments received as part of their medical history assessment at Screening.

Subjects with a history of hepatitis B or hepatitis C infection prior to study entry will be tested for hepatitis B and hepatitis C reactivation at Week 16. Subjects who receive

therapeutic corticosteroids prior to Week 16 do not need to complete the Week 16 reactivation assessment; instead, they will be tested for hepatitis B and hepatitis C reactivation at the time points listed in Table 9.1.6.

A liver ultrasound and LTs at Screening will identify any significant hepatic dysfunction, which is defined as:

- More than 3x the normal ALT level
- More than 3x the normal bilirubin level
- More than 3x the normal Alkaline phosphatase level.
- INR ≥ 1.4 .
- Thrombocytopenia under 100 x 10⁹/L
- Liver ultrasound results indicative of a liver cirrhosis

Liver tests will be monitored on a regular basis, at the time points indicated in Table 9.1.1, Table 9.1.2, Table 9.1.3, Table 9.1.4, and Table 9.1.5. At each time point, the following LTs should be assessed:

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

Patients with ALT > 1.5 ULN during the study may undergo additional evaluations (eg, imaging studies including MRI or ultrasound, additional blood tests, and/or liver biopsy) at the discretion of the investigator.

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.

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Systolic blood pressure, diastolic blood pressure, heart rate, respiration rate, and temperature will be assessed at Screening, Baseline, and at the beginning of each visit during the Post-Infusion Follow-Up and Safety Follow-Up periods. On the day of the BMN 270 Infusion, vital signs will be monitored prior to infusion, during the infusion every 15 minutes (\pm 5 minutes), following the infusion hourly (\pm 5 minutes) for 6 hours and then every 2 hours (\pm 15 minutes) for 6 hours and then at 4 hour intervals (\pm 15 minutes).

A complete physical examination is necessary during Screening/Baseline, at Week 16 and 52 and at the End of Years visits thereafter. A complete physical examination will include general appearance (head, eyes, ears, nose, and throat), cardiovascular, dermatologic, lymphatic, respiratory, gastrointestinal, genitourinary, musculoskeletal, and neurologic systems.

At other visits, brief physical examinations may be performed at the discretion of the investigator based on the subject's clinical condition. A brief physical examination will include general appearance, cardiovascular, respiratory, neurologic, dermatologic, musculoskeletal, and gastrointestinal assessments. Particular attention should be given to signs of bleeding, as well as assessing possible hemarthroses.

Height will be recorded at Screening only. Weight will be recorded at Screening, at Weeks 26 and 52 during Year 1, and then at the second Q12W visit each year and at every End of Years visit during Years 2-5.

9.7.8.6 Vector Shedding

Vector shedding has been extensively studied in all similar clinical trials performed to date. (Nathwani, 2014, N.Engl.J.Med.); (Manno, 2006, Nat.Med.); (Schenk-Braat, 2007, J.Gene Med.); (Croteau, 2004, Ann.Occup.Hyg.). In the literature referenced above, including Haemophilia B clinical studies utilizing AAV2 and AAV8, vector was no longer detectable after 40 days in blood, saliva, urine or stool, but in one study was detected in the seminal fluid but not in motile sperm (Manno, 2006, Nat.Med.). In these studies, the amount of vector present in these bodily fluids involved an extremely small fraction of the infused dose. More recent data from an ongoing AAV-FIX study demonstrates persistence of the vector in both the blood and the semen for at least 39 weeks (Miesbach, 2016, Haemophilia).

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 PCR at the time points indicated in Table 9.1.2, Table 9.1.3, Table 9.1.4, and Table 9.1.5. Fluids tested will include:

- Blood
- Saliva
- Semen
- Urine
- Stool

Vector shedding will also be extensively studied in the present clinical trial, every other week between Weeks 4-16, then every 4 weeks to Week 52 until at least 3 consecutive negative results are obtained. Testing of semen will continue through Week 12, even if 3 consecutive negative results have been recorded in that compartment prior to that timepoint. Subjects who have not had 3 consecutive negative samples by Week 52 should continue to have PCR testing every 4 weeks until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor). Subjects who meet the definition of treatment failure and wish to follow an abbreviated schedule (refer to Section 12.5.3 but who have not cleared vector shedding from all fluids must still provide samples for assessment until vector shedding has cleared: every 4 weeks (during Year 2), or every 6 weeks (during Years 3-5).

Contraception use may need to be extended beyond 26 weeks in individual subjects based on observed vector shedding in semen. After 6 months, subjects may stop contraception use only if they have had 3 consecutive negative semen samples (upon consultation between the Investigator and Medical Monitor).

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

10 REPORTING ADVERSE EVENTS

10.1 Safety Parameters and Definitions

Safety assessments will consist of monitoring and recording protocol-defined AEs and SAEs; measurement of protocol-specified haematology, 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, a reportable adverse event (AE) is any untoward medical occurrence (eg, sign, symptom, illness, disease or injury) in a subject administered the study-drug or other protocol-imposed intervention, regardless of attribution. This includes the following:

- AEs not previously observed in the subject that emerge during the course of the study.
- Pre-existing medical conditions judged by the Investigator to have worsened in severity or frequency or changed in character during the study.
- Complications that occur as a result of non-drug protocol-imposed interventions (eg, AEs related to screening procedures).

An adverse drug reaction is any AE for which there is a reasonable possibility that the study-drug caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the study-drug and the AE.

Whenever possible, it is preferable to record a diagnosis as the AE term rather than a series of terms relating to a diagnosis.

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 meets 1 or more of the following criteria:

- Is fatal
- Is life threatening
- Note: Life-threatening refers to an event that places the subject at immediate risk of death. This definition does not include a reaction that, had it occurred in a more severe form, might have caused death.
- Requires or prolongs inpatient hospitalization.
- 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 intervention to prevent one of the above consequences (eg, anaphylaxis)

All adverse events that do not meet any of the criteria for SAEs should be regarded as non-serious AEs.

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 $ALT \ge 1.5x$ ULN, regardless of whether that triggers an initiation or modification of corticosteroid treatment
- Thromboembolic event

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 treatment, only SAEs associated with any protocol-imposed interventions will be reported. After informed consent is obtained and the first administration of study drug, the reporting period for all non-serious AEs and SAEs begins and continues for approximately 5 years or until study discontinuation/termination, whichever is longer. The criteria for determining, and the reporting of SAEs is provided in Section 10.1.1.1.

10.3.2 Eliciting Adverse Events

Investigators will seek information on AEs, SAEs, and EOSI at each subject contact by specific questioning and, as appropriate, by examination. Information on all AEs and SAEs and EOSI, should be recorded in the subject's medical record and on the 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 10.1.1.1 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 10.1.1.1. 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 severity of each will be assessed using the defined categories in Table 10.3.3.2.1.

The Investigator will determine the severity of each AE and SAE and EOSI using the NCI CTCAE v4. 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 as stated below.

Table 10.3.3.2.1: Adverse Event Grading (Severity) Scale

Grade	Description	
1	Mild: asymptomatic or mild symptoms; clinical or diagnostic observat indicated	ions only; intervention not
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 or debilitating: consequences; urgent intervention indicated	Grade 4 and 5 AEs should always be
5	Death related to AE	reported as SAEs

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

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

10.3.3.3 Causality

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

Table 10.3.3.3.1: Causality Attribution Guidance

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

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

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

The investigator's assessment of causality for individual AE reports is part of the study documentation process. Regardless of the Investigator's assessment of causality for individual AE reports, the Sponsor will promptly evaluate all reported SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators and applicable regulatory authorities.

10.4 Procedures for Recording Adverse Events

10.4.1 Recording Adverse Events on a eCRF

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

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

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

10.4.1.1 Diagnosis versus Signs and Symptoms

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 haemorrhage 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.

10.4.1.4 Abnormal Laboratory Values

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

Any laboratory result abnormality fulfilling the criteria for a SAE or EOSI should be reported as such, and recorded in the AE eCRF. Any laboratory result abnormality of CTCAE Grade 4 or 5 should be recorded as an SAE in the AE eCRF.

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

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

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

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

For purposes of this study, laboratory tests showing a decreased level of hFVIII activity should not be reported as adverse events unless signs of worsening are observed.

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.

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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 document 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 10.1.1.1).

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 procedure or assessment
- Undergo a diagnostic or elective surgical procedure for a pre-existing medical condition that has not changed
- Insert an in-dwelling IV catheter (such as a Port-a-Cath or other brand) for administration of study drug or FVIII replacement therapy.
- Receive scheduled therapy (study drug or otherwise) for the study indication

10.4.1.8 Deaths

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

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

10.4.1.9 Pregnancy

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

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

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

10.5 Reporting Requirements

10.5.1 Expedited Reporting Requirements

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

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

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

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10.5.2 Ethics Committee Reporting Requirements

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

10.6 Follow-up of Subjects after Adverse Events

The Investigator should follow all unresolved AEs and SAEs until the events are resolved or have stabilized, the subject is lost to follow-up, or it has been determined that the study treatment or participation is not the cause of the AE/SAE. Resolution of AEs and SAEs (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, 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 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 treatment.

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 treatment. 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

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protect the patients against any immediate hazard. The Sponsor shall forthwith inform the competent authorities of those new events and the measures taken and shall ensure that the IRB/IEC/REB is notified at the same time."

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

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

- Immediate need to revise the IP administration (eg, modified dose amount or frequency not defined in protocol)
- 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 ,	MA MB BChir MSc	
Address:	Biomarin (UK) Ltd.		
	10 Bloomsbury Way		
	London WC1A 2SL		
Phone	PI	(office)	
	PI	(mobile)	
E-mail:	PI		

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

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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 will be performed within 28 days (+ 14 days) of BMN 270 infusion while baseline assessments will take place within 7 days of BMN 270 infusion (Day 1). Should the screening visit occur within 7 days of the drug infusion, physical examination, vital signs, blood chemistry, LTs, haematology, urine tests, coagulation screen, and CRP do not need to be repeated at Baseline.

The following procedures will be performed during the Screening Period:

- Full medical history, including haemophilia A history, hepatitis B, hepatitis C, and HIV.
 - Subjects with a history of hepatitis B or hepatitis C will be asked for information about the treatments received. Any prior pharmacokinetics information obtained while the subject was receiving prophylactic or on-demand FVIII therapy prior to the study should also be collected. For subjects who have already enrolled in 270-201, this information should be collected at the next regularly scheduled study visit (or at least prior to the subject's completion of study participation).
- 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)
- Electrocardiogram
- Chest X-ray
- Liver Ultrasound
- Samples for hFVIII Assays
 - Baseline hFVIII activity chromogenic substrate (plasma)

- o Baseline hFVIII activity level one-stage clotting assay
- hFVIII coagulation activity exploratory assay
- hFVIII inhibitor level (Bethesda assay with Nijmegen modification)
- o hFVIII total antibody assay
- hFVIII antigen (ELISA)
- Blood sample for AAV5 Assays
 - o AAV5 antibody titer
 - o AAV5 transduction inhibition assay
- Screen for hepatitis B, hepatitis C, and HIV if required (subjects with documented negative results 30 days prior to informed consent being obtained do not need to be retested)
- Blood chemistry, haematology, coagulation screen, and CRP (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)
- Von Willebrand Factor Antigen (VWF:Ag)
- Blood samples for Biomarker testing (including HLA genotyping, FVIII genotyping status, TNFα and IL10a single nucleotide polymorphisms)

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 sample for AAV5 Assays
 - o AAV5 antibody titer
 - o AAV5 transduction inhibition assay
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- Urine Tests (refer to Table 9.7.8.2.1)
- Liver Tests (refer to Table 9.7.8.3.1)

12.3 Baseline Visit

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

- Physical examination
- Assessment of Adverse Events and Concomitant Medications
- Documentation of bleeding episodes and FVIII usage (by either subject or clinical information)
- Distribution of subject diaries and training in diary completion
- Blood chemistry, haematology, coagulation screen, and CRP (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)
- PBMC collection for CTL baseline
- Direct Thrombin test
- PCR of vector DNA in blood, saliva, urine, semen, and stools
- Exploratory biomarker assessments
- Haemo-QoL-A QoL assessment

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 24 hours for the BMN 270 Infusion Visit. The following procedures will be performed during the BMN 270 Infusion Visit:

- Physical examination
- Assessment of Adverse Events and Concomitant Medications
- Blood sample for AAV5 Assays (must be performed before the BMN 270 infusion)

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- o AAV5 antibody titer
- AAV5 transduction inhibition assay
- BMN 270 Infusion
- Vital Signs
 - Vital signs will be recorded prior to BMN 270 infusion and then every 15 minutes (± 5 minutes) during BMN 270 infusion. Following infusion, vital signs will be monitored every 1 hour (± 5 minutes) for the first 6 hours, every 2 hours (± 15 minutes) for the next 6 hours, and then at 4 hour (± 15 minutes) intervals for the remainder of the subject's stay in the clinic.

12.5 BMN 270 Infusion Follow-Up Visits

After BMN 270 has been infused, subjects will return to the study site every week $(\pm 48 \text{ hours})$ for 16 weeks, when the following procedures will be completed:

12.5.1 Once per week (Weeks 1 through 16)

The following procedures will be performed at one visit per week from Weeks 1 through 16:

- Physical examination
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Vital Signs
- Liver Tests (refer to Table 9.7.8.3.1) central laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- Samples for FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
 - FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level
 - FVIII antigen (ELISA)

Note: If a subject has used FVIII within 72 hours of a measurement day, all efforts should be made to obtain FVIII activity measurements when a 72-hour interval without FVIII use is achieved. The 72-hour wash-out period is only intended for

subjects who have achieved FVIII \geq 5 IU/dL at 16 weeks after BMN 270 infusion and who have not resumed standard of care FVIII replacement therapy.

- Central assessment of FVIII activity level should be performed 1x/week from Week 1 through Week 16
- Liver Tests (refer to Table 9.7.8.3.1) local laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
- PBMC collection

12.5.2 Week 1 – Day 2 and Day 4

On Day 2 and Day 4 of Week 1, the following procedures will be performed:

- PCR of vector DNA in blood, saliva, urine, semen, and stools (Day 2 and Day 4)
- Samples for FVIII Assays (Day 4 only) central laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
 - FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level
 - o FVIII antigen (ELISA)

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

- Liver Tests (refer to Table 9.7.8.3.1) (Day 4 only) central laboratory assessment
- Liver Tests (refer to Table 9.7.8.3.1) (Day 4 only) local laboratory assessment
- FVIII activity level (Day 4 only) local laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)

12.5.3 Week 1 – Day 8

On Day 8, the following procedures will be performed:

- PCR of vector DNA in blood, saliva, urine, semen, and stools
- Direct Thrombin test
- Haemo-QoL-A QoL assessment

12.5.4 Every 2 Weeks

Every 2 weeks (Weeks 2, 4, 6, 8, 10, 12, 14 and 16), the following procedures will be performed:

- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.8.2.1) (not assessed at Week 14)
- PCR of vector DNA in blood, saliva, urine, semen, and stools (not collected at Week 2)
 - Collection to occur until at least 3 consecutive negative results are obtained. Semen samples should continue to be collected and tested through Week 12, even if 3 consecutive negative results in that compartment have been recorded prior to that timepoint.

12.5.5 Weeks 4, 8, 12, and 16

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

- Urine Tests (refer to Table 9.7.8.2.1)
- VWF:Ag
- FVIII antibody titer
- Exploratory biomarker assessments

12.5.6 Week 16

At Week 16, the following procedures will be performed:

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

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

• AAV5 antibody titer

12.5.8 Weeks 2, 3, 4, and 16

At Weeks 2, 3, 4, and 16, the following procedure will be performed:

• Haemo-QoL-A QoL assessment

12.5.9 Week 13

At Week 13, the following procedure will be performed:

• Direct Thrombin test

12.6 Safety Follow-Up – Weeks 17-36

After the Post-Infusion Follow-Up visits are complete, subjects will return to the study site for Safety Follow-Up visits from Weeks 17 through Week 36 (\pm 48 hours), when the following procedures will be completed:

12.6.1 Once per week (Weeks 17 through 36)

Once per week from Week 17 through Week 36, the following procedures will be performed:

- Physical examination
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Vital Signs
- Liver Tests (refer to Table 9.7.8.3.1) central laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
 - FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - FVIII antigen (ELISA)

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

- Liver Tests (refer to Table 9.7.8.3.1) local laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)

12.6.2 Once per week (Weeks 17 through 20)

Once per week from Week 17 through Week 20, the following procedures will be performed:

• PBMC collection

12.6.3 Every 2 weeks (Weeks 21 through 36)

Every 2 weeks (Weeks 22, 24, 26, 28, 30, 32, 34, and 36), the following procedures will be performed:

• PBMC collection

12.6.4 Every 4 Weeks

Every 4 weeks (Weeks 20, 24, 28, 32, and 36), the following procedures will be performed:

- Exploratory biomarker assessments
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- Urine Tests (refer to Table 9.7.8.2.1)
- VWF:Ag
- AAV5 antibody titer
- PCR of vector DNA in blood, saliva, urine, semen, and stools
 - Sample testing during Safety Follow-Up is not required if at least
 3 consecutive samples are clear during the Post-Infusion Follow-Up period.

Every 8 weeks (Weeks 20, 28, and 36), the following procedure will be performed:

• FVIII antibody titer

12.6.6 Week 26

At Week 26, the following procedure will be performed:

- Direct Thrombin test
- Weight

12.6.7 Week 28

At Week 28, the following procedure will be performed:

• Haemo-QoL-A QoL assessment

12.7 Safety Follow-Up – Weeks 37-52

Subjects will return every 2 weeks (Week 38, 40, 42, 44, 46, 48, 50, and 52) from Week $37-52 (\pm 1 \text{ week})$, when the following procedures will be completed:

12.7.1 Once per visit

At Weeks 38, 40, 42, 44, 46, 48, 50, and 52, the following procedures will be performed:

- Physical examination
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Vital Signs
- Liver Tests (refer to Table 9.7.8.3.1) local laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
- Liver Tests (refer to Table 9.7.8.3.1) central laboratory assessment
 - LTs may be monitored more or less frequently based (and in particular when ALT values are >1.5x ULN) on discussion between the Medical Monitor and the Investigator and review of subject data.

- FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - o FVIII activity level (chromogenic substrate assay)
 - FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - FVIII antigen (ELISA)

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

12.7.2 Every 4 Weeks

Every 4 weeks (Weeks 40, 44, 48, and 52), the following procedures will be performed:

- Exploratory biomarker assessments
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- Urine Tests (refer to Table 9.7.8.2.1)
- AAV5 antibody titer
- VWF:Ag
- PCR of vector DNA in blood, saliva, urine, semen, and stools
 - Sample testing during Safety Follow-Up is not required if at least 3 consecutive samples are clear during the Post-Infusion Follow-Up period. Subjects who have not had 3 consecutive negative samples by Week 52 should continue to have PCR testing every 4 weeks until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor).

12.7.3 Every 8 Weeks

Every 8 weeks (Weeks 44 and 52), the following procedure will be performed:

- PBMC collection
- FVIII antibody titer

12.7.4 Week 38 and 52

At Week 38 and Week 52, the following procedure will be performed:

• Direct Thrombin test

12.7.5 Week 52

At Week 52, the following procedure will be performed:

- Haemo-QoL-A QoL assessment
- Weight

12.8 Safety Follow-Up – Years 2-5

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

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

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

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

During Year 2, every 4 weeks (\pm 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) local laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)

- Liver Tests (refer to Table 9.7.8.3.1) central laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
 - FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - FVIII antigen (ELISA)

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

- PCR of vector DNA in blood, saliva, urine, semen, and stools (if required)
 - Sample testing during Year 2 is not required if at least 3 consecutive samples are negative during the Post-Infusion Follow-Up period in Weeks 1-52.
 Subjects who have not had 3 consecutive negative semen samples by Week 52 should continue to have PCR testing of semen every 4 weeks during Year 2 until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor).
 - Subjects who meet the definition of treatment failure and wish to follow an abbreviated schedule but who have not cleared vector shedding from all fluids must still provide samples for assessment every 4 weeks during Year 2 until vector shedding has cleared (in such a case, these subjects do not need to perform other assessments except for PCR sample delivery scheduled at these timepoints).

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

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

- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Liver Tests (refer to Table 9.7.8.3.1) local laboratory assessment

- LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
- Liver Tests (refer to Table 9.7.8.3.1) central laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
 - FVIII coagulation activity exploratory assay
 - Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - FVIII antigen (ELISA)

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

- PCR of vector DNA in blood, saliva, urine, semen, and stools (if required)
 - Sample testing during Years 3-5 is not required if at least 3 consecutive samples are negative during the Post-Infusion Follow-Up period in Weeks 1-52 and/or Year 2. Subjects who have not had 3 consecutive negative semen samples by Week 52 should continue to have PCR testing of semen every 6 weeks during Years 3-5 until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor).
 - Subjects who meet the definition of treatment failure and wish to follow an abbreviated schedule but who have not cleared vector shedding from all fluids must still provide samples for assessment every 6 weeks during Years 3-5 until vector shedding has cleared (in such a case, these subjects do not need to perform other assessments except for PCR sample delivery scheduled at these timepoints).

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

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

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

For each of these years, the last study visit listed (Week 104, Week 156, Week 208, and Week 260) will serve as an End of Year visit.

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

- Brief physical examination (at every 12 week visits) or complete physical examination (at End of Year visits)
- Weight (at Week 76, Week 128, Week 180, Week 232, and End of Year visits only)
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Liver Tests (refer to Table 9.7.8.3.1) local laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
- Liver Tests (refer to Table 9.7.8.3.1) central laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
 - FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for FVIII inhibitor level

• FVIII antigen (ELISA)

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

- Vital Signs
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
 - ABO blood typing assessment should be performed at the next regularly scheduled study visit (or at least prior to the end of the subject's participation in the study)
- Urine Tests (refer to Table 9.7.8.2.1)
- AAV5 antibody titer
- FVIII antibody titer
- PBMC collection
- VWF:Ag
- Exploratory biomarker assessments
- Haemo-QoL-A QOL assessment (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 negative during the Post-Infusion Follow-Up period in Weeks 1-52. Subjects who have not had 3 consecutive negative semen samples by Week 52 should continue to have PCR testing of semen every 4 weeks (during Year 2) or every 6 weeks (during Years 3-5) until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor).

12.9 Liver Biopsy Substudy - Years 1-5

For the optional liver biopsy substudy (refer to Table 9.1.7), the following procedures will be performed at the following times:

- Within 28 days before Biopsy Day
 - Informed consent
 - Liver ultrasound

- Brief physical examination
- Hematology, Coagulation, and Chemistry Assessments (refer to Table 9.7.8.2.1)
- Liver Tests (refer to Table 9.7.8.3.1)
- Within 7 Days before Biopsy Day
 - o FibroScan

- o Local laboratory FVIII activity level assessment
- Pre-biopsy consultation with investigator (treating hematologist). This may need to be repeated/extended if the subject's FVIII activity levels need adjustment before the biopsy, at the discretion of the investigator (treating hematologist).
- 1 Day before Biopsy Day
 - Hematology, Coagulation, and Chemistry Assessments (refer to Table 9.7.8.2.1)
 - Liver Tests (refer to Table 9.7.8.3.1) local laboratory assessment
 - Brief physical examination
 - o Local laboratory FVIII activity level assessment
 - Subjects must have a FVIII activity level of at least 50 IU/dL (or higher, depending on local guidelines and/or investigator discretion). 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".
- Biopsy Day
 - Brief physical examination
 - Local laboratory FVIII activity level assessment (performed pre-biopsy)

- Subjects must have a FVIII activity level of at least 50 IU/dL (or higher, depending on local guidelines and/or investigator discretion). 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".
- Liver Tests (refer to Table 9.7.8.3.1) local laboratory assessment (prebiopsy)
- Liver Biopsy (refer to Laboratory Manual for guidelines for biopsy procedure and handling of biopsy samples)
 - If only a small amount of tissue is obtained at the time of the biopsy, the subject may be asked to consent for a second pass.

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.

12.10 Early Termination Visit

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

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

- Physical examination
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Vital Signs
- Blood chemistry, haematology, coagulation screen, and CRP (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) local laboratory assessment
- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage clotting assay)

- FVIII activity level (chromogenic substrate assay)
- Liver Tests (refer to Table 9.7.8.3.1) central laboratory assessment
- FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
 - FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - FVIII antigen (ELISA)

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

- AAV5 antibody titer
- FVIII antibody titer
- PBMC collection
- VWF:Ag
- PCR of vector DNA in blood, saliva, urine, semen, and stools
 - Sample testing at the ETV is not required if at least 3 consecutive samples are clear during the Post-Infusion Follow-Up period.
- Exploratory biomarker assessment
- Haemo-QoL-A QOL assessment

12.11 End of Study

The study will end after the last subject completes the last Safety Follow-Up visit (Week 260). 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.

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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, any applicable randomization procedures, source document requirements, eCRFs, monitoring requirements, and procedures for reporting AEs, including SAEs.

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

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

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14 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

14.1 Statistical and Analytical Plans

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

14.1.1 Interim Analyses

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

14.1.2 Procedures for Accounting for Missing, Unused and Spurious Data

Missing data will not be imputed.

14.2 Primary and Secondary Efficacy Analysis

The subjects will be followed in a longitudinal manner and all the relevant information will be collected. The analysis of the data will be descriptive in nature. Descriptive statistics include the number of subjects, mean, median, standard deviation, minimum, and maximum for continuous variables and count and percent for categorical variables. Efficacy variables will be summarized by dose cohort at each time point. Relationship between dose and efficacy results will be examined.

Data collected in a longitudinal manner may be analyzed using longitudinal methods such as mixed effect model which takes into account the correlation among the observation taken at various time points within a participant. Efficacy is a secondary endpoint, defined as biologically active hFVIII at ≥ 5 IU/dL by chromogenic substrate assay and/or one-stage clotting assay as measured by the central laboratory at 16 weeks following study treatment. hFVIII activity will be assessed weekly during the study period. We can only assess the true steady state of hFVIII protein produced from BMN 270 after a minimum of 72 hours has elapsed since the last infusion of FVIII protein concentrates.

14.3 Liver Biopsy Substudy Analysis

A separate report presenting and discussing analyses of the exploratory objectives for the optional liver biopsy substudy will be prepared.

14.4 Immunogenicity

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

14.5 Pharmacodynamic Analyses

The FVIII antigen and activity level as measured by an ELISA (antigen level) and by a one-stage clotting assay and/or chromogenic substrate assay (activity level), will be used for plasma profiles; FVIII activity will be used to determine PD parameters. Traditional PK analysis is not applicable.

If supported by FVIII activity data, non-compartmental analysis and observation will be used to estimate individual PD parameter values of C_b (baseline), C_{ss} (steady state), T_{ss} (time to steady state), C(t) and AUC(0-t) where t is 16 weeks. Other parameters that may be used to describe individual FVIII protein and activity plasma profiles are C_{max} (maximum concentration) and C_{avg} (average concentration, AUC(0-t)/t). The parameters will be summarized using descriptive statistics.

14.6 Safety Analysis

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

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

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

Detailed statistical methods will be provided in the SAP.

14.7 Determination of Sample Size

No formal sample size calculations based on statistical power were performed.

The sample size is determined based upon clinical consideration and could detect a strong clinical efficacy signal. Up to 15 subjects may be dosed in the study; the actual number of subjects will depend on the criteria for dose escalation.

14.8 Analysis Populations

The Safety analysis population is defined as all enrolled subjects who receive any study drug. The analysis of safety data will be performed on Safety Set.

The Full Analysis Set (FAS) is defined as all enrolled subjects who receive study drug and have at least one Baseline and post-Baseline assessment. The FAS will be used for efficacy analysis.

14.9 Changes in the Conduct of the Study or Planned Analyses

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

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

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

Note: If discrepancies exist between the text of the statistical analysis as planned in the protocol, and the final SAP, a protocol amendment will not be issued and the SAP will prevail.

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15 DATA REVIEW BOARD

There will be no formal DMC for this study, however a safety and efficacy evaluation board (the Data Review Board [DRB]) composed of the investigator representatives and the Sponsor will be established.

The DRB will review safety and efficacy on an ongoing basis. The DRB will meet prior to dose escalation or dose expansion to assess available subject safety and efficacy data and make recommendations with regards to the conduct of study. Should a safety signal arise, including one which may warrant a halt of study enrollment, the DRB will promptly convene for further assessment of subject safety. Notification of all DRB meetings and meeting outcomes will be sent to participating sites.

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16 COMPENSATION, INSURANCE AND INDEMNITY

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

The Investigator should contact BioMarin immediately upon notification that a study subject has been injured by the IP 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 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 subject has followed the Investigator's instructions, BioMarin will pay for reasonable and necessary medical services to treat the injuries caused by the IP or study procedures, if these costs are not covered by health insurance or another third party that usually pays these costs. In some jurisdictions, BioMarin is obligated by law to pay for study-related injuries without prior recourse to third party payer billing. If this is the case, BioMarin will comply with the law.

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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 CRF casebook to verify its accuracy.

CRFs 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 CRF instructions, blank data fields are not acceptable.

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

BioMarin's policy is that study data on the CRFs 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 an Investigator or institution refuses to allow access to subject records because of confidentiality, arrangements must be made to allow an "interview" style of data verification.

A CRA designated by BioMarin will compare the CRFs 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 CRA, 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 CRA 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 CRF 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 CRFs 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.

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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 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).

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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 R2 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 patients.
- He or she will personally conduct or supervise the study.
- He or she will inform any potential patients, 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 R2 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 R2 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 R2 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 R2 Section 4.9 are kept, and those records are available for inspection in accordance with 21 CFR 312.68 and/or ICH E6 R2 Section 4.9.7.
- The IRB/IEC/REB complies with the requirements of 21 CFR Part 56, ICH E6 R2 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 patients or others are reported to the IRB/IEC/REB. Additionally, he or she will not make any changes in the research without IRB/IEC/REB approval, except where necessary to eliminate apparent immediate hazards to human patients.
- 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 R2.

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23 SIGNATURE PAGE

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

Protocol Number: 270-201 Amendment 8

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 R2, as stated in the protocol, and other information supplied to me.

Investigator Signature		Date
Printed name		
Accepted for the Sponsor:	DocuSigned by:	
Medical Monitor Signature	Date	
Printed name: Pl	, MA MB BChir MSc, <mark>Pl</mark>	, Clinical Science

24 PROTOCOL AMENDMENT TEXT REVISIONS

The following table summarizes the revisions made to the protocol and relates the changes to the appropriate rationale (See page 2). Text that has been added or inserted is indicated by <u>underlined</u> font, and deleted text is indicated by <u>strikethrough</u> font.

Section No./Title	Revision	Rationale
Synopsis (Study Rationale)	Liver Biopsy Substudy RationaleThe pattern of response in hFVIII activity observed so far after administration of BMN 270 demonstrates peak expressionlevels during the first 6-12 months post-treatment followed by a decline to a steady-state level of expression in the second yearof follow-up, with mean hFVIII activity levels remaining above the lower limit of normal (50 IU/dL). One of the explanationsmay 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, andit is these circularized DNA species that are thought to be associated with long-term, persistent expression of the gene productin target cells. Examination of transduced hepatocytes from subjects treated with BMN 270 in the 270-201 study will help toestablish 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 hepaticenzymes released into the blood stream. Transient post-treatment elevations in ALT levels have been observed in somesubjects, as well as inter-subject variability in post-therapy hFVIII levels. Neither the reasons for, nor the significance of, theALT elevations or variations in response to FVIII gene therapy are known. Moreover, the effects of BMN 270 on hepatictissue structure and function are also currently unknown.The purpose of this exploratory substudy is to provide a better understanding of the long-term gene expression related tocircularized genomes, health of the liver, and variation in hFVIII levels	1
Synopsis (Objectives)	The exploratory objectives of the liver biopsy substudy are: • To examine the histopathology of the liver following BMN 270 therapy, including assessing for possible safety findings (eg, fibrosis, fatty liver disease, lymphocytic invasion) • To quantify FVIII DNA, RNA, and protein expression within hepatocytes • To determine which forms of rAAV vector DNA are present at the time of biopsy. • To determine the transduction pattern of BMN 270 in humans (ie, peri-portal hepatocytes, central vein hepatocytes)	1

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Section No./Title	Revision	Rationale
Synopsis (Study Design and Plan)		
Synopsis (Inclusion and Exclusion Criteria)	Individuals eligible to participate in the liver biopsy substudy must meet all of the following criteria: 5. Currently enrolled in 270-201 6. Received BMN 270 infusion at least 1 year prior to enrollment in the substudy 7. Able to sign informed consent and comply with requirements of the substudy 8. FVIII activity at least >50 IU/dL (or higher, depending on local guidelines and/or Investigator discretion) within 24 hours prior to the liver biopsy being performed. (FVIII 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 to an appropriate level, under the supervision/instruction of the Investigator. Individuals who meet any of the following exclusion criteria will not be eligible to participate in the liver biopsy substudy: 9. Assessed by the investigator or a hepatologist as having a medical condition such that undergoing a liver biopsy would be contraindicated. These conditions could include (but are not limited to): • Significant thrombocytopenia (platelet count < 100 x 10 ⁹ /L) • Evidence of significant ascites	1

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Section No./Title	Revision	Rationale
	<u>Abnormalities detected on liver ultrasound (performed within 90 days of procedure) that would preclude safe</u> performance of the biopsy.	
Synopsis (Criteria for Evaluation)	Liver Biopsy Substudy: The following exploratory assessments will be performed as part of the optional liver biopsy substudy: • Morphologic/pathogenic changes after FVIII gene transduction or any change that may be associated with sustained ALT rise • Determine quantities of liver FVIII-SQ DNA/RNA • Determine forms of vector DNA in liver at the time of biopsy • Determine percentage of hepatocytes expressing FVIII protein • Determine hepatic liver transcriptome at single nuclei level if sufficient material is obtained • Identify the forms of vector DNA in the liver • Examination of potential stress inducing cellular pathways • Other exploratory assessment to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to hemophilia A, coagulation, and/or AAV gene transfer	1
7.3.1/Liver Biopsy Substudy Rationale	The 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 in the second year of follow-up, with mean hFVIII activity levels remaining above the lower limit of normal (50 IU/dL). 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 270-201 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 some subjects, as well as inter-subject variability in post-therapy hFVIII 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.	1

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Section No./Title	Revision	Rationale
	The purpose of this exploratory substudy is to provide a better understanding of the long-term gene expression related to genome circularization, health of the liver, and variation in hFVIII levels observed after gene therapy with BMN 270. Whilst consenting subjects may not derive any direct benefit themselves by participating in the substudy, the overall findings could aid future patients by helping to characterize the means by which long-term efficacy is achieved and the safety of liver-directed gene therapy.	
7.4.1.1/Liver Biopsy Substudy 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 substudy will have a comprehensive pre-/post-biopsy surveillance plan according to the standard procedures at the institution. 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 substudy is optional and will not have any effect on the subject's continued participation in 270-201. 	1
8/Study Objectives	The exploratory objectives of the liver biopsy substudy are: • To examine the histopathology of the liver following BMN 270 therapy, including assessing for possible safety findings (eg, fibrosis, fatty liver disease, lymphocytic invasion)	1

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Section No./Title	Revision	Rationale
	<u>To quantify FVIII DNA, RNA, and protein expression within hepatocytes</u>	
	• To determine which forms of rAAV genomic DNA (eg, concatemers) are present at the time of biopsy	
	• To determine the transduction pattern in humans (ie, peri-portal hepatocytes, central vein hepatocytes)	
9.1/Overall Study	Liver Biopsy Substudy Design	1
Design and Plan	All subjects enrolled in 270-201 and who are at least one year post-BMN 270 infusion are eligible for the optional liver biopsy substudy. Subjects who consent to participate in the substudy will have a liver biopsy via either the transjugular or percutaneous (ultrasound-guided) route, according to the standard procedures of the institution. To enhance safety, all subjects will have an ultrasound examination of the liver within 3 months prior to the procedure (to ensure there are no pathological findings such as bile duct obstruction that might interfere with the safe performance of the liver biopsy) and a FibroScan of the liver within one week before the liver biopsy (to correlate with any potential histopathologic findings of fibrosis on the biopsy). Subjects who consent should have their FVIII levels monitored/adjusted by the Investigator to enable the procedure to be performed safely. This may require the administration of exogenous FVIII replacement products in order to achieve the desired FVIII activity. The target FVIII activity level within 24 hours prior to the liver biopsy is at the discretion of the Investigator and/or according to local guidelines, but at a minimum should be at the lower limit of the normal range (ie, at least 50 IU/dL). Table 9.1.7 presents the schedule of assessments for participation in the liver biopsy substudy.	
Table 9.1.5/Safety Follow-Up	The Direct Thrombin Test has been removed from this schedule of events and footnote g.	2
Table 9.1.7/Liver Biopsy Substudy	Table 9.1.7 has been added as part of this amendment.	1
9.3.3/Liver Biopsy Substudy Inclusion and Exclusion Criteria	 <u>Individuals eligible to participate in the liver biopsy substudy must meet all of the following criteria:</u> <u>Currently enrolled in 270-201</u> <u>Received BMN 270 infusion at least 1 year prior to enrollment in the substudy</u> <u>Able to sign informed consent and comply with requirements of the substudy</u> 	1

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Section No./Title	Revision	Rationale
	 12. FVIII activity at least >50 IU/dL (or higher, depending on local guidelines and/or Investigator discretion) within 24 hours prior to the liver biopsy being performed. (FVIII 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 to an appropriate level, under the supervision/instruction of the Investigator. Individuals who meet any of the following exclusion criteria will not be eligible to participate in the liver biopsy substudy: 	
	 3. <u>Assessed by the investigator or a hepatologist as having a medical condition such that undergoing a liver biopsy would be contraindicated. These conditions could include (but are not limited to):</u> Significant thrombocytopenia (platelet count < 100 x 10⁹/L) 	
	 Evidence of significant ascites <u>Abnormalities detected on liver ultrasound (performed within 90 days of procedure) that would preclude safe</u> performance of the biopsy. 	
9.7.6/Exploratory Assessments	Liver biopsy samples collected as part of the exploratory substudy may also be tested to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to hemophilia A, coagulation, and/or AAV gene transfer. Subjects participating in the substudy 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.	1
<u>9.7.7.1/Liver Biopsy</u> <u>Substudy</u>	The objectives of the liver biopsy substudy are considered exploratory.Subjects who consent to the procedure will have a liver biopsy via either the transjugular or percutaneous (ultrasound-guided)route, according to the standard procedures of the institution. To enhance safety, all subjects will have an ultrasound exam ofthe liver within 28 days prior to the procedure (to ensure there is no obstruction to the liver that would interfere with the liverbiopsy) and a FibroScan of the liver within one week before the liver biopsy (to correlate any histopathologic findings on thebiopsy). Subjects will also undergo a pre-biopsy consultation with the investigator (treating hematologist).Within 24 hours prior to the biopsy being performed, subjects must have a FVIII activity level of at least 50 IU/dL (or higher,depending on local guidelines and/or investigator discretion). FVIII activity levels for this purpose should be assessed at thelocal laboratory within 7 days before the biopsy, and again the day before the biopsy. As needed, subjects may be treated withadditional exogenous FVIII replacement products in order to increase their FVIII activity levels to an appropriate level, under	1

Section No./Title	Revision	Rationale
	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".	
	The liver biopsy should be performed in the morning, 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 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 and/or according to local guidelines.	
	Safety findings arising from the histopathological analysis of the biopsy sample are subject to Adverse Event reporting (Section 10), and such findings should be further assessed and followed-up as clinically appropriate and in order to safeguard the subject's ongoing medical care (this should be done in consultation with a hepatologist and/or other specialist clinicians if required). In the event fibrotic changes being observed on the biopsy sample, additional follow-up Fibroscans may be considered (with the frequency of subsequent scans at the discretion of the Investigator and/or hepatologist).	
10.4.1.7/Hospitalization, Prolonged Hospitalization, or Surgery	 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 <u>efficacy measurement procedure or assessment</u> 	1
12.8.3/Years 2-5 –	At the every 12 week and End of Year visits, the following procedures will be performed:	2
Every 12 Weeks and End of Year Visits	Direct Thrombin test	
<u>12.9/Liver Biopsy</u> Substudy – Years 1-5	For the optional liver biopsy substudy (refer to Table 9.1.7), the following procedures will be performed at the following times:	1
	<u>Within 28 days before Biopsy Day</u>	
	• <u>Informed consent</u>	
	• Liver ultrasound	
	 Liver ultrasound does not need to be performed if an ultrasound result from the prior 3 months is already available 	

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Section No./Title	Revision	Rationale
	• Brief physical examination	
	• <u>Hematology, Coagulation, and Chemistry Assessments (refer to Table 9.7.8.2.1)</u>	
	• <u>Liver Tests (refer to Table 9.7.8.3.1)</u>	
	<u>Within 7 Days before Biopsy Day</u>	
	o <u>FibroScan</u>	
	• Local laboratory FVIII activity level assessment	
	 <u>Pre-biopsy consultation with investigator (treating hematologist)</u>. This may need to be repeated/extended if the subject's FVIII activity levels need adjustment before the biopsy, at the discretion of the investigator (treating hematologist). 	
	• <u>1 Day before Biopsy Day</u>	
	• <u>Hematology, Coagulation, and Chemistry Assessments (refer to Table 9.7.8.2.1)</u>	
	• <u>Liver Tests (refer to Table 9.7.8.3.1) – local laboratory assessment</u>	
	• Brief physical examination	
	 <u>Local laboratory FVIII activity level assessment</u> 	
	 Subjects must have a FVIII activity level of at least 50 IU/dL (or higher, depending on local guidelines and/or investigator discretion). 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". 	
	• <u>Biopsy Day</u>	
	• Brief physical examination	

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Section No./Title	Revision	Rationale
	 Local laboratory FVIII activity level assessment (performed pre-biopsy) Subjects must have a FVIII activity level of at least 50 IU/dL (or higher, depending on local guidelines and/or investigator discretion). 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". Liver Tests (refer to Table 9.7.8.3.1) – local laboratory assessment (pre-biopsy) Liver Biopsy (refer to Laboratory Manual for guidelines for biopsy procedure and handling of biopsy samples) If only a small amount of tissue is obtained at the time of the biopsy, the subject may be asked to consent for a second pass. 	
12.10/Early Termination Visit	At the Early Termination visit, as many of the following assessments as possible should be done: Direct Thrombin test 	2
<u>14.3/Liver Biopsy</u> Substudy Analysis	A separate report presenting and discussing analyses of the exploratory objectives for the optional liver biopsy substudy will <u>be prepared.</u>	1
21/References	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 1 December 2018).	1

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1/2, Dose-Escalation, Safety, Tolerability and Efficacy Study of BMN 270, an Adenovirus-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII in Patients with Severe Haemophilia A
Protocol Number:	270-201
Active Investigational Product:	AAV5-hFVIII-SQ
IND/European Union Drug Regulating Authorities Clinical Trials (EudraCT) Number:	2014-003880-38
Indication:	Haemophilia A
Sponsor:	BioMarin Pharmaceutical Inc.
	105 Digital Drive
	Novato, CA 94949
Development Phase:	Phase 1/2
Sponsor's Responsible Medical Monitor:	PI, MA MB BChir MSc BioMarin (UK) Ltd. 10 Bloomsbury Way London, WC1A 2SL
Duration of Subject Participation:	Approximately 264 weeks
Dose:	Varied
Study Population:	Males aged 18 or older
Date of Original Protocol:	10 February 2015
Date of Amendment 1:	06 March 2015
Date of Amendment 2:	26 May 2015
Date of Amendment 3:	06 November 2015
Date of Amendment 4:	02 September 2016
Date of Amendment 5:	14 February 2017
Date of Amendment 6:	21 December 2017
Date of Amendment 7:	10 October 2018

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This study will be conducted according to the principles of Good Clinical Practice as described in the U.S. Code of Federal Regulations and the International Conference on Harmonisation Guidelines, including the archiving of essential documents



CLINICAL STUDY PROTOCOL AMENDMENT SUMMARY

Amendment: 7

Date: 10 October 2018

RATIONALE AND SUMMARY OF MAJOR CHANGES

A summary of major changes covered by Amendment 7 to the BMN 270-201 protocol is provided below.

1. Efavirenz, lamivudine, and experimental hemophilia treatments (emicizumab, fitusiran, and concizumab) have been added to the list of prohibited concomitant medications.

Rationale: An HIV-positive subject in Study 270-302 developed markedly elevated transaminase levels after receiving 4E13 vg/kg of BMN 270. The subject was receiving HAART treatment that included efavirenz and lamivudine for his HIV infection, and it is hypothesized that the combination of BMN 270, one or more of his HAART medications, and/or unsuspected underlying hepatic disease may have contributed to the subject's elevated transaminase levels. Experimental hemophilia treatments are prohibited during the study as they could affect the assessment of FVIII levels in 270-201 subjects.

2. The timing of assessment visits during Years 2-5 has been modified.

Rationale: The original timing (which required visits on every 4 week, every 6 week, and every 3 month schedules) created burdens on sites in trying to align visits within allowed visit windows to minimize subject burden. The revised timing (which has substituted visits every 12 weeks and at specified end of year timepoints for the every 3 month visits) has simplified the calendar of visits and should ease site burden.

3. An abbreviated visit schedule has been made available during Years 2-5 for subjects who are considered to have not responded to BMN 270 therapy.

Rationale: 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, enable subjects to follow an abbreviated visit schedule after Week 52 of the study by attending only the Q12W and End of Year visits during Years 2-5.

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

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vector shedding has cleared (but do not need to perform other assessments at those study visits).

4. Additional details have been included concerning information to be collected as part of the medical history.

Rationale: In subjects with a history of hepatitis B or hepatitis C infection, information on the specific treatments received for that infection should be collected. In addition, any previous pharmacokinetic data collected at the time the subject was receiving on-demand or prophylactic FVIII treatment should be collected. This additional history data could help explain a subject's FVIII response (or lack of FVIII response) to BMN 270. As all subjects have already gone through Screening and reported medical history during 270-201, this additional history should be collected at the next regularly scheduled study visit (or at least prior to the end of the subject's participation in the study).

5. Language concerning when to consider restarting FVIII prophylaxis following BMN 270 infusion has been modified.

Rationale: The decision for reinstitution of FVIII prophylaxis should be based on clinical grounds (eg, the advent of bleeding episodes), in consultation with the Medical Monitor. The need to reinstitute FVIII prophylaxis if the FVIII activity is below a certain level post-BMN 270 has not yet been clinically established but will be informed by results from this study.

6. Language was added to include ABO testing.

Rationale: ABO blood type results will be obtained to potentially correlate with FVIII activity level results in an exploratory manner. This assessment should be completed at the next regularly scheduled study visit (or at least prior to the end of the subject's participation in the study).

7. Clarified that vector shedding assessments, if required, can be performed at the every 6 week visits during Years 3-5.

Rationale: Previously, the protocol called for vector shedding assessments, if required, to be done every 4 weeks after Week 52 until clearance. During Years 3-5, when subjects are being assessed for FVIII and liver function every 6 weeks, an every 4-week schedule for vector shedding would add to subject burden. Obtaining results every 6 weeks is sufficient to monitor vector shedding for subject safety and also aligns these assessments with the FVIII and liver test assessment visits.

8. Assessment of dermatologic and musculoskeletal systems has been added to the brief physical examination.

Rationale: Both organ systems are routinely assessed as part of comprehensive hemophilia care visits.

9. Testing of the exploratory samples for the Direct Thrombin Activity Test has been clarified as optional.

Rationale: While exploratory samples for Direct Thrombin Activity Test will be collected at the time points indicated in the protocol, analysis of these samples will be optional.

10. Subjects will be advised to abstain from blood or sperm donation after BMN 270 infusion until there is no further evidence of vector shedding.

Rationale: Vector shedding in the blood and semen following BMN 270 infusion has been observed, which could serve for vector transmission if subjects were to donate blood or semen following the BMN 270 infusion.

11. In the event of a positive Bethesda assay result during Years 3-5, an additional sample has been added to be collected within 4 weeks of the visit where the positive result was obtained.

Rationale: During Years 3-5, samples are being regularly collected every 6 weeks. However, to align with EMA guidance (which suggests that a confirmatory test on a second sample should be done within a month after a positive Bethesda assay result), language has been added to require the site to conduct an unscheduled visit within 4 weeks after the date when the positive Bethesda result was obtained.

12. Twice weekly evaluation of liver function tests (LFTs) has been added during times when a subject's ALT is \geq 3x ULN.

Rationale: The decision is based on clinical experience with subject LFT elevations and use of oral corticosteroids in 270-201. More frequent LFT monitoring may be undertaken following review of a subject's data and upon discussion between the investigator and the medical monitor. However, in order to enhance subject safety, the protocol has been modified to mandate twice weekly LFT monitoring when a subject's ALT is \geq 3x ULN.

13. The identity of the medical monitor has been updated.

14. Minor administrative changes have been made for consistency and clarity.

Specific changes included in this amendment, including the Synopsis, since Amendment 6 (approved 21 December 2017) are outlined in Section 24.



2 SYNOPSIS

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

PROTOCOL NUMBER:

270-201

STUDY SITES:

Approximately 6-10 sites worldwide.

PHASE OF DEVELOPMENT:

Phase 1/2

STUDY RATIONALE:

Haemophilia 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 cascade. This disorder can be either inherited, due to a new mutation 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 is largely governed by the level of residual expression. Severe HA is classified as FVIII activity less than 1% of wild type (< 1 IU/dL), moderate disease comprises 1-5% of wild type activity and the mild form is 5-40% activity. The clinical manifestations of severe HA remain frequent spontaneous bleeding episodes, predominantly in joints and soft tissues, with a substantially increased risk of death from haemorrhage when the brain is involved. 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 treatment (mean of 1 to 7 episodes/year with prophylaxis and up to 30 to 50 episodes/year for on demand treatment). The consequence of multiple bleeding events is the development of an underlying pathology that contributes to 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

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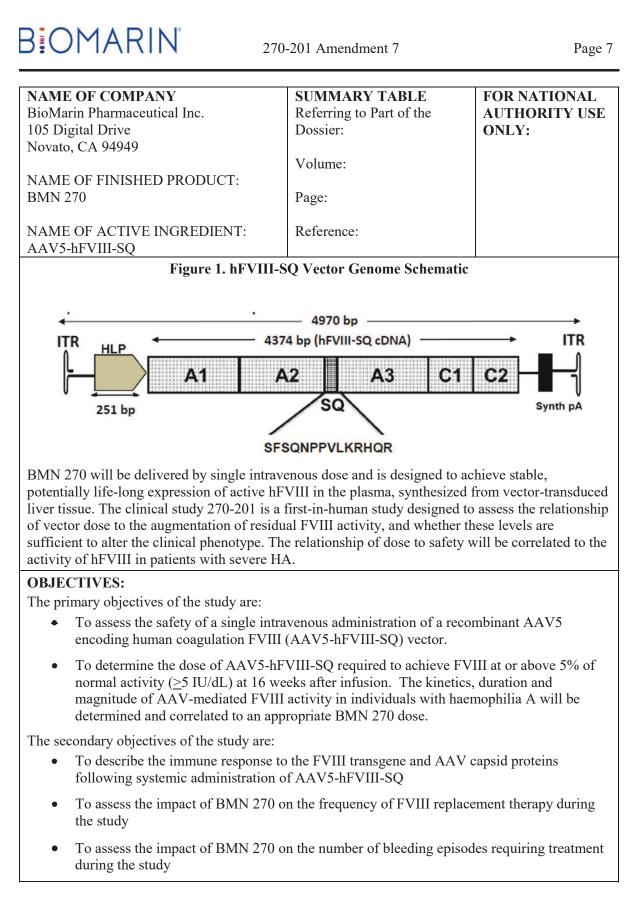
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maintaining activity levels above 1% trough. However, these longer acting FVIIIs remain dependent on multiple infusions to maintain critical levels of FVIII activity in severe HA patients. There is therefore a strong unmet need for a fully preventive treatment of HA to give patients a FVIII level compatible with a normal and haemorrhage-free life.

Gene therapy offers the potential of disease-modifying therapy by continuous endogenous production of active FVIII following a single intravenous administration of a vector with the appropriate gene sequence. Haemophilia 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 modest increases in the level of FVIII (any increase of the plasma level by 2 ng/ml induces an increase in activity of 1%) can ameliorate the severe form of the disease. Thus, relatively small changes in endogenous FVIII activity results in clinically relevant improvements in disease phenotype. Finally, the 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 for specific tissues such as the liver (for serotypes 2, 5 and 8 among others). Indeed, an on-going gene therapy clinical trial for a related disorder, haemophilia B, has established that stable (>36 months) expression of human factor IX at levels that are sufficient for conversion of their bleeding phenotype from severe to moderate or mild is achievable following a single peripheral vein administration of AAV-8 vector. Several participants in this trial have been able to discontinue factor prophylaxis without suffering spontaneous haemorrhages, 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 liver-selective promoter (Figure 1).



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STUDY DESIGN AND PLAN:

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

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

Cohort 1: 6E12 vector genomes [vg] per kilogram of body weight, given as a single intravenous dose (iv)

Cohort 2: 2E13 vg per kilogram, iv

Cohort 3: 6E13 vg per kilogram, iv

Cohort 4: 4E13 vg per kilogram, iv

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

Cohorts 1-3

The first 3 cohorts will be enrolled sequentially, allowing a period of 3 weeks or more between cohorts. Dose escalation may occur after a single subject has been safely dosed if the resulting FVIII activity at the Week 3 visit is < 5 IU/dL in both the one-stage clotting and chromogenic substrate assays. Three weeks is expected to be the time the expression will be close to the maximum. This escalation paradigm is intended to minimize the subject numbers exposed to subtherapeutic doses.

Approximately three weeks after an injection, the decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and a panel of investigators participating in the study, the Data Review Board (DRB).

If the FVIII activity reaches $\geq 5 \text{ IU/dL}$ at the Week 3 visit, then the remaining subjects in the cohort will be enrolled without the need to wait for 3 weeks between subjects.

Subject 1 will be dosed by intravenous infusion with 6E12 vector genomes [vg] per kilogram of body weight. If the FVIII activity level does not reach ≥ 5 IU/dL at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 1 and enrollment into Cohort 2 will initiate with Subject 2 at the next dose (2E13 vg/kg).

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If the FVIII activity level in the first subject treated in Cohort 2 does not reach ≥ 5 IU/dL at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 2 and enrollment into Cohort 3 (6E13) will initiate with the next subject. If the FVIII activity level in the first subject treated in Cohort 3 does not reach ≥ 5 IU/dL at the Week 3 visit in both assays, then the Data Review Board (DRB) will recommend whether to continue to add subjects to the cohort and/or whether to continue the study.

For the first subject treated in each of the first 3 cohorts, if the activity level reaches \geq 5 IU/dL and no safety issue is found, then up to four subjects will be enrolled in the Cohort, though, the adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

Cohort 4

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

There will be an ongoing review of individual patient safety and efficacy data by the medical monitor and the DRB. The adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

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

In subjects who experience recurrent bleeding episodes, the Investigator and Medical Monitor will discuss whether to resume prior FVIII prophylaxis. Subjects who do not respond to BMN 270 treatment (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, follow an abbreviated visit schedule after Week 52, as applicable and at the discretion of the Investigator. Because subjects develop neutralizing immunity upon exposure to the capsid, re-challenge of vector is not a likely treatment option and these subjects have effectively a single opportunity for therapy using this AAV capsid. Efficacy will be determined by FVIII activity at 16 weeks post dose. Safety will be evaluated for approximately 5 years after dosing. Any safety signal may trigger a review of the data and possible additional immunogenicity studies that include an assessment of cellular immune responses using collected peripheral blood mononuclear cells (PBMC).

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NUME	BER OF SUBJECTS PLANNED:			
	5 subjects may enroll into the study; v levels seen in each Cohort.	the actual number of subjects w	ill depend on the FVIII	
DIAG	NOSIS AND ALL CRITERIA FOR	R INCLUSION AND EXCLUS	ION:	
Individ	uals eligible to participate in this stud	ly must meet all of the following	g criteria:	
 Males that are 18 years or older with established severe haemophilia A as evidenced by their medical history. Patients will be considered as severe if their base FVIII level is 1 IU/dL or less 				
2.	 Treated/exposed to FVIII concentrates or cryoprecipitate for a minimum of 150 exposure days (EDs) 			
3.	3. Greater or equal to 12 bleeding episodes only if receiving on-demand therapy over the previous 12 months. Does not apply to patients on prophylaxis			
4.	. Able to sign informed consent and comply with requirements of the trial			
5.				
6.	6. Sexually active patients must be willing to use an acceptable method of contraception such as double barrier, including hormonal contraception for at least 6 months post-treatment. After 6 months, subjects may stop contraception use only if they have had 3 consecutive negative semen samples.			
Individ the stud	uals who meet any of the following e dy:	exclusion criteria will not be elig	ible to participate in	
1.	Detectable pre-existing immunity to inhibition or AAV5 total antibodies	the AAV5 capsid as measured l	by AAV5 transduction	
2.	Any evidence of active infection or	any immunosuppressive disorde	er.	
3.	HIV positive	_		
4.	Significant liver dysfunction as defi	ned by abnormal elevation of:		
	• ALT (alanine transaminase) to 3	3 times the upper limit of normal	l;	
	 Bilirubin above 3 times the upper limit of normal; 			

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• Alkaline phosphatase above 3 ti	mes the upper limit of normal; o	r			
• INR (international normalized r	atio) ≥ 1.4				
5. Potential participants who have had	a liver biopsy in the past 3 years	are excluded if they			
had significant fibrosis of 3 or 4 as r	rated on a scale of 0-4				
6. Evidence of any bleeding disorder n	ot related to Haemophilia A				
7. Platelet count of $< 100 \text{ x } 10^{9}/\text{L}$					
8. Creatinine $\geq 1.5 \text{ mg/dL}$					
9. Liver cirrhosis of any etiology as as	sessed by liver ultrasound				
10. Hepatitis B if surface antigen is pos	itive				
11. Hepatitis C if RNA is positive					
12. Treatment with any IP within 30 day	ys prior to the end of the screening	ng period			
13. Any disease or condition at the physician's discretion that would prevent the patient from fully complying with the requirements of the study including possible corticosteroid treatment outlined in the protocol. The physician may exclude patients unwilling or unable to agree on not using alcohol for the 16-week period following the viral infusion.					
14. Prior treatment with any vector or g	ene transfer agent				
15. Major surgery planned in the 16-we	ek period following the viral info	usion			
16. Use of systemic immunosuppressive infusion	16. Use of systemic immunosuppressive agents or live vaccines within 30 days before the viral infusion				
INVESTIGATIONAL PRODUCT(S), DC	SE, ROUTE AND REGIMEN	1:			
Each subject will receive a single injection of infusion will depend on the dose level.	of BMN 270 as an intravenous in	fusion. The volume of			
REFERENCE THERAPY(IES), DOSE, F	ROUTE AND REGIMEN:				
The study is open label with comparison of FVIII activity to baseline values. No reference therapy					
will be evaluated in this study.					
DURATION OF TREATMENT:					

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

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CRITERIA FOR EVALUATION:

Safety:

The following safety outcome measurements will be assessed:

- Incidence of adverse events (AEs), including serious AEs (SAEs)
- Change in clinical laboratory tests (serum chemistry and haematology)
- Change in vital signs
- Change in physical examination
- Vector shedding
- Liver tests (LTs, including ALT, AST, GGT, LDH, bilirubin, alkaline phosphatase)
- Immune response to FVIII transgene and AAV capsid proteins

No major toxicity is expected based on preclinical studies in mice and monkeys. Each subject will have comprehensive surveillance monitoring of LTs (at local labs, once per week for Weeks 1-36, then once every 2 weeks from Week 37-52) during Year 1. LTs will be monitored every 4 weeks during Year 2, and then every 6 weeks for Years 3-5 post-dose in the safety extension; the frequency and duration of LT testing may be changed based on discussion between the Medical Monitor and the Investigator and review of subject data.

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

Efficacy:

The primary efficacy measure will be to assess plasma FVIII activity. The efficacy goal of the study is to establish the dose relationship to FVIII activity \geq 5 IU/dL at 16 weeks post BMN 270 administration.

Secondary efficacy measures include assessing the impact of BMN 270 on the frequency of FVIII replacement therapy and on the number of bleeding episodes during the study. Subjects will be asked to keep a subject diary to record the details in these areas.

Pharmacodynamics:

The FVIII antigen and activity level as measured by an ELISA (antigen level) and by one-stage clotting and/or chromogenic substrate assay (activity level), will be used for plasma profiles; FVIII activity will be used to determine PD parameters. Traditional PK analysis is not applicable. If supported by the FVIII activity data, non-compartmental analysis and observation will be used to estimate individual values of Cb (baseline concentration), Css (steady state concentration), Tss (time to steady state), C(t) and AUC(0-t) where t is 16 weeks.

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STATISTICAL METHODS:

The sample size is based upon clinical considerations and could detect a strong clinical efficacy signal. Up to 15 subjects may be dosed in the study. The subjects will be followed in a longitudinal manner and all the relevant information will be collected. The analysis of the data will be descriptive in nature but data collected in a longitudinal manner may be analyzed using longitudinal methods such as mixed effect model which takes into account the correlation among the observation taken at various time points within a participant. Efficacy is a secondary endpoint, defined as biologically active FVIII at ≥ 5 IU/dL by chromogenic substrate assay and/or one-stage clotting assay at 16 weeks following study treatment. FVIII activity will be assessed weekly during the study period. We can only assess the true steady state of FVIII protein produced from BMN 270 after a minimum of 72 hours has elapsed since the last infusion of FVIII protein concentrates.

Analysis of neutralizing antibody response and other immunological parameters as well as vector shedding will be primarily descriptive and involve both inter-participant and intra-participant comparisons across doses.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

AAV	adeno-associated virus
ADL	activities of daily living
ADR	adverse drug reaction
AE	adverse event
ALT	alanine transaminase
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BPV	BioMarin Pharmacovigilance
BU	Bethesda Unit
CFR	Code of Federal Regulations
CRA	clinical research associate
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DRB	Data Review Board
eCRF	electronic case report form
ED	exposure days
EOSI	events of special interest
ETV	early termination visit
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
FIH	first-in-human
FVIII	coagulation factor VIII
FXa	coagulation factor Xa
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
HA	Haemophilia A
hFVIII	human coagulation factor VIII
HIPAA	Health Insurance Portability and Accountability Act
IB	investigator brochure
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for
	Registration of Pharmaceuticals for Human Use
ICH E6	ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6
IEC	independent ethics committee

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IND	Investigational New Drug (application)
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IV	intravenous
LT	liver test
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	no-observed-adverse-effect level
PBMC	peripheral blood mononuclear cells
PD	pharmacodynamics
PEG	polyethylene glycol
РК	Pharmacokinetics
PRO	patient-reported outcome
rhFVIII	recombinant human FVIII protein
REB	research ethics board
SAE	serious adverse event
SAP	statistical analysis plan
SDV	source data verification
ULN	upper limit of normal
vg	vector genomes
VWF:Ag	von Willebrand factor Antigen

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]).

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

5 ETHICS

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

5.1 Institutional Review Board or Independent Ethics Committee

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

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

5.2 Ethical Conduct of Study

It is expected that Investigators understand and comply with the protocol. This includes, but is not limited to: establishing and meeting enrollment commitments, including providing eligible subjects for study enrollment; adhering to 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)

Specifically, this study is based on adequately performed laboratory and animal experimentation. The study will be conducted under a protocol reviewed and approved by an IRB/IEC/REB and will be conducted by scientifically and medically qualified persons. The benefits of the study are in proportion to the 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), United States Code of Federal Regulations (CFR) 21 CFR §50, European Clinical Trial Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC, and other applicable local regulations, will be obtained for each subject prior to entering the subject into the study. The Investigator will prepare the ICF and provide the documents to BioMarin for approval prior to submission to the IRB/IEC/REB approval. BioMarin and the IRB/IEC/REB must approve the documents before they are implemented. A copy of the approved ICF, and if applicable, a copy of the approved subject information sheet and all ICFs translated to a language other than the native language of the clinical site must also be received by BioMarin or designee prior to any study-specific procedures being performed.

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

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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 US Food and Drug Administration (FDA) Form FDA 1572 and a Financial Disclosure Form. All sub-Investigators must be listed on Form FDA 1572. Financial Disclosure Forms must also be completed for all sub-Investigators listed on the Form FDA 1572 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.

Liver tests (LTs) will be performed at the local laboratories associated with the study sites. Local laboratory results of LTs will be used to trigger corticosteroid treatment as needed (refer to Section 9.4.8.2). In case of discrepant results between local and central laboratories, the Investigator and Medical Monitor will decide further action. Safety labs evaluations (including LTs) will be performed at the central lab, while bioanalytical samples will be performed at the appropriate specialty lab. Refer to the Laboratory Manual for more details.

7 INTRODUCTION

Haemophilia A (HA) is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males (Nathwani, 1992, Baillieres Clin.Haematol.). It is caused by mutations in the factor VIII (FVIII) gene that codes for FVIII protein, an essential cofactor in the coagulation cascade. 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 haemorrhage. Treatment in Western (Berntorp, 2012, Haemophilia.) countries consists of intravenous injection of plasma derived or recombinant FVIII protein concentrates at the time of a bleed, 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 haemophilia A patients. These individuals develop debilitating arthropathy and have a substantially increased risk of death from haemorrhage in life (Stonebraker, 2010, Haemophilia.). Chemical modification or bioengineering of FVIII may improve half-life to 18-19 hours (Kaufman, 2013, Blood). However, these long acting FVIII variants do not eliminate the need for lifelong FVIII protein administration (Hay, 2012, Blood).

Gene therapy offers the potential of disease-modifying therapy by continuous endogenous production of human FVIII following a single administration of vector. Haemophilia 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, Haemophilia.); thus the therapeutic goal for gene therapy is a modest increase in hFVIII. Finally, the consequences of gene transfer can be assessed using simple quantitative rather than qualitative endpoints that can be easily assayed in most clinical laboratories.

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

7.1 Nonclinical Studies

The nonclinical program supports a single IV administration of BMN 270, the planned clinical route of administration, for the treatment of Haemophilia A in male patients. This

nonclinical program took into account the guidelines and reflection papers for gene therapy medicinal products under EMA Advanced Therapies. 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 (normal CD-1 mouse, B and T cell deficient mouse model of haemophilia 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.

The primary PD of BMN 270 was assessed in a series of non-GLP single dose studies in a FVIII KO x Rag2 mouse model of severe Haemophilia A that recapitulates the change in coagulation observed in the human severe disease population without interfering cross species immunogenicity. PD activity and expression of hFVIII was assessed for durations up to 13-weeks in the FVIII KO x Rag2 mouse given dose range of 2E11 through 2E14 vector genomes (vg)/kg. Low levels of plasma hFVIII were observed in mice given 2E12 vg/kg after eight-weeks, post dose. Plasma hFVIII activity using bleeding time as an endpoint was evaluated in the FVIII KO x Rag2 mouse given up to 2E13 and 1E14 vg/kg BMN 270 at 8 weeks, post dose. BMN 270 related correction of bleeding times showed a dose relationship that was similar to that observed in FVIII KO x Rag2 mice given matched IU levels of Refacto[®].

All cynomolgus monkeys used in this program were screened for neutralizing anti-AAV5 activity prior to study enrollment. PD activity and plasma hFVIII concentrations were evaluated in the cynomolgus monkey given up to 6E13 vg/kg BMN 270 for eight weeks. Peak expression of hFVIII was observed three to six weeks post administration with a subsequent decrease in expression presumably due to immunogenicity though not necessarily correlated to antibody titer.

The normal mouse was utilized in the GLP toxicology study to assess the safety profile of BMN 270 without the background of disease progression and in sufficient number per parameter. The GLP single dose toxicity study in normal CD-1 mice given 6E12 and 6E13 vg/kg with a 4 and 13-week follow up period monitored clinical pathology, defined potential target organs, immunogenicity, gene expression and activity. No changes in liver function were observed. In a single dose PD study in monkey given BMN 270, formation of anti-AAV5 total antibodies was observed at Week 8 with relatively low formation of anti-hFVIII total antibodies. No changes in liver function was observed.

The overall nonclinical safety profile includes formation of anti-AAV5 total antibodies with relatively lower formation of anti-hFVIII total antibodies. Immunogenicity against the AAV capsid and hFVIII is an anticipated finding for BMN 270 treatment and will be monitored in

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the nonclinical and clinical programs. Though not observed in the nonclinical species, liver toxicity utilizing clinical pathology parameters will be monitored in the clinical program based on previous literature. Cellular immune response will also be monitored.

Additionally, the BMN 270 transgene product has a final sequence closely matching that of the protein replacement treatment, Refacto® and therefore the safety profile of the BMN 270 transgene product is anticipated to be similar to Refacto® and have no unique FVIII-specific target organs of toxicity. The AAV5 capsid has not been modified and therefore no unique capsid-specific safety findings are anticipated. Because the biodistribution pattern of AAV5 after IV administration is consistent across species, BioMarin will confirm the nonclinical distribution pattern of BMN 270 during clinical development. Biodistribution of the AAV5 capsid has been documented to predominately target the liver with relatively lower levels of transduction observed in the lung, kidney, spleen, testes and blood compartment depending on the species and timing of administration. Liver targeted distribution of a similar AAV5 Factor IX gene therapy product was observed in the rhesus macaque monkey with low levels of vector genomes detected in spleen, kidney and testis (Nathwani, 2006, Blood). Despite distribution to non-liver organs, no expression of Factor IX was detected in these tissues. Additionally, distribution to the testis was observed in another study in monkeys given an AAV5-codon-optimized human porphobilinogen deaminase; however, vector genomes in the semen were only transiently observed within one week but not thereafter (Paneda, 2013, Hum.Gene Ther.).

Both normal and disease model mice and a limited number of monkeys were utilized to establish proof of concept, species scaling and dose response in order to select the first-in-human (FIH) dose of 6E12 vg/kg. This dose represents 10-fold safety factor from the no observed adverse effect level (NOAEL) in the GLP enabling nonclinical toxicology study in mice.

7.2 Previous Clinical Studies

This is the first clinical study for BMN 270.

BioMarin's program for haemophilia A builds on previous clinical trials of AAV-mediated gene transfer for a related condition, haemophilia B, that were conducted with an AAV2 vector (Manno, 2003, Blood) and an AAV8 vector (Nathwani, 2011, N.Engl.J.Med.), (Nathwani, 2014, N.Engl.J.Med.). The large size of the FVIII cDNA was shortened and a preclinical validation of this approach was performed with an AAV8 vector (McIntosh, 2013, Blood).

AAV serotype 5 is being tested in other clinical trials and was reportedly well tolerated without treatment-related serious adverse events in a recent phase 1 study for treatment of Acute Intermittent Porphyria (D'Avola, 2014, J.Hepatol.). In addition, AAV using other serotypes have been used in 105 clinical studies to date and no safety issue specific to the vector was ever reported.

7.3 Study Rationale

Haemophilia A (HA) is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males (Mannucci, 2001, N.Engl.J.Med.). It is caused by deficiency in the activity of coagulation factor VIII (FVIII), an essential cofactor in the intrinsic coagulation cascade. This disorder can be either inherited, due to a new mutation 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 is largely governed by the level of residual expression. Severe HA is classified as FVIII activity less than 1% of wild type (< 1 IU/dL), moderate disease comprises 1-5% of wild type activity and the mild form is 5-40% activity. The clinical manifestations of severe HA remain frequent spontaneous bleeding episodes, predominantly in joints and soft tissues, with a substantially increased risk of death from haemorrhage when the brain is involved.

Treatment of severe HA presently consists of intravenous injection of plasma derived or recombinant human FVIII protein (rhFVIII) concentrates both as prophylaxis 2-4 times per week, and at the time of a bleed, to prevent or control bleeding episodes, respectively. The half-life for FVIII (12-18 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 treatment (mean of 1 to 7 episodes/year with prophylaxis and up to 30 to 50 episodes/year for on demand treatment) (Nagel, 2011, Haemophilia.). The consequence of multiple bleeding events is the development of an underlying pathology that contributes to debilitating multiple-joint arthropathy and substantially increased risk of death (Nagel, 2011, Haemophilia). Chemical modification (eg, direct conjugation of polyethylene glycol (PEG) polymers) and bioengineering of FVIII (eg, FVIII-Fc fusion proteins) improve half-life by approximately 50%, and thus, show promise in reduced dosing and maintaining activity levels above 1% trough (Stonebraker, 2010, Haemophilia.), (Mahlangu, 2014, Blood). However, these longer acting FVIIIs remain dependent on multiple infusions to maintain critical levels of FVIII activity in severe HA patients. There is therefore a strong unmet need for a fully preventive treatment of HA to give patients a FVIII level compatible with a normal and haemorrhage-free life.

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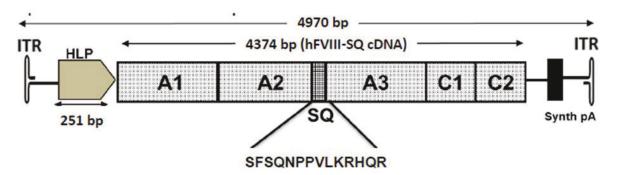
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Gene therapy offers the potential of disease-modifying therapy by continuous endogenous production of active FVIII following a single intravenous administration of a vector with the appropriate gene sequence. Haemophilia A is well suited for a gene 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 modest increases in the level of FVIII (any increase of the plasma level by 2 ng/ml induces an increase in activity of 1%) can ameliorate the severe form of the disease. Thus, relatively small changes in endogenous FVIII activity results in clinically relevant improvements in disease phenotype. Finally, the 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 (Mannucci, 2001, N.Engl.J.Med.). They have an excellent and well defined safety profile, and can direct long term transgene expression with tropism for specific tissues such as the liver (Nathwani, 2005, Curr.Hematol.Rep.) for serotypes 2, 5 and 8 among others). Indeed, an on-going gene therapy clinical trial for a related disorder, haemophilia B, has established that stable (>36 months) expression of human factor IX at levels that are sufficient for conversion of their bleeding phenotype from severe to moderate or mild is achievable following a single peripheral vein administration of AAV-8 vector (Nathwani, 2014, N.Engl.J.Med.). Several participants in this trial have been able to discontinue factor prophylaxis without suffering spontaneous haemorrhages, 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, 2011, Mol.Ther.), (Bainbridge, 2008, N.Engl.J.Med.), (Maguire, 2009, Lancet); (Simonelli, 2010, Mol.Ther.).

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





BMN 270 will be delivered by single intravenous dose and is designed to achieve stable, potentially life-long expression of active FVIII in the plasma, synthesized from vector-transduced liver tissue. The clinical study BMN 270-201 is a first-in-human study designed to assess the relationship of vector dose to the augmentation of residual FVIII activity, and whether these levels are sufficient to alter the clinical phenotype. The relationship of dose to safety will be correlated to the activity of FVIII in patients with severe HA.

7.4 Summary of Overall Risks and Benefits

The majority of subjects in the ongoing 270-201 clinical study who have received 4E13 or 6E13 vg/kg doses of BMN 270 have had Grade 1 asymptomatic elevations in ALT. For most subjects, the elevations have reached only slightly above the upper limit of normal (ULN). Based on the effectiveness of transient oral corticosteroid used to suppress a presumed Class 1 (cytotoxic T-cell) response in prior studies with hepatic transduction with AAV vectors (Mingozzi, 2013), subjects were treated with 7-32 weeks of oral corticosteroids prophylactically or in response to the elevations in ALT to ensure preservation of the transduced hepatocytes. Using this approach, no sustained loss of FVIII activity has been observed in subjects with ALT elevations, consistent with maintaining a high level of hepatocyte function. Moreover, the rise in ALT levels were not accompanied by significant or lasting aberrations in other liver tests such as AST, bilirubin or albumin, indicating that extent of toxicity is limited. There has been one HIV-positive subject in the ongoing 270-302 clinical study who experienced Grade 3 asymptomatic elevations in ALT and AST, which has been attributed to an interaction between one or more of his antiretroviral therapy medications and/or unsuspected underlying hepatic disease with BMN 270. In addition, there has been one subject with Gilbert's syndrome in the ongoing 270-301 clinical study who has experienced Grade 3 asymptomatic elevations in ALT and AST. These cases have led to the exclusion of subsequent HIV-positive subjects and requirement of liver tests at Screening Proprietary and Confidential 10 October 2018

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that are <1.25 times the upper limit of the normal range in the ongoing 270-301 and 270-302 clinical studies. Of note, two HIV-positive subjects in 270-301 and one presumed Gilbert's syndrome subject in 270-201 have received BMN 270 without experiencing any elevations in ALT to date. Overall, the literature and clinical 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, 2016).

The current data available for BMN 270 does not yet permit comprehensive assessment of the benefit:risk profile of this investigational drug. Given the monitoring measures in place in the clinical protocol(s) to minimize the risk to subjects participating in the existing studies, the identified risks are justified by the anticipated benefits that may be afforded to subjects. Each subject in 270-201 will have a comprehensive surveillance plan that monitors LTs during the study, and elevations in LT will be addressed according to the guidelines set forth in the protocol. Safety will be assessed by adverse event reporting and clinical laboratory assessments.

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

Dose selection: The benefit of this study can only be enhanced by selecting a starting dose that maximizes the opportunity of observing a therapeutic effect, and therefore, reducing the possibility of a sub-therapeutic effect. With this consideration in mind, the starting dose 6E12 vg/kg was selected using overall data from the pre-clinical studies conducted in mice (normal and disease model, Rag2 -/- x FVIII -/-) and monkey. A detectable pharmacological response based on activity was observed at 6E12 vg/kg. A 10-fold safety margin based upon the NOAEL was observed in the GLP 13-week study in normal mouse at the highest dose administered. A 30-fold safety margin in an 8-week dose response study in disease model mice based on histology was observed at the highest dose administered. No BMN 270-related changes in clinical observations or chemistry was observed in the monkey at doses up to 6E13 vg/kg, a 10-fold safety margin after 8-weeks. Overall, no BMN 270-related findings, except expected formation of anti-AAV5 antibodies, were observed at the highest administered doses of 6E13, 2E14 and 6E13 vg/kg in the normal mouse, disease model mouse and monkey, respectively.

Based on these key pre-clinical findings it can be suggested that the proposed starting dose of 6E12 vg/kg should not pose any risk or safety concerns to subjects with the best chance of benefiting the subject therapeutically.

8 STUDY OBJECTIVES

The primary objectives of the study are:

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

The secondary objectives of the study are:

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

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

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

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

- Cohort 1: 6E12 vector genomes [vg] per kilogram of body weight, given as a single intravenous dose (iv)
- Cohort 2: 2E13 vg per kilogram, iv
- Cohort 3: 6E13 vg per kilogram, iv
- Cohort 4: 4E13 vg per kilogram, iv

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

Cohorts 1-3

The first three cohorts will be enrolled sequentially, allowing a period of 3 weeks or more between cohorts. Dose escalation may occur after a single subject in a cohort has been safely dosed if the resulting FVIII activity at the Week 3 visit is < 5 IU/dL in both assays. Three weeks is expected to be the time the expression will be close to the maximum. This escalation paradigm is intended to minimize the subject numbers exposed to subtherapeutic doses. The decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and a panel of investigators participating in the study.

If the FVIII activity reaches ≥ 5 IU/dL at the Week 3 visit, then the remaining subjects in the cohort will be enrolled without the need to wait for 3 weeks between subjects.

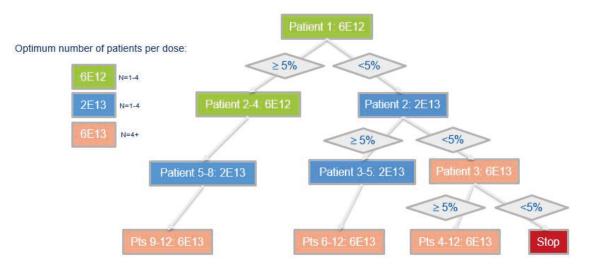


Figure 9.1.1: Flow Chart of Dose Escalation Scheme for Cohorts 1 to 3

Subject 1 (Cohort 1) will be dosed by intravenous infusion with 6E12 vg/kg of body weight. If the FVIII activity level does not reach 5 IU/dL or greater (expressed as % in Figure 9.1.1) at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 1 and enrollment into Cohort 2 will initiate with Subject 2 at the next dose (2E13 vg/kg).

If the FVIII activity level in the first subject treated in Cohort 2 does not reach \geq 5 IU/dL at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 2 and enrollment into Cohort 3 (6E13) will initiate with the next subject.

If the FVIII activity level in the first subject treated in Cohort 3 does not reach \geq 5 IU/dL at the Week 3 visit in both assays, then the DRB will recommend whether to continue to add subjects to the cohort and/or whether to continue the study.

For the first subject treated in each of the first 3 cohorts, if the activity level reaches \geq 5 IU/dL and no safety issue is found, then up to four subjects will be enrolled in the Cohort, though the adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

<u>Cohort 4</u>

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

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There will be an ongoing review of individual patient safety and efficacy data by the medical monitor and the Data Review Board (DRB). The adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

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

In subjects who experience recurrent bleeding episodes, the Investigator and Medical Monitor will discuss whether to resume prior FVIII prophylaxis. Subjects who do not respond to BMN 270 treatment (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, follow an abbreviated visit schedule after Week 52, as applicable and at the discretion of the Investigator.

Because subjects develop neutralizing immunity upon exposure to the capsid, re-challenge of vector is not a likely treatment option and these subjects have effectively a single opportunity for therapy using this AAV capsid. Efficacy will be determined by FVIII activity at 16 weeks post dose. Safety will be evaluated for approximately 5 years after dosing. Any safety signal may trigger a review of the data and possible additional immunogenicity studies that include an assessment of cellular immune responses using collected PBMC. Additionally, if any of the events listed in Section 9.3.3.1 occur, enrollment into the trial will be halted to complete an extensive safety analysis. Notification of the study enrollment halt will be sent by the Sponsor to the participating sites via telephone and email immediately after becoming aware of a safety concern. This will ensure no additional subjects are dosed until the signal has been completely evaluated. If, following safety review by the DRB and the Sponsor, it is deemed appropriate to restart dosing, a request to restart dosing with pertinent data will be submitted to the health authority.

A summary of events and assessments are provided by visit in Table 9.1.1 for Screening, Baseline and BMN 270 Infusion, in Table 9.1.2 for Post-Infusion Follow-up, and in Table 9.1.3 and Table 9.1.4 for Safety Follow-up.

Table 9.1.6, dealing with the apeutic corticosteroid use in the event of elevated LTs, is discussed in Section 9.4.8.2.

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	Pri	BMN 270				
Assessment	Screening ⁱ (Day -28 to Day -1)	Smart Rescreening ⁱ (Day -28 to Day -1)	Baseline (Day -7 to Day -1) ^h	Infusion Visit (Day 1) ¹		
Informed consent	X					
Medical History	Х					
Physical Examination ^a	Х		Х	Х		
Height and Weight ^a	Х					
Vital Signs	Х	Х		Х		
Assessment of Adverse Events and Concomitant Medications	Х	Х	Х	Х		
Documentation of bleeding episodes and FVIII usage (by either subject or clinical information)	Х	Х	Х			
Distribution of subject diaries and training in their use			Х			
Electrocardiogram	Х					
Chest X-ray	Х					
Liver Ultrasound	Х					
hFVIII Assays ^b	Х	Xj				
AAV5 Assays ^c	Х	Х		Х		
Screen for Hepatitis B, Hepatitis C, HIV ^d	Х					
Blood chemistry, haematology, coagulation screen, and CRPe	Х	Х	X			
Urine Tests ^e	Х	Х	Х			
Liver Tests ^e	Х	Х	Х			
PBMC collection for CTL baseline			Х			
Von Willebrand Factor Antigen (VWF:Ag)	Х					
Direct Thrombin Test			Х			
PCR of vector DNA in blood, saliva, urine, semen, and stools			Х			
Biomarker testing ^f	Х					
Exploratory biomarker assessments ^g			Х			
Haemo-QoL-A Quality of Life (QoL) assessment			Х			
BMN 270 Infusion				Х		

Table 9.1.1: Schedule of Events – Screening and Infusion

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- ^a Complete physical examination should be done at Screening. Brief physical examination may be done at Baseline and at the BMN 270 Infusion Visit. Height will be recorded at Screening only. Weight will be recorded at Screening and then every 6 months thereafter.
- ^b Includes baseline hFVIII activity (chromogenic substrate assay and one-stage clotting assay), hFVIII coagulation activity exploratory assay, hFVIII inhibitor level (Bethesda assay with Nijmegen modification), hFVIII total antibody titer, and hFVIII antigen (ELISA).
- ^c Screening (done during Screening) and testing (at Infusion Visit) of AAV5 pre-existing immunity may include plasma samples for 3 assays (in vivo transduction inhibition, in vitro transduction inhibition and AAV5 total antibody assays). Sample collection on the day of the infusion visit must be performed before the BMN 270 infusion is given.
- ^d Patients with documented negative results within the last 30 days do not need to be retested.
- ^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.
- $^{\rm f}$ Includes HLA genotyping, FVIII genotyping, TNF α and IL10a single nucleotide polymorphisms.
- ^g 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 Direct Thrombin Activity test and any other exploratory assessments) will be performed only as deemed necessary by the Sponsor.
- ^h Should the screening visit occur within 7 days of the drug infusion, physical examination, blood chemistry, LTs, haematology, urine tests, coagulation screen, and CRP do not need to be repeated at Baseline.
- ⁱ Smart rescreening should only be performed if a patient has been determined to be eligible for the study and is unable to complete the Baseline assessments and Infusion prior to the closing of the original Screening window. Subjects who undergo smart rescreening must complete the rescreening assessments and receive the infusion within 90 days of signing the original consent. Subjects who do not complete dosing within 90 days will be required to re-consent and undergo all screening procedures. Subjects may not undergo smart rescreening more than once.
- ^j Only the hFVIII inhibitor level (Bethesda assay with Nijmegen modification) assay must be done at smart rescreening.
- ^k Assessments on the day of infusion must be performed prior to the infusion. 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), following the infusion hourly (± 5 minutes) for 6 hours and then every 2 hours (± 15 minutes) for 6 hours and then at 4 hour intervals (± 15 minutes).

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	Follow-Up After BMN 270 Administration – Weeks*																	
		Week 1																
Assessment	D2	D4	D8	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Physical examination ^a			Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)			Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Vital Signs			Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Blood chemistry, haematology, coagulation screen, and CRP ^b				Х		Х		Х		Х		Х		Х				Х
Urine Tests ^b						Х				Х				Х				Х
Liver Tests (local) ^b		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
FVIII assays (local) ^c		X	Х	Х	X	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Liver Tests (central) ^b		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
FVIII assays (central) ^d		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
FVIII antibody titer						Х				Х				Х				Х
PCR of vector DNA in blood, saliva, urine, semen, and stools ^e	X	Х	Х			Х		Х		Х		Х		Х		Х		Х
Exploratory biomarker assessments ^f						Х				Х				Х				Х
Haemo-QoL-A QoL assessment			Х	Х	Х	Х												Х
AAV5 antibody titer										Х								Х
Testing for reactivation of hepatitis B and hepatitis C																		Xg
PBMC collection			Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Von Willebrand Factor Antigen (VWF:Ag)						Х				Х				Х				Х
Direct Thrombin test			Х												Х			

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

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 * Visit windows are $\pm\,48$ hours (and include the Day 4 visit)

^a Brief physical examination should be done at all weekly visits except Week 16, where a complete physical examination should be performed. Refer to Section 9.7.8.5.

^b Refer to Table 9.7.8.2.1 for laboratory assessments to be included, and to Table 9.7.8.3.1 for liver tests. LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) 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 \geq 3x ULN. Patients with ALT > 1.5 ULN during the study may undergo additional evaluations (eg, imaging studies including MRI or ultrasound, additional blood tests, and/or liver biopsy) at the discretion of the investigator. Additional testing of FVIII and LTs during any study week may be performed if: (1) the ALT has increased to above ULN; (2) Increases in ALT values from prior assessment are accompanied by declines in FVIII activity level; or after a discussion between the Medical Monitor and the Investigator based on a review of subject data. If FVIII levels and/or ALT values are stable over the course of several weeks, assessment of FVIII activity and ALT levels may be adjusted based on discussion between the Medical Monitor and the Investigator.

- ^c Includes hFVIII activity level (one-stage clotting assay and chromogenic substrate 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 standard of care 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 Includes hFVIII activity level (one-stage clotting assay and chromogenic substrate assay), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, hFVIII coagulation activity exploratory assay, and hFVIII antigen (ELISA). If a subject has used FVIII within 72 hours of a measurement day, all efforts should be made to obtain FVIII activity measurements when a 72-hour interval without FVIII use is achieved; the 72-hour wash-out period is only intended for subjects who have achieved FVIII \geq 5 IU/dL at 16 weeks after BMN 270 infusion and who have not resumed standard of care 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 Collection to occur on Day 2 and 4 following BMN 270 infusion, and then until at least 3 consecutive negative results are obtained. Collection and testing of semen samples must continue through Week 12, even if 3 consecutive negative samples in that compartment have already been recorded.

^f 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 Direct Thrombin Activity test and any other exploratory assessments) will be performed only as deemed necessary by the Sponsor.

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

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	Follow-Up After BMN 270 Administration – Weeks*															
Assessment	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
Physical examination ^a	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	X	Х	Х	Х
Weight										Х						
Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)	X	Х	Х	Х	Х	Х	Х	Х	Х	Х	X	Х	Х	Х	Х	X
Vital Signs	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Blood chemistry, haematology, coagulation screen, and $\mathrm{CRP}^{\mathrm{b}}$				X				Х				Х				X
Urine Tests ^b				Х				Х				Х				Х
Liver Tests (local) ^b	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	X	Х	Х	Х
FVIII assays (local) ^c	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Liver Tests (central) ^b	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
FVIII assays (central) ^d	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
FVIII antibody titer				Х								Х				
PCR of vector DNA in blood, saliva, urine, semen, and stools ^e				Х				Х				Х				X
Exploratory biomarker assessments ^f				Х				Х				Х				Х
Haemo-QoL-A QoL assessment												Х				
AAV5 antibody titer				Х				Х				Х				Х
PBMC collection	Х	Х	Х	Х		Х		Х		Х		Х		Х		Х
Von Willebrand Factor Antigen (VWF:Ag)				Х				Х				Х				Х
Direct Thrombin test										Х						

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

* Visit windows are \pm 48 hours

^a Brief physical examination should be done at all weekly visits. Refer to Section 9.7.8.5.

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^b Refer to Table 9.7.8.2.1 for laboratory assessments to be included, and to Table 9.7.8.3.1 for liver tests. LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) 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 \geq 3x ULN. Patients with ALT > 1.5 ULN during the study may undergo additional evaluations (eg, imaging studies including MRI or ultrasound, additional blood tests, and/or liver biopsy) at the discretion of the investigator. Additional testing of FVIII and LTs during any study week may be performed if: (1) the ALT has increased to above ULN; (2) Increases in ALT values from prior assessment are accompanied by declines in FVIII activity level; or after a discussion between the Medical Monitor and the Investigator based on a review of subject data. If FVIII levels and/or ALT values are stable over the course of several weeks, assessment of FVIII activity and ALT levels may be adjusted based on discussion between the Medical Monitor and the Investigator.

^c Includes hFVIII activity level (one-stage clotting and chromogenic substrate 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 \geq 5 IU/dL at 16 weeks after BMN 270 infusion and who have not resumed standard of care 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 Includes hFVIII activity level (one-stage clotting and chromogenic substrate assay), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, hFVIII coagulation activity exploratory assay, and hFVIII antigen (ELISA). If a subject has used FVIII within 72 hours of a measurement day, all efforts should be made to obtain FVIII activity measurements when a 72-hour interval without FVIII use is achieved; the 72-hour wash-out period is only intended for subjects who have achieved FVIII \geq 5 IU/dL at 16 weeks after BMN 270 infusion and who have not resumed standard of care 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 Collection for each matrix to occur until at least 3 consecutive negative results are obtained.

^f 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 Direct Thrombin Activity test and any other exploratory assessments) will be performed only as deemed necessary by the Sponsor.

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	Year 1 – Weeks*												
Assessment	33	34	35	36	38	40	42	44	46	48	50	52	
Physical examination ^a	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	
Weight ^a												Х	
Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)	Х	X	Х	Х	Х	Х	Х	Х	X	X	X	X	
Vital Signs	Х	Х	Х	Х	Х	Х	Х	Х	Х	X	X	Х	
Blood chemistry, haematology, coagulation screen, and CRP ^b				Х		Х		Х		X		Х	
Urine Tests ^b				Х		Х		Х		Х		Х	
Liver Tests (local) ^b	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	X	Х	
FVIII assays (local) ^c	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	
Liver Tests (central) ^b	Х	X	Х	Х	Х	Х	Х	Х	Х	X	X	Х	
FVIII assays (central) ^d	Х	Х	Х	Х	Х	Х	Х	Х	Х	X	X	Х	
AAV5 antibody titer				Х		Х		Х		X		Х	
FVIII antibody titer				Х				Х				Х	
PBMC Collection (for determination of FVIII and Capsid specific CTL activity)		X		Х				Х				X	
Von Willebrand Factor Antigen (VWF:Ag)				Х		Х		Х		X		Х	
Direct Thrombin Test					Х							Х	
PCR of vector DNA in blood, saliva, urine, semen, and stools ^e				Х		Х		Х		Х		Х	
Exploratory biomarker assessments ^f				Х		Х		Х		Х		Х	
Haemo-QoL-A QoL assessment												Х	

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

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

^a Complete physical examination should be performed at Week 52; brief physical examination may be performed at other study visits. Refer to Section 9.7.8.5.

^b Refer to Table 9.7.8.2.1 for laboratory assessments to be included, and to Table 9.7.8.3.1 for liver tests. LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) 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

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subject's ALT is \geq 3x ULN. Patients with ALT > 1.5 ULN during the study may undergo additional evaluations (eg, imaging studies including MRI or ultrasound, additional blood tests, and/or liver biopsy) at the discretion of the investigator. Additional testing of FVIII and LTs during any study week may be performed if: (1) the ALT has increased to above ULN or increased by > 10 U/L from prior assessment; (2) Increases in ALT values from prior assessment are accompanied by declines in FVIII activity level; or after a discussion between the Medical Monitor and the Investigator based on a review of subject data. If FVIII levels and/or ALT values are stable over the course of several weeks, assessment of FVIII activity and ALT levels may be adjusted based on discussion between the Medical Monitor and the Investigator.

- ^c Includes hFVIII activity level (one-stage clotting and chromogenic substrate 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 \geq 5 IU/dL at 16 weeks after BMN 270 infusion and who have not resumed standard of care 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 Includes hFVIII activity level (one-stage clotting and chromogenic substrate assay), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, hFVIII coagulation activity exploratory assay, and hFVIII antigen (ELISA). If a subject has used FVIII within 72 hours of a measurement day, all efforts should be made to obtain FVIII activity measurements when a 72 hour interval without FVIII use is achieved; the 72-hour wash-out period is only intended for subjects who have achieved FVIII \geq 5 IU/dL at 16 weeks after BMN 270 infusion and who have not resumed standard of care 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 Sample testing during Safety Follow-Up is not required if at least 3 consecutive samples are cleared during the Post-Infusion Follow-Up period.

^f 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 Direct Thrombin Activity test and any other exploratory assessments) will be performed only as deemed necessary by the Sponsor.

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	Years 2-5*	Year 2* Q4W ^h	Years 3-5* Q6W ^h	End of Year Visit				
				Year 2	Year 3	Year 4	Year 5	ETV
Assessment	Q12W			W104	W156	W208	W260	
Physical examination ^a	Xa				Х	(a		Х
Weight ^a	Xa				Х	^{(a}		Х
Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)	Х	Х	X		2	K		Х
Vital Signs	Х				2	K		Х
Blood chemistry, haematology, coagulation screen, and CRP ^b	Х				2	K		Х
Urine Tests ^b	Х				2	K		Х
Liver Tests (local) ^b	Х	Х	Х		2	K		Х
FVIII assays (local) ^c	Х	Х	Х		2	K		Х
Liver Tests (central) ^b	Х	Х	Х		2	K		Х
FVIII assays (central) ^d	Х	Х	Х		2	K		Х
AAV5 antibody titer	Х				2	K		Х
FVIII antibody titer	Х				2	K		Х
PBMC Collection (for determination of FVIII and Capsid specific CTL activity)	Х				2	K		Х
Von Willebrand Factor Antigen (VWF:Ag)	Х				2	K		Х
Direct Thrombin Test	Х				2	K		Х
PCR of vector DNA in blood, saliva, urine, semen, and stools ^e	Xe	Xe	Xe		Х	(e		Х
Exploratory biomarker assessments ^g	Х				2	K		Х
Haemo-QoL-A QoL assessment	Xf				Σ	ζf		Х

Table 9.1.5: Schedule of Events – Safety Follow-Up (Years 2-5)

* Visit windows are ± 2 weeks for visits in Years 2-5. The Q6W visits during Years 3-5 should restart after each End of Year visit (eg, the first Q6W visit during Year 3 should be ~6 weeks after the End of Year 2 visit).

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- ^a Complete physical examination should be performed at the End of Year visits; brief physical examination may be performed at other study visits. Weight should be recorded at the second Q12W visit each year and at every End of Year visit during Years 2-5.
- ^b Refer to Table 9.7.8.2.1 for laboratory assessments to be included, and to Table 9.7.8.3.1 for liver tests. LTs may be monitored more or less frequently (and in particular when ALT values are \geq 1.5x ULN) 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 \geq 3x ULN. Patients with ALT \geq 1.5x ULN during the study may undergo additional evaluations (eg, imaging studies including MRI or ultrasound, additional blood tests, and/or liver biopsy) at the discretion of the investigator. Additional testing of FVIII and LTs during any study week may be performed if: (1) the ALT has increased to above ULN or increased by > 10 U/L from prior assessment; (2) Increases in ALT values from prior assessment are accompanied by declines in FVIII activity level; or after a discussion between the Medical Monitor and the Investigator based on a review of subject data. If FVIII levels and/or ALT values are stable over the course of several weeks, assessment of FVIII activity and ALT levels may be adjusted based on discussion between the Medical Monitor and the Investigator. During Years 2-5 of the Post-Infusion Follow-Up period, urine tests and blood, chemistry, and coagulation tests should be performed at the second Q12W visit each year and at every End of Year visit.
- ^c Includes hFVIII activity level (one-stage clotting and chromogenic substrate 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 standard of care FVIII replacement therapy. If FVIII levels are elevated or stable over the course of several weeks, assessment of FVIII activity may be adjusted based on discussion between the Medical Monitor and the Investigator. A d-dimer may be considered under circumstances in which FVIII activity levels are above the normal physiological range and/or if there is a concern for a venous thromboembolism. If a subject tests positive in the Bethesda assay (with Nijmegen modification) during Years 3-5, a fresh sample should be collected within 4 weeks of the initial visit that had a positive result.
- ^d Includes hFVIII activity level (one-stage clotting and chromogenic substrate assay), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, hFVIII coagulation activity exploratory assay, and hFVIII antigen (ELISA). If a subject has used FVIII within 72 hours of a measurement day, all efforts should be made to obtain FVIII activity measurements when a 72 hour interval without FVIII use is achieved; the 72-hour wash-out period is only intended for subjects who have achieved FVIII \geq 5 IU/dL at 16 weeks after BMN 270 infusion and who have not resumed standard of care 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) in 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 Safety Follow-Up is not required if at least 3 consecutive samples are cleared during the Post-Infusion Follow-Up period. Subjects who have not had 3 consecutive negative samples by Week 52 should continue to have PCR testing every 4 weeks (during Year 2) or every 6 weeks (during Years 3-5) until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor).
- ^fHaemo-QoL-A QoL assessment during Years 2-5 of Safety Follow-up should be performed at the second Q12W visit each year and at every End of Year visit.
- ^g 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 Direct Thrombin Activity test and any other exploratory assessments) will be performed only as deemed necessary by the Sponsor.

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^h Subjects who meet the definition of treatment failure to BMN 270 therapy after Week 52 may omit the Q4W and Q6W visits during Years 2-5, and must attend only the Q12W and End of Year visits. Such subjects following the abbreviated schedule who have not yet cleared vector shedding in all fluids must still provide samples Q4W (during Year 2) or Q6W (during Years 3-5) until vector shedding has been cleared (but do not need to do other scheduled assessments at those visit dates).

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	Steroid Treatment Period ^d									Post-Steroid Period ^c						
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11 ^b	Week 1	Week 2	Week 3	Week 4	Week 13
Therapeutic corticosteroids (dose in mg/day) ^a	60 mg	60 mg	40 mg	40 mg	30 mg	30 mg	20 mg	20 mg	15 mg	10 mg	5 mg					
FVIII activity testing												Х	Х	Х	Х	
Liver testing												Х	Х	Х	Х	
Hepatitis B testing ^e						Х						Х				Х
HCV Viral Load ^e						Х						Х				Х

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

^a Therapeutic corticosteroids may be initiated when a subject's ALT value is ≥ 1.5x ULN or based on review of FVIII and liver enzyme data after consultation between the Investigator and the Medical Monitor.

^b Following initiation or completion of steroid regimen, if ALT elevation ≥ 1.5x ULN is reported, steroid management decisions will based on discussions between the Investigator and Medical Monitor. Modification of the steroid regimen may take into consideration possible confounders for the ALT elevation and impact on FVIII expression.

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

^d Regardless of the assessments listed in the Schedule of Assessments (Table 9.1.2, Table 9.1.3, or Table 9.1.4), subjects initiated on corticosteroids will only be required to have laboratory evaluations on a weekly basis.

^e Should only be performed in subjects with a history of hepatitis B or hepatitis C prior to study entry.

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9.2 Discussion of Study Design, Including Choice of Control Group

Study 270-201 is designed to be a first-in-man, phase 1/2 open-label, dose escalation study in patients with severe haemophilia A. Four doses of BMN 270 will be evaluated and the dose escalation decision tree for Cohorts 1-3 is summarized in Figure 9.1.1.

The decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and the DRB.

There will be no control group. Parameters for each subject will be compared to a pre-treatment assessment of safety (liver function) and efficacy (number of bleeds, use of replacement therapy).

As AAV based treatment always leads to anti-capsid immune response, no true control group (for example with an empty AAV) is possible.

9.3 Selection of Study Population

Up to 15 severe haemophilia A patients may enroll into the study; the actual number of patients will depend on the criteria for dose escalation.

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 criteria:

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

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 immunity to the AAV5 capsid as measured by AAV5 transduction inhibition or AAV5 total antibodies
- 2. Any evidence of active infection or any immunosuppressive disorder.
- 3. HIV positive
- 4. Significant liver dysfunction as defined by abnormal elevation of:
- 5. ALT (alanine transaminase) to 3 times the upper limit of normal;
- 6. Bilirubin above 3 times the upper limit of normal;
- 7. Alkaline phosphatase above 3 times the upper limit of normal; or
- 8. INR (international normalized ratio) \geq 1.4.
- 9. Potential participants who have had a liver biopsy in the past 3 years are excluded if they had significant fibrosis of 3 or 4 as rated on a scale of 0-4
- 10. Evidence of any bleeding disorder not related to Haemophilia A
- 11. Platelet count of $< 100 \text{ x } 10^9/\text{L}$
- 12. Creatinine \geq 1.5 mg/dL
- 13. Liver cirrhosis of any etiology as assessed by liver ultrasound
- 14. Hepatitis B if surface antigen is positive
- 15. Hepatitis C if RNA is positive
- 16. Treatment with any IP within 30 days prior to the end of the screening period
- 17. Any disease or condition at the physician's discretion that would prevent the patient from fully complying with the requirements of the study including possible corticosteroid treatment outlined in the protocol. The physician may exclude patients unwilling or unable to agree on not using alcohol for the 16-week period following the viral infusion.
- 18. Prior treatment with any gene transfer agent
- 19. Major surgery planned in the 16-week period following the viral infusion
- 20. Use of immunosuppressive agents or live vaccines within 30 days before the viral infusion

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. A subject's participation in the study may be discontinued at any time at the discretion 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.

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 admitted into the study or does not meet entry criteria
- Subject is lost to follow-up

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

The Investigator or designee must explain to each subject, before enrollment into the study, that for evaluation of study results, the subject's protected health information obtained during the study may be shared with the study Sponsor, regulatory agencies, and IRB/IEC/REB. It is the Investigator's (or designee's) responsibility to obtain written permission to use protected health information per country-specific regulations, such as the Health Insurance Portability and Accountability Act (HIPAA) in the US, from each subject. If permission to use protected health information is withdrawn, it is the Investigator's responsibility to obtain a written request, to ensure that no further data will be collected from the subject and the subject will be removed from the study.

9.3.3.1 Study Safety Evaluation Criteria

If any of the following events occur in a subject in the study who has received BMN 270 infusion, enrollment into the trial will be put on halt to complete an extensive safety analysis per Section 9.1.

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- Any ALT elevation > 5x ULN for at least 2 consecutive weeks after administration of BMN 270, in the absence of a definitive alternate etiology for the increase
- The occurrence of Grade 3 or higher adverse events (excluding ALT elevation) assessed as related to study drug, including liver failure and clinical hepatitis
- The detection of neutralizing antibodies to hFVIII following BMN 270 infusion
- The detection of AAV vector DNA in the semen of a participant in 3 consecutive samples (which are at least 2 weeks apart) more than 52 weeks after BMN 270 infusion, as discussed in Section 9.7.8.6
- The occurrence of a malignancy excluding skin cancers at any point after BMN 270 infusion

If the following event occurs in a subject in the study who has received BMN 270 infusion, a DRB review and analysis of safety data will be undertaken to determine whether the enrollment into the trial will be put on halt:

• Grade 2 adverse event assessed as related to study drug that persists for at least 7 days

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 CRF pages. In legal jurisdictions where use of initials is not permitted, a substitute identifier will be used.

Subjects who withdraw from the study will not be replaced.

9.3.5 Duration of Subject Participation

The duration of this study will be approximately 264 weeks. This includes 4 weeks of screening, 1 day of BMN 270 infusion, 16 weeks of Post-Infusion Follow-Up, and 244 weeks of Safety Follow-Up. A primary endpoint analysis on safety and efficacy will be performed at 16 weeks.

9.4 Treatments

BioMarin or its designee will provide the study site with study drug sufficient for study completion. BioMarin is responsible for shipping study drug to clinical sites.

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.



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 2 mL polypropylene cryovial. Each vial contains 1.1 mL of AAV5-hFVIII-SQ at a concentration of 2E13 vector genomes per mL in a pH 7.4 phosphate buffer.

The study drug label includes the following information: lot number, required storage conditions, a precautionary statement, expiry date, study number, and BioMarin name and address. Labelling will be done according to country specific requirements.

9.4.3 Storage

At the study site, all IP must be stored under the conditions specified in the IB 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

After a physical examination performed by the PI or designee, participants will be admitted on the day of BMN 270 infusion. 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. An electric syringe pump will be used to infuse through an in-line, low protein binding 0.22 micron filter. BMN 270 will be infused through the catheter using an appropriate infusion pump at a constant rate of 4 ml/min while monitoring the vital signs (pulse, blood pressure, respiration rate and temperature) at 15 minute (\pm 5 minutes) intervals. The anticipated maximum interval from initiation of thawing of BMN 270 to completion of the infusion is 4 hours, although the IP has been shown to be stable at room temperature for 6 hours.

Following completion of the infusion, vital signs will be monitored hourly (\pm 5 minutes) for 6 hours and then every 2 hours (\pm 15 minutes) for 6 hours and then at 4 hour intervals. If the vital signs are stable the catheter will be removed 20-24 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 24 hours to observe for any immediate toxicity of the procedure. After 24 hours, participants 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.

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 Sponsor will be required prior to enrollment of each study subject. Upon their enrollment into the study, subjects will be assigned a unique subject number and dose level by the Sponsor.

Cohorts 1 to 3 are enrolled serially and their dose is defined in Section 9.4.6.2 below. Escalation is based on FVIII activity 3 weeks after injection. Cohorts may receive the next higher dose if subjects in the previous cohort does not meet the activity criteria, or the same dose if subjects in the previous cohort meets the activity criteria. Subjects in Cohort 4 will all be enrolled at a single dose.

9.4.6 Selection of Doses Used in the Study

The starting dose was based on the expression of hFVIII observed in nonclinical studies of mice and monkeys. The starting dose has a significant safety margin (10-fold) from NOAEL in mice. The dose escalation is half-logs based.

9.4.6.1 Selection of Timing of Dose for Each Subject

A minimum of three weeks are required between subjects, to allow for evaluation of safety and expression of hFVIII. After three weeks, depending on the activity level, the choice of the dose for the next subject will be made as described below.

9.4.6.2 Selection of Dose for Each Subject

The starting dose was determined by expression of hFVIII observed in mice and monkeys and a scale up factor based on previous experience, an improved purification process over previous trials (thus potentially decreasing the risk of immune response), and a new evaluation of the titer (PCR performed after hairpin removal).

For Cohorts 1 to 3, approximately three weeks after an injection, the decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and the DRB.

Subject 1 (Cohort 1) will be dosed by intravenous infusion with 6E12 vg/kg of body weight. If the FVIII activity level does not reach 5 IU/dL or greater (expressed as % in Figure 9.1.1)

at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 1 and enrollment into Cohort 2 will initiate with Subject 2 at the next dose (2E13 vg/kg).

If the FVIII activity level in the first subject treated in Cohort 2 does not reach \geq 5 IU/dL at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 2 and enrollment into Cohort 3 (6E13) will initiate with the next subject.

If the FVIII activity level in the first subject treated in Cohort 3 does not reach \geq 5 IU/dL at the Week 3 visit in both assays, then the DRB will recommend whether to continue to add subjects to the cohort and/or whether to continue the study.

For the first subject treated in each of the first 3 cohorts, if the activity level reaches \geq 5 IU/dL and no safety issue is found, then up to four subjects will be enrolled in that cohort, though the adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

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

There will be an ongoing review of individual patient safety and efficacy data by the medical monitor and the DRB. The adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

Refer to Figure 9.1.1 for a visual representation of the study design for Cohorts 1-3

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 CRF. The Investigator may prescribe additional medications 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 CRF.

The following medications are prohibited starting 30 days before Screening:

- Live vaccines
- Systemic immunosuppressive agents
- Emicizumab
- Fitusiran
- Concizumab
- Efavirenz
- Lamivudine

Subjects who begin antiretroviral therapy following BMN 270 infusion and during their participation in 270-201 must have their antiretroviral medication regimen approved by the Investigator and Medical Monitor prior to starting antiretroviral treatment.

Medications which are predominately metabolized by the liver (eg, acetaminophen) and alcohol should, whenever possible, be avoided for the first 52 weeks of the study, and particularly within 48 hours prior to lab work.

9.4.8.1 Concomitant Haemophilia Treatments

Subjects on "on demand" therapy for FVIII will continue their treatment at will. Subjects on prophylactic FVIII therapy will discontinue their treatment starting the day of infusion and switch to an "on demand" schedule. FVIII can always be taken as needed by the subject, who will carefully record his treatment and bleeding episodes in his diary. In addition, information on FVIII usage by medical history will be collected (if available) from subjects for the 6 month period immediately preceding study enrollment.

9.4.8.2 Glucocorticoid Treatment of Elevated Hepatic Transaminases

During the Post-Infusion Follow-up Period and the Safety Follow-Up Period, each subject will have comprehensive surveillance plan monitoring of LTs (at local labs, once per week for Weeks 1-36, then once every 2 weeks from Week 37-52). LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.

9.4.8.2.1 Therapeutic Corticosteroids

In general, therapeutic corticosteroids may be initiated when a subject's ALT value is $\geq 1.5x$ ULN, or based on review of FVIII and liver enzyme data after consultation between the Medical Monitor and the Investigator.

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Reports of raised LTs (defined as $ALT \ge 1.5x$ ULN) should be made to the BioMarin medical monitor within 30 minutes of the lab value being available. Local laboratory results of LTs will be used to trigger corticosteroid treatment as needed. In case of discrepant results between local and central laboratories, the Investigator and Medical Monitor will decide further action.

Following initiation or completion of therapeutic corticosteroids, if ALT elevation $\geq 1.5x$ ULN is reported, steroid management decisions will based on discussions between the Investigator and Medical Monitor. Modification of the steroid regimen may take into consideration possible confounders for the ALT elevation and impact on FVIII expression.

Treatment with prednisolone will be initiated at a dose of 60 mg per day and then gradually tapered (60 mg daily for the first 2 weeks, then 40 mg the next 2 weeks, then 30 mg the next two weeks, then 20 mg the next two weeks, then 15 mg for the next week, then 10 mg for the next week, then 5 mg for the next week, then stop, for a total treatment of 11 weeks) (refer to Table 9.1.6).

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

Management and monitoring of reactions to corticosteroids should be determined by the Investigator's clinical judgment in consultation with the Sponsor's Medical Monitor. This includes the contraindicated use of NSAIDs during corticosteroid treatment, and specific monitoring not already covered by the schedule of events. For the subjects with a past medical history of hepatitis B or hepatitis C prior to study entry, Hepatitis B status and HCV viral load will be rechecked 6 weeks after the start of corticosteroid treatment, and then 1 week and 13 weeks after the completion of corticosteroid treatment. All adverse events should be reported as outlined in Section 10 of the protocol.

9.4.9 Treatment Compliance

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

9.5 Investigational Product Accountability

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

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9.5.1 Return and Disposition of Clinical Supplies

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

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

All study drug and related materials should be stored, inventoried, reconciled, and destroyed or returned according to applicable state and federal regulations and study procedures.

9.6 Dietary or Other Protocol Restrictions

There are no dietary or other protocol restrictions for this 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 samples.

9.7 Safety and Efficacy Variables

As this is a first-in-man study, the primary endpoint of safety will be assessed as explained in Section 9.7.8.

The primary efficacy measure will be to assess plasma FVIII activity. The efficacy goal of the study is to establish the dose relationship to FVIII activity \geq 5 IU/dL at 16 weeks post BMN 270 administration.

9.7.1 Safety and Efficacy Measurements Assessed

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

9.7.2 Primary Efficacy Variables

The primary efficacy measure will be the plasma FVIII activity monitored on a regular basis after BMN 270 dose. The efficacy goal of the protocol is to ascertain the dose range of

BMN 270 required to convert severe HA patients to expression of FVIII at 5 IU/dL or above, (ie, a mild severity). This is associated in natural history studies with clinically superior long term outcomes (Den Ujil, 2011, Haemophilia).

The following assays (assessed by the central laboratory) will be used to measure the primary efficacy variable:

- FVIII activity (chromogenic substrate assay)
- FVIII activity by one-stage clotting 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 standard of care FVIII replacement therapy.

The FVIII activity level in both assays and the number of subjects with FVIII activity ≥ 5 IU/dL in at least one of the two assays will be summarized.

FVIII activity assays will also be performed at the local laboratory at the time points indicated in Table 9.1.2, Table 9.1.3, and Table 9.1.4, but will be used in conjunction with local lab LT assessments to monitor subject safety and need for initiation of therapeutic corticosteroid dosing; local laboratory FVIII activity assessments will not be used to assess efficacy or to measure the primary efficacy outcome of the study.

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, follow an abbreviated visit schedule after Week 52, as applicable and at the discretion of the Investigator.

Timing of assessment by these assays is provided in Table 9.1.2, Table 9.1.3, and Table 9.1.4. Details on performing the assays are included in the Laboratory Manual.

9.7.3 Secondary Efficacy Variables

Secondary efficacy measures will be the reduction in the frequency of factor replacement therapy, and reduction in the number of bleeding episodes. 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.

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

9.7.4 Immunogenicity

Immunogenicity assays will be performed on plasma. The assays will include detection of anti-capsid, and anti-FVIII total antibody, and determination of neutralizing antibodies against FVIII. Any increase in total antibody level, especially during the time period of 5-12 weeks, will be compared with FVIII activity measurements. Any abnormality of the liver parameters will lead to a retrospective immunogenicity assessment to determine anti-FVIII and capsid specific CTL. Anti-FVIII and capsid specific CTL assays will be performed on collected PBMCs.

Timing of assessment by these assays is provided in Table 9.1.2, Table 9.1.3, and Table 9.1.4.

9.7.5 Pharmacodynamics

The hFVIII antigen and activity level will be measured by an ELISA (antigen) and by one-stage clotting and/or chromogenic substrate assay (activity). Individual antigen and activity plasma plots will be prepared to assess changes over 16 weeks. FVIII activity measurements will be used to determine PD parameters.

If supported by FVIII activity data, non-compartmental analysis and observation will be used to estimate individual values of C_b (baseline concentration), C_{ss} (steady state concentration), T_{ss} (time to steady state), C(t) and AUC(0-t) where t is 16 weeks. Other parameters that may be used to describe individual FVIII protein and activity plasma profiles are C_{max} (maximum concentration) and C_{avg} (average concentration, AUC(0-t)/t). The PD parameters and dose will be used to assess clinical pharmacology.

Sample collection times are indicated in Table 9.1.2, Table 9.1.3, and Table 9.1.4.

9.7.6 Exploratory Assessments

Blood samples will be collected at the time points indicated in Table 9.1.1, Table 9.1.2, Table 9.1.3, and Table 9.1.4 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.

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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 may be used for exploratory use once the primary use has been completed.

On an exploratory basis, samples may be fractionated prior to shedding analysis in order to better characterize the presence and location of vector DNA and/or vector capsid within each matrix. The fractionation may be performed with samples collected specifically for shedding analysis (saliva, blood, semen, urine, faeces), or by using exploratory samples, such as plasma, PBMCs, and red blood cells, collected under the study protocol.

9.7.7 Haemo-QoL-A Quality of Life Assessment

The Haemo-QoL-A is a patient-reported outcome (PRO) questionnaire which will be used to assess subject quality of life (QoL) during the study. Assessments will occur at the time points listed in the Schedules of Assessments.

Details regarding the QoL assessment will be included in the Study Reference Manual.

9.7.8 Safety Variables

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

9.7.8.1 Adverse Events

The occurrence of AEs will be assessed continuously from the time the subject signs the ICF. The determination, evaluation and reporting of AEs will be performed as outlined in Section 10. Assessments of AEs will occur at the time points shown in Table 9.1.1, Table 9.1.2, Table 9.1.3, and Table 9.1.4.

9.7.8.2 Clinical Laboratory Assessments

Specific visits for obtaining clinical laboratory assessment samples are provided in Table 9.1.1, Table 9.1.2, Table 9.1.3, Table 9.1.4, and Table 9.1.5. The scheduled clinical laboratory tests are listed in Table 9.7.8.2.1. Refer to the Study Reference Manual 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 the cause of the abnormality is determined, the value returns to baseline or to within normal limits, or the Investigator determines that the abnormal value is no longer clinically significant.

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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 CRF.



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Blood Chemistry	Haematology	Urine Tests	Other
Albumin	Haemoglobin	Appearance	CRP
BUN	Haematocrit	Color	
Calcium	WBC count	pН	Coagulation Screen
			including:
Chloride	RBC count	Specific gravity	APTT
Total cholesterol	Platelet count	Ketones	PT/INR
CO ₂	Differential cell count	Protein	TT
СРК	ABO blood typing*	Glucose	
Creatinine		Bilirubin	
Glucose		Nitrite	
Phosphorus		Urobilinogen	
Potassium		Haemoglobin	
Total protein			
Sodium			
Uric Acid			

Table 9.7.8.2.1: Clinical Laboratory Tests

BUN, blood urea nitrogen; CO₂, carbon dioxide; 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. * ABO blood typing assessment should be completed at the next regularly scheduled study visit (or at least prior to the end of the subject's participation in the study).

9.7.8.3 Liver and Hepatitis Testing

Subjects will be screened for evidence of previous hepatitis B or hepatitis C infection at Screening. Subjects with documented results showing an absence of active hepatitis B or hepatitis C infection (as measured by positive surface antigen for hepatitis B or positive RNA testing for hepatitis C) 30 days prior to providing signed informed consent do not need to be screened again.

Evidence of ongoing hepatitis B or hepatitis C infection is exclusionary. Subjects with a history of hepatitis B or hepatitis C will be asked for information about the treatments received as part of their medical history assessment at Screening.

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

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A liver ultrasound and LTs at Screening will identify any significant hepatic dysfunction, which is defined as:

- More than 3x the normal ALT level
- More than 3x the normal bilirubin level
- More than 3x the normal Alkaline phosphatase level.
- INR \geq 1.4.
- Thrombocytopoenia under 100 x 10⁹/L
- Liver ultrasound results indicative of a liver cirrhosis

Liver tests will be monitored on a regular basis, at the time points indicated in Table 9.1.1, Table 9.1.2, Table 9.1.3, Table 9.1.4, and Table 9.1.5. 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

Patients with ALT > 1.5 ULN during the study may undergo additional evaluations (eg, imaging studies including MRI or ultrasound, additional blood tests, and/or liver biopsy) at the discretion of the investigator.

9.7.8.4 HIV Testing

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

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

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

Systolic blood pressure, diastolic blood pressure, heart rate, respiration rate, and temperature will be assessed at Screening, Baseline, and at the beginning of each visit during the Post-Infusion Follow-Up and Safety Follow-Up periods. On the day of the BMN 270 Infusion, vital signs will be monitored prior to infusion, during the infusion every

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15 minutes (\pm 5 minutes), following the infusion hourly (\pm 5 minutes) for 6 hours and then every 2 hours (\pm 15 minutes) for 6 hours and then at 4 hour intervals (\pm 15 minutes).

A complete physical examination is necessary during Screening/Baseline, at Week 16 and 52 and at the End of Years visits thereafter. A complete physical examination will include general appearance (head, eyes, ears, nose, and throat), cardiovascular, dermatologic, lymphatic, respiratory, gastrointestinal, genitourinary, musculoskeletal, and neurologic systems.

At other visits, brief physical examinations may be performed at the discretion of the investigator based on the subject's clinical condition. A brief physical examination will include general appearance, cardiovascular, respiratory, neurologic, dermatologic, musculoskeletal, and gastrointestinal assessments. Particular attention should be given to signs of bleeding, as well as assessing possible hemarthroses.

Height will be recorded at Screening only. Weight will be recorded at Screening, at Weeks 26 and 52 during Year 1, and then at the second Q12W visit each year and at every End of Years visit during Years 2-5.

9.7.8.6 Vector Shedding

Vector shedding has been extensively studied in all similar clinical trials performed to date. (Nathwani, 2014, N.Engl.J.Med.); (Manno, 2006, Nat.Med.); (Schenk-Braat, 2007, J.Gene Med.); (Croteau, 2004, Ann.Occup.Hyg.). In the literature referenced above, including Haemophilia B clinical studies utilizing AAV2 and AAV8, vector was no longer detectable after 40 days in blood, saliva, urine or stool, but in one study was detected in the seminal fluid but not in motile sperm (Manno, 2006, Nat.Med.). In these studies, the amount of vector present in these bodily fluids involved an extremely small fraction of the infused dose. More recent data from an ongoing AAV-FIX study demonstrates persistence of the vector in both the blood and the semen for at least 39 weeks (Miesbach, 2016, Haemophilia).

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 PCR at the time points indicated in Table 9.1.2, Table 9.1.3, Table 9.1.4, and Table 9.1.5. Fluids tested will include:

- Blood
- Saliva
- Semen
- Urine

• Stool

Vector shedding will also be extensively studied in the present clinical trial, every other week between Weeks 4-16, then every 4 weeks to Week 52 until at least 3 consecutive negative results are obtained. Testing of semen will continue through Week 12, even if 3 consecutive negative results have been recorded in that compartment prior to that timepoint. Subjects who have not had 3 consecutive negative samples by Week 52 should continue to have PCR testing every 4 weeks until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor). Subjects who meet the definition of treatment failure and wish to follow an abbreviated schedule (refer to Section 12.5.3 but who have not cleared vector shedding from all fluids must still provide samples for assessment until vector shedding has cleared: every 4 weeks (during Year 2), or every 6 weeks (during Years 3-5).

Contraception use may need to be extended beyond 26 weeks in individual subjects based on observed vector shedding in semen. After 6 months, subjects may stop contraception use only if they have had 3 consecutive negative semen samples (upon consultation between the Investigator and Medical Monitor).

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

10 REPORTING ADVERSE EVENTS

10.1 Safety Parameters and Definitions

Safety assessments will consist of monitoring and recording protocol-defined AEs and SAEs; measurement of protocol-specified haematology, 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, a reportable adverse event (AE) is any untoward medical occurrence (eg, sign, symptom, illness, disease or injury) in a subject administered the study-drug or other protocol-imposed intervention, regardless of attribution. This includes the following:

- AEs not previously observed in the subject that emerge during the course of the study.
- Pre-existing medical conditions judged by the Investigator to have worsened in severity or frequency or changed in character during the study.
- Complications that occur as a result of non-drug protocol-imposed interventions (eg, AEs related to screening procedures).

An adverse drug reaction is any AE for which there is a reasonable possibility that the study-drug caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the study-drug and the AE.

Whenever possible, it is preferable to record a diagnosis as the AE term rather than a series of terms relating to a diagnosis.

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 meets 1 or more of the following criteria:

- Is fatal
- Is life threatening
- Note: Life-threatening refers to an event that places the subject at immediate risk of death. This definition does not include a reaction that, had it occurred in a more severe form, might have caused death.
- Requires or prolongs inpatient hospitalization.
- 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 intervention to prevent one of the above consequences (eg, anaphylaxis)

All adverse events that do not meet any of the criteria for SAEs should be regarded as non-serious AEs.

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 $ALT \ge 1.5x$ ULN, regardless of whether that triggers an initiation or modification of corticosteroid treatment
- Thromboembolic event

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 treatment, only SAEs associated with any protocol-imposed interventions will be reported. After informed consent is obtained and the first administration of study drug, the reporting period for all non-serious AEs and SAEs begins and continues for approximately 5 years or until study discontinuation/termination, whichever is longer. The criteria for determining, and the reporting of SAEs is provided in Section 10.1.1.1.

10.3.2 Eliciting Adverse Events

Investigators will seek information on AEs, SAEs, and EOSI at each subject contact by specific questioning and, as appropriate, by examination. Information on all AEs and SAEs and EOSI, should be recorded in the subject's medical record and on the 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 10.1.1.1 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 10.1.1.1. 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 severity of each will be assessed using the defined categories in Table 10.3.3.2.1.

The Investigator will determine the severity of each AE and SAE and EOSI using the NCI CTCAE v4. 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 as stated below.

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 or debilitating: consequences; urgent intervention indicated	Grade 4 and 5 AEs should always be		
5	Death related to AE reported as SAEs			

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

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

10.3.3.3 Causality

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

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

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

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

The investigator's assessment of causality for individual AE reports is part of the study documentation process. Regardless of the Investigator's assessment of causality for individual AE reports, the Sponsor will promptly evaluate all reported SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators and applicable regulatory authorities.

10.4 Procedures for Recording Adverse Events

10.4.1 Recording Adverse Events on a eCRF

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

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

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

10.4.1.1 Diagnosis versus Signs and Symptoms

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 haemorrhage 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.

10.4.1.4 Abnormal Laboratory Values

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

Any laboratory result abnormality fulfilling the criteria for a SAE or EOSI should be reported as such, and recorded in the AE eCRF. Any laboratory result abnormality of CTCAE Grade 4 or 5 should be recorded as an SAE in the AE eCRF.

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

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

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

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

For purposes of this study, laboratory tests showing a decreased level of hFVIII activity should not be reported as adverse events unless signs of worsening are observed.

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.

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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 document 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 10.1.1.1).

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 changed
- Insert an in-dwelling IV catheter (such as a Port-a-Cath or other brand) for administration of study drug or FVIII replacement therapy.
- Receive scheduled therapy (study drug or otherwise) for the study indication

10.4.1.8 Deaths

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

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

10.4.1.9 Pregnancy

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

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

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

10.5 Reporting Requirements

10.5.1 Expedited Reporting Requirements

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

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

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

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10.5.2 Ethics Committee Reporting Requirements

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

10.6 Follow-up of Subjects after Adverse Events

The Investigator should follow all unresolved AEs and SAEs until the events are resolved or have stabilized, the subject is lost to follow-up, or it has been determined that the study treatment or participation is not the cause of the AE/SAE. Resolution of AEs and SAEs (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, 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 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 treatment.

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 treatment. 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

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protect the patients against any immediate hazard. The Sponsor shall forthwith inform the competent authorities of those new events and the measures taken and shall ensure that the IRB/IEC/REB is notified at the same time."

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

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

- Immediate need to revise the IP administration (eg, modified dose amount or frequency not defined in protocol)
- 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	, MA MB BChir MSc
Address:		(UK) Ltd. sbury Way /C1A 2SL
Phone	PI PI	(office) (mobile)
E-mail:	PI	

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

BOMARIN

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 will be performed within 28 days (\pm 14 days) of BMN 270 infusion while baseline assessments will take place within 7 days of BMN 270 infusion (Day 1). Should the screening visit occur within 7 days of the drug infusion, physical examination, vital signs, blood chemistry, LTs, haematology, urine tests, coagulation screen, and CRP do not need to be repeated at Baseline.

The following procedures will be performed during the Screening Period:

- Full medical history, including haemophilia A history, hepatitis B, hepatitis C, and HIV. Subjects with a history of hepatitis B or hepatitis C will be asked for information about the treatments received. Any prior pharmacokinetics information obtained while the subject was receiving prophylactic or on-demand FVIII therapy prior to the study should also be collected. For subjects who have already enrolled in 270-201, this information should be collected at the next regularly scheduled study visit (or at least prior to the subject's completion of study participation).
- 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)
- Electrocardiogram
- Chest X-ray
- Liver Ultrasound
- Samples for hFVIII Assays
 - Baseline hFVIII activity chromogenic substrate (plasma)
 - Baseline hFVIII activity level one-stage clotting assay
 - o hFVIII coagulation activity exploratory assay

- o hFVIII inhibitor level (Bethesda assay with Nijmegen modification)
- hFVIII total antibody assay
- hFVIII antigen (ELISA)
- Blood sample for AAV5 Assays
 - o AAV5 antibody titer
 - o AAV5 transduction inhibition assay
- Screen for hepatitis B, hepatitis C, and HIV if required (subjects with documented negative results 30 days prior to informed consent being obtained do not need to be retested)
- Blood chemistry, haematology, coagulation screen, and CRP (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)
- Von Willebrand Factor Antigen (VWF:Ag)
- Blood samples for Biomarker testing (including HLA genotyping, FVIII genotyping status, TNFα and IL10a single nucleotide polymorphisms)

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 sample for AAV5 Assays
 - AAV5 antibody titer

- AAV5 transduction inhibition assay
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- Urine Tests (refer to Table 9.7.8.2.1)
- Liver Tests (refer to Table 9.7.8.3.1)

12.3 Baseline Visit

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

- Physical examination
- Assessment of Adverse Events and Concomitant Medications
- Documentation of bleeding episodes and FVIII usage (by either subject or clinical information)
- Distribution of subject diaries and training in diary completion
- Blood chemistry, haematology, coagulation screen, and CRP (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)
- PBMC collection for CTL baseline
- Direct Thrombin test
- PCR of vector DNA in blood, saliva, urine, semen, and stools
- Exploratory biomarker assessments
- Haemo-QoL-A QoL assessment

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 24 hours for the BMN 270 Infusion Visit. The following procedures will be performed during the BMN 270 Infusion Visit:

- Physical examination
- Assessment of Adverse Events and Concomitant Medications
- Blood sample for AAV5 Assays (must be performed before the BMN 270 infusion)
 - o AAV5 antibody titer
 - AAV5 transduction inhibition assay

- BMN 270 Infusion
- Vital Signs
 - Vital signs will be recorded prior to BMN 270 infusion and then every 15 minutes (± 5 minutes) during BMN 270 infusion. Following infusion, vital signs will be monitored every 1 hour (± 5 minutes) for the first 6 hours, every 2 hours (± 15 minutes) for the next 6 hours, and then at 4 hour (± 15 minutes) intervals for the remainder of the subject's stay in the clinic.

12.5 BMN 270 Infusion Follow-Up Visits

After BMN 270 has been infused, subjects will return to the study site every week $(\pm 48 \text{ hours})$ for 16 weeks, when the following procedures will be completed:

12.5.1 Once per week (Weeks 1 through 16)

The following procedures will be performed at one visit per week from Weeks 1 through 16:

- Physical examination
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Vital Signs
- Liver Tests (refer to Table 9.7.8.3.1) central laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- Samples for FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
 - FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level
 - FVIII antigen (ELISA)

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

- Central assessment of FVIII activity level should be performed 1x/week from Week 1 through Week 16
- Liver Tests (refer to Table 9.7.8.3.1) local laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
- PBMC collection

12.5.2 Week 1 – Day 2 and Day 4

On Day 2 and Day 4 of Week 1, the following procedures will be performed:

- PCR of vector DNA in blood, saliva, urine, semen, and stools (Day 2 and Day 4)
- Samples for FVIII Assays (Day 4 only) central laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
 - FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level
 - FVIII antigen (ELISA)

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

- Liver Tests (refer to Table 9.7.8.3.1) (Day 4 only) central laboratory assessment
- Liver Tests (refer to Table 9.7.8.3.1) (Day 4 only) local laboratory assessment
- FVIII activity level (Day 4 only) local laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)

12.5.3 Week 1 – Day 8

On Day 8, the following procedures will be performed:

- PCR of vector DNA in blood, saliva, urine, semen, and stools
- Direct Thrombin test
- Haemo-QoL-A QoL assessment

12.5.4 Every 2 Weeks

Every 2 weeks (Weeks 2, 4, 6, 8, 10, 12, 14 and 16), the following procedures will be performed:

- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.8.2.1) (not assessed at Week 14)
- PCR of vector DNA in blood, saliva, urine, semen, and stools (not collected at Week 2)
 - Collection to occur until at least 3 consecutive negative results are obtained. Semen samples should continue to be collected and tested through Week 12, even if 3 consecutive negative results in that compartment have been recorded prior to that timepoint.

12.5.5 Weeks 4, 8, 12, and 16

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

- Urine Tests (refer to Table 9.7.8.2.1)
- VWF:Ag
- FVIII antibody titer
- Exploratory biomarker assessments

12.5.6 Week 16

At Week 16, the following procedures will be performed:

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

12.5.7 Weeks 8 and 16

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

• AAV5 antibody titer

At Weeks 2, 3, 4, and 16, the following procedure will be performed:

• Haemo-QoL-A QoL assessment

12.5.9 Week 13

At Week 13, the following procedure will be performed:

• Direct Thrombin test

12.6 Safety Follow-Up – Weeks 17-36

After the Post-Infusion Follow-Up visits are complete, subjects will return to the study site for Safety Follow-Up visits from Weeks 17 through Week 36 (\pm 48 hours), when the following procedures will be completed:

12.6.1 Once per week (Weeks 17 through 36)

Once per week from Week 17 through Week 36, the following procedures will be performed:

- Physical examination
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Vital Signs
- Liver Tests (refer to Table 9.7.8.3.1) central laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - o FVIII activity level (chromogenic substrate assay)
 - FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - FVIII antigen (ELISA)

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

- Liver Tests (refer to Table 9.7.8.3.1) local laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)

12.6.2 Once per week (Weeks 17 through 20)

Once per week from Week 17 through Week 20, the following procedures will be performed:

• PBMC collection

12.6.3 Every 2 weeks (Weeks 21 through 36)

Every 2 weeks (Weeks 22, 24, 26, 28, 30, 32, 34, and 36), the following procedures will be performed:

• PBMC collection

12.6.4 Every 4 Weeks

Every 4 weeks (Weeks 20, 24, 28, 32, and 36), the following procedures will be performed:

- Exploratory biomarker assessments
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- Urine Tests (refer to Table 9.7.8.2.1)
- VWF:Ag
- AAV5 antibody titer
- PCR of vector DNA in blood, saliva, urine, semen, and stools
 - Sample testing during Safety Follow-Up is not required if at least
 3 consecutive samples are clear during the Post-Infusion Follow-Up period.

12.6.5 Every 8 Weeks

Every 8 weeks (Weeks 20, 28, and 36), the following procedure will be performed:

• FVIII antibody titer

12.6.6 Week 26

At Week 26, the following procedure will be performed:

- Direct Thrombin test
- Weight

12.6.7 Week 28

At Week 28, the following procedure will be performed:

• Haemo-QoL-A QoL assessment

12.7 Safety Follow-Up – Weeks 37-52

Subjects will return every 2 weeks (Week 38, 40, 42, 44, 46, 48, 50, and 52) from Week $37-52 (\pm 1 \text{ week})$, when the following procedures will be completed:

12.7.1 Once per visit

At Weeks 38, 40, 42, 44, 46, 48, 50, and 52, the following procedures will be performed:

- Physical examination
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Vital Signs
- Liver Tests (refer to Table 9.7.8.3.1) local laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
- Liver Tests (refer to Table 9.7.8.3.1) central laboratory assessment
 - LTs may be monitored more or less frequently based (and in particular when ALT values are >1.5x ULN) on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
 - FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for FVIII inhibitor level

• FVIII antigen (ELISA)

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

12.7.2 Every 4 Weeks

Every 4 weeks (Weeks 40, 44, 48, and 52), the following procedures will be performed:

- Exploratory biomarker assessments
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- Urine Tests (refer to Table 9.7.8.2.1)
- AAV5 antibody titer
- VWF:Ag
- PCR of vector DNA in blood, saliva, urine, semen, and stools
 - Sample testing during Safety Follow-Up is not required if at least
 3 consecutive samples are clear during the Post-Infusion Follow-Up period.
 Subjects who have not had 3 consecutive negative samples by Week 52
 should continue to have PCR testing every 4 weeks until 3 consecutive
 negative samples are documented (or upon consultation between the
 Investigator and Medical Monitor).

12.7.3 Every 8 Weeks

Every 8 weeks (Weeks 44 and 52), the following procedure will be performed:

- PBMC collection
- FVIII antibody titer

12.7.4 Week 38 and 52

At Week 38 and Week 52, the following procedure will be performed:

• Direct Thrombin test

12.7.5 Week 52

At Week 52, the following procedure will be performed:

• Haemo-QoL-A QoL assessment

• Weight

12.8 Safety Follow-Up – Years 2-5

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

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

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

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

During Year 2, every 4 weeks (\pm 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) local laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
- Liver Tests (refer to Table 9.7.8.3.1) central laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)

- o FVIII coagulation activity exploratory assay
- o Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
- FVIII antigen (ELISA)

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

- PCR of vector DNA in blood, saliva, urine, semen, and stools (if required)
 - Sample testing during Year 2 is not required if at least 3 consecutive samples are negative during the Post-Infusion Follow-Up period in Weeks 1-52.
 Subjects who have not had 3 consecutive negative semen samples by Week 52 should continue to have PCR testing of semen every 4 weeks during Year 2 until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor).
 - Subjects who meet the definition of treatment failure and wish to follow an abbreviated schedule but who have not cleared vector shedding from all fluids must still provide samples for assessment every 4 weeks during Year 2 until vector shedding has cleared (in such a case, these subjects do not need to perform other assessments except for PCR sample delivery scheduled at these timepoints).

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

During Years 3-5, every 6 weeks (\pm 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) local laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
- Liver Tests (refer to Table 9.7.8.3.1) central laboratory assessment

- LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
 - FVIII coagulation activity exploratory assay
 - Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - FVIII antigen (ELISA)

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

- PCR of vector DNA in blood, saliva, urine, semen, and stools (if required)
 - Sample testing during Years 3-5 is not required if at least 3 consecutive samples are negative during the Post-Infusion Follow-Up period in Weeks 1-52 and/or Year 2. Subjects who have not had 3 consecutive negative semen samples by Week 52 should continue to have PCR testing of semen every 6 weeks during Years 3-5 until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor).
 - Subjects who meet the definition of treatment failure and wish to follow an abbreviated schedule but who have not cleared vector shedding from all fluids must still provide samples for assessment every 6 weeks during Years 3-5 until vector shedding has cleared (in such a case, these subjects do not need to perform other assessments except for PCR sample delivery scheduled at these timepoints).

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

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

- Year 2 Week 64, Week 76, Week 88, Week 104
- Year 3 Week 116, Week 128, Week 140, Week 156
- Year 4 Week 168, Week 180, Week 192, Week 208

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• Year 5 – Week 220, Week 232, Week 244, Week 260

For each of these years, the last study visit listed (Week 104, Week 156, Week 208, and Week 260) will serve as an End of Year visit.

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

- Brief physical examination (at every 12 week visits) or complete physical examination (at End of Year visits)
- Weight (at Week 76, Week 128, Week 180, Week 232, and End of Year visits only)
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Liver Tests (refer to Table 9.7.8.3.1) local laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
- Liver Tests (refer to Table 9.7.8.3.1) central laboratory assessment
 - LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
 - FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - FVIII antigen (ELISA)

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

• Vital Signs

- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
 - ABO blood typing assessment should be performed at the next regularly scheduled study visit (or at least prior to the end of the subject's participation in the study)
- Urine Tests (refer to Table 9.7.8.2.1)
- AAV5 antibody titer
- FVIII antibody titer
- PBMC collection
- VWF:Ag
- Direct Thrombin test
- Exploratory biomarker assessments
- Haemo-QoL-A QOL assessment (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 negative during the Post-Infusion Follow-Up period in Weeks 1-52. Subjects who have not had 3 consecutive negative semen samples by Week 52 should continue to have PCR testing of semen every 4 weeks (during Year 2) or every 6 weeks (during Years 3-5) until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor).

12.9 Early Termination Visit

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

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

- Physical examination
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Vital Signs
- Blood chemistry, haematology, coagulation screen, and CRP (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) local laboratory assessment
- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
- Liver Tests (refer to Table 9.7.8.3.1) central laboratory assessment
- FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage clotting assay)
 - FVIII activity level (chromogenic substrate assay)
 - o FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - FVIII antigen (ELISA)

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

- AAV5 antibody titer
- FVIII antibody titer
- PBMC collection
- VWF:Ag
- Direct Thrombin test
- PCR of vector DNA in blood, saliva, urine, semen, and stools
 - Sample testing at the ETV is not required if at least 3 consecutive samples are clear during the Post-Infusion Follow-Up period.
- Exploratory biomarker assessment
- Haemo-QoL-A QOL assessment

12.10 End of Study

The study will end after the last subject completes the last Safety Follow-Up visit (Week 260). 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

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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.

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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, any applicable randomization procedures, source document requirements, eCRFs, monitoring requirements, and procedures for reporting AEs, including SAEs.

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

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

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14 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

14.1 Statistical and Analytical Plans

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

14.1.1 Interim Analyses

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

14.1.2 Procedures for Accounting for Missing, Unused and Spurious Data

14.2 Missing data will not be imputed.

14.3 Primary and Secondary Efficacy Analysis

The subjects will be followed in a longitudinal manner and all the relevant information will be collected. The analysis of the data will be descriptive in nature. Descriptive statistics include the number of subjects, mean, median, standard deviation, minimum, and maximum for continuous variables and count and percent for categorical variables. Efficacy variables will be summarized by dose cohort at each time point. Relationship between dose and efficacy results will be examined.

Data collected in a longitudinal manner may be analyzed using longitudinal methods such as mixed effect model which takes into account the correlation among the observation taken at various time points within a participant. Efficacy is a secondary endpoint, defined as biologically active hFVIII at ≥ 5 IU/dL by chromogenic substrate assay and/or one-stage clotting assay as measured by the central laboratory at 16 weeks following study treatment. hFVIII activity will be assessed weekly during the study period. We can only assess the true steady state of hFVIII protein produced from BMN 270 after a minimum of 72 hours has elapsed since the last infusion of FVIII protein concentrates.

14.4 Immunogenicity

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

14.5 Pharmacodynamic Analyses

The FVIII antigen and activity level as measured by an Elisa (antigen level) and by a one-stage clotting assay and/or chromogenic substrate assay (activity level), will be used for

plasma profiles; FVIII activity will be used to determine PD parameters. Traditional PK analysis is not applicable.

If supported by FVIII activity data, non-compartmental analysis and observation will be used to estimate individual PD parameter values of C_b (baseline), C_{ss} (steady state), T_{ss} (time to steady state), C(t) and AUC(0-t) where t is 16 weeks. Other parameters that may be used to describe individual FVIII protein and activity plasma profiles are C_{max} (maximum concentration) and C_{avg} (average concentration, AUC(0-t)/t). The parameters will be summarized using descriptive statistics.

14.6 Safety Analysis

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

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

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

Detailed statistical methods will be provided in the SAP.

14.7 Determination of Sample Size

No formal sample size calculations based on statistical power were performed.

The sample size is determined based upon clinical consideration and could detect a strong clinical efficacy signal. Up to 15 subjects may be dosed in the study; the actual number of subjects will depend on the criteria for dose escalation.

14.8 Analysis Populations

The Safety analysis population is defined as all enrolled subjects who receive any study drug. The analysis of safety data will be performed on Safety Set.

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The Full Analysis Set (FAS) is defined as all enrolled subjects who receive study drug and have at least one Baseline and post-Baseline assessment. The FAS will be used for efficacy analysis.

14.9 Changes in the Conduct of the Study or Planned Analyses

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

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

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

Note: If discrepancies exist between the text of the statistical analysis as planned in the protocol, and the final SAP, a protocol amendment will not be issued and the SAP will prevail.

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15 DATA REVIEW BOARD

There will be no formal DMC for this study, however a safety and efficacy evaluation board (the Data Review Board [DRB]) composed of the investigator representatives and the Sponsor will be established.

The DRB will review safety and efficacy on an ongoing basis. The DRB will meet prior to dose escalation or dose expansion to assess available subject safety and efficacy data and make recommendations with regards to the conduct of study. Should a safety signal arise, including one which may warrant a halt of study enrollment, the DRB will promptly convene for further assessment of subject safety. Notification of all DRB meetings and meeting outcomes will be sent to participating sites.

16 COMPENSATION, INSURANCE AND INDEMNITY

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

The Investigator should contact BioMarin immediately upon notification that a study subject has been injured by the IP 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 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 subject has followed the Investigator's instructions, BioMarin will pay for reasonable and necessary medical services to treat the injuries caused by the IP or study procedures, if these costs are not covered by health insurance or another third party that usually pays these costs. In some jurisdictions, BioMarin is obligated by law to pay for study-related injuries without prior recourse to third party payer billing. If this is the case, BioMarin will comply with the law.

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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 CRF casebook to verify its accuracy.

CRFs 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 CRF instructions, blank data fields are not acceptable.

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

BioMarin's policy is that study data on the CRFs 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 an Investigator or institution refuses to allow access to subject records because of confidentiality, arrangements must be made to allow an "interview" style of data verification.

A CRA designated by BioMarin will compare the CRFs 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 CRA, 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 CRA 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 CRF 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 CRFs 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

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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.

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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 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).

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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 R2 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 patients.
- He or she will personally conduct or supervise the study.
- He or she will inform any potential patients, 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 R2 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 R2 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 R2 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 R2 Section 4.9 are kept, and those records are available for inspection in accordance with 21 CFR 312.68 and/or ICH E6 R2 Section 4.9.7.
- The IRB/IEC/REB complies with the requirements of 21 CFR Part 56, ICH E6 R2 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 patients or others are reported to the IRB/IEC/REB. Additionally, he or she will not make any changes in the research without IRB/IEC/REB approval, except where necessary to eliminate apparent immediate hazards to human patients.
- 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 R2.

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23 SIGNATURE PAGE

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

Protocol Number: 270-201, Amendment 7

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 R2, as stated in the protocol, and other information supplied to me.

Investigator Signature			Date
Deinte durante			
Printed name			
Accepted for the Sponsor:	DocuSigned by:		
Medical Monitor Signature	Ι	Date	
Printed name:	, MA MB BChir MSc, <mark>Pl</mark>	, Clin	nical Science

24 PROTOCOL AMENDMENT TEXT REVISIONS

The following table summarizes the revisions made to the protocol and relates the changes to the appropriate rationale (See pages 2-3). Text that has been added or inserted is indicated by <u>underlined</u> font, and deleted text is indicated by strikethrough font.

Section No./Title	Revision	Rationale
Synopsis (Study Design and Plan)	As the relationship between activity assay results of the BMN 270 gene product and bleeding remains to be established, Investigators should strive to minimize bias by avoiding consideration of FVIII activity levels by themselves or subjects in the reporting of bleeding episodes and FVIII usage.	5, 14
	In subjects who experience recurrent bleeding episodes, the Investigator and Medical Monitor will discuss whether to resume prior FVIII prophylaxis. Subjects who do not respond to BMN 270 treatment (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, follow an abbreviated visit schedule after Week 52, as applicable and at the discretion of the Investigator. Because subjects develop neutralizing immunity upon exposure to the capsid, re-challenge of vector is not a likely treatment option and these subjects have effectively a single opportunity for therapy using this AAV capsid. Efficacy will be determined by FVIII activity at 16 weeks post dose. Safety will be evaluated for approximately	
	5 years after dosing. Any safety signal may trigger a review of the data and possible additional immunogenicity studies that include an assessment of cellular immune responses using collected peripheral blood mononuclear cells (PBMC).	
7.4/Summary of Overall Risks and Benefits	Safety will be assessed by adverse event reporting and clinical laboratory assessment. Based on prior human studies with peripheral injections of AAV vectors, there is no known safety risk of AAV gene therapy. However, a mild asymptomatic transaminitis was observed at week 7-12 after administration in humans with an AAV8 FIX, providing the rationale for the	14
	following surveillance plan . Each subject will have a comprehensive surveillance plan that monitors LFTs during the study. The majority of subjects in the ongoing 270-201 clinical study who have received 4E13 or 6E13 vg/kg doses of BMN 270 have had Grade 1 asymptomatic elevations in ALT. For most subjects, the elevations have reached only slightly above the upper limit of normal (ULN). Based on the effectiveness of transient oral corticosteroid used to suppress a presumed Class 1	
	(cytotoxic T-cell) response in prior studies with hepatic transduction with AAV vectors (Mingozzi, 2013), subjects were treated with 7-32 weeks of oral corticosteroids prophylactically or in response to the elevations in ALT to ensure preservation of the transduced hepatocytes. Using this approach, no sustained loss of FVIII activity has been observed in subjects with ALT elevations, consistent with maintaining a high level of hepatocyte function. Moreover, the rise in ALT levels were not accompanied by significant or lasting aberrations in other liver tests such as AST, bilirubin or albumin, indicating that extent	

Section No./Title	Revision	Rationale
	of toxicity is limited. There has been one HIV-positive subject in the ongoing 270-302 clinical study who experienced Grade 3	
	asymptomatic elevations in ALT and AST, which has been attributed to an interaction between one or more of his	
	antiretroviral therapy medications and/or unsuspected underlying hepatic disease with BMN 270. In addition, there has been	
	one subject with Gilbert's syndrome in the ongoing 270-301 clinical study who has experienced Grade 3 asymptomatic	
	elevations in ALT and AST. These cases have led to the exclusion of subsequent HIV-positive subjects and requirement of	
	liver tests at Screening that are <1.25 times the upper limit of the normal range in the ongoing 270-301 and 270-302 clinical	
	studies. Of note, two HIV-positive subjects in 270-301 and one presumed Gilbert's syndrome subject in 270-201 have	
	received BMN 270 without experiencing any elevations in ALT to date. Overall, the literature and clinical 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,	
	<u>2016; Miesbach, 2016; Pasi, 2017).</u>	
	The current data available for BMN 270 does not yet permit comprehensive assessment of the benefit:risk profile of this	
	investigational drug. Given the monitoring measures in place in the clinical protocol(s) to minimize the risk to subjects	
	participating in the existing studies, the identified risks are justified by the anticipated benefits that may be afforded to	
	subjects. Each subject in 270-201 will have a comprehensive surveillance plan that monitors LTs during the study, and	
	elevations in LT will be addressed according to the guidelines set forth in the protocol. Safety will be assessed by adverse	
	event reporting and clinical laboratory assessments.	
9.1/Overall Study	As the relationship between activity assay results of the BMN 270 gene product and bleeding remains to be established,	5, 14
Design and Plan	Investigators should strive to minimize bias by avoiding consideration of FVIII activity levels by themselves or subjects in the	·
	reporting of bleeding episodes and FVIII usage.	
	In subjects who experience recurrent bleeding episodes, the Investigator and Medical Monitor will discuss whether to resume	
	prior FVIII prophylaxis. Subjects who do not respond to BMN 270 treatment (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, follow an abbreviated visit schedule after Week 52, as applicable and at the	
	discretion of the Investigator.	

Section No./Title	Revision	Rationale
Table 9.1.1, Table 9.1.2, Table 9.1.3	Table 9.1.1, Table 9.1.2, and Table 9.1.3 have been updated to reflect the changes made elsewhere in the protocol.	4, 6, 9, 12, 14
Table 9.1.1 (Footnotes)	^g 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 <u>(including those for Direct Thrombin Activity test and any other exploratory assessments)</u> will be performed only as deemed necessary by the Sponsor.	9
Table 9.1.2 (Footnotes)	 ^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 function tests. LFTsLTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) 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. Patients with ALT > 1.5 ULN during the study may undergo additional evaluations (e.g.,e.g. imaging studies including MRI or ultrasound, additional blood tests, and/or liver biopsy) at the discretion of the investigator. Additional testing of FVIII and LTs during any study week may be performed if: (1) the ALT has increased to above ULN; (2) Increases in ALT values from prior assessment are accompanied by declines in FVIII activity level; or after a discussion between the Medical Monitor and the Investigator. ^f 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 Direct Thrombin Activity test and any other exploratory assessments) will be performed only as deemed necessary by the Sponsor. 	9, 12, 14
Table 9.1.3 (Footnotes)	^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 function tests. <u>LFTsLTs</u> may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) 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. Patients with ALT > 1.5 ULN during the study may undergo additional	9, 12, 14

Section No./Title	Revision	Rationale
	 evaluations (e.g., eg, imaging studies including MRI or ultrasound, additional blood tests, and/or liver biopsy) at the discretion of the investigator. Additional testing of FVIII and LTs during any study week may be performed if: (1) the ALT has increased to above ULN; (2) Increases in ALT values from prior assessment are accompanied by declines in FVIII activity level; or after a discussion between the Medical Monitor and the Investigator based on a review of subject data. If FVIII levels and/or ALT values are stable over the course of several weeks, assessment of FVIII activity and ALT levels may be adjusted based on discussion between the Medical Monitor and the Investigator. ^e Collection for each matrix to occur until at least 3 consecutive negative results are obtained. ^f 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 Direct Thrombin Activity test and any other exploratory assessments) will be 	
Table 9.1.4 and Table 9.1.5	performed only as deemed necessary by the Sponsor. Table 9.1.4 and Table 9.1.5 and their associated footnotes have been modified/added to reflect changes made elsewhere in the protocol.	2, 3, 6, 9, 11, 12, 14
9.4.8/Prior and Concomitant Medications	The following medications are prohibited starting 30 days before Screening: • Emicizumab • Fitusiran • Concizumab • Efavirenz • Lamivudine Subjects who begin antiretroviral therapy following BMN 270 infusion and during their participation in 270-201 must have their antiretroviral medication regimen approved by the Investigator and Medical Monitor prior to starting antiretroviral treatment.	1

Section No./Title	Revision	Rationale
9.4.9/Treatment Compliance	Study drug will be administered to subjects at the study site by a qualified professional. The quantity dispensed, returned, used, lost, etc. must be recorded on the <u>a</u> dispensing log provided for the study. Sites will be instructed to return or destroy all used and unused study drug containers.	
9.5/IP Accountability	The Investigator or designee is responsible for maintaining accurate records (including dates and quantities) of IP(s) received and IP lost or accidentally or deliberately destroyed. The Investigator or designee must retain all unused or expired study supplies until the study monitor (on-site CRA) has confirmed the accountability data, if allowed by local SOPs.	14
9.5.1/Return and Disposition of Clinical Supplies	Unused study drug must be kept in a secure location for accountability and reconciliation by the study monitor. The Investigator or designee must provide an explanation for any destroyed or missing study drug or study materials- <u>(or must be referenced in their institution SOPs)</u> .	14
9.6/Dietary or Other Protocol Restrictions	Subjects should be advised to abstain from any blood or sperm donation after BMN 270 infusion, until there is no further evidence of vector shedding from PCR analysis of samples.	
9.7.2/Primary Efficacy Variables	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, follow an abbreviated visit schedule after Week 52, as applicable and at the discretion of the Investigator.	3
9.7.3/Secondary Efficacy Variables	In subjects who experience recurrent bleeding episodes, the Investigator and Medical Monitor will discuss whether to resume prior FVIII prophylaxis.	5
Table 9.7.8.2.1	Table 9.7.8.2.1 (and its footnotes) have been updated to reflect changes made elsewhere in the protocol.	6
9.7.8.3/Liver and Hepatitis Testing		
9.7.8.5/Vital Signs, Physical Examinations and Other Safety Observations	A complete physical examination is necessary during Screening/Baseline, at Week 16 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. at the End of	2, 8, 14

Section No./Title	Revision	Rationale		
	<u>Years visits thereafter.</u> A complete physical examination will include general appearance (head, eyes, ears, nose, and throat), cardiovascular, dermatologic, lymphatic, respiratory, gastrointestinal, genitourinary, musculoskeletal, and neurologic systems. <u>At other visits, brief physical examinations may be performed at the discretion of the investigator based on the subject's clinical condition.</u> A brief physical examination will include general appearance, cardiovascular, respiratory, neurologic, <u>dermatologic, musculoskeletal, and gastrointestinal assessments</u> . <u>Particular attention should be given to signs of bleeding, as well as assessing possible hemarthroses</u> .			
	Height will be recorded at Screening only. Weight will be recorded at Screening, at Weeks 26 and 52 during Year 1, and then at the second Q12W visit each year and at every 6 months thereafter End of Years visit during Years 2-5.			
9.7.8.6/Vector Shedding	Vector shedding will also be extensively studied in the present clinical trial, every other week between Weeks 4-16, then every 4 weeks to Week 52 until at least 3 consecutive negative results are obtained. Testing of semen will continue through Week 12, even if 3 consecutive negative results have been recorded in that compartment prior to that timepoint. Subjects who have not had 3 consecutive negative samples by Week 52 should continue to have PCR testing every 4 weeks until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor). Subjects who meet the definition of treatment failure and wish to follow an abbreviated schedule (refer to Section 12.5.3) but who have not cleared vector shedding from all fluids must still provide samples for assessment until vector shedding has cleared: every 4 weeks (during Year 2), or every 6 weeks (during Years 3-5). Contraception use may need to be extended beyond 26 weeks in individual subjects based on observed vector shedding in semen. After 6 months, subjects may stop contraception use only if they have had 3 consecutive negative semen samples-(upon consultation between the Investigator and Medical Monitor).	3, 7, 14		
10.1.1/Adverse Events	Bleeding events that are normal events of haemophilia (ie, bleeding events which occur only because the subject is a haemophiliac) should not be recorded as AEs but will instead be captured in subject diaries. Bleeding events that occur where a normal (ie, non-haemophiliac) patient would bleed, such as bleeding as a result of major trauma, should be recorded as adverse events. All bleeding events which meet criteria for being serious should be reported as serious adverse events (SAEs) whether or not they are bleeding events that are normal sequelae of haemophilia.	14		

Section No./Title	Revision	Rationale
<u>10.1.1.1/Bleeding and</u> <u>Suspected Bleeding</u> <u>Events</u>	 <u>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:</u> <u>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).</u> 	14
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 liver enzymes (ALT) ≥ 1.5x ULN, regardless of whether that triggers an initiation or modification of corticosteroid treatment <u>Thromboembolic event</u> 	14
10.4.1.4/Abnormal Laboratory Values	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: • Leading to a change in study medication (e.g. dose modification, interruption or permanent discontinuation)	14
10.4.1.7/Hospitalization, Prolonged Hospitalization, or Surgery	on, 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: • Hospitalization solely for the purpose of insertion of Insert an in-dwelling IV catheter (such as a Port-a-Cath or other brand) for administration of study drug will not be considered an SAE or FVIII replacement therapy.	
10.4.1.9/Pregnancy	Pregnancy in a partner should be reported within 24 hours of the site becoming aware of the pregnancy by entering the information on the Pregnancy eCRF and submitting to BPV within 24 hours of the site becoming aware of the event. The Investigator must make every effort to follow the subject's partner (with that partner's consent) through resolution of the pregnancy (delivery or termination) and to report the resolution on the Pregnancy Follow-up Form in the study reference materials.eCRF.	14
10.9/BioMarin Contact Information	Contact information for the medical monitor is as follows:	13

Section No./Title	Revision	Rationale
	Name: Mitra Tavakkoli, MD, PharmD <u>Address: 105 Digital Drive</u> <u>Novato, CA 94949 USA</u> <u>Phone: +1 (415) 257-5974</u> <u>E-mail: fatemeh.tavakkoli@bmrn.com</u>	
	Name: Nina Mitchell, MA MB BChir MSc Address: Biomarin (UK) Ltd. 10 Bloomsbury Way London WC1A 2SL Phone: +44 (0) 207 420 3414 (office) +44 (0) 7761 659 535 (mobile) E-mail: nina.mitchell@bmrn.com	
12.2/Screening Visit	 The following procedures will be performed during the Screening Period: Full medical history, including haemophilia A history, hepatitis B, hepatitis C, and HIV. <u>Subjects with a history of hepatitis B or hepatitis C will be asked for information about the treatments received. Any prior pharmacokinetics information obtained while the subject was receiving prophylactic or on-demand FVIII therapy prior to the study should also be collected. For subjects who have already enrolled in 270-201, this information should be collected at the next regularly scheduled study visit (or at least prior to the subject's completion of study participation).</u> 	4
12.8/Safety Follow-Up (Years 2-5)	Subjects who do not respond to BMN 270 treatment (ie, treatment failure, manifesting as either failure to achieve FVIII activity ≥ 5 IU/dL by Week 52 or inability to maintain independence from prophylactic FVIII replacement therapy due to joint bleeding episodes, in the judgment of the Investigator) may, at the Investigator's discretion and after discussion with the Medical Monitor, follow an abbreviated visit schedule after Week 52 of the study by attending only the Q12W and End of 	3, 7

Section No./Title	Revision	Rationale
12.8.1/Year 2 – Every 4 Weeks	Physical examination	
	 Complete Physical Examination will be performed every 52 weeks; Brief Physical Examinations may be performed at other visits. 	
	Vital Signs Exploratory biomarker assessments	
	 <u>PCR of vector DNA in blood, saliva, urine, semen, and stools (if required)</u> 	
	 Sample testing during Year 2 is not required if at least 3 consecutive samples are negative during the Post- Infusion Follow-Up period in Weeks 1-52. Subjects who have not had 3 consecutive negative semen samples by Week 52 should continue to have PCR testing of semen every 4 weeks during Year 2 until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor). 	
	 Subjects who meet the definition of treatment failure and wish to follow an abbreviated schedule but who have not cleared vector shedding from all fluids must still provide samples for assessment every 4 weeks during Year 2 until vector shedding has cleared (in such a case, these subjects do not need to perform other assessments except for PCR sample delivery scheduled at these timepoints). 	
12.8.2/Years 3-5 –	During Years 3-5, every 6 weeks (± 2 weeks), the following procedures will be performed:	2, 7, 14
Every 6 Weeks	Physical examination	
	 Complete Physical Examination will be performed every 52 weeks; Brief Physical Examinations may be performed at other visits. 	
	Vital Signs	
	Exploratory biomarker assessments	
	• <u>PCR of vector DNA in blood, saliva, urine, semen, and stools (if required)</u>	

Section No./Title	Revision	Rationale		
	 Sample testing during Years 3-5 is not required if at least 3 consecutive samples are negative during the Post-Infusion Follow-Up period in Weeks 1-52 and/or Year 2. Subjects who have not had 3 consecutive negative semen samples by Week 52 should continue to have PCR testing of semen every 6 weeks during Years 3-5 until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor). Subjects who meet the definition of treatment failure and wish to follow an abbreviated schedule but who 			
	have not cleared vector shedding from all fluids must still provide samples for assessment every 6 weeks during Years 3-5 until vector shedding has cleared (in such a case, these subjects do not need to perform other assessments except for PCR sample delivery scheduled at these timepoints).			
12.8.3/Years 2-5 –	During Years 2-5, every 3 months (± 2 weeks), the following procedures will be performed:	2, 3, 7, 11,		
Every 3 Months Every 12 Weeks and End of	During Years 2-5, subjects will be asked to return to the study site for visits at the following study weeks (± 2 weeks):	14		
Year Visits	• Year 2 – Week 64, Week 76, Week 88, Week 104			
	• Year 3 – Week 116, Week 128, Week 140, Week 156			
	• <u>Year 4 – Week 168, Week 180, Week 192, Week 208</u>			
	• <u>Year 5 – Week 220, Week 232, Week 244, Week 260</u>			
	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:			
	• Brief physical examination (at every 12 week visits) or complete physical examination (at End of Year visits)			
	• Weight (at Week 76, Week 128, Week 180, Week 232, and End of Year visits only)			
	• <u>Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)</u>			
	• Liver Tests (refer to Table 9.7.8.3.1) – local laboratory assessment			
	 <u>LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based</u> on discussion between the Medical Monitor and the Investigator and review of subject data. 			

Section No./Title	Revision	Rationale
	<u>FVIII activity level – local laboratory assessment</u>	
	• <u>FVIII activity level (one-stage clotting assay)</u>	
	• FVIII activity level (chromogenic substrate assay)	
	• Liver Tests (refer to Table 9.7.8.3.1) – central laboratory assessment	
	 <u>LTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based</u> on discussion between the Medical Monitor and the Investigator and review of subject data. 	
	• <u>FVIII Assays – central laboratory assessment</u>	
	• <u>FVIII activity level (one-stage clotting assay)</u>	
	• <u>FVIII activity level (chromogenic substrate assay)</u>	
	• FVIII coagulation activity exploratory assay	
	o Bethesda assay (with Nijmegen modification) for FVIII inhibitor level	
	• <u>FVIII antigen (ELISA)</u>	
	Note: If a subject has used FVIII within 72 hours of a measurement day, all efforts should be made to obtain FVIII activity measurements when a 72-hour interval without FVIII use is achieved; the 72-hour wash-out period is only intended for subjects who have achieved FVIII \geq 5 IU/dL at 16 weeks after BMN 270 infusion and who have not resumed standard of care FVIII replacement therapy.	
	<u>Vital Signs</u>	
	• Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.8.2.1)	
	• <u>ABO blood typing assessment should be performed at the next regularly scheduled study visit (or at least</u> prior to the end of the subject's participation in the study)	
	• Exploratory biomarker assessments	
	• Haemo-QoL-A QOL assessment (at Week 76, Week 128, Week 180, Week 232, and End of Year visits only)	
	• <u>PCR of vector DNA in blood, saliva, urine, semen, and stools (if required)</u>	

Section No./Title	Revision	Rationale
	 Sample testing during Years 2-5 is not required if at least 3 consecutive samples are negative during the Post-Infusion Follow-Up period in Weeks 1-52. Subjects who have not had 3 consecutive negative semen samples by Week 52 should continue to have PCR testing of semen every 4 weeks (during Year 2) or every 6 weeks (during Years 3-5) until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor). 	
12.8.4/Years 2-5 – Every 6 Months	Every six months starting at the Week 78 visit (ie, 26 weeks after the Week 52 visit at the end of Year 1 of the Safety Follow- up period), the following procedures will be performed: Haemo QoL A QOL assessment Weight	2
12.8.5/Years 2-5 Every 4 Weeks	 Every four weeks during Years 2-5, the following procedure may be performed: PCR of vector DNA in blood, saliva, urine, semen, and stools Sample testing during Years 2-5 is not required if at least 3 consecutive samples are clear during the Post-Infusion Follow Up period. Subjects who have not had 3 consecutive negative samples by Week 52 should continue to have PCR testing every 4 weeks during Years 2-5 until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor). 	2

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1/2, Dose-Escalation, Safety, Tolerability and Efficacy Study of BMN 270, an Adenovirus-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII in Patients with Severe Haemophilia A		
Protocol Number:	270-201		
Active Investigational Product:	AAV5-hFVIII-SQ		
IND/European Union Drug Regulating Authorities Clinical Trials (EudraCT) Number:	2014-003880-38		
Indication:	Haemophilia A		
Sponsor:	BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949		
Development Phase:	Phase 1/2		
Sponsor's Responsible Medical Monitor:	Pl, MD, PharmDPlBioMarin Pharmaceutical Inc.105 Digital DriveNovato, CA 94949		
Duration of Subject Participation:	Approximately 264 weeks		
Dose:	Varied		
Study Population:	Males aged 18 or older		
Date of Original Protocol:	10 February 2015		
Date of Amendment 1:	06 March 2015		
Date of Amendment 2:	26 May 2015		
Date of Amendment 3:	06 November 2015		
Date of Amendment 4:	02 September 2016		
Date of Amendment 5:	14 February 2017		
Date of Amendment 6:	21 December 2017		

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May not be divulged, published, or otherwise disclosed to others without prior written approval from BioMarin.

This study will be conducted according to the principles of Good Clinical Practice as described in the U.S. Code of Federal Regulations and the International Conference on Harmonisation Guidelines, including the archiving of essential documents

Proprietary and Confidential

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CLINICAL STUDY PROTOCOL AMENDMENT SUMMARY

Amendment: 6

Date: 21 December 2017

RATIONALE AND SUMMARY OF MAJOR CHANGES

A summary of major changes covered by Amendment 6 to the BMN 270-201 protocol is provided below.

1. The frequency of liver function and FVIII testing has been increased during the Years 2-5 follow-up period. Testing will be performed every 4 weeks (+ 2 weeks) during year 2, and every 6 weeks (± 2 weeks) during years 3-5.

Rationale: To maintain adequate surveillance of potential hepatocyte injury and trending of FVIII activity beyond Week 52 post-BMN 270 infusion, the frequency of liver function and FVIII testing has been increased during the Years 2-5 follow-up period from every 3 months beyond Week 52. A brief physical examination, assessment of vital signs, and review of adverse events, concomitant medications, and diaries of FVII usage and bleeding events will also occur at these visits.

2. Exploratory biomarker sampling has been extended beyond Week 24. Samples will now be collected every 4 weeks through the end of Year 2, and then every 6 weeks during Years 3-5.

Rationale: Additional biomarker sampling will permit further analysis of exploratory endpoints during the study.

3. Clarified that the 72-hour washout period prior to assessment of FVIII levels is necessary only for subjects who have achieved FVIII levels ≥ 5 IU/dL by Week 16 after BMN 270 infusion and have not resumed standard of care FVIII replacement therapy.

Rationale: The current language in the protocol states: 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 proposed language is to make it more clear that the 72 hour wash-out period prior to FVIII assessment is not intended for the subjects who have resumed standard of care FVIII replacement therapy.

- 4. Clarified that testing for reactivation of hepatitis B and hepatitis C at Week 16 is necessary only in subjects who have a past medical history of hepatitis B or hepatitis C prior to study entry.
- 5. Minor administrative changes have been made for consistency and clarity.

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6. The identity of the medical monitor has been updated.

Specific changes included in this amendment, including the Synopsis, since Amendment 5 (approved 14 February 2017) are outlined in Section 24.

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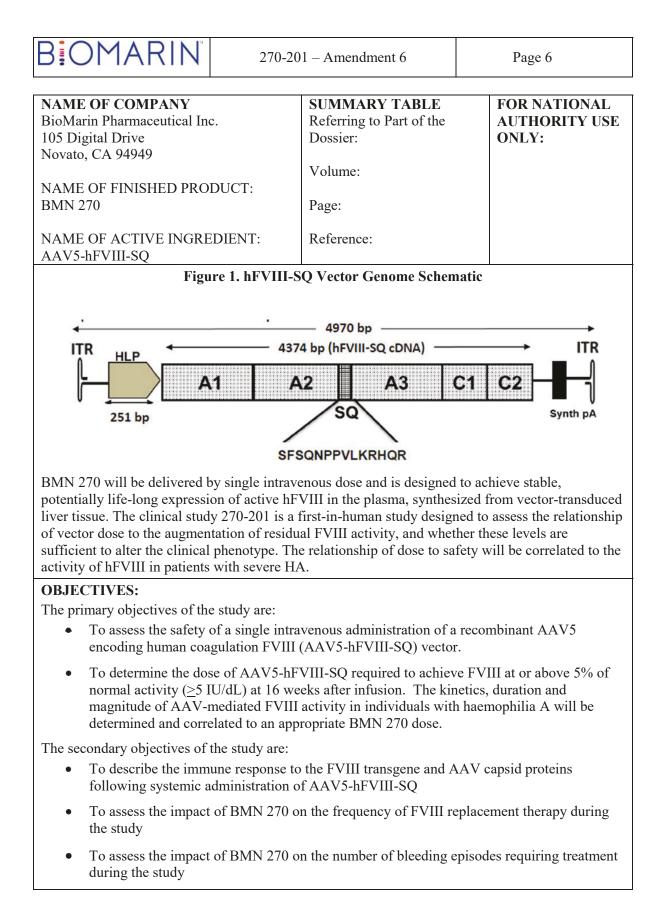
2 SYNOPSIS

NAME OF COMPANY BioMarin Pharmaceutical Inc.	SUMMARY TABLE Referring to Part of the	FOR NATIONAL AUTHORITY USE				
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NAME OF ACTIVE INGREDIENT: AAV5-hFVIII-SQ	Reference:					
TITLE OF STUDY:						
A Phase 1/2, Dose-Escalation, Safety, Toler Adenovirus-Associated Virus Vector–Media with Severe Haemophilia A						
PROTOCOL NUMBER:						
270-201						
STUDY SITES:						
Approximately 6-10 sites worldwide.						
PHASE OF DEVELOPMENT:						
Phase 1/2						
STUDY RATIONALE:	is blooding disorder that offects	opprovimately 1 in				
5,000 males. It is caused by deficiency in the essential cofactor in the intrinsic coagulation	Haemophilia 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 cascade. This disorder can be either inherited, due to a new mutation or an acquired immunologic process, leading to insufficient quantities of FVIII or a					
phenotype of HA patients is largely governe classified as FVIII activity less than 1% of v 1-5% of wild type activity and the mild form severe HA remain frequent spontaneous ble	ed by the level of residual expressivild type (< 1 IU/dL), moderate in is 5-40% activity. The clinical eding episodes, predominantly in	sion. Severe HA is disease comprises manifestations of n joints and soft				
tissues, with a substantially increased risk of						
Treatment of severe HA presently consists of recombinant human FVIII protein (rhFVIII)	5 1					
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 treatment (mean of 1 to 7 episodes/year with prophylaxis and up						
to 30 to 50 episodes/year for on demand trea	atment). The consequence of mu	ltiple bleeding events				
is the development of an underlying patholo						
arthropathy and substantially increased risk conjugation of polyethylene glycol (PEG) p						
fusion proteins) improve half-life by approx						

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dosing and maintaining activity levels above 1% trough. However, these longer acting FVIIIs					
remain dependent on multipl					
patients. There is therefore a					
patients a FVIII level compa-		-			
Gene therapy offers the poter					
production of active FVIII for					
appropriate gene sequence. H					
clinical manifestations are at					
minute amounts (200 ng/ml) in the plasma. Tightly regulated control of gene expression is not					
essential, and modest increases in the level of FVIII (any increase of the plasma level by 2 ng/ml					
induces an increase in activity of 1%) can ameliorate the severe form of the disease. Thus,					
relatively small changes in en					
in disease phenotype. Finally					
quantitative rather than quali	tative endpoints	s that are easily assayed us	ing 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 for specific tissues such as the liver (for serotypes 2, 5 and 8 among others). Indeed, an on-going gene therapy clinical trial for a related disorder, haemophilia B, has established that stable (>36 months) expression of human factor IX at levels that are sufficient for conversion of their bleeding phenotype from severe to moderate or mild is achievable following a single peripheral vein administration of AAV-8 vector. Several participants in this trial have been able to discontinue factor prophylaxis without suffering spontaneous haemorrhages, 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 liver-selective promoter (Figure 1).



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AAV5-hFVIII-SQ			
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STUDY DESIGN AND PLAN:

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

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

Cohort 1: 6E12 vector genomes [vg] per kilogram of body weight, given as a single intravenous dose (iv)

Cohort 2: 2E13 vg per kilogram, iv

Cohort 3: 6E13 vg per kilogram, iv

Cohort 4: 4E13 vg per kilogram, iv

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

Cohorts 1-3

The first 3 cohorts will be enrolled sequentially, allowing a period of 3 weeks or more between cohorts. Dose escalation may occur after a single subject has been safely dosed if the resulting FVIII activity at the Week 3 visit is < 5 IU/dL in both the one-stage aPTT and chromogenic assays. Three weeks is expected to be the time the expression will be close to the maximum. This escalation paradigm is intended to minimize the subject numbers exposed to subtherapeutic doses. Approximately three weeks after an injection, the decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and a panel of investigators participating in the study, the Data Review Board (DRB).

If the FVIII activity reaches \geq 5 IU/dL at the Week 3 visit, then the remaining subjects in the cohort will be enrolled without the need to wait for 3 weeks between subjects.

Subject 1 will be dosed by intravenous infusion with 6E12 vector genomes [vg] per kilogram of body weight. If the FVIII activity level does not reach ≥ 5 IU/dL at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 1 and enrollment into Cohort 2 will initiate with Subject 2 at the next dose (2E13 vg/kg).

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If the FVIII activity level in the first subject treated in Cohort 2 does not reach ≥ 5 IU/dL at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 2 and enrollment into Cohort 3 (6E13) will initiate with the next subject. If the FVIII activity level in the first subject treated in Cohort 3 does not reach ≥ 5 IU/dL at the Week 3 visit in both assays, then the Data Review Board (DRB) will recommend whether to continue to add subjects to the cohort and/or whether to continue the study.

For the first subject treated in each of the first 3 cohorts, if the activity level reaches ≥ 5 IU/dL and no safety issue is found, then up to four subjects will be enrolled in the Cohort, though, the adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

<u>Cohort 4</u>

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

There will be an ongoing review of individual patient safety and efficacy data by the medical monitor and the DRB. The adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

Because subjects develop neutralizing immunity upon exposure to the capsid, re-challenge of vector is not a likely treatment option and these subjects have effectively a single opportunity for therapy using this AAV capsid. Efficacy will be determined by FVIII activity at 16 weeks post dose. Safety will be evaluated for approximately 5 years after dosing. Any safety signal may trigger a review of the data and possible additional immunogenicity studies that include an assessment of cellular immune responses using collected peripheral blood mononuclear cells (PBMC).

NUMBER OF SUBJECTS PLANNED:

Up to 15 subjects may enroll into the study; the actual number of subjects will depend on the FVIII activity levels seen in each Cohort.

DIAGNOSIS AND ALL CRITERIA FOR INCLUSION AND EXCLUSION:

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

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BioMa 105 Di	C OF COMPANY rin Pharmaceutical Inc. gital Drive o, CA 94949	SUMMARY TABLE Referring to Part of the Dossier: Volume:	FOR NATIONAL AUTHORITY USE ONLY:		
NAME BMN 2	C OF FINISHED PRODUCT: 270	Page:			
AAV5	COF ACTIVE INGREDIENT: hFVIII-SQ	Reference:			
1.	Males that are 18 years or older with their medical history. Patients will 1 IU/dL or less				
2.	Treated/exposed to FVIII concentra days (EDs)	tes or cryoprecipitate for a n	minimum of 150 exposure		
3.	Greater or equal to 12 bleeding epis previous 12 months. Does not apply				
4.	Able to sign informed consent and c	comply with requirements o	f the trial		
5.	5. No history of inhibitor, and results from a modified Nijmegen Bethesda assay of less than 0.6 Bethesda Units (BU) on 2 consecutive occasions at least one week apart within the past 12 months				
6.	6. Sexually active patients must be willing to use an acceptable method of contraception such as double barrier, including hormonal contraception for at least 6 months post-treatment. After 6 months, subjects may stop contraception use only if they have had 3 consecutive negative semen samples.				
Individ the stud	uals who meet any of the following e dy:	exclusion criteria will not be	e eligible to participate in		
1.	Detectable pre-existing immunity to inhibition or AAV5 total antibodies		ared by AAV5 transduction		
2.	Any evidence of active infection or	any immunosuppressive dis	sorder.		
3.	HIV positive				
4.	Significant liver dysfunction as defi	ned by abnormal elevation	of:		
	• ALT (alanine transaminase) to 3	3 times the upper limit of no	ormal;		
	• Bilirubin above 3 times the upp	er limit of normal;			
	• Alkaline phosphatase above 3 ti	mes the upper limit of norm	nal; or		
	• INR (international normalized r	$atio) \ge 1.4$			
5.	5. Potential participants who have had a liver biopsy in the past 3 years are excluded if they had significant fibrosis of 3 or 4 as rated on a scale of 0-4				
6.	Evidence of any bleeding disorder r	not related to Haemophilia A	Α		
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NAME OF COMPANY BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949	SUMMARY TABLE Referring to Part of the Dossier: Volume:	FOR NATIONAL AUTHORITY USE ONLY:		
NAME OF FINISHED PRODUCT: BMN 270	Page:			
NAME OF ACTIVE INGREDIENT: AAV5-hFVIII-SQ	Reference:			
7. Platelet count of $< 100 \times 10^9/L$				
8. Creatinine $\geq 1.5 \text{ mg/dL}$				
9. Liver cirrhosis of any etiology as assessed by liver ultrasound				
10. Hepatitis B if surface antigen is positive				
11. Hepatitis C if RNA is positive				
12. Treatment with any IP within 30 days prior to the end of the screening period				
13. Any disease or condition at the physician's discretion that would prevent the patient from fully complying with the requirements of the study including possible corticosteroid treatment outlined in the protocol. The physician may exclude patients unwilling or unable to agree on not using alcohol for the 16-week period following the viral infusion.				
14. Prior treatment with any vector	or gene transfer agent			
15. Major surgery planned in the 10	6-week period following the viral	infusion		
16. Use of systemic immunosuppre infusion	essive agents or live vaccines with	hin 30 days before the viral		
INVESTIGATIONAL PRODUCT(S)), DOSE, ROUTE AND REGIN	IEN:		
Each subject will receive a single inject infusion will depend on the dose level.	ion of BMN 270 as an intravenou	us infusion. The volume of		
REFERENCE THERAPY(IES), DOS				
The study is open label with comparison will be evaluated in this study.	n of FVIII activity to baseline val	lues. No reference therapy		
DURATION OF TREATMENT:				
BMN 270 is given as a single dose by it	ntravenous infusion.			

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BioMarin Pharmaceutical Inc		Referring to Part of the	AUTHORITY USE	
105 Digital Drive		Dossier:	ONLY:	
Novato, CA 94949				
,		Volume:		
NAME OF FINISHED PROI	DUCT:			
BMN 270				
NAME OF ACTIVE INGRE	DIENT:	Reference:		
AAV5-hFVIII-SQ				
CRITERIA FOR EVALUA	TION:			
Safety:				

The following safety outcome measurements will be assessed:

- Incidence of adverse events (AEs), including serious AEs (SAEs)
- Change in clinical laboratory tests (serum chemistry and haematology)
- Change in vital signs
- Change in physical examination
- Vector shedding
- Liver function tests (LFTs, including ALT, AST, GGT, LDH, bilirubin, alkaline phosphatase)
- Immune response to FVIII transgene and AAV capsid proteins

No major toxicity is expected based on preclinical studies in mice and monkeys. Each subject will have comprehensive surveillance monitoring of LFTs (at local labs, once per week for Weeks 1-36, then once every 2 weeks from Week 37-52) during Year 1. LFTs will be monitored every 4 weeks during Year 2, and then every 6 weeks for Years 3-5 post-dose in the safety extension; the frequency and duration of LFT testing may be changed based on discussion between the Medical Monitor and the Investigator and review of subject data.

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

Efficacy:

The primary efficacy measure will be to assess plasma FVIII activity. The efficacy goal of the study is to establish the dose relationship to FVIII activity \geq 5 IU/dL at 16 weeks post BMN 270 administration.

Secondary efficacy measures include assessing the impact of BMN 270 on the frequency of FVIII replacement therapy and on the number of bleeding episodes during the study. Subjects will be asked to keep a subject diary to record the details in these areas.

Pharmacodynamics:

The FVIII antigen and activity level as measured by an ELISA (antigen level) and by one-stage APTT and/or chromogenic FXa assay (activity level), will be used for plasma profiles; FVIII activity will be used to determine PD parameters. Traditional PK analysis is not applicable.

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105 Digital Drive	Dossier:	ONLY:	
Novato, CA 94949			
	Volume:		
NAME OF FINISHED PRODU	JCT:		
BMN 270	Page:		
	5		
NAME OF ACTIVE INGRED	IENT: Reference:		
AAV5-hFVIII-SQ			
	ity data, non-compartmental analysis an	d observation will be used	

to estimate individual values of Cb (baseline concentration), Css (steady state concentration), Tss (time to steady state), C(t) and AUC(0-t) where t is 16 weeks.

STATISTICAL METHODS:

The sample size is based upon clinical considerations and could detect a strong clinical efficacy signal. Up to 15 subjects may be dosed in the study. The subjects will be followed in a longitudinal manner and all the relevant information will be collected. The analysis of the data will be descriptive in nature but data collected in a longitudinal manner may be analyzed using longitudinal methods such as mixed effect model which takes into account the correlation among the observation taken at various time points within a participant. Efficacy is a secondary endpoint, defined as biologically active FVIII at ≥ 5 IU/dL by chromogenic FXa assay and/or one-stage APTT assay at 16 weeks following study treatment. FVIII activity will be assessed weekly during the study period. We can only assess the true steady state of FVIII protein produced from BMN 270 after a minimum of 72 hours has elapsed since the last infusion of FVIII protein concentrates.

Analysis of neutralizing antibody response and other immunological parameters as well as vector shedding will be primarily descriptive and involve both inter-participant and intra-participant comparisons across doses.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

AAV	adeno-associated virus
ADL	activities of daily living
ADR	adverse drug reaction
AE	adverse event
ALT	alanine transaminase
APTT	activated partial thromboplastin time
BPV	BioMarin Pharmacovigilance
BU	Bethesda Unit
CFR	Code of Federal Regulations
CRA	clinical research associate
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DRB	Data Review Board
eCRF	electronic case report form
ED	exposure days
EOSI	events of special interest
ETV	early termination visit
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIH	first-in-human
FVIII	coagulation factor VIII
FXa	coagulation factor Xa
GCP	Good Clinical Practice
HA	Haemophilia A
hFVIII	human coagulation factor VIII
HIPAA	Health Insurance Portability and Accountability Act
IB	investigator brochure
ICF	informed consent form
ICH	
	International Conference on Harmonisation of Technical Requirements for
	Registration of Pharmaceuticals for Human Use
ICH E6	Registration of Pharmaceuticals for Human Use ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6
	Registration of Pharmaceuticals for Human Use
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INR	international normalized ratio	
IP	investigational product	
IRB	institutional review board	
IV	intravenous	
LFT	liver function test	
MedDRA	Medical Dictionary for Regulatory Activities	
NOAEL	no-observed-adverse-effect level	
PBMC	peripheral blood mononuclear cells	
PD	pharmacodynamics	
PEG	polyethylene glycol	
РК	Pharmacokinetics	
PRO	patient-reported outcome	
rhFVIII	recombinant human FVIII protein	
REB	research ethics board	
SAE	serious adverse event	
SAP	statistical analysis plan	
SDV	source data verification	
ULN	upper limit of normal	
vg	vector genomes	
VWF:Ag	von Willebrand factor Antigen	

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]).

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

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5 ETHICS

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

5.1 Institutional Review Board or Independent Ethics Committee

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

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

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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 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)

Specifically, this study is based on adequately performed laboratory and animal experimentation. The study will be conducted under a protocol reviewed and approved by an IRB/IEC/REB and will be conducted by scientifically and medically qualified persons. The benefits of the study are in proportion to the 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), United States Code of Federal Regulations (CFR) 21 CFR §50, European Clinical Trial Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC, and other applicable local regulations, will be obtained for each subject prior to entering the subject into the study. The Investigator will prepare the ICF and provide the documents to BioMarin for approval prior to submission to the IRB/IEC/REB approval. BioMarin and the IRB/IEC/REB must approve the documents before they are implemented. A copy of the approved ICF, and if applicable, a copy of the approved subject information sheet and all ICFs translated to a language other than the native language of the clinical site must also be received by BioMarin or designee prior to any study-specific procedures being performed.

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

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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 US Food and Drug Administration (FDA) Form FDA 1572 and a Financial Disclosure Form. All sub-Investigators must be listed on Form FDA 1572. Financial Disclosure Forms must also be completed for all sub-Investigators listed on the Form FDA 1572 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.

Liver function tests (LFTs) will be performed at the local laboratories associated with the study sites. Local laboratory results of LFTs will be used to trigger corticosteroid treatment as needed (refer to Section 9.4.8.2). In case of discrepant results between local and central laboratories, the Investigator and Medical Monitor will decide further action. Safety labs evaluations (including LFTs) will be performed at the central lab, while bioanalytical samples will be performed at the appropriate specialty lab. Refer to the Laboratory Manual for more details.

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7 INTRODUCTION

Haemophilia A (HA) is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males (Nathwani, 1992, Baillieres Clin.Haematol.). It is caused by mutations in the factor VIII (FVIII) gene that codes for FVIII protein, an essential cofactor in the coagulation cascade. 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 haemorrhage. Treatment in Western (Berntorp, 2012, Haemophilia.) countries consists of intravenous injection of plasma derived or recombinant FVIII protein concentrates at the time of a bleed, 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 haemophilia A patients. These individuals develop debilitating arthropathy and have a substantially increased risk of death from haemorrhage in life (Stonebraker, 2010, Haemophilia.). Chemical modification or bioengineering of FVIII may improve half-life to 18-19 hours (Kaufman, 2013, Blood). However, these long acting FVIII variants do not eliminate the need for lifelong FVIII protein administration (Hay, 2012, Blood).

Gene therapy offers the potential of disease-modifying therapy by continuous endogenous production of human FVIII following a single administration of vector. Haemophilia 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, Haemophilia.); thus the therapeutic goal for gene therapy is a modest increase in hFVIII. Finally, the consequences of gene transfer can be assessed using simple quantitative rather than qualitative endpoints that can be easily assayed in most clinical laboratories.

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

7.1 Nonclinical Studies

The nonclinical program supports a single IV administration of BMN 270, the planned clinical route of administration, for the treatment of Haemophilia A in male patients. This

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nonclinical program took into account the guidelines and reflection papers for gene therapy medicinal products under EMA Advanced Therapies. 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 (normal CD-1 mouse, B and T cell deficient mouse model of haemophilia 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.

The primary PD of BMN 270 was assessed in a series of non-GLP single dose studies in a FVIII KO x Rag2 mouse model of severe Haemophilia A that recapitulates the change in coagulation observed in the human severe disease population without interfering cross species immunogenicity. PD activity and expression of hFVIII was assessed for durations up to 13-weeks in the FVIII KO x Rag2 mouse given dose range of 2E11 through 2E14 vector genomes (vg)/kg. Low levels of plasma hFVIII were observed in mice given 2E12 vg/kg after eight-weeks, post dose. Plasma hFVIII activity using bleeding time as an endpoint was evaluated in the FVIII KO x Rag2 mouse given up to 2E13 and 1E14 vg/kg BMN 270 at 8 weeks, post dose. BMN 270 related correction of bleeding times showed a dose relationship that was similar to that observed in FVIII KO x Rag2 mice given matched IU levels of Refacto[®].

All cynomolgus monkeys used in this program were screened for neutralizing anti-AAV5 activity prior to study enrollment. PD activity and plasma hFVIII concentrations were evaluated in the cynomolgus monkey given up to 6E13 vg/kg BMN 270 for eight weeks. Peak expression of hFVIII was observed three to six weeks post administration with a subsequent decrease in expression presumably due to immunogenicity though not necessarily correlated to antibody titer.

The normal mouse was utilized in the GLP toxicology study to assess the safety profile of BMN 270 without the background of disease progression and in sufficient number per parameter. The GLP single dose toxicity study in normal CD-1 mice given 6E12 and 6E13 vg/kg with a 4 and 13-week follow up period monitored clinical pathology, defined potential target organs, immunogenicity, gene expression and activity. No changes in liver function were observed. In a single dose PD study in monkey given BMN 270, formation of anti-AAV5 total antibodies was observed at Week 8 with relatively low formation of anti-hFVIII total antibodies. No changes in liver function was observed.

The overall nonclinical safety profile includes formation of anti-AAV5 total antibodies with relatively lower formation of anti-hFVIII total antibodies. Immunogenicity against the AAV capsid and hFVIII is an anticipated finding for BMN 270 treatment and will be monitored in

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the nonclinical and clinical programs. Though not observed in the nonclinical species, liver toxicity utilizing clinical pathology parameters will be monitored in the clinical program based on previous literature. Cellular immune response will also be monitored.

Additionally, the BMN 270 transgene product has a final sequence closely matching that of the protein replacement treatment, Refacto[®] and therefore the safety profile of the BMN 270 transgene product is anticipated to be similar to Refacto® and have no unique FVIII-specific target organs of toxicity. The AAV5 capsid has not been modified and therefore no unique capsid-specific safety findings are anticipated. Because the biodistribution pattern of AAV5 after IV administration is consistent across species, BioMarin will confirm the nonclinical distribution pattern of BMN 270 during clinical development. Biodistribution of the AAV5 capsid has been documented to predominately target the liver with relatively lower levels of transduction observed in the lung, kidney, spleen, testes and blood compartment depending on the species and timing of administration. Liver targeted distribution of a similar AAV5 Factor IX gene therapy product was observed in the rhesus macaque monkey with low levels of vector genomes detected in spleen, kidney and testis (Nathwani, 2006, Blood). Despite distribution to non-liver organs, no expression of Factor IX was detected in these tissues. Additionally, distribution to the testis was observed in another study in monkeys given an AAV5-codon-optimized human porphobilinogen deaminase; however, vector genomes in the semen were only transiently observed within one week but not thereafter (Paneda, 2013, Hum.Gene Ther.).

Both normal and disease model mice and a limited number of monkeys were utilized to establish proof of concept, species scaling and dose response in order to select the first-in-human (FIH) dose of 6E12 vg/kg. This dose represents 10-fold safety factor from the no observed adverse effect level (NOAEL) in the GLP enabling nonclinical toxicology study in mice.

7.2 Previous Clinical Studies

This is the first clinical study for BMN 270.

BioMarin's program for haemophilia A builds on previous clinical trials of AAV-mediated gene transfer for a related condition, haemophilia B, that were conducted with an AAV2 vector (Manno, 2003, Blood) and an AAV8 vector (Nathwani, 2011, N.Engl.J.Med.), (Nathwani, 2014, N.Engl.J.Med.). The large size of the FVIII cDNA was shortened and a preclinical validation of this approach was performed with an AAV8 vector (McIntosh, 2013, Blood).

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AAV serotype 5 is being tested in other clinical trials and was reportedly well tolerated without treatment-related serious adverse events in a recent phase 1 study for treatment of Acute Intermittent Porphyria (D'Avola, 2014, J.Hepatol.). In addition, AAV using other serotypes have been used in 105 clinical studies to date and no safety issue specific to the vector was ever reported.

7.3 Study Rationale

Haemophilia A (HA) is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males (Mannucci, 2001, N.Engl.J.Med.). It is caused by deficiency in the activity of coagulation factor VIII (FVIII), an essential cofactor in the intrinsic coagulation cascade. This disorder can be either inherited, due to a new mutation 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 is largely governed by the level of residual expression. Severe HA is classified as FVIII activity less than 1% of wild type (< 1 IU/dL), moderate disease comprises 1-5% of wild type activity and the mild form is 5-40% activity. The clinical manifestations of severe HA remain frequent spontaneous bleeding episodes, predominantly in joints and soft tissues, with a substantially increased risk of death from haemorrhage when the brain is involved.

Treatment of severe HA presently consists of intravenous injection of plasma derived or recombinant human FVIII protein (rhFVIII) concentrates both as prophylaxis 2-4 times per week, and at the time of a bleed, to prevent or control bleeding episodes, respectively. The half-life for FVIII (12-18 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 treatment (mean of 1 to 7 episodes/year with prophylaxis and up to 30 to 50 episodes/year for on demand treatment) (Nagel, 2011, Haemophilia.). The consequence of multiple bleeding events is the development of an underlying pathology that contributes to debilitating multiple-joint arthropathy and substantially increased risk of death (Nagel, 2011, Haemophilia). Chemical modification (e.g. direct conjugation of polyethylene glycol (PEG) polymers) and bioengineering of FVIII (e.g. FVIII-Fc fusion proteins) improve half-life by approximately 50%, and thus, show promise in reduced dosing and maintaining activity levels above 1%trough (Stonebraker, 2010, Haemophilia.), (Mahlangu, 2014, Blood). However, these longer acting FVIIIs remain dependent on multiple infusions to maintain critical levels of FVIII activity in severe HA patients. There is therefore a strong unmet need for a fully preventive treatment of HA to give patients a FVIII level compatible with a normal and haemorrhage-free life.

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Gene therapy offers the potential of disease-modifying therapy by continuous endogenous production of active FVIII following a single intravenous administration of a vector with the appropriate gene sequence. Haemophilia 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 modest increases in the level of FVIII (any increase of the plasma level by 2 ng/ml induces an increase in activity of 1%) can ameliorate the severe form of the disease. Thus, relatively small changes in endogenous FVIII activity results in clinically relevant improvements in disease phenotype. Finally, the 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 (Mannucci, 2001, N.Engl.J.Med.). They have an excellent and well defined safety profile, and can direct long term transgene expression with tropism for specific tissues such as the liver (Nathwani, 2005, Curr.Hematol.Rep.) for serotypes 2, 5 and 8 among others). Indeed, an on-going gene therapy clinical trial for a related disorder, haemophilia B, has established that stable (>36 months) expression of human factor IX at levels that are sufficient for conversion of their bleeding phenotype from severe to moderate or mild is achievable following a single peripheral vein administration of AAV-8 vector (Nathwani, 2014, N.Engl.J.Med.). Several participants in this trial have been able to discontinue factor prophylaxis without suffering spontaneous haemorrhages, 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, 2011, Mol.Ther.), (Bainbridge, 2008, N.Engl.J.Med.), (Maguire, 2009, Lancet); (Simonelli, 2010, Mol.Ther.).

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

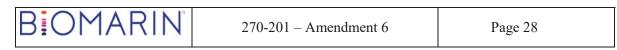
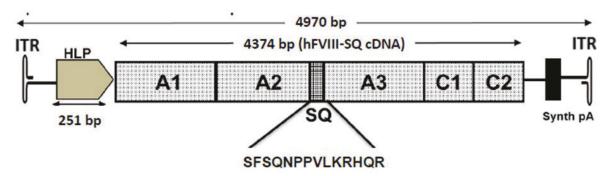


Figure 7.3.1: hFVIII-SQ Vector Genome Schematic



BMN 270 will be delivered by single intravenous dose and is designed to achieve stable, potentially life-long expression of active FVIII in the plasma, synthesized from vector-transduced liver tissue. The clinical study BMN 270-201 is a first-in-human study designed to assess the relationship of vector dose to the augmentation of residual FVIII activity, and whether these levels are sufficient to alter the clinical phenotype. The relationship of dose to safety will be correlated to the activity of FVIII in patients with severe HA.

7.4 Summary of Overall Risks and Benefits

Safety will be assessed by adverse event reporting and clinical laboratory assessment. Based on prior human studies with peripheral injections of AAV vectors, there is no known safety risk of AAV gene therapy. However, a mild asymptomatic transaminitis was observed at week 7-12 after administration in humans with an AAV8-FIX, providing the rationale for the following surveillance plan (Nathwani, 2011, Mol.Ther.). Each subject will have a comprehensive surveillance plan that monitors LFTs during the study.

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

Dose selection: The benefit of this study can only be enhanced by selecting a starting dose that maximizes the opportunity of observing a therapeutic effect, and therefore, reducing the possibility of a sub-therapeutic effect. With this consideration in mind, the starting dose 6E12 vg/kg was selected using overall data from the pre-clinical studies conducted in mice (normal and disease model, Rag2 -/- x FVIII -/-) and monkey. A detectable pharmacological response based on activity was observed at 6E12 vg/kg. A 10-fold safety margin based upon the NOAEL was observed in the GLP 13-week study in normal mouse at the highest dose administered. A 30-fold safety margin in an 8-week dose response study in disease model mice based on histology was observed at the highest dose administered. No BMN 270-related

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changes in clinical observations or chemistry was observed in the monkey at doses up to 6E13 vg/kg, a 10-fold safety margin after 8-weeks. Overall, no BMN 270-related findings, except expected formation of anti-AAV5 antibodies, were observed at the highest administered doses of 6E13, 2E14 and 6E13 vg/kg in the normal mouse, disease model mouse and monkey, respectively.

Based on these key pre-clinical findings it can be suggested that the proposed starting dose of 6E12 vg/kg should not pose any risk or safety concerns to subjects with the best chance of benefiting the subject therapeutically.

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8 STUDY OBJECTIVES

The primary objectives of the study are:

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

The secondary objectives of the study are:

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

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9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

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

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

- Cohort 1: 6E12 vector genomes [vg] per kilogram of body weight, given as a single intravenous dose (iv)
- Cohort 2: 2E13 vg per kilogram, iv
- Cohort 3: 6E13 vg per kilogram, iv
- Cohort 4: 4E13 vg per kilogram, iv

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

Cohorts 1-3

The first three cohorts will be enrolled sequentially, allowing a period of 3 weeks or more between cohorts. Dose escalation may occur after a single subject in a cohort has been safely dosed if the resulting FVIII activity at the Week 3 visit is < 5 IU/dL in both assays. Three weeks is expected to be the time the expression will be close to the maximum. This escalation paradigm is intended to minimize the subject numbers exposed to subtherapeutic doses. The decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and a panel of investigators participating in the study.

If the FVIII activity reaches ≥ 5 IU/dL at the Week 3 visit, then the remaining subjects in the cohort will be enrolled without the need to wait for 3 weeks between subjects.

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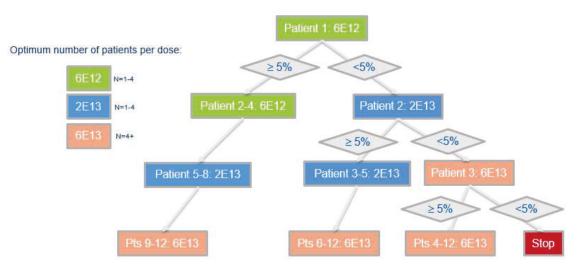


Figure 9.1.1: Flow Chart of Dose Escalation Scheme for Cohorts 1 to 3

Subject 1 (Cohort 1) will be dosed by intravenous infusion with 6E12 vg/kg of body weight. If the FVIII activity level does not reach 5 IU/dL or greater (expressed as % in Figure 9.1.1) at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 1 and enrollment into Cohort 2 will initiate with Subject 2 at the next dose (2E13 vg/kg).

If the FVIII activity level in the first subject treated in Cohort 2 does not reach \geq 5 IU/dL at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 2 and enrollment into Cohort 3 (6E13) will initiate with the next subject.

If the FVIII activity level in the first subject treated in Cohort 3 does not reach \geq 5 IU/dL at the Week 3 visit in both assays, then the DRB will recommend whether to continue to add subjects to the cohort and/or whether to continue the study.

For the first subject treated in each of the first 3 cohorts, if the activity level reaches \geq 5 IU/dL and no safety issue is found, then up to four subjects will be enrolled in the Cohort, though the adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

Cohort 4

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

There will be an ongoing review of individual patient safety and efficacy data by the medical monitor and the Data Review Board (DRB). The adaptive nature of this trial allows the DRB Proprietary and Confidential 21 December 2017

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to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

Because subjects develop neutralizing immunity upon exposure to the capsid, re-challenge of vector is not a likely treatment option and these subjects have effectively a single opportunity for therapy using this AAV capsid. Efficacy will be determined by FVIII activity at 16 weeks post dose. Safety will be evaluated for approximately 5 years after dosing. Any safety signal may trigger a review of the data and possible additional immunogenicity studies that include an assessment of cellular immune responses using collected PBMC. Additionally, if any of the events listed in Section 9.3.3.1 occur, enrollment into the trial will be halted to complete an extensive safety analysis. Notification of the study enrollment halt will be sent by the Sponsor to the participating sites via telephone and email immediately after becoming aware of a safety concern. This will ensure no additional subjects are dosed until the signal has been completely evaluated. If, following safety review by the DRB and the Sponsor, it is deemed appropriate to restart dosing, a request to restart dosing with pertinent data will be submitted to the health authority.

A summary of events and assessments are provided by visit in Table 9.1.1 for Screening, Baseline and BMN 270 Infusion, in Table 9.1.2 for Post-Infusion Follow-up, and in Table 9.1.3 and Table 9.1.4 for Safety Follow-up.

Table 9.1.5, dealing with the apeutic corticosteroid use in the event of elevated LFTs, is discussed in Section 9.4.8.2.

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Table 9.1.1: Schedule of Events – Screening and Infusion

	Prie	Prior to BMN 270 Infusion					
Assessment	Screening ⁱ (Day -28 to Day -1)	Smart Rescreening ⁱ (Day -28 to Day -1)	Baseline (Day -7 to Day -1) ^h	Infusion Visit (Day 1) ^k			
Informed consent	X						
Medical History	Х						
Physical Examination ^a	Х		Х	Х			
Height and Weight ^a	X						
Vital Signs	X	Х		X			
Assessment of Adverse Events and Concomitant Medications	X	Х	Х	X			
Documentation of bleeding episodes and FVIII usage (by either subject or clinical information)	X	Х	Х				
Distribution of subject diaries and training in their use			Х				
Electrocardiogram	X						
Chest X-ray	Х						
Liver Ultrasound	X						
hFVIII Assays ^b	Х	Xj					
AAV5 Assays ^c	X	X		Х			
Screen for Hepatitis B, Hepatitis C, HIV ^d	X						
Blood chemistry, haematology, coagulation screen, and CRPe	X	Х	Х				
Urine Tests ^e	Х	Х	Х				
Liver Function Tests ^e	Х	Х	Х				
PBMC collection for CTL baseline			Х				
Von Willebrand Factor Antigen (VWF:Ag)	Х						
Direct Thrombin Test			Х				
PCR of vector DNA in blood, saliva, urine, semen, and stools			Х				
Biomarker testing ^f	Х						
Exploratory biomarker assessments ^g			Х				
Haemo-QoL-A Quality of Life (QoL) assessment			Х				
BMN 270 Infusion				Х			

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^a Complete physical examination should be done at Screening. Brief physical examination may be done at Baseline and at the BMN 270 Infusion Visit. Height will be recorded at Screening only. Weight will be recorded at Screening and then every 6 months thereafter.

- ^b Includes baseline hFVIII activity (chromogenic FXa and one-stage APTT assays), hFVIII coagulation activity exploratory assay, hFVIII inhibitor level (Bethesda assay with Nijmegen modification), hFVIII total antibody titer, and hFVIII antigen (ELISA).
- ^c Screening (done during Screening) and testing (at Infusion Visit) of AAV5 pre-existing immunity may include plasma samples for 3 assays (in vivo transduction inhibition, in vitro transduction inhibition and AAV5 total antibody assays). Sample collection on the day of the infusion visit must be performed before the BMN 270 infusion is given.

^d Patients with documented negative results within the last 30 days do not need to be retested.

- ^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 function tests.
- ^f Includes HLA genotyping, FVIII genotyping, TNFα and IL10a single nucleotide polymorphisms.
- ^g 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 will be performed only as deemed necessary by the Sponsor.
- ^h Should the screening visit occur within 7 days of the drug infusion, physical examination, blood chemistry, LFTs, haematology, urine tests, coagulation screen, and CRP do not need to be repeated at Baseline.
- ⁱ Smart rescreening should only be performed if a patient has been determined to be eligible for the study and is unable to complete the Baseline assessments and Infusion prior to the closing of the original Screening window. Subjects who undergo smart rescreening must complete the rescreening assessments and receive the infusion within 90 days of signing the original consent. Subjects who do not complete dosing within 90 days will be required to re-consent and undergo all screening procedures. Subjects may not undergo smart rescreening more than once.
- ^j Only the hFVIII inhibitor level (Bethesda assay with Nijmegen modification) assay must be done at smart rescreening.
- ^k Assessments on the day of infusion must be performed prior to the infusion. 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), following the infusion hourly (± 5 minutes) for 6 hours and then every 2 hours (± 15 minutes) for 6 hours and then at 4 hour intervals (± 15 minutes).

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

					F	ollow-	Up Af	fter BN	AN 27	0 Adm	inistra	tion –	Week	s*																																										
	,	Week 1		Week 1		Week 1		Week 1		Week 1		Week 1		Week 1		Week 1		Week 1		Week 1		Week 1		Week 1		Week 1		Week 1		Week 1		Week 1		Week 1		Week 1		Week 1		Week 1		Week 1														
Assessment	D2	D4	D8	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16																																						
Physical examination ^a			Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х																																						
Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)			Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х																																						
Vital Signs			Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х																																						
Blood chemistry, haematology, coagulation screen, and CRP ^b				Х		Х		Х		Х		Х		Х				Х																																						
Urine Tests ^b						Х				Х				Х				Х																																						
Liver Function Tests (local) ^b		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х																																						
FVIII assays (local) ^c		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х																																						
Liver Function Tests (central) ^b		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х																																						
FVIII assays (central) ^d		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х																																						
FVIII antibody titer						Х				Х				Х				Х																																						
PCR of vector DNA in blood, saliva, urine, semen, and stools ^e	X	Х	Х			Х		Х		Х		Х		Х		Х		Х																																						
Exploratory biomarker assessments ^f						Х				Х				Х				Х																																						
Haemo-QoL-A QoL assessment			Х	Х	Х	Х												Х																																						
AAV5 antibody titer										Х								Х																																						
Testing for reactivation of hepatitis B and hepatitis C																		Xg																																						
PBMC collection			Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х																																						
Von Willebrand Factor Antigen (VWF:Ag)						Х				Х				Х				Х																																						
Direct Thrombin test			Х												Х																																									

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* Visit windows are \pm 48 hours (and include the Day 4 visit)

- ^a Brief physical examination should be done at all weekly visits except Week 16, where a complete physical examination should be performed. Refer to Section 9.7.8.5.
- ^b Refer to Table 9.7.8.2.1 for laboratory assessments to be included, and to Table 9.7.8.3.1 for liver function tests. LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data. Patients with ALT > 1.5 ULN during the study may undergo additional evaluations (e.g., imaging studies including MRI or ultrasound, additional blood tests, and/or liver biopsy) at the discretion of the investigator.
- ^c Includes hFVIII activity level (one-stage APTT and FXa chromogenic 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 \geq 5 IU/dL at 16 weeks after BMN 270 infusion and who have not resumed standard of care 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 Includes hFVIII activity level (one-stage APTT and FXa chromogenic assay), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, hFVIII coagulation activity exploratory assay, and hFVIII antigen (ELISA). If a subject has used FVIII within 72 hours of a measurement day, all efforts should be made to obtain FVIII activity measurements when a 72-hour interval without FVIII use is achieved; the 72-hour wash-out period is only intended for subjects who have achieved FVIII \geq 5 IU/dL at 16 weeks after BMN 270 infusion and who have not resumed standard of care 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 Collection to occur on Day 2 and 4 following BMN 270 infusion, and then until at least 3 consecutive negative results are obtained. Collection and testing of semen samples must continue through Week 12, even if 3 consecutive negative samples in that compartment have already been recorded.
- ^f 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 will be performed only as deemed necessary by the Sponsor.
- ^g Testing for reactivation of hepatitis B and hepatitis C at Week 16, for subjects with a past medical history of Hepatitis B or Hepatitis C prior to study entry, should be performed only in subjects who have not received therapeutic corticosteroids prior to Week 16; subjects who have received therapeutic corticosteroids will have hepatitis B and hepatitis C testing at the time points indicated in Table 9.1.5.

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

	Follow-Up After BMN 270 Administration – Weeks*															
Assessment		18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
Physical examination ^a	X	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	X	Х	Х	Х
Weight										Х						
Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)	X	X	Х	Х	X	Х	Х	Х	Х	Х	Х	Х	X	Х	Х	X
Vital Signs	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Blood chemistry, haematology, coagulation screen, and CRP ^b				X				X				X				X
Urine Tests ^b				Х				Х				Х				Х
Liver Function Tests (local) ^b	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
FVIII assays (local) ^c	X	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	X	Х	Х	Х
Liver Function Tests (central) ^b	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
FVIII assays (central) ^d	X	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
FVIII antibody titer				Х								Х				
PCR of vector DNA in blood, saliva, urine, semen, and stools ^e				Х				Х				X				X
Exploratory biomarker assessments ^f				Х				Х				Х				Х
Haemo-QoL-A QoL assessment												Х				
AAV5 antibody titer				X				Х				Х				Х
PBMC collection	Х	Х	Х	Х		Х		Х		Х		Х		Х		Х
Von Willebrand Factor Antigen (VWF:Ag)				Х				Х				Х				Х
Direct Thrombin test										Х						

* Visit windows are \pm 48 hours

^a Brief physical examination should be done at all weekly visits. Refer to Section 9.7.8.5.

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^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 function tests. LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data. Patients with ALT > 1.5 ULN during the study may undergo additional evaluations (e.g., imaging studies including MRI or ultrasound, additional blood tests, and/or liver biopsy) at the discretion of the investigator.

- ^c Includes hFVIII activity level (one-stage APTT and FXa chromogenic 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 \geq 5 IU/dL at 16 weeks after BMN 270 infusion and who have not resumed standard of care 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 Includes hFVIII activity level (one-stage APTT and FXa chromogenic assay), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, hFVIII coagulation activity exploratory assay, and hFVIII antigen (ELISA). If a subject has used FVIII within 72 hours of a measurement day, all efforts should be made to obtain FVIII activity measurements when a 72-hour interval without FVIII use is achieved; the 72-hour wash-out period is only intended for subjects who have achieved FVIII \geq 5 IU/dL at 16 weeks after BMN 270 infusion and who have not resumed standard of care 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 Collection to occur until at least 3 consecutive negative results are obtained.

^f 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 will be performed only as deemed necessary by the Sponsor.

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Table 9.1.4: Schedule of Events – Safety Follow-Up

					Ye	ear 1 -	- Weel	KS *					Years 2-5*	Year 2*	Years 3-5*	ETV
Assessment	33	34	35	36	38	40	42	44	46	48	50	52	Q3M	Q4W	Q6W	
Physical examination ^a	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х		Х	Х	Х
Weight ^a												Х	Xa			
Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)	Х	X	Х	Х	Х	Х	X	X	X	Х	Х	X		X	Х	Х
Vital Signs	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х		Х	Х	Х
Blood chemistry, haematology, coagulation screen, and $CRP^{\rm b}$				Х		Х		Х		Х		X	Х			Х
Urine Tests ^b				Х		Х		Х		Х		Х	Х			Х
Liver Function Tests (local) ^b	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х		Х	Х	Х
FVIII assays (local) ^c	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х		Х	Х	Х
Liver Function Tests (central) ^b	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х		Х	Х	Х
FVIII assays (central) ^d	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х		Х	Х	Х
AAV5 antibody titer				Х		Х		Х		Х		Х	Х			Х
FVIII antibody titer				Х				Х				Х	Х			X
PBMC Collection (for determination of FVIII and Capsid specific CTL activity)		Х		Х				Х				Х	Х			Х
Von Willebrand Factor Antigen (VWF:Ag)				Х		Х		Х		Х		Х	Х			Х
Direct Thrombin Test					Х							Х	Х			Х
PCR of vector DNA in blood, saliva, urine, semen, and stools ^e				Х		Х		Х		Х		Х	Xe			X
Exploratory biomarker assessments ^g				Х		Х		Х		Х		Х		Х	Х	Х
Haemo-QoL-A QoL assessment												Х	Xf			Х

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* Visit windows are ± 48 hours through Week 36, then ±1 week until Week 52 and ± 2 weeks for visits in Years 2-5. For LFT, FVIII, and exploratory biomarker testing during Years 2-5, the visit windows are every 4 weeks (+ 2 weeks) during Year 2, and every 6 weeks (±2 weeks) during Years 3-5.

^a Complete physical examination should be performed at Week 52 and every 52 weeks thereafter; brief physical examination may be performed at other study visits. Refer to Section 9.7.8.5. During Years 2-5, weight should be performed every 6 months.

^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 function tests. LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data. Patients with ALT > 1.5 ULN during the study may undergo additional evaluations (e.g., imaging studies including MRI or ultrasound, additional blood tests, and/or liver biopsy) at the discretion of the investigator.

- ^c Includes hFVIII activity level (one-stage APTT and chromogenic FXa 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 \geq 5 IU/dL at 16 weeks after BMN 270 infusion and who have not resumed standard of care 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 Includes hFVIII activity level (one-stage APTT and chromogenic FXa assay), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, hFVIII coagulation activity exploratory assay, and hFVIII antigen (ELISA). If a subject has used FVIII within 72 hours of a measurement day, all efforts should be made to obtain FVIII activity measurements when a 72 hour interval without FVIII use is achieved; the 72-hour wash-out period is only intended for subjects who have achieved FVIII \geq 5 IU/dL at 16 weeks after BMN 270 infusion and who have not resumed standard of care 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) in 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 Safety Follow-Up is not required if at least 3 consecutive samples are cleared during the Post-Infusion Follow-Up period. Subjects who have not had 3 consecutive negative samples by Week 52 should continue to have PCR testing every 4 weeks until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor).
- ^fHaemo-QoL-A QoL assessment during Years 2-5 of Safety Follow-up should be performed at every other visit (every 6 months) starting with the Week 78 visit (ie, 26 weeks after the Week 52 visit at the end of Year 1 of the Safety Follow-up period).
- ^g 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 will be performed only as deemed necessary by the Sponsor.

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 Table 9.1.5:
 Schedule of Events – Therapeutic Corticosteroids

	Steroid Treatment Period ^d											Post-Steroid Period ^c				
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11 ^b	Week 1	Week 2	Week 3	Week 4	Week 13
Therapeutic corticosteroids (dose in mg/day) ^a	60 mg	60 mg	40 mg	40 mg	30 mg	30 mg	20 mg	20 mg	15 mg	10 mg	5 mg					
FVIII activity testing												Х	Х	Х	Х	
Liver function testing												Х	Х	Х	Х	
Hepatitis B testing ^e						Х						Х				X
HCV Viral Load ^e						Х						Х				X

^a Therapeutic corticosteroids may be initiated when a subject's ALT value is ≥ 1.5x ULN or based on review of FVIII and liver enzyme data after consultation between the Investigator and the Medical Monitor.

^b Following initiation or completion of steroid regimen, if ALT elevation ≥ 1.5x ULN is reported, steroid management decisions will based on discussions between the Investigator and Medical Monitor. Modification of the steroid regimen may take into consideration possible confounders for the ALT elevation and impact on FVIII expression.

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

^d Regardless of the assessments listed in the Schedule of Assessments (Table 9.1.2, Table 9.1.3, or Table 9.1.4), subjects initiated on corticosteroids will only be required to have laboratory evaluations on a weekly basis.

^e Should only be performed in subjects with a history of hepatitis B or hepatitis C prior to study entry.

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9.2 Discussion of Study Design, Including Choice of Control Group

Study 270-201 is designed to be a first-in-man, phase 1/2 open-label, dose escalation study in patients with severe haemophilia A. Four doses of BMN 270 will be evaluated and the dose escalation decision tree for Cohorts 1-3 is summarized in Figure 9.1.1.

The decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and the DRB.

There will be no control group. Parameters for each subject will be compared to a pre-treatment assessment of safety (liver function) and efficacy (number of bleeds, use of replacement therapy).

As AAV based treatment always leads to anti-capsid immune response, no true control group (for example with an empty AAV) is possible.

9.3 Selection of Study Population

Up to 15 severe haemophilia A patients may enroll into the study; the actual number of patients will depend on the criteria for dose escalation.

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 criteria:

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

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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 immunity to the AAV5 capsid as measured by AAV5 transduction inhibition or AAV5 total antibodies
- 2. Any evidence of active infection or any immunosuppressive disorder.
- 3. HIV positive
- 4. Significant liver dysfunction as defined by abnormal elevation of:
 - ALT (alanine transaminase) to 3 times the upper limit of normal;
 - Bilirubin above 3 times the upper limit of normal;
 - Alkaline phosphatase above 3 times the upper limit of normal; or
 - INR (international normalized ratio) \geq 1.4.
- 5. Potential participants who have had a liver biopsy in the past 3 years are excluded if they had significant fibrosis of 3 or 4 as rated on a scale of 0-4
- 6. Evidence of any bleeding disorder not related to Haemophilia A
- 7. Platelet count of $< 100 \times 10^9/L$
- 8. Creatinine $\geq 1.5 \text{ mg/dL}$
- 9. Liver cirrhosis of any etiology as assessed by liver ultrasound
- 10. Hepatitis B if surface antigen is positive
- 11. Hepatitis C if RNA is positive
- 12. Treatment with any IP within 30 days prior to the end of the screening period
- 13. Any disease or condition at the physician's discretion that would prevent the patient from fully complying with the requirements of the study including possible corticosteroid treatment outlined in the protocol. The physician may exclude patients unwilling or unable to agree on not using alcohol for the 16-week period following the viral infusion.
- 14. Prior treatment with any gene transfer agent
- 15. Major surgery planned in the 16-week period following the viral infusion
- 16. Use of immunosuppressive agents or live vaccines within 30 days before the viral infusion

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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. A subject's participation in the study may be discontinued at any time at the discretion 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.

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 admitted into the study or does not meet entry criteria
- Subject is lost to follow-up

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

The Investigator or designee must explain to each subject, before enrollment into the study, that for evaluation of study results, the subject's protected health information obtained during the study may be shared with the study Sponsor, regulatory agencies, and IRB/IEC/REB. It is the Investigator's (or designee's) responsibility to obtain written permission to use protected health information per country-specific regulations, such as the Health Insurance Portability and Accountability Act (HIPAA) in the US, from each subject. If permission to use protected health information is withdrawn, it is the Investigator's responsibility to obtain a written request, to ensure that no further data will be collected from the subject and the subject will be removed from the study.

9.3.3.1 Study Safety Evaluation Criteria

If any of the following events occur in a subject in the study who has received BMN 270 infusion, enrollment into the trial will be put on halt to complete an extensive safety analysis per Section 9.1.

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- Any ALT elevation > 5x ULN for at least 2 consecutive weeks after administration of BMN 270, in the absence of a definitive alternate etiology for the increase
- The occurrence of Grade 3 or higher adverse events (excluding ALT elevation) assessed as related to study drug, including liver failure and clinical hepatitis
- The detection of neutralizing antibodies to hFVIII following BMN 270 infusion
- The detection of AAV vector DNA in the semen of a participant in 3 consecutive samples (which are at least 2 weeks apart) more than 52 weeks after BMN 270 infusion, as discussed in Section 9.7.8.6
- The occurrence of a malignancy excluding skin cancers at any point after BMN 270 infusion

If the following event occurs in a subject in the study who has received BMN 270 infusion, a DRB review and analysis of safety data will be undertaken to determine whether the enrollment into the trial will be put on halt:

• Grade 2 adverse event assessed as related to study drug that persists for at least 7 days

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 CRF pages. In legal jurisdictions where use of initials is not permitted, a substitute identifier will be used.

Subjects who withdraw from the study will not be replaced.

9.3.5 Duration of Subject Participation

The duration of this study will be approximately 264 weeks. This includes 4 weeks of screening, 1 day of BMN 270 infusion, 16 weeks of Post-Infusion Follow-Up, and 244 weeks of Safety Follow-Up. A primary endpoint analysis on safety and efficacy will be performed at 16 weeks.

9.4 Treatments

BioMarin or its designee will provide the study site with study drug sufficient for study completion. BioMarin is responsible for shipping study drug to clinical sites.

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.

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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 2 mL polypropylene cryovial. Each vial contains 1.1 mL of AAV5-hFVIII-SQ at a concentration of 2E13 vector genomes per mL in a pH 7.4 phosphate buffer.

The study drug label includes the following information: lot number, required storage conditions, a precautionary statement, expiry date, study number, and BioMarin name and address. Labelling will be done according to country specific requirements.

9.4.3 Storage

At the study site, all IP must be stored under the conditions specified in the IB 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

After a physical examination performed by the PI or designee, participants will be admitted on the day of BMN 270 infusion. An IV catheter will be inserted into a suitable peripheral vein (e.g. 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. An electric syringe pump will be used to infuse through an in-line, low protein binding 0.22 micron filter. BMN 270 will be infused through the catheter using an appropriate infusion pump at a constant rate of 4 ml/min while monitoring the vital signs (pulse, blood pressure, respiration rate and temperature) at 15 minute (\pm 5 minutes) intervals. The anticipated maximum interval from initiation of thawing of BMN 270 to completion of the infusion is 4 hours, although the IP has been shown to be stable at room temperature for 6 hours.

Following completion of the infusion, vital signs will be monitored hourly (\pm 5 minutes) for 6 hours and then every 2 hours (\pm 15 minutes) for 6 hours and then at 4 hour intervals. If the vital signs are stable the catheter will be removed 20-24 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 24 hours to observe for any immediate toxicity of the procedure. After 24 hours, participants will be

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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.

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 Sponsor will be required prior to enrollment of each study subject. Upon their enrollment into the study, subjects will be assigned a unique subject number and dose level by the Sponsor.

Cohorts 1 to 3 are enrolled serially and their dose is defined in Section 9.4.6.2 below. Escalation is based on FVIII activity 3 weeks after injection. Cohorts may receive the next higher dose if subjects in the previous cohort does not meet the activity criteria, or the same dose if subjects in the previous cohort meets the activity criteria. Subjects in Cohort 4 will all be enrolled at a single dose.

9.4.6 Selection of Doses Used in the Study

The starting dose was based on the expression of hFVIII observed in nonclinical studies of mice and monkeys. The starting dose has a significant safety margin (10-fold) from NOAEL in mice. The dose escalation is half-logs based.

9.4.6.1 Selection of Timing of Dose for Each Subject

A minimum of three weeks are required between subjects, to allow for evaluation of safety and expression of hFVIII. After three weeks, depending on the activity level, the choice of the dose for the next subject will be made as described below.

9.4.6.2 Selection of Dose for Each Subject

The starting dose was determined by expression of hFVIII observed in mice and monkeys and a scale up factor based on previous experience, an improved purification process over previous trials (thus potentially decreasing the risk of immune response), and a new evaluation of the titer (PCR performed after hairpin removal).

For Cohorts 1 to 3, approximately three weeks after an injection, the decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and the DRB.

Subject 1 (Cohort 1) will be dosed by intravenous infusion with 6E12 vg/kg of body weight. If the FVIII activity level does not reach 5 IU/dL or greater (expressed as % in Figure 9.1.1)

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at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 1 and enrollment into Cohort 2 will initiate with Subject 2 at the next dose (2E13 vg/kg).

If the FVIII activity level in the first subject treated in Cohort 2 does not reach \geq 5 IU/dL at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 2 and enrollment into Cohort 3 (6E13) will initiate with the next subject.

If the FVIII activity level in the first subject treated in Cohort 3 does not reach \geq 5 IU/dL at the Week 3 visit in both assays, then the DRB will recommend whether to continue to add subjects to the cohort and/or whether to continue the study.

For the first subject treated in each of the first 3 cohorts, if the activity level reaches \geq 5 IU/dL and no safety issue is found, then up to four subjects will be enrolled in that cohort, though the adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

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

There will be an ongoing review of individual patient safety and efficacy data by the medical monitor and the DRB. The adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

Refer to Figure 9.1.1 for a visual representation of the study design for Cohorts 1-3

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 CRF. The Investigator may prescribe additional medications 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 CRF.

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The following medications are prohibited starting 30 days before Screening:

- Live vaccines
- Systemic immunosuppressive agents

Medications which are predominately metabolized by the liver (e.g., acetaminophen) and alcohol should, whenever possible, be avoided for the first 52 weeks of the study, and particularly within 48 hours prior to lab work.

9.4.8.1 Concomitant Haemophilia Treatments

Subjects on "on demand" therapy for FVIII will continue their treatment at will. Subjects on prophylactic FVIII therapy will discontinue their treatment starting the day of infusion and switch to an "on demand" schedule. FVIII can always be taken as needed by the subject, who will carefully record his treatment and bleeding episodes in his diary. In addition, information on FVIII usage by medical history will be collected (if available) from subjects for the 6 month period immediately preceding study enrollment.

9.4.8.2 Glucocorticoid Treatment of Elevated Hepatic Transaminases

During the Post-Infusion Follow-up Period and the Safety Follow-Up Period, each subject will have comprehensive surveillance plan monitoring of LFTs (at local labs, once per week for Weeks 1-36, then once every 2 weeks from Week 37-52). LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.

9.4.8.2.1 Therapeutic Corticosteroids

In general, therapeutic corticosteroids may be initiated when a subject's ALT value is $\geq 1.5x$ ULN, or based on review of FVIII and liver enzyme data after consultation between the Medical Monitor and the Investigator.

Reports of raised LFTs (defined as $ALT \ge 1.5x$ ULN) should be made to the BioMarin medical monitor within 30 minutes of the lab value being available. Local laboratory results of LFTs will be used to trigger corticosteroid treatment as needed. In case of discrepant results between local and central laboratories, the Investigator and Medical Monitor will decide further action.

Following initiation or completion of therapeutic corticosteroids, if ALT elevation $\geq 1.5x$ ULN is reported, steroid management decisions will based on discussions between the Investigator and Medical Monitor. Modification of the steroid regimen may take into consideration possible confounders for the ALT elevation and impact on FVIII expression.

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Treatment with prednisolone will be initiated at a dose of 60 mg per day and then gradually tapered (60 mg daily for the first 2 weeks, then 40 mg the next 2 weeks, then 30 mg the next two weeks, then 20 mg the next two weeks, then 15 mg for the next week, then 10 mg for the next week, then 5 mg for the next week, then stop, for a total treatment of 11 weeks) (refer to Table 9.1.5).

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

Management and monitoring of reactions to corticosteroids should be determined by the Investigator's clinical judgment in consultation with the Sponsor's Medical Monitor. This includes the contraindicated use of NSAIDs during corticosteroid treatment, and specific monitoring not already covered by the schedule of events. For the subjects with a past medical history of hepatitis B or hepatitis C prior to study entry, Hepatitis B status and HCV viral load will be rechecked 6 weeks after the start of corticosteroid treatment, and then 1 week and 13 weeks after the completion of corticosteroid treatment. All adverse events should be reported as outlined in Section 10 of the protocol.

9.4.9 Treatment Compliance

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

9.5 Investigational Product Accountability

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

9.5.1 Return and Disposition of Clinical Supplies

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

Unused study drug may be destroyed on site, per the site's standard operating procedures, but only after BioMarin has granted approval for drug destruction. The monitor must account for all study drug in a formal reconciliation process prior to study drug destruction. All study drug destroyed on site must be documented. Documentation must be provided to BioMarin

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and retained in the Investigator study files. If a site is unable to destroy study drug appropriately, the site can return unused study drug to BioMarin upon request. The return of study drug or study drug materials must be accounted for on a study drug return form provided by BioMarin.

All study drug and related materials should be stored, inventoried, reconciled, and destroyed or returned according to applicable state and federal regulations and study procedures.

9.6 Dietary or Other Protocol Restrictions

There are no dietary or other protocol restrictions for this study.

9.7 Safety and Efficacy Variables

As this is a first-in-man study, the primary endpoint of safety will be assessed as explained in Section 9.7.8.

The primary efficacy measure will be to assess plasma FVIII activity. The efficacy goal of the study is to establish the dose relationship to FVIII activity \geq 5 IU/dL at 16 weeks post BMN 270 administration.

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

The primary efficacy measure will be the plasma FVIII activity monitored on a regular basis after BMN 270 dose. The efficacy goal of the protocol is to ascertain the dose range of BMN 270 required to convert severe HA patients to expression of FVIII at 5 IU/dL or above, i.e., a mild severity. This is associated in natural history studies with clinically superior long term outcomes (Den Ujil, 2011, Haemophilia).

The following assays (assessed by the central laboratory) will be used to measure the primary efficacy variable:

- FVIII activity (chromogenic FXa assay)
- FVIII activity by one-stage APTT (Activated Partial Thromboplastin Time)

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

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 \geq 5 IU/dL at 16 weeks after BMN 270 infusion and who have not resumed standard of care FVIII replacement therapy.

The FVIII activity level in both assays and the number of subjects with FVIII activity ≥ 5 IU/dL in at least one of the two assays will be summarized.

FVIII activity assays will also be performed at the local laboratory at the time points indicated in Table 9.1.2, Table 9.1.3, and Table 9.1.4, but will be used in conjunction with local lab LFT assessments to monitor subject safety and need for initiation of therapeutic corticosteroid dosing; local laboratory FVIII activity assessments will not be used to assess efficacy or to measure the primary efficacy outcome of the study.

Timing of assessment by these assays is provided in Table 9.1.2, Table 9.1.3, and Table 9.1.4. Details on performing the assays are included in the Laboratory Manual.

9.7.3 Secondary Efficacy Variables

Secondary efficacy measures will be the reduction in the frequency of factor replacement therapy, and reduction in the number of bleeding episodes. 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.

9.7.4 Immunogenicity

Immunogenicity assays will be performed on plasma. The assays will include detection of anti-capsid, and anti-FVIII total antibody, and determination of neutralizing antibodies against FVIII. Any increase in total antibody level, especially during the time period of 5-12 weeks, will be compared with FVIII activity measurements. Any abnormality of the liver parameters will lead to a retrospective immunogenicity assessment to determine anti-FVIII and capsid specific CTL. Anti-FVIII and capsid specific CTL assays will be performed on collected PBMCs.

Timing of assessment by these assays is provided in Table 9.1.2, Table 9.1.3, and Table 9.1.4.

9.7.5 Pharmacodynamics

The hFVIII antigen and activity level will be measured by an ELISA (antigen) and by one-stage APTT and/or chromogenic FXa assay (activity). Individual antigen and activity plasma plots will be prepared to assess changes over 16 weeks. FVIII activity measurements will be used to determine PD parameters.

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If supported by FVIII activity data, non-compartmental analysis and observation will be used to estimate individual values of C_b (baseline concentration), C_{ss} (steady state concentration), T_{ss} (time to steady state), C(t) and AUC(0-t) where t is 16 weeks. Other parameters that may be used to describe individual FVIII protein and activity plasma profiles are C_{max} (maximum concentration) and C_{avg} (average concentration, AUC(0-t)/t). The PD parameters and dose will be used to assess clinical pharmacology.

Sample collection times are indicated in Table 9.1.2, Table 9.1.3, and Table 9.1.4.

9.7.6 Exploratory Assessments

Blood samples will be collected at the time points indicated in Table 9.1.1, Table 9.1.2, Table 9.1.3, and Table 9.1.4 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 may be used for exploratory use once the primary use has been completed.

On an exploratory basis, samples may be fractionated prior to shedding analysis in order to better characterize the presence and location of vector DNA and/or vector capsid within each matrix. The fractionation may be performed with samples collected specifically for shedding analysis (saliva, blood, semen, urine, faeces), or by using exploratory samples, such as plasma, PBMCs, and red blood cells, collected under the study protocol.

9.7.7 Haemo-QoL-A Quality of Life Assessment

The Haemo-QoL-A is a patient-reported outcome (PRO) questionnaire which will be used to assess subject quality of life (QoL) during the study. Assessments will occur at the time points listed in the Schedules of Assessments.

Details regarding the QoL assessment will be included in the Study Reference Manual.

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.

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9.7.8.1 Adverse Events

The occurrence of AEs will be assessed continuously from the time the subject signs the ICF. The determination, evaluation and reporting of AEs will be performed as outlined in Section 10. Assessments of AEs will occur at the time points shown in Table 9.1.1, Table 9.1.2, Table 9.1.3, and Table 9.1.4.

9.7.8.2 Clinical Laboratory Assessments

Specific visits for obtaining clinical laboratory assessment samples are provided in Table 9.1.1, Table 9.1.2, Table 9.1.3, and Table 9.1.4. The scheduled clinical laboratory tests are listed in Table 9.7.8.2.1. Refer to the Study Reference Manual 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 the cause of the abnormality is determined, the value returns to baseline or to within normal limits, or 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 CRF.

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Blood Chemistry	Haematology	Urine Tests	Other
Albumin	Haemoglobin	Appearance	CRP
BUN	Haematocrit	Color	
Calcium	WBC count	рН	Coagulation Screen including:
Chloride	RBC count	Specific gravity	APTT
Total cholesterol	Platelet count	Ketones	PT/INR
CO_2	Differential cell count	Protein	TT
СРК		Glucose	
Creatinine		Bilirubin	
Glucose		Nitrite	
Phosphorus		Urobilinogen	
Potassium		Haemoglobin	
Total protein			
Sodium			
Uric Acid			

Table 9.7.8.2.1: Clinical Laboratory Tests

BUN, blood urea nitrogen; CO₂, carbon dioxide; 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.

9.7.8.3 Liver Function and Hepatitis Testing

Subjects will be screened for evidence of previous hepatitis B or hepatitis C infection at Screening. Subjects with documented results showing an absence of active hepatitis B or hepatitis C infection (as measured by positive surface antigen for hepatitis B or positive RNA testing for hepatitis C) 30 days prior to providing signed informed consent do not need to be screened again.

Evidence of ongoing hepatitis B or hepatitis C infection is exclusionary. Subjects who have cleared a hepatitis B infection or are seronegative do not need to receive the hepatitis B vaccination.

Subjects with a history of hepatitis B or hepatitis C infection prior to study entry will be tested for hepatitis B and hepatitis C reactivation at Week 16. Subjects who receive therapeutic corticosteroids prior to Week 16 do not need to complete the Week 16 reactivation assessment; instead, they will be tested for hepatitis B and hepatitis C reactivation at the time points listed in Table 9.1.5.

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A liver ultrasound and liver function testing at Screening will identify any significant hepatic dysfunction, which is defined as:

- More than 3x the normal ALT level
- More than 3x the normal bilirubin level
- More than 3x the normal Alkaline phosphatase level.
- INR ≥ 1.4 .
- Thrombocytopoenia under $100 \ge 10^9/L$
- Liver ultrasound results indicative of a liver cirrhosis

Liver function tests will be monitored on a regular basis, at the time points indicated in Table 9.1.1, Table 9.1.2, Table 9.1.3, and Table 9.1.4. At each time point, the following LFTs should be assessed:

Liver Function Tests			
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

Patients with ALT > 1.5 ULN during the study may undergo additional evaluations (e.g., imaging studies including MRI or ultrasound, additional blood tests, and/or liver biopsy) at the discretion of the investigator.

9.7.8.4 HIV Testing

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

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

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

Systolic blood pressure, diastolic blood pressure, heart rate, respiration rate, and temperature will be assessed at Screening, Baseline, and at the beginning of each visit during the Post-Infusion Follow-Up and Safety Follow-Up periods. On the day of the BMN 270 Infusion, vital signs will be monitored prior to infusion, during the infusion every

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15 minutes (\pm 5 minutes), following the infusion hourly (\pm 5 minutes) for 6 hours and then every 2 hours (\pm 15 minutes) for 6 hours and then at 4 hour intervals (\pm 15 minutes).

A complete physical examination is necessary during Screening/Baseline, at Week 16 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, respiratory, neurologic, and gastrointestinal assessments.

Height will be recorded at Screening only. Weight will be recorded at Screening and then every 6 months thereafter.

9.7.8.6 Vector Shedding

Vector shedding has been extensively studied in all similar clinical trials performed to date. (Nathwani, 2014, N.Engl.J.Med.); (Manno, 2006, Nat.Med.); (Schenk-Braat, 2007, J.Gene Med.); (Croteau, 2004, Ann.Occup.Hyg.). In the literature referenced above, including Haemophilia B clinical studies utilizing AAV2 and AAV8, vector was no longer detectable after 40 days in blood, saliva, urine or stool, but in one study was detected in the seminal fluid but not in motile sperm (Manno, 2006, Nat.Med.). In these studies, the amount of vector present in these bodily fluids involved an extremely small fraction of the infused dose. More recent data from an ongoing AAV-FIX study demonstrates persistence of the vector in both the blood and the semen for at least 39 weeks (Miesbach, 2016, Haemophilia).

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 PCR at the time points indicated in Table 9.1.2, Table 9.1.3, and Table 9.1.4. Fluids tested will include:

- Blood
- Saliva
- Semen
- Urine
- Stool

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Vector shedding will also be extensively studied in the present clinical trial, every other week between Weeks 4-16, then every 4 weeks to Week 52 until at least 3 consecutive negative results are obtained. Testing of semen will continue through Week 12, even if 3 consecutive negative results have been recorded in that compartment prior to that timepoint. Subjects who have not had 3 consecutive negative samples by Week 52 should continue to have PCR testing every 4 weeks until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor).

Contraception use may need to be extended beyond 26 weeks in individual subjects based on observed vector shedding in semen. After 6 months, subjects may stop contraception use only if they have had 3 consecutive negative semen samples.

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

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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 haematology, 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, a reportable adverse event (AE) is any untoward medical occurrence (e.g., sign, symptom, illness, disease or injury) in a subject administered the study-drug or other protocol-imposed intervention, regardless of attribution. This includes the following:

- AEs not previously observed in the subject that emerge during the course of the study.
- Pre-existing medical conditions judged by the Investigator to have worsened in severity or frequency or changed in character during the study.
- Complications that occur as a result of non-drug protocol-imposed interventions (eg, AEs related to screening procedures).

An adverse drug reaction is any AE for which there is a reasonable possibility that the study-drug caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the study-drug and the AE.

Bleeding events that are normal events of haemophilia (ie, bleeding events which occur only because the subject is a haemophiliac) should not be recorded as AEs but will instead be captured in subject diaries. Bleeding events that occur where a normal (ie, non-haemophiliac) patient would bleed, such as bleeding as a result of major trauma, should be recorded as adverse events. All bleeding events which meet criteria for being serious should be reported as serious adverse events (SAEs) whether or not they are bleeding events that are normal sequelae of haemophilia.

Whenever possible, it is preferable to record a diagnosis as the AE term rather than a series of terms relating to a diagnosis.

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10.2 Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that at any dose meets 1 or more of the following criteria:

- Is fatal
- Is life threatening

Note: Life-threatening refers to an event that places the subject at immediate risk of death. This definition does not include a reaction that, had it occurred in a more severe form, might have caused death.

- Requires or prolongs inpatient hospitalization.
- 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 intervention to prevent one of the above consequences (e.g. anaphylaxis)

All adverse events that do not meet any of the criteria for SAEs should be regarded as nonserious AEs.

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 liver enzymes (ALT) that triggers an initiation or modification of corticosteroid treatment

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 treatment, only SAEs associated with any protocol-imposed interventions will be reported. After informed consent is obtained and the first administration of study drug, the reporting period for all non-serious AEs and SAEs begins and continues for approximately 5 years or until study discontinuation/termination, whichever is longer. The criteria for determining, and the reporting of SAEs is provided in Section 10.2.

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10.3.2 Eliciting Adverse Events

Investigators will seek information on AEs, SAEs, and EOSI at each subject contact by specific questioning and, as appropriate, by examination. Information on all AEs and SAEs and EOSI, should be recorded in the subject's medical record and on the 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 severity of each will be assessed using the defined categories in Table 10.3.3.2.1.

The Investigator will determine the severity of each AE and SAE and EOSI using the NCI CTCAE v4. 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 as stated below.

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Table 10.3.3.2.1: Adverse Event Grading (Severity) Scale

Grade	Description	
1	Mild: asymptomatic or mild symptoms; clinical or diagnostic observation indicated	ons only; intervention not
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 or debilitating: consequences; urgent intervention indicated	Grade 4 and 5 AEs should always be
5	Death related to AE	reported as SAEs

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

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

10.3.3.3 Causality

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

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

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

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

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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

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 haemorrhage 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.

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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.

10.4.1.4 Abnormal Laboratory Values

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

Any laboratory result abnormality fulfilling the criteria for a SAE or EOSI should be reported as such, and recorded in the AE eCRF. Any laboratory result abnormality of CTCAE Grade 4 or 5 should be recorded as an SAE in the AE eCRF.

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

- Accompanied by clinical symptoms
- Leading to a change in study medication (e.g. dose modification, interruption or permanent discontinuation)
- Requiring a change in concomitant therapy (e.g. 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 hFVIII activity should not be reported as adverse events unless signs of worsening are observed.

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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 document 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 changed
- Hospitalization solely for the purpose of insertion of an in-dwelling IV catheter (such as a Port-a-Cath or other brand) for administration of study drug will not be considered an SAE.
- 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

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is unknown and cannot be ascertained at the time of reporting, record "Unexplained Death" or "Death of Unknown Cause" on the AE eCRF.

10.4.1.9 Pregnancy

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

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

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

If the EDC is unavailable, all SAEs should be reported to BPV by completing the SAE Report Form and faxing or emailing the completed form to BPV within 24 hours of the site

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becoming aware of the event. Once the EDC is available, the information should be entered in the AE eCRF.

10.5.2 Ethics Committee Reporting Requirements

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

10.6 Follow-up of Subjects after Adverse Events

The Investigator should follow all unresolved AEs and SAEs until the events are resolved or have stabilized, the subject is lost to follow-up, or it has been determined that the study treatment or participation is not the cause of the AE/SAE. Resolution of AEs and SAEs (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, 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 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 treatment.

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 treatment. 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

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investigational medicinal product where that new event is likely to affect the safety of the patients, the Sponsor and the Investigator shall take appropriate urgent safety measures to protect the patients against any immediate hazard. The Sponsor shall forthwith inform the competent authorities of those new events and the measures taken and shall ensure that the IRB/IEC/REB is notified at the same time."

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

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

- Immediate need to revise the IP administration (eg, modified dose amount or frequency not defined in protocol)
- 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

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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:	ГІ
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, PharmD
Address:	105 Digital Driv	/e
	Novato, CA 949	049 USA
Phone: E-mail:	PI	

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

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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 will be performed within 28 days (\pm 14 days) of BMN 270 infusion while baseline assessments will take place within 7 days of BMN 270 infusion (Day 1). Should the screening visit occur within 7 days of the drug infusion, physical examination, vital signs, blood chemistry, LFTs, haematology, urine tests, coagulation screen, and CRP do not need to be repeated at Baseline.

The following procedures will be performed during the Screening Period:

- Full medical history, including haemophilia A history, hepatitis B, hepatitis C, and HIV.
- 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)
- Electrocardiogram
- Chest X-ray
- Liver Ultrasound
- Samples for hFVIII Assays
 - Baseline hFVIII activity chromogenic FXa (plasma)
 - Baseline hFVIII activity level one-stage APTT assay
 - o hFVIII coagulation activity exploratory assay
 - o hFVIII inhibitor level (Bethesda assay with Nijmegen modification)
 - hFVIII total antibody assay
 - hFVIII antigen (ELISA)

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- Blood sample for AAV5 Assays
 - o AAV5 antibody titer
 - AAV5 transduction inhibition assay
- Screen for hepatitis B, hepatitis C, and HIV if required (subjects with documented negative results 30 days prior to informed consent being obtained do not need to be retested)
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- Urine Tests (refer to Table 9.7.8.2.1)
- Liver Function Tests (refer to Table 9.7.8.3.1)
- Von Willebrand Factor Antigen (VWF:Ag)
- Blood samples for Biomarker testing (including HLA genotyping, FVIII genotyping status, TNFα and IL10a single nucleotide polymorphisms)

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 sample for AAV5 Assays
 - AAV5 antibody titer
 - AAV5 transduction inhibition assay
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.8.2.1)

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

12.3 Baseline Visit

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

- Physical examination
- Assessment of Adverse Events and Concomitant Medications
- Documentation of bleeding episodes and FVIII usage (by either subject or clinical information)
- Distribution of subject diaries and training in diary completion
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- Urine Tests (refer to Table 9.7.8.2.1)
- Liver Function Tests (refer to Table 9.7.8.3.1)
- PBMC collection for CTL baseline
- Direct Thrombin test
- PCR of vector DNA in blood, saliva, urine, semen, and stools
- Exploratory biomarker assessments
- Haemo-QoL-A QoL assessment

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 24 hours for the BMN 270 Infusion Visit. The following procedures will be performed during the BMN 270 Infusion Visit:

- Physical examination
- Assessment of Adverse Events and Concomitant Medications
- Blood sample for AAV5 Assays (must be performed before the BMN 270 infusion)
 - o AAV5 antibody titer
 - AAV5 transduction inhibition assay
- BMN 270 Infusion
- Vital Signs

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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 the first 6 hours, every 2 hours (± 15 minutes) for the next 6 hours, and then at 4 hour (± 15 minutes) intervals for the remainder of the subject's stay in the clinic.

12.5 BMN 270 Infusion Follow-Up Visits

After BMN 270 has been infused, subjects will return to the study site every week $(\pm 48 \text{ hours})$ for 16 weeks, when the following procedures will be completed:

12.5.1 Once per week (Weeks 1 through 16)

The following procedures will be performed at one visit per week from Weeks 1 through 16:

- Physical examination
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Vital Signs
- Liver Function Tests (refer to Table 9.7.8.3.1) central laboratory assessment
 - LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- Samples for FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage APTT)
 - FVIII activity level (chromogenic FXa assay)
 - FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level
 - FVIII antigen (ELISA)

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

• Central assessment of FVIII activity level should be performed 1x/week from Week 1 through Week 16

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- Liver Function Tests (refer to Table 9.7.8.3.1) local laboratory assessment
 - LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage APTT)
 - FVIII activity level (chromogenic FXa assay)
- PBMC collection

12.5.2 Week 1 – Day 2 and Day 4

On Day 2 and Day 4 of Week 1, the following procedures will be performed:

- PCR of vector DNA in blood, saliva, urine, semen, and stools (Day 2 and Day 4)
- Samples for FVIII Assays (Day 4 only) central laboratory assessment
 - FVIII activity level (one-stage APTT)
 - FVIII activity level (chromogenic FXa assay)
 - FVIII coagulation activity exploratory assay
 - Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level
 - FVIII antigen (ELISA)

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

- Liver Function Tests (refer to Table 9.7.8.3.1) (Day 4 only) central laboratory assessment
- Liver Function Tests (refer to Table 9.7.8.3.1) (Day 4 only) local laboratory assessment
- FVIII activity level (Day 4 only) local laboratory assessment
 - FVIII activity level (one-stage APTT)
 - FVIII activity level (chromogenic FXa assay)

12.5.3 Week 1 – Day 8

On Day 8, the following procedures will be performed:

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

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- Direct Thrombin test
- Haemo-QoL-A QoL assessment

12.5.4 Every 2 Weeks

Every 2 weeks (Weeks 2, 4, 6, 8, 10, 12, 14 and 16), the following procedures will be performed:

- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.8.2.1) (not assessed at Week 14)
- PCR of vector DNA in blood, saliva, urine, semen, and stools (not collected at Week 2)
 - Collection to occur until at least 3 consecutive negative results are obtained. Semen samples should continue to be collected and tested through Week 12, even if 3 consecutive negative results in that compartment have been recorded prior to that timepoint.

12.5.5 Weeks 4, 8, 12, and 16

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

- Urine Tests (refer to Table 9.7.8.2.1)
- VWF:Ag
- FVIII antibody titer
- Exploratory biomarker assessments

12.5.6 Week 16

At Week 16, the following procedures will be performed:

- Test for hepatitis B and hepatitis C reactivation (in subjects with a history of hepatitis B or hepatitis C infection prior to study entry)
 - Subjects who receive therapeutic corticosteroids prior to Week 16 do not need to complete the Week 16 reactivation assessment; instead, they will be tested for hepatitis B and hepatitis C reactivation at the time points listed in Table 9.1.5.

12.5.7 Weeks 8 and 16

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

• AAV5 antibody titer

12.5.8 Weeks 2, 3, 4, and 16

At Weeks 2, 3, 4, and 16, the following procedure will be performed:

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• Haemo-QoL-A QoL assessment

12.5.9 Week 13

At Week 13, the following procedure will be performed:

• Direct Thrombin test

12.6 Safety Follow-Up – Weeks 17-36

After the Post-Infusion Follow-Up visits are complete, subjects will return to the study site for Safety Follow-Up visits from Weeks 17 through Week 36 (\pm 48 hours), when the following procedures will be completed:

12.6.1 Once per week (Weeks 17 through 36)

Once per week from Week 17 through Week 36, the following procedures will be performed:

- Physical examination
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Vital Signs
- Liver Function Tests (refer to Table 9.7.8.3.1) central laboratory assessment
 - LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage APTT)
 - FVIII activity level (chromogenic FXa assay)
 - FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - FVIII antigen (ELISA)

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

• Liver Function Tests (refer to Table 9.7.8.3.1) – local laboratory assessment

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- LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage APTT)
 - FVIII activity level (chromogenic FXa assay)

12.6.2 Once per week (Weeks 17 through 20)

Once per week from Week 17 through Week 20, the following procedures will be performed:

• PBMC collection

12.6.3 Every 2 weeks (Weeks 21 through 36)

Every 2 weeks (Weeks 22, 24, 26, 28, 30, 32, 34, and 36), the following procedures will be performed:

• PBMC collection

12.6.4 Every 4 Weeks

Every 4 weeks (Weeks 20, 24, 28, 32, and 36), the following procedures will be performed:

- Exploratory biomarker assessments
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- Urine Tests (refer to Table 9.7.8.2.1)
- VWF:Ag
- AAV5 antibody titer
- PCR of vector DNA in blood, saliva, urine, semen, and stools
 - Sample testing during Safety Follow-Up is not required if at least
 3 consecutive samples are clear during the Post-Infusion Follow-Up period.

12.6.5 Every 8 Weeks

Every 8 weeks (Weeks 20, 28, and 36), the following procedure will be performed:

• FVIII antibody titer

12.6.6 Week 26

At Week 26, the following procedure will be performed:

• Direct Thrombin test

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• Weight

12.6.7 Week 28

At Week 28, the following procedure will be performed:

• Haemo-QoL-A QoL assessment

12.7 Safety Follow-Up – Weeks 37-52

Subjects will return every 2 weeks (Week 38, 40, 42, 44, 46, 48, 50, and 52) from Week $37-52 (\pm 1 \text{ week})$, when the following procedures will be completed:

12.7.1 Once per visit

At Weeks 38, 40, 42, 44, 46, 48, 50, and 52, the following procedures will be performed:

- Physical examination
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Vital Signs
- Liver Function Tests (refer to Table 9.7.8.3.1) local laboratory assessment
 - LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage APTT)
 - FVIII activity level (chromogenic FXa assay)
- Liver Function Tests (refer to Table 9.7.8.3.1) central laboratory assessment
 - LFTs may be monitored more or less frequently based (and in particular when ALT values are >1.5x ULN) on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage APTT)
 - FVIII activity level (chromogenic FXa assay)
 - FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - FVIII antigen (ELISA)

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

12.7.2 Every 4 Weeks

Every 4 weeks (Weeks 40, 44, 48, and 52), the following procedures will be performed:

- Exploratory biomarker assessments
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- Urine Tests (refer to Table 9.7.8.2.1)
- AAV5 antibody titer
- VWF:Ag
- PCR of vector DNA in blood, saliva, urine, semen, and stools
 - Sample testing during Safety Follow-Up is not required if at least 3 consecutive samples are clear during the Post-Infusion Follow-Up period. Subjects who have not had 3 consecutive negative samples by Week 52 should continue to have PCR testing every 4 weeks until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor).

12.7.3 Every 8 Weeks

Every 8 weeks (Weeks 44 and 52), the following procedure will be performed:

- PBMC collection
- FVIII antibody titer

12.7.4 Week 38 and 52

At Week 38 and Week 52, the following procedure will be performed:

• Direct Thrombin test

12.7.5 Week 52

At Week 52, the following procedure will be performed:

- Haemo-QoL-A QoL assessment
- Weight

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12.8 Safety Follow-Up – Years 2-5

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

12.8.1 Year 2 – Every 4 Weeks

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

- Physical examination
 - Complete Physical Examination will be performed every 52 weeks; Brief Physical Examinations may be performed at other visits.
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Vital Signs
- Liver Function Tests (refer to Table 9.7.8.3.1) local laboratory assessment
 - LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage APTT)
 - FVIII activity level (chromogenic FXa assay)
- Liver Function Tests (refer to Table 9.7.8.3.1) central laboratory assessment
 - LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage APTT)
 - FVIII activity level (FXa chromogenic assay)
 - FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - o FVIII antigen (ELISA)

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

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• Exploratory biomarker assessments

12.8.2 Years 3-5 – Every 6 Weeks

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

- Physical examination
 - Complete Physical Examination will be performed every 52 weeks; Brief Physical Examinations may be performed at other visits.
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Vital Signs
- Liver Function Tests (refer to Table 9.7.8.3.1) local laboratory assessment
 - LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage APTT)
 - FVIII activity level (chromogenic FXa assay)
- Liver Function Tests (refer to Table 9.7.8.3.1) central laboratory assessment
 - LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage APTT)
 - FVIII activity level (FXa chromogenic assay)
 - FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - FVIII antigen (ELISA)

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

• Exploratory biomarker assessments

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12.8.3 Years 2-5 – Every 3 Months

During Years 2-5, every 3 months (\pm 2 weeks), the following procedures will be performed:

- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- Urine Tests (refer to Table 9.7.8.2.1)
- AAV5 antibody titer
- FVIII antibody titer
- PBMC collection
- VWF:Ag
- Direct Thrombin test

12.8.4 Years 2-5 – Every 6 Months

Every six months starting at the Week 78 visit (ie, 26 weeks after the Week 52 visit at the end of Year 1 of the Safety Follow-up period), the following procedures will be performed:

- Haemo-QoL-A QOL assessment
- Weight

12.8.5 Years 2-5 – Every 4 Weeks

Every four weeks during Years 2-5, the following procedure may be performed:

- PCR of vector DNA in blood, saliva, urine, semen, and stools
 - Sample testing during Years 2-5 is not required if at least 3 consecutive samples are clear during the Post-Infusion Follow-Up period. Subjects who have not had 3 consecutive negative samples by Week 52 should continue to have PCR testing every 4 weeks during Years 2-5 until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor).

12.9 Early Termination Visit

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

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

• Physical examination

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- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Vital Signs
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- Urine Tests (refer to Table 9.7.8.2.1)
- Liver Function Tests (refer to Table 9.7.8.3.1) local laboratory assessment
- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage APTT)
 - FVIII activity level (chromogenic FXa assay)
- Liver Function Tests (refer to Table 9.7.8.3.1) central laboratory assessment
- FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage APTT)
 - FVIII activity level (chromogenic FXa assay)
 - FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - FVIII antigen (ELISA)

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

- AAV5 antibody titer
- FVIII antibody titer
- PBMC collection
- VWF:Ag
- Direct Thrombin test
- PCR of vector DNA in blood, saliva, urine, semen, and stools
 - Sample testing at the ETV is not required if at least 3 consecutive samples are clear during the Post-Infusion Follow-Up period.
- Exploratory biomarker assessment
- Haemo-QoL-A QOL assessment

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12.10 End of Study

The study will end after the last subject completes the last Safety Follow-Up visit (Week 260). 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.

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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, any applicable randomization procedures, source document requirements, eCRFs, monitoring requirements, and procedures for reporting AEs, including SAEs.

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

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

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14 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

14.1 Statistical and Analytical Plans

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

14.1.1 Interim Analyses

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

14.1.2 Procedures for Accounting for Missing, Unused and Spurious Data

14.2 Missing data will not be imputed.

14.3 Primary and Secondary Efficacy Analysis

The subjects will be followed in a longitudinal manner and all the relevant information will be collected. The analysis of the data will be descriptive in nature. Descriptive statistics include the number of subjects, mean, median, standard deviation, minimum, and maximum for continuous variables and count and percent for categorical variables. Efficacy variables will be summarized by dose cohort at each time point. Relationship between dose and efficacy results will be examined.

Data collected in a longitudinal manner may be analyzed using longitudinal methods such as mixed effect model which takes into account the correlation among the observation taken at various time points within a participant. Efficacy is a secondary endpoint, defined as biologically active hFVIII at \geq 5 IU/dL by chromogenic FXa and/or one-stage APTT assay as measured by the central laboratory at 16 weeks following study treatment. hFVIII activity will be assessed weekly during the study period. We can only assess the true steady state of hFVIII protein produced from BMN 270 after a minimum of 72 hours has elapsed since the last infusion of FVIII protein concentrates.

14.4 Immunogenicity

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

14.5 Pharmacodynamic Analyses

The FVIII antigen and activity level as measured by an Elisa (antigen level) and by a one-stage APTT and/or chromogenic FXa assay (activity level), will be used for plasma

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profiles; FVIII activity will be used to determine PD parameters. Traditional PK analysis is not applicable.

If supported by FVIII activity data, non-compartmental analysis and observation will be used to estimate individual PD parameter values of C_b (baseline), C_{ss} (steady state), T_{ss} (time to steady state), C(t) and AUC(0-t) where t is 16 weeks. Other parameters that may be used to describe individual FVIII protein and activity plasma profiles are C_{max} (maximum concentration) and C_{avg} (average concentration, AUC(0-t)/t). The parameters will be summarized using descriptive statistics.

14.6 Safety Analysis

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

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

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

Detailed statistical methods will be provided in the SAP.

14.7 Determination of Sample Size

No formal sample size calculations based on statistical power were performed.

The sample size is determined based upon clinical consideration and could detect a strong clinical efficacy signal. Up to 15 subjects may be dosed in the study; the actual number of subjects will depend on the criteria for dose escalation.

14.8 Analysis Populations

The Safety analysis population is defined as all enrolled subjects who receive any study drug. The analysis of safety data will be performed on Safety Set.

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The Full Analysis Set (FAS) is defined as all enrolled subjects who receive study drug and have at least one Baseline and post-Baseline assessment. The FAS will be used for efficacy analysis.

14.9 Changes in the Conduct of the Study or Planned Analyses

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

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

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

Note: If discrepancies exist between the text of the statistical analysis as planned in the protocol, and the final SAP, a protocol amendment will not be issued and the SAP will prevail.

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15 DATA REVIEW BOARD

There will be no formal DMC for this study, however a safety and efficacy evaluation board (the Data Review Board [DRB]) composed of the investigator representatives and the Sponsor will be established.

The DRB will review safety and efficacy on an ongoing basis. The DRB will meet prior to dose escalation or dose expansion to assess available subject safety and efficacy data and make recommendations with regards to the conduct of study. Should a safety signal arise, including one which may warrant a halt of study enrollment, the DRB will promptly convene for further assessment of subject safety. Notification of all DRB meetings and meeting outcomes will be sent to participating sites.

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16 COMPENSATION, INSURANCE AND INDEMNITY

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

The Investigator should contact BioMarin immediately upon notification that a study subject has been injured by the IP 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 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 subject has followed the Investigator's instructions, BioMarin will pay for reasonable and necessary medical services to treat the injuries caused by the IP or study procedures, if these costs are not covered by health insurance or another third party that usually pays these costs. In some jurisdictions, BioMarin is obligated by law to pay for study-related injuries without prior recourse to third party payer billing. If this is the case, BioMarin will comply with the law.

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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 CRF casebook to verify its accuracy.

CRFs 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 CRF instructions, blank data fields are not acceptable.

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

BioMarin's policy is that study data on the CRFs 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 an Investigator or institution refuses to allow access to subject records because of confidentiality, arrangements must be made to allow an "interview" style of data verification.

A CRA designated by BioMarin will compare the CRFs 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 CRA, 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 CRA 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 CRF 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 CRFs 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

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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.

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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.

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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.

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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 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).

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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 R2 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 patients.
- He or she will personally conduct or supervise the study.
- He or she will inform any potential patients, 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 R2 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 R2 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 R2 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 R2 Section 4.9 are kept, and those records are available for inspection in accordance with 21 CFR 312.68 and/or ICH E6 R2 Section 4.9.7.
- The IRB/IEC/REB complies with the requirements of 21 CFR Part 56, ICH E6 R2 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 patients or others are reported to the IRB/IEC/REB. Additionally, he or she will not make any changes in the research without IRB/IEC/REB approval, except where necessary to eliminate apparent immediate hazards to human patients.
- 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 R2.

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23 SIGNATURE PAGE

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

Protocol Number: 270-201, Amendment 6

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 R2, as stated in the protocol, and other information supplied to me.

Investigator Signature		Date
Printed name:		
Accepted for the Sponsor:	DocuSigned by:	
Medical Monitor Signature		Date
Printed name: Pl	, MD, PharmD, ^{Pl}	

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24 PROTOCOL AMENDMENT TEXT REVISIONS

The following table summarizes the revisions made to the protocol and relates the changes to the appropriate rationale (See pages 2-3). Text that has been added or inserted is indicated by <u>underlined</u> font, and deleted text is indicated by strikethrough font.

Section No./Title	Text Revisions	<u>Rationale</u>
Synopsis/Study Design and Plan	The starting dose was based on the expression and safety of FVIII observed in nonclinical studies of mice and monkeys. The starting dose has a significant 10-fold safety margin (10-fold) from no observed adverse effect level (NOAEL) in non-human primates.	5
Synopsis/Criteria for Evaluation	LFTs will be monitored every three months <u>4 weeks during Year 2, and then every 6 weeks</u> for up to Years 3-5-years post-dose in the safety extension; the frequency and duration of LFT testing may be changed based on discussion between the Medical Monitor and the Investigator and review of subject data.	1
9.1/Overall Study Design and Plan	The starting dose was based on the expression and safety of FVIII observed in nonclinical studies of mice and monkeys. The starting dose has a significant10-fold safety margin-(10-fold) from no observed adverse effect level (NOAEL) in non-human primates.	5
Table 9.1.1 (Footnotes)	^g Blood samples will be collected from subjects to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to Haemophilia A-disease., coagulation, and/or AAV gene transfer, and to develop assays used for these evaluations. Subjects may choose to opt out of the exploratory genetic/genomic research being done to study or try to discover genes that are not yet known to be associated with hemophilia A. While exploratory samples will be collected at the time points indicated above, testing on-of these samples is optional-will be performed only as deemed necessary by the Sponsor.	5
Table 9.1.2 (Footnotes)	^c Includes hFVIII activity level (one-stage APTT and FXa chromogenic 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 standard of care 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.	3, 4, 5
	^d Includes hFVIII activity level (one-stage APTT and FXa chromogenic assay), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, hFVIII coagulation activity exploratory assay, and hFVIII antigen (ELISA). 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	

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Section No./Title	Text Revisions	Rationale
	<u>have not resumed standard of care FVIII replacement therapy</u> . 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.	
	^f Blood samples will be collected from subjects to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to Haemophilia A-disease, coagulation, and/or AAV gene transfer, and to develop assays used for these evaluations. Subjects may choose to opt out of the exploratory genetic/genomic research being done to study or try to discover genes that are not yet known to be associated with hemophilia A. While exploratory samples will be collected at the time points indicated above, testing on of these samples is optional-will be performed only as deemed necessary by the Sponsor.	
	^g Testing for reactivation of hepatitis B and hepatitis C at Week 16, for subjects with a past medical history of Hepatitis B or Hepatitis C prior to study entry, should be performed only in subjects who have not received therapeutic corticosteroids prior to Week 16; subjects who have received therapeutic corticosteroids will have hepatitis B and hepatitis C testing at the time points indicated in Table 9.1.5.	
Table 9.1.3	Table 9.1.3 has been updated to be consistent with changes made elsewhere in the protocol.	2
Table 9.1.3 (Footnotes)	 ^c Includes hFVIII activity level (one-stage APTT and FXa chromogenic 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 standard of care 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 Includes hFVIII activity level (one-stage APTT and FXa chromogenic assay), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, hFVIII coagulation activity exploratory assay, and hFVIII antigen (ELISA). 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 standard of care 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. 	2, 3, 5
	^f Blood samples will be collected from subjects to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to Haemophilia A-disease, coagulation, and/or AAV gene transfer, and to develop assays used for these evaluations. Subjects may choose to opt out of the exploratory genetic/genomic research being done to study or try to discover genes that are not yet known to be	

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Section No./Title	Text Revisions	<u>Rationale</u>
	associated with hemophilia A. While exploratory samples will be collected at the time points indicated above, testing on of these samples is	
	optional will be performed only as deemed necessary by the Sponsor.	
Table 9.1.4	Table 9.1.4 has been updated to be consistent with changes made elsewhere in the protocol.	1, 2, 3
Table 9.1.4 (Footnotes)	* Visit windows are ± 48 hours through Week 36, then ±1 week until Week 52 and ± 2 weeks for visits in Years 2-5. For LFT, FVIII, and exploratory biomarker testing during Years 2-5, the visit windows are every 4 weeks (+ 2 weeks) during Year 2, and every 6 weeks (±2 weeks) during Years 3-5.	1, 2, 3, 5
	^c Includes hFVIII activity level (one-stage APTT and chromogenic FXa 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 standard of care 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 Includes hFVIII activity level (one-stage APTT and chromogenic FXa assay), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, hFVIII coagulation activity exploratory assay, and hFVIII antigen (ELISA). 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. <u>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 standard of care FVIII replacement therapy.</u> 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) in years 3-5, a fresh sample should be collected within 4 weeks of the initial visit that had a positive result. ^g Blood samples will be collected to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to hemophilia A, 	
	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 will be performed only as deemed necessary by the Sponsor.	
Table 9.1.5 (Footnotes)	^e Should only be performed in subjects with a history of hepatitis B or hepatitis C prior to study entry.	4

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Section No./Title	Text Revisions	<u>Rationale</u>
9.4.8.2.1/Therapeutic Corticosteroids	For subjects with a past medical history of hepatitis B or hepatitis C prior to study entry, Hepatitis B status and HCV viral load will be rechecked 6 weeks after the start of corticosteroid treatment, and then 1 week and 13 weeks after the completion of corticosteroid treatment.	4
9.7.2/Primary Efficacy Variable	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. <u>The 72-hour wash-out period is only intended for subjects who have achieved FVIII \geq 5 IU/dL at 16 weeks after BMN 270 infusion and who have not resumed standard of care FVIII replacement therapy.</u>	3
9.7.6/Exploratory Assessments	Blood samples will be collected from subjects at the time points indicated in Table 9.1.1, Table 9.1.2, Table 9.1.3, and Table 9.1.4 to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to Haemophilia A disease. The exploratory genetic/genomic testing is optional. 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.	5
9.7.8.3/Liver Function and Hepatitis Testing	Subjects with a history of hepatitis B or hepatitis C infection prior to study entry will be tested for hepatitis B and hepatitis C reactivation at Week 16.	4
10.4.1.4/Abnormal Laboratory Values	Any laboratory result abnormality fulfilling the criteria for a SAE or EOSI should be reported as such, <u>and recorded in addition</u> to being the AE eCRF. Any laboratory result abnormality of CTCAE Grade 4 or 5 should be recorded as an <u>AESAE</u> in the AE eCRF.	5
10.9/BioMarin Contact Information	Contact information for the medical monitor is as follows: Name: Liron WalshMitra Tavakkoli, MD, PharmD Address: 105 Digital Drive Novato, CA 94949 USA Phone: +1 (415) 455 7870257-5974 E-mail: liron.walsh Jiron.walsh fatemeh.tavakkoli@bmrn.com	5
12.5.1/Once per Week (Weeks 1-16)	 The following procedures will be performed at one visit per week from Weeks 1 through 16: Samples for FVIII Assays – central laboratory assessment 	6

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Section No./Title	Text Revisions	<u>Rationale</u>
	Note: If a subject has used FVIII within 72 hours of a measurement day, all efforts should be made to obtain FVIII activity measurements when a 72-hour interval without FVIII use is achieved. The 72-hour wash-out period is only intended for subjects who have achieved FVIII \geq 5 IU/dL at 16 weeks after BMN 270 infusion and who have not resumed standard of care FVIII replacement therapy.	
12.5.1/Week 1 – Day 2 and Day 4	 On Day 2 and Day 4 of Week 1, the following procedures will be performed: Samples for FVIII Assays (Day 4 only) – central laboratory assessment Note: 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. <u>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 standard of care FVIII replacement therapy.</u> 	3
12.5.6/Week 16	 At Week 16, the following procedures will be performed: Test for hepatitis B and hepatitis C reactivation (in subjects with a history of hepatitis B or hepatitis C infection prior to study entry) Subjects will be tested for hepatitis B and hepatitis C reactivation at Week 16. Subjects who receive therapeutic corticosteroids prior to Week 16 do not need to complete the Week 16 reactivation at the time points listed in Table 9.1.5. 	4, 5
12.6.1/Once per Week (Weeks 17 through 36)	 Once per week from Week 17 through Week 36, the following procedures will be performed: FVIII Assays – central laboratory assessment Note: 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. <u>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 standard of care FVIII replacement therapy.</u> 	3
12.6.4/Every 4 Weeks	 Every 4 weeks (Weeks 20, 24, 28, 32, and 36), the following procedures will be performed: Exploratory biomarker assessments (Weeks 20 and 24 only) 	2

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Section No./Title	Text Revisions	<u>Rationale</u>
12.7.1/Once per visit	At Weeks 38, 40, 42, 44, 46, 48, 50, and 52, the following procedures will be performed:	3
	• FVIII Assays – central laboratory assessment	
	Note: If a subject has used FVIII within 72 hours of a measurement day, all efforts should be made to obtain FVIII activity	
	measurements when a 72-hour interval without FVIII use is achieved. The 72-hour wash-out period is only intended for	
	subjects who have achieved FVIII \geq 5 IU/dL at 16 weeks after BMN 270 infusion and who have not resumed standard of care FVIII replacement therapy.	
12.7.2/Every 4 Weeks	Every 4 weeks (Weeks 40, 44, 48, and 52), the following procedures will be performed:	2
	Exploratory biomarker assessments	
12.8/Safety Follow-	During Years 2-5 of Safety Follow-up, subjects will be assessed every 3 months (± 2 weeks). At these times, the following	5
Up	procedures will be completed:	
<u>12.8.1/Year 2 – Every</u>	During Year 2, every 4 weeks (+ 2 weeks), the following procedures will be performed:	1, 2, 3, 5
<u>4 Weeks</u>	<u>Physical examination</u>	
	• Complete Physical Examination will be performed every 52 weeks; Brief Physical Examinations may be	
	performed at other visits.	
	 Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and <u>FVIII use</u>) 	
	• <u>Vital Signs</u>	
	• Liver Function Tests (refer to Table 9.7.8.3.1) – local laboratory assessment	
	 LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data. 	
	<u>FVIII activity level – local laboratory assessment</u>	
	• <u>FVIII activity level (one-stage APTT)</u>	
	 <u>FVIII activity level (chromogenic FXa assay)</u> 	

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 <u>Liver Function Tests (refer to Table 9.7.8.3.1) – central laboratory assessment</u> <u>LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.</u> <u>FVIII Assays – central laboratory assessment</u> <u>FVIII activity level (one-stage APTT)</u> <u>FVIII activity level (FXa chromogenic assay)</u> <u>FVIII coagulation activity exploratory assay</u> <u>Bethesda assay (with Nijmegen modification) for FVIII inhibitor level</u> 	
 <u>FVIII antigen (ELISA)</u> <u>Note: 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 standard of care FVIII replacement therapy.</u> <u>Exploratory biomarker assessments</u> 	
 During Years 3-5, every 6 weeks (± 2 weeks), the following procedures will be performed: Physical examination Complete Physical Examination will be performed every 52 weeks; Brief Physical Examinations may be performed at other visits. Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use) Vital Signs Liver Function Tests (refer to Table 9.7.8.3.1) – local laboratory assessment LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data. 	1, 2, 3, 5
	on discussion between the Medical Monitor and the Investigator and review of subject data. • FVIII Assays – central laboratory assessment • FVIII activity level (one-stage APTT) • FVIII activity level (FXa chromogenic assay) • FVIII coagulation activity exploratory assay • Bethesda assay (with Nijmegen modification) for FVIII inhibitor level • FVIII antigen (ELISA) Note: 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 standard of care FVIII replacement therapy. • Exploratory biomarker assessments During Years 3-5, every 6 weeks (± 2 weeks), the following procedures will be performed: • Physical examination mill be performed every 52 weeks; Brief Physical Examinations may be performed at other visits. • Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use) • Vital Signs • Liver Function Tests (refer to Table 9.7.8.3.1) – local laboratory assessment • LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5.x ULN) based

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Section No./Title	Text Revisions	<u>Rationale</u>
	 <u>FVIII activity level (one-stage APTT)</u> <u>FVIII activity level (chromogenic FXa assay)</u> <u>Liver Function Tests (refer to Table 9.7.8.3.1) – central laboratory assessment</u> 	
	 <u>LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based</u> on discussion between the Medical Monitor and the Investigator and review of subject data. <u>FVIII Assays – central laboratory assessment</u> <u>FVIII activity level (one-stage APTT)</u> 	
	 FVIII activity level (FXa chromogenic assay) FVIII coagulation activity exploratory assay Bethesda assay (with Nijmegen modification) for FVIII inhibitor level FVIII antigen (ELISA) Note: 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 standard of care FVIII replacement therapy. Exploratory biomarker assessments 	
12.8.3/ Every Visit <u>Years 2-5 – Every 3</u> <u>Months</u>	 Every <u>During Years 2-5, every 3</u> months (± 2 weeks), the following procedures will be performed: Physical examination Complete Physical Examination will be performed every 52 weeks; Brief Physical Examinations may be performed at other visits. Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use) 	1, 3, 5
	 Vital Signs Liver Function Tests (refer to Table 9.7.8.3.1) local laboratory assessment 	

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Section No./Title	Text Revisions	<u>Rationale</u>
	 LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data. 	
	FVIII activity level local laboratory assessment	
	○ FVIII activity level (one stage APTT)	
	○ FVIII activity level (chromogenic FXa assay)	
	Liver Function Tests (refer to Table 9.7.8.3.1) central laboratory assessment	
	 LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data. 	
	FVIII Assays — central laboratory assessment	
	↔ FVIII activity level (one stage APTT)	
	○ FVIII activity level (FXa chromogenic assay)	
	 FVIII coagulation activity exploratory assay 	
	 Bethesda assay (with Nijmegen modification) for FVIII inhibitor level 	
	↔ FVIII antigen (ELISA)	
	Note: 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.	
12.8.4/ Every Other Visit <u>Years 2-5 –</u> Every 6 Months	Every six months starting at the Week 78 visit (ie, 26 weeks after the Week 52 visit at the end of Year 1 of the Safety Follow-up period), the following procedure procedures will be performed:	5
$\frac{12.8.5/\text{Years } 2-5}{\text{Factors } 4 \text{ We also}}$	Every four weeks during Years 2-5, the following procedure may be performed:	5
Every 4 Weeks	PCR of vector DNA in blood, saliva, urine, semen, and stools	
	 Sample testing during Years 2-5 is not required if at least 3 consecutive samples are clear during the Post- Infusion Follow-Up period. Subjects who have not had 3 consecutive negative samples by Week 52 should continue to have PCR testing every 4 weeks during Years 2-5 until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor). 	

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Section No./Title	Text Revisions	<u>Rationale</u>
12.9/Early Termination Visit	 At the Early Termination visit, as many of the following assessments as possible should be done: FVIII Assays – central laboratory assessment Note: 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 standard of care FVIII replacement therapy. Exploratory biomarker assessment 	2, 3
22.1/Conduct of Study and Protection of Human Patients	 In accordance with FDA Form 1572 and/or principles of ICH E6 R2 GCP, the Investigator will ensure that: He or she will inform any potential patients, 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 R2 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 R2 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 R2 Section 4.11. He or she will ensure that Adequate and accurate records in accordance with 21 CFR 312.62 and to make/or ICH E6 R2 Section 4.9.1. He or she will ensure that Adequate and accurate records in accordance with 21 CFR 312.62 and to make/or ICH E6 R2 Section 4.9.7. The IRB/IEC/REB complies with the requirements of 21 CFR Part 56, ICH E6 R2 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 patients or others are reported to the IRB/IEC/REB approval, except where necessary to eliminate apparent immediate hazards to human patients. 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 R2. 	5

BOMARIN

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1/2, Dose-Escalation, Safety, Tolerability and Efficacy Study of BMN 270, an Adenovirus-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII in Patients with Severe Haemophilia A
Protocol Number:	270-201
Active Investigational Product:	AAV5-hFVIII-SQ
IND/European Union Drug Regulating Authorities Clinical Trials (EudraCT) Number:	2014-003880-38
Indication:	Haemophilia A
Sponsor:	BioMarin Pharmaceutical Inc.
	105 Digital Drive
	Novato, CA 94949
Development Phase:	Phase 1/2
Sponsor's Responsible Medical Monitor:	Pl , MD Pl BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949
Duration of Subject Participation:	Approximately 264 weeks
Dose:	Varied
Study Population:	Males aged 18 or older
Date of Original Protocol:	10 February 2015
Date of Amendment 1:	06 March 2015
Date of Amendment 2:	26 May 2015
Date of Amendment 3:	06 November 2015
Date of Amendment 4:	02 September 2016
Date of Amendment 5:	14 February 2017

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May not be divulged, published, or otherwise disclosed to others without prior written approval from BioMarin.

This study will be conducted according to the principles of Good Clinical Practice as described in the U.S. Code of Federal Regulations and the International Conference on Harmonisation Guidelines, including the archiving of essential documents

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CLINICAL STUDY PROTOCOL AMENDMENT SUMMARY

Amendment: 5

Date: 14 February 2017

RATIONALE AND SUMMARY OF MAJOR CHANGES

A summary of major changes covered by Amendment 5 to the BMN 270-201 protocol is provided below.

1. Twice weekly testing (at the local laboratories) of FVIII and ALT levels during Weeks 1-20 has been reduced to once weekly testing.

Rationale: Current data from subjects enrolled in the study support a reduced frequency of local ALT and FVIII assessments in order to maintain adequate surveillance of hepatocyte injury and FVIII activity. The accumulated data suggest that week-to-week increases in ALT (if observed) are mild, and as such timely administration of corticosteroids will not be impacted by a reduction to once weekly testing. As already stipulated in the protocol, an observed increase in ALT, or decline in FVIII activity, may require an adjustment to the monitoring schedule as needed based on individual subject data (ie, increased monitoring in case of increases in ALT) and upon discussion between the Investigator and the Medical Monitor.

2. The frequency of PBMC collection has been increased to weekly through Week 20, then every other week through Week 36.

Rationale: Previous FIX gene-therapy clinical studies have demonstrated an association between increases in ALT and declines in FIX expression, which are thought to be due to a cell-mediated immune response to transduced hepatocytes (Manno, 2006, Nat.Med.) (Mingozzi, 2013, Blood); (Nathwani, 2014, N.Engl.J.Med.); (Nathwani, 2011, Mol.Ther.). An analysis of this immune response requires the collection of peripheral blood mononuclear cells (PBMC), which is part of the current schedule of assessments. The transient nature of the reported data indicates we may need to sample more frequently to identify a potential cell-mediated immune response to transduced hepatocytes. The frequency of PBMC collection has been increased from every 4 weeks to weekly through Week 20, then to every 2 weeks through Week 36.

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3. Subjects will be required to continue to provide semen samples for PCR analysis through Week 12, even if they have already had 3 consecutive negative results in semen prior to that timepoint.

Rationale: A monitoring period of at least 12 weeks is required for semen to conform with regulatory guidances for shedding analysis, which recommend monitoring for at least one complete cycle of spermatogenesis (mean: 74 days, 95% CI interval: 70-78 days) (Heller and Clermont, 1964; Heller, 1969). Collection and testing of semen for vector DNA will therefore be continued through Week 12, regardless of whether the semen fluid compartment is considered to have cleared (i.e., the subject has had 3 consecutive negative sample tests). This new minimal monitoring period should account for the potentially delayed appearance of vector DNA in semen if a sperm progenitor cell had been transduced.

4. Language has been added to allow exploratory fractionation of collected samples (such as plasma, PBMCs, and red blood cells).

Rationale: On an exploratory basis, samples may be fractionated prior to shedding analysis in order to better characterize the presence and location of vector DNA and/or vector capsid within each matrix. The fractionation may be performed with a portion of samples designated for shedding analysis (saliva, blood, semen, urine, faeces), or by using exploratory samples, such as plasma, PBMCs, and red blood cells, collected under the study protocol.

5. Minor administrative changes have been made for consistency and clarity.

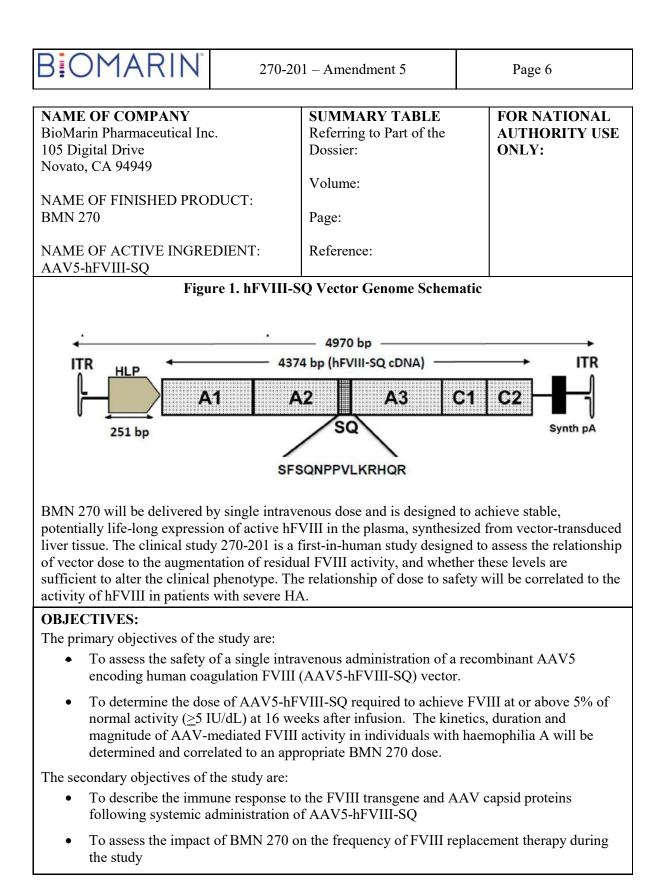
Specific changes included in this amendment, including the Synopsis, since Amendment 4 (approved 2 September 2016) are outlined in Section 24.

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2 SYNOPSIS

NAME OF COMPANY BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949	SUMMARY TABLE Referring to Part of the Dossier: Volume:	FOR NATIONAL AUTHORITY USE ONLY:	
NAME OF FINISHED PRODUCT: BMN 270	Page:		
NAME OF ACTIVE INGREDIENT: AAV5-hFVIII-SQ	Reference:		
TITLE OF STUDY: A Phase 1/2, Dose-Escalation, Safety, Toler Adenovirus-Associated Virus Vector–Media with Severe Haemophilia A			
PROTOCOL NUMBER:			
270-201			
STUDY SITES: Approximately 6-10 sites worldwide.			
PHASE OF DEVELOPMENT:			
Phase 1/2 STUDY RATIONALE: Haemophilia 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 cascade. This disorder can be either inherited, due to a new mutation 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 is largely governed by the level of residual expression. Severe HA is classified as FVIII activity less than 1% of wild type (< 1 IU/dL), moderate disease comprises 1-5% of wild type activity and the mild form is 5-40% activity. The clinical manifestations of severe HA remain frequent spontaneous bleeding episodes, predominantly in joints and soft tissues, with a substantially increased risk of death from haemorrhage when the brain is involved. 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 treatment). The consequence of multiple bleeding events is the development of an underlying pathology that contributes to debilitating multiple-joint arthropathy and substantially increased risk of death. Chemical modification (e.g. direct conjugation of polyethylene glycol (PEG) polymers) and bioengineering of FVIII (e.g. FVIII-Fc fusion proteins) improve half-life by approximately 50%, and thus, show promise in reduced			

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NAME OF COMPANY BioMarin Pharmaceutical Inc 105 Digital Drive Novato, CA 94949	SUMMARY TABLE Referring to Part of the Dossier: Volume:	FOR NATIONAL AUTHORITY USE ONLY:
NAME OF FINISHED PROE BMN 270		
NAME OF ACTIVE INGREI AAV5-hFVIII-SQ	DIENT: Reference:	
BMN 270 Page: NAME OF ACTIVE INGREDIENT: Reference:		treatment of HA to give life. tinuous endogenous on of a vector with the placement approach because duct (FVIII) that circulates in of gene expression is not ne plasma level by 2 ng/ml of the disease. Thus, ally relevant improvements e assessed using validated ing established laboratory een evaluated, but y have an excellent and well vith tropism for specific ed, an on-going gene therapy stable (>36 months) on of their bleeding single peripheral vein been able to discontinue when they undertook ment has resulted in a



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NAME OF COMPANY		SUMMARY TABLE		FOR NATIONAL
BioMarin Pharmaceutical Ind	с.	Referring to Part of the		AUTHORITY USE
105 Digital Drive		Dossier:		ONLY:
Novato, CA 94949				
		Volume:		
NAME OF FINISHED PRODUCT:				
BMN 270		Page:		
NAME OF ACTIVE INGRE	EDIENT:	Reference:		
AAV5-hFVIII-SQ				
• To assess the impact of BMN 270 on the number of bleeding episodes requiring treatment				

• To assess the impact of BMN 270 on the number of bleeding episodes requiring treatment during the study

STUDY DESIGN AND PLAN:

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

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

Cohort 1: 6E12 vector genomes [vg] per kilogram of body weight, given as a single intravenous dose (iv)

Cohort 2: 2E13 vg per kilogram, iv

Cohort 3: 6E13 vg per kilogram, iv

Cohort 4: 4E13 vg per kilogram, iv

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

Cohorts 1-3

The first 3 cohorts will be enrolled sequentially, allowing a period of 3 weeks or more between cohorts. Dose escalation may occur after a single subject has been safely dosed if the resulting FVIII activity at the Week 3 visit is < 5 IU/dL in both the one-stage aPTT and chromogenic assays. Three weeks is expected to be the time the expression will be close to the maximum. This escalation paradigm is intended to minimize the subject numbers exposed to subtherapeutic doses.

Approximately three weeks after an injection, the decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and a panel of investigators participating in the study, the Data Review Board (DRB).

If the FVIII activity reaches \geq 5 IU/dL at the Week 3 visit, then the remaining subjects in the cohort will be enrolled without the need to wait for 3 weeks between subjects.

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

Subject 1 will be dosed by intravenous infusion with 6E12 vector genomes [vg] per kilogram of body weight. If the FVIII activity level does not reach ≥ 5 IU/dL at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 1 and enrollment into Cohort 2 will initiate with Subject 2 at the next dose (2E13 vg/kg).

If the FVIII activity level in the first subject treated in Cohort 2 does not reach ≥ 5 IU/dL at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 2 and enrollment into Cohort 3 (6E13) will initiate with the next subject. If the FVIII activity level in the first subject treated in Cohort 3 does not reach ≥ 5 IU/dL at the Week 3 visit in both assays, then the Data Review Board (DRB) will recommend whether to continue to add subjects to the cohort and/or whether to continue the study.

For the first subject treated in each of the first 3 cohorts, if the activity level reaches \geq 5 IU/dL and no safety issue is found, then up to four subjects will be enrolled in the Cohort, though, the adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

<u>Cohort 4</u>

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

There will be an ongoing review of individual patient safety and efficacy data by the medical monitor and the DRB. The adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

Because subjects develop neutralizing immunity upon exposure to the capsid, re-challenge of vector is not a likely treatment option and these subjects have effectively a single opportunity for therapy using this AAV capsid. Efficacy will be determined by FVIII activity at 16 weeks post dose. Safety will be evaluated for approximately 5 years after dosing. Any safety signal may trigger a review of the data and possible additional immunogenicity studies that include an assessment of cellular immune responses using collected peripheral blood mononuclear cells (PBMC).

NUMBER OF SUBJECTS PLANNED:

Up to 15 subjects may enroll into the study; the actual number of subjects will depend on the FVIII activity levels seen in each Cohort.

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BioMar 105 Dig	OF COMPANY rin Pharmaceutical Inc gital Drive , CA 94949		SUMMARY TABLE Referring to Part of the Dossier: Volume:	FOR NATIONAL AUTHORITY USE ONLY:	
NAME BMN 2	OF FINISHED PROI 70	DUCT:	Page:		
	OF ACTIVE INGRE hFVIII-SQ	DIENT:	Reference:		
DIAGN	NOSIS AND ALL CF	RITERIA FOR	R INCLUSION AND EXC	CLUSION:	
Individ	uals eligible to particip	pate in this stud	ly must meet all of the follo	owing criteria:	
1.			n established severe haemo be considered as severe if t		
2.	2. Treated/exposed to FVIII concentrates or cryoprecipitate for a minimum of 150 exposure days (EDs)			minimum of 150 exposure	
3.	3. Greater or equal to 12 bleeding episodes only if receiving on-demand therapy over the previous 12 months. Does not apply to patients on prophylaxis				
4.	Able to sign informed consent and comply with requirements of the trial				
5.	5. No history of inhibitor, and results from a modified Nijmegen Bethesda assay of less than 0.6 Bethesda Units (BU) on 2 consecutive occasions at least one week apart within the pa 12 months				
6. Sexually active patients must be willing to use an acceptable method of contraception such as double barrier, including hormonal contraception for at least 6 months post-treatment. After 6 months, subjects may stop contraception use only if they have had 3 consecutive negative semen samples.					
Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study:					
1.	1. Detectable pre-existing immunity to the AAV5 capsid as measured by AAV5 transduction inhibition or AAV5 total antibodies				
2.	. Any evidence of active infection or any immunosuppressive disorder.				
3.					
4.	. Significant liver dysfunction as defined by abnormal elevation of:			of:	
	• ALT (alanine tran	nsaminase) to 3	times the upper limit of ne	ormal;	
	• Bilirubin above 3 times the upper limit of normal;				
	• Alkaline phosphatase above 3 times the upper limit of normal; or			nal; or	
	• INR (international	al normalized ra	atio) ≥ 1.4		

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NAME OF COMPANY BioMarin Pharmaceutical Inc 105 Digital Drive	SUMMARY TABLE Referring to Part of the Dossier:			
Novato, CA 94949 NAME OF FINISHED PROI				
BMN 270	Page:			
NAME OF ACTIVE INGRE AAV5-hFVIII-SQ				
	who have had a liver biopsy in the pass s of 3 or 4 as rated on a scale of 0-4	at 3 years are excluded if they		
6. Evidence of any blee	ling disorder not related to Haemophil	ia A		
7. Platelet count of < 10	$0 \ge 10^{9}/L$			
8. Creatinine $\geq 1.5 \text{ mg/c}$	L			
9. Liver cirrhosis of any etiology as assessed by liver ultrasound				
10. Hepatitis B if surface antigen is positive				
11. Hepatitis C if RNA is positive				
12. Treatment with any IP within 30 days prior to the end of the screening period				
13. Any disease or condition at the physician's discretion that would prevent the patient from fully complying with the requirements of the study including possible corticosteroid treatment outlined in the protocol. The physician may exclude patients unwilling or unable to agree on not using alcohol for the 16-week period following the viral infusion.				
14. Prior treatment with any vector or gene transfer agent				
15. Major surgery planne	15. Major surgery planned in the 16-week period following the viral infusion			
16. Use of systemic immunosuppressive agents or live vaccines within 30 days before the viral infusion				
INVESTIGATIONAL PRODUCT(S), DOSE, ROUTE AND REGIMEN: Each subject will receive a single injection of BMN 270 as an intravenous infusion. The volume of infusion will depend on the dose level.				
REFERENCE THERAPY(IES), DOSE, ROUTE AND REGIMEN:				
The study is open label with comparison of FVIII activity to baseline values. No reference therapy will be evaluated in this study.				
	DURATION OF TREATMENT:			
BMN 270 is given as a single	dose by intravenous infusion.			

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NAME OF COMPANY BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949	SUMMARY TABLE Referring to Part of the Dossier:	FOR NATIONAL AUTHORITY USE ONLY:		
NAME OF FINISHED PRODUCT: BMN 270	Volume: Page:			
NAME OF ACTIVE INGREDIENT: AAV5-hFVIII-SQ	Reference:			
CRITERIA FOR EVALUATION:				
<u>Safety:</u> The following safety outcome measure	ments will be assessed.			
ç ,)		
 Incidence of adverse events (AEs), including serious AEs (SAEs) Change in clinical laboratory tests (serum chemistry and haematology) 				
 Change in vital signs 				
 Change in physical examination 				
 Vector shedding 				
 Vector shedding Liver function tests (LFTs, including ALT, AST, GGT, LDH, bilirubin, alkaline phosphatase) 				
• Immune response to FVIII transgene and AAV capsid proteins				
No major toxicity is expected based on have comprehensive surveillance moni 1-36, then once every 2 weeks from W three months for up to 5 years post-dos testing may be changed based on discu- review of subject data.	toring of LFTs (at local labs, once Veek 37-52) during Year 1. LFTs v e in the safety extension; the frequession between the Medical Monito	e per week for Weeks will be monitored every uency and duration of LF or and the Investigator an		
There will be a detailed assessment of cellular and humoral responses to AAV5 capsid and FVIII				
protein.				
<u>Efficacy:</u> The primary efficacy measure will be to study is to establish the dose relationsh administration.				
Secondary efficacy measures include assessing the impact of BMN 270 on the frequency of FVI replacement therapy and on the number of bleeding episodes during the study. Subjects will be asked to keep a subject diary to record the details in these areas.				

Pharmacodynamics:

The FVIII antigen and activity level as measured by an ELISA (antigen level) and by one-stage APTT and/or chromogenic FXa assay (activity level), will be used for plasma profiles; FVIII activity will be used to determine PD parameters. Traditional PK analysis is not applicable.

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NAME OF COMPANY	SUMMARY TABLE	FOR NATIONAL		
BioMarin Pharmaceutical Inc.	Referring to Part of the	AUTHORITY USE		
105 Digital Drive	Dossier:	ONLY:		
Novato, CA 94949				
	Volume:			
NAME OF FINISHED PRODU	CT:			
BMN 270	Page:			
NAME OF ACTIVE INGREDIE	NT: Reference:			
AAV5-hFVIII-SQ				
If supported by the FVIII activity data, non-compartmental analysis and observation will be used				
to estimate individual values of Cb (baseline concentration), Css (steady state concentration), Tss				
(time to steady state), C(t) and AUC(0-t) where t is 16 weeks.				

STATISTICAL METHODS:

The sample size is based upon clinical considerations and could detect a strong clinical efficacy signal. Up to 15 subjects may be dosed in the study. The subjects will be followed in a longitudinal manner and all the relevant information will be collected. The analysis of the data will be descriptive in nature but data collected in a longitudinal manner may be analyzed using longitudinal methods such as mixed effect model which takes into account the correlation among the observation taken at various time points within a participant. Efficacy is a secondary endpoint, defined as biologically active FVIII at ≥ 5 IU/dL by chromogenic FXa assay and/or one-stage APTT assay at 16 weeks following study treatment. FVIII activity will be assessed weekly during the study period. We can only assess the true steady state of FVIII protein produced from BMN 270 after a minimum of 72 hours has elapsed since the last infusion of FVIII protein concentrates.

Analysis of neutralizing antibody response and other immunological parameters as well as vector shedding will be primarily descriptive and involve both inter-participant and intra-participant comparisons across doses.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

AAV	adeno-associated virus
ADL	activities of daily living
ADR	adverse drug reaction
AE	adverse event
ALT	alanine transaminase
APTT	activated partial thromboplastin time
BPV	BioMarin Pharmacovigilance
BU	Bethesda Unit
CFR	Code of Federal Regulations
CRA	clinical research associate
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DRB	Data Review Board
eCRF	electronic case report form
ED	exposure days
EOSI	events of special interest
ETV	early termination visit
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIH	first-in-human
FVIII	coagulation factor VIII
FXa	coagulation factor Xa
GCP	Good Clinical Practice
HA	Haemophilia A
hFVIII	human coagulation factor VIII
HIPAA	Health Insurance Portability and Accountability Act
IB	investigator brochure
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for
	Registration of Pharmaceuticals for Human Use
ICH E6	ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6
IEC	independent ethics committee
IND	Investigational New Drug (application)

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INR	internatio	onal normalized ratio	
IP	investiga	tional product	
IRB	institutio	nal review board	
IV	intraveno	bus	
LFT	liver fun	ction test	
MedDRA	Medical	Dictionary for Regulatory Activities	
NOAEL	no-obser	ved-adverse-effect level	
PBMC	periphera	al blood mononuclear cells	
PD	pharmac	odynamics	
PEG	polyethy	lene glycol	
РК	Pharmac	okinetics	
PRO	patient-r	eported outcome	
rhFVIII	recombin	nant human FVIII protein	
REB	research	ethics board	
SAE	serious a	dverse event	
SAP	statistica	l analysis plan	
SDV	source da	ata verification	
ULN	upper lin	nit of normal	
vg	vector ge	enomes	
VWF:Ag	von Will	ebrand factor Antigen	

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]).

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

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5 ETHICS

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

5.1 Institutional Review Board or Independent Ethics Committee

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

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

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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 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)

Specifically, this study is based on adequately performed laboratory and animal experimentation. The study will be conducted under a protocol reviewed and approved by an IRB/IEC/REB and will be conducted by scientifically and medically qualified persons. The benefits of the study are in proportion to the 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), United States Code of Federal Regulations (CFR) 21 CFR §50, European Clinical Trial Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC, and other applicable local regulations, will be obtained for each subject prior to entering the subject into the study. The Investigator will prepare the ICF and provide the documents to BioMarin for approval prior to submission to the IRB/IEC/REB approval. BioMarin and the IRB/IEC/REB must approve the documents before they are implemented. A copy of the approved ICF, and if applicable, a copy of the approved subject information sheet and all ICFs translated to a language other than the native language of the clinical site must also be received by BioMarin or designee prior to any study-specific procedures being performed.

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

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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 US Food and Drug Administration (FDA) Form FDA 1572 and a Financial Disclosure Form. All sub-Investigators must be listed on Form FDA 1572. Financial Disclosure Forms must also be completed for all sub-Investigators listed on the Form FDA 1572 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.

Liver function tests (LFTs) will be performed at the local laboratories associated with the study sites. Local laboratory results of LFTs will be used to trigger corticosteroid treatment as needed (refer to Section 9.4.8.2). In case of discrepant results between local and central laboratories, the Investigator and Medical Monitor will decide further action. Safety labs evaluations (including LFTs) will be performed at the central lab, while bioanalytical samples will be performed at the appropriate specialty lab. Refer to the Laboratory Manual for more details.

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7 INTRODUCTION

Haemophilia A (HA) is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males (Nathwani, 1992, Baillieres Clin.Haematol.). It is caused by mutations in the factor VIII (FVIII) gene that codes for FVIII protein, an essential cofactor in the coagulation cascade. 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 haemorrhage. Treatment in Western (Berntorp, 2012, Haemophilia.) countries consists of intravenous injection of plasma derived or recombinant FVIII protein concentrates at the time of a bleed, 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 haemophilia A patients. These individuals develop debilitating arthropathy and have a substantially increased risk of death from haemorrhage in life (Stonebraker, 2010, Haemophilia.). Chemical modification or bioengineering of FVIII may improve half-life to 18-19 hours (Kaufman, 2013, Blood). However, these long acting FVIII variants do not eliminate the need for lifelong FVIII protein administration (Hay, 2012, Blood).

Gene therapy offers the potential of disease-modifying therapy by continuous endogenous production of human FVIII following a single administration of vector. Haemophilia 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, Haemophilia.); thus the therapeutic goal for gene therapy is a modest increase in hFVIII. Finally, the consequences of gene transfer can be assessed using simple quantitative rather than qualitative endpoints that can be easily assayed in most clinical laboratories.

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

7.1 Nonclinical Studies

The nonclinical program supports a single IV administration of BMN 270, the planned clinical route of administration, for the treatment of Haemophilia A in male patients. This

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nonclinical program took into account the guidelines and reflection papers for gene therapy medicinal products under EMA Advanced Therapies. 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 (normal CD-1 mouse, B and T cell deficient mouse model of haemophilia 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.

The primary PD of BMN 270 was assessed in a series of non-GLP single dose studies in a FVIII KO x Rag2 mouse model of severe Haemophilia A that recapitulates the change in coagulation observed in the human severe disease population without interfering cross species immunogenicity. PD activity and expression of hFVIII was assessed for durations up to 13-weeks in the FVIII KO x Rag2 mouse given dose range of 2E11 through 2E14 vector genomes (vg)/kg. Low levels of plasma hFVIII were observed in mice given 2E12 vg/kg after eight-weeks, post dose. Plasma hFVIII activity using bleeding time as an endpoint was evaluated in the FVIII KO x Rag2 mouse given up to 2E13 and 1E14 vg/kg BMN 270 at 8 weeks, post dose. BMN 270 related correction of bleeding times showed a dose relationship that was similar to that observed in FVIII KO x Rag2 mice given matched IU levels of Refacto[®].

All cynomolgus monkeys used in this program were screened for neutralizing anti-AAV5 activity prior to study enrollment. PD activity and plasma hFVIII concentrations were evaluated in the cynomolgus monkey given up to 6E13 vg/kg BMN 270 for eight weeks. Peak expression of hFVIII was observed three to six weeks post administration with a subsequent decrease in expression presumably due to immunogenicity though not necessarily correlated to antibody titer.

The normal mouse was utilized in the GLP toxicology study to assess the safety profile of BMN 270 without the background of disease progression and in sufficient number per parameter. The GLP single dose toxicity study in normal CD-1 mice given 6E12 and 6E13 vg/kg with a 4 and 13-week follow up period monitored clinical pathology, defined potential target organs, immunogenicity, gene expression and activity. No changes in liver function were observed. In a single dose PD study in monkey given BMN 270, formation of anti-AAV5 total antibodies was observed at Week 8 with relatively low formation of anti-hFVIII total antibodies. No changes in liver function was observed.

The overall nonclinical safety profile includes formation of anti-AAV5 total antibodies with relatively lower formation of anti-hFVIII total antibodies. Immunogenicity against the AAV capsid and hFVIII is an anticipated finding for BMN 270 treatment and will be monitored in

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the nonclinical and clinical programs. Though not observed in the nonclinical species, liver toxicity utilizing clinical pathology parameters will be monitored in the clinical program based on previous literature. Cellular immune response will also be monitored.

Additionally, the BMN 270 transgene product has a final sequence closely matching that of the protein replacement treatment, Refacto[®] and therefore the safety profile of the BMN 270 transgene product is anticipated to be similar to Refacto[®] and have no unique FVIII-specific target organs of toxicity. The AAV5 capsid has not been modified and therefore no unique capsid-specific safety findings are anticipated. Because the biodistribution pattern of AAV5 after IV administration is consistent across species, BioMarin will confirm the nonclinical distribution pattern of BMN 270 during clinical development. Biodistribution of the AAV5 capsid has been documented to predominately target the liver with relatively lower levels of transduction observed in the lung, kidney, spleen, testes and blood compartment depending on the species and timing of administration. Liver targeted distribution of a similar AAV5 Factor IX gene therapy product was observed in the rhesus macaque monkey with low levels of vector genomes detected in spleen, kidney and testis (Nathwani, 2006, Blood). Despite distribution to non-liver organs, no expression of Factor IX was detected in these tissues. Additionally, distribution to the testis was observed in another study in monkeys given an AAV5-codon-optimized human porphobilinogen deaminase; however, vector genomes in the semen were only transiently observed within one week but not thereafter (Paneda, 2013, Hum.Gene Ther.).

Both normal and disease model mice and a limited number of monkeys were utilized to establish proof of concept, species scaling and dose response in order to select the first-in-human (FIH) dose of 6E12 vg/kg. This dose represents 10-fold safety factor from the no observed adverse effect level (NOAEL) in the GLP enabling nonclinical toxicology study in mice.

7.2 Previous Clinical Studies

This is the first clinical study for BMN 270.

BioMarin's program for haemophilia A builds on previous clinical trials of AAV-mediated gene transfer for a related condition, haemophilia B, that were conducted with an AAV2 vector (Manno, 2003, Blood) and an AAV8 vector (Nathwani, 2011, N.Engl.J.Med.), (Nathwani, 2014, N.Engl.J.Med.). The large size of the FVIII cDNA was shortened and a preclinical validation of this approach was performed with an AAV8 vector (McIntosh, 2013, Blood).

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AAV serotype 5 is being tested in other clinical trials and was reportedly well tolerated without treatment-related serious adverse events in a recent phase 1 study for treatment of Acute Intermittent Porphyria (D'Avola, 2014, J.Hepatol.). In addition, AAV using other serotypes have been used in 105 clinical studies to date and no safety issue specific to the vector was ever reported.

7.3 Study Rationale

Haemophilia A (HA) is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males (Mannucci, 2001, N.Engl.J.Med.). It is caused by deficiency in the activity of coagulation factor VIII (FVIII), an essential cofactor in the intrinsic coagulation cascade. This disorder can be either inherited, due to a new mutation 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 is largely governed by the level of residual expression. Severe HA is classified as FVIII activity less than 1% of wild type (< 1 IU/dL), moderate disease comprises 1-5% of wild type activity and the mild form is 5-40% activity. The clinical manifestations of severe HA remain frequent spontaneous bleeding episodes, predominantly in joints and soft tissues, with a substantially increased risk of death from haemorrhage when the brain is involved.

Treatment of severe HA presently consists of intravenous injection of plasma derived or recombinant human FVIII protein (rhFVIII) concentrates both as prophylaxis 2-4 times per week, and at the time of a bleed, to prevent or control bleeding episodes, respectively. The half-life for FVIII (12-18 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 treatment (mean of 1 to 7 episodes/year with prophylaxis and up to 30 to 50 episodes/year for on demand treatment) (Nagel, 2011, Haemophilia.). The consequence of multiple bleeding events is the development of an underlying pathology that contributes to debilitating multiple-joint arthropathy and substantially increased risk of death (Nagel, 2011, Haemophilia). Chemical modification (e.g. direct conjugation of polyethylene glycol (PEG) polymers) and bioengineering of FVIII (e.g. FVIII-Fc fusion proteins) improve half-life by approximately 50%, and thus, show promise in reduced dosing and maintaining activity levels above 1%trough (Stonebraker, 2010, Haemophilia.), (Mahlangu, 2014, Blood). However, these longer acting FVIIIs remain dependent on multiple infusions to maintain critical levels of FVIII activity in severe HA patients. There is therefore a strong unmet need for a fully preventive treatment of HA to give patients a FVIII level compatible with a normal and haemorrhage-free life.

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Gene therapy offers the potential of disease-modifying therapy by continuous endogenous production of active FVIII following a single intravenous administration of a vector with the appropriate gene sequence. Haemophilia 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 modest increases in the level of FVIII (any increase of the plasma level by 2 ng/ml induces an increase in activity of 1%) can ameliorate the severe form of the disease. Thus, relatively small changes in endogenous FVIII activity results in clinically relevant improvements in disease phenotype. Finally, the 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 (Mannucci, 2001, N.Engl.J.Med.). They have an excellent and well defined safety profile, and can direct long term transgene expression with tropism for specific tissues such as the liver (Nathwani, 2005, Curr.Hematol.Rep.) for serotypes 2, 5 and 8 among others). Indeed, an on-going gene therapy clinical trial for a related disorder, haemophilia B, has established that stable (>36 months) expression of human factor IX at levels that are sufficient for conversion of their bleeding phenotype from severe to moderate or mild is achievable following a single peripheral vein administration of AAV-8 vector (Nathwani, 2014, N.Engl.J.Med.). Several participants in this trial have been able to discontinue factor prophylaxis without suffering spontaneous haemorrhages, 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, 2011, Mol.Ther.), (Bainbridge, 2008, N.Engl.J.Med.), (Maguire, 2009, Lancet); (Simonelli, 2010, Mol.Ther.).

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

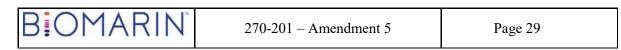
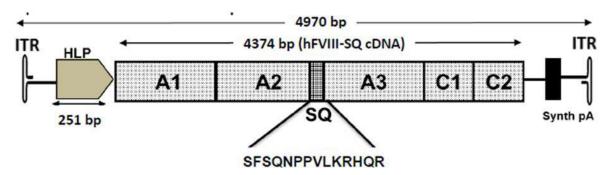


Figure 7.3.1: hFVIII-SQ Vector Genome Schematic



BMN 270 will be delivered by single intravenous dose and is designed to achieve stable, potentially life-long expression of active FVIII in the plasma, synthesized from vector-transduced liver tissue. The clinical study BMN 270-201 is a first-in-human study designed to assess the relationship of vector dose to the augmentation of residual FVIII activity, and whether these levels are sufficient to alter the clinical phenotype. The relationship of dose to safety will be correlated to the activity of FVIII in patients with severe HA.

7.4 Summary of Overall Risks and Benefits

Safety will be assessed by adverse event reporting and clinical laboratory assessment. Based on prior human studies with peripheral injections of AAV vectors, there is no known safety risk of AAV gene therapy. However, a mild asymptomatic transaminitis was observed at week 7-12 after administration in humans with an AAV8-FIX, providing the rationale for the following surveillance plan (Nathwani, 2011, Mol.Ther.). Each subject will have a comprehensive surveillance plan that monitors LFTs during the study.

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

Dose selection: The benefit of this study can only be enhanced by selecting a starting dose that maximizes the opportunity of observing a therapeutic effect, and therefore, reducing the possibility of a sub-therapeutic effect. With this consideration in mind, the starting dose 6E12 vg/kg was selected using overall data from the pre-clinical studies conducted in mice (normal and disease model, Rag2 -/- x FVIII -/-) and monkey. A detectable pharmacological response based on activity was observed at 6E12 vg/kg. A 10-fold safety margin based upon the NOAEL was observed in the GLP 13-week study in normal mouse at the highest dose administered. A 30-fold safety margin in an 8-week dose response study in disease model mice based on histology was observed at the highest dose administered. No BMN 270-related

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changes in clinical observations or chemistry was observed in the monkey at doses up to 6E13 vg/kg, a 10-fold safety margin after 8-weeks. Overall, no BMN 270-related findings, except expected formation of anti-AAV5 antibodies, were observed at the highest administered doses of 6E13, 2E14 and 6E13 vg/kg in the normal mouse, disease model mouse and monkey, respectively.

Based on these key pre-clinical findings it can be suggested that the proposed starting dose of 6E12 vg/kg should not pose any risk or safety concerns to subjects with the best chance of benefiting the subject therapeutically.

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8 STUDY OBJECTIVES

The primary objectives of the study are:

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

The secondary objectives of the study are:

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

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9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

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

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

- Cohort 1: 6E12 vector genomes [vg] per kilogram of body weight, given as a single intravenous dose (iv)
- Cohort 2: 2E13 vg per kilogram, iv
- Cohort 3: 6E13 vg per kilogram, iv
- Cohort 4: 4E13 vg per kilogram, iv

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

Cohorts 1-3

The first three cohorts will be enrolled sequentially, allowing a period of 3 weeks or more between cohorts. Dose escalation may occur after a single subject in a cohort has been safely dosed if the resulting FVIII activity at the Week 3 visit is < 5 IU/dL in both assays. Three weeks is expected to be the time the expression will be close to the maximum. This escalation paradigm is intended to minimize the subject numbers exposed to subtherapeutic doses. The decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and a panel of investigators participating in the study.

If the FVIII activity reaches ≥ 5 IU/dL at the Week 3 visit, then the remaining subjects in the cohort will be enrolled without the need to wait for 3 weeks between subjects.

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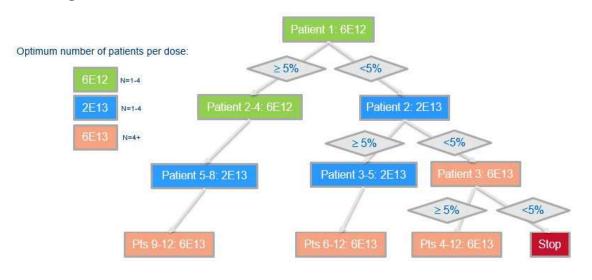


Figure 9.1.1: Flow Chart of Dose Escalation Scheme for Cohorts 1 to 3

Subject 1 (Cohort 1) will be dosed by intravenous infusion with 6E12 vg/kg of body weight. If the FVIII activity level does not reach 5 IU/dL or greater (expressed as % in Figure 9.1.1) at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 1 and enrollment into Cohort 2 will initiate with Subject 2 at the next dose (2E13 vg/kg).

If the FVIII activity level in the first subject treated in Cohort 2 does not reach \geq 5 IU/dL at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 2 and enrollment into Cohort 3 (6E13) will initiate with the next subject.

If the FVIII activity level in the first subject treated in Cohort 3 does not reach \geq 5 IU/dL at the Week 3 visit in both assays, then the DRB will recommend whether to continue to add subjects to the cohort and/or whether to continue the study.

For the first subject treated in each of the first 3 cohorts, if the activity level reaches \geq 5 IU/dL and no safety issue is found, then up to four subjects will be enrolled in the Cohort, though the adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

Cohort 4

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

There will be an ongoing review of individual patient safety and efficacy data by the medical monitor and the Data Review Board (DRB). The adaptive nature of this trial allows the DRB Proprietary and Confidential 14 February 2017

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to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

Because subjects develop neutralizing immunity upon exposure to the capsid, re-challenge of vector is not a likely treatment option and these subjects have effectively a single opportunity for therapy using this AAV capsid. Efficacy will be determined by FVIII activity at 16 weeks post dose. Safety will be evaluated for approximately 5 years after dosing. Any safety signal may trigger a review of the data and possible additional immunogenicity studies that include an assessment of cellular immune responses using collected PBMC. Additionally, if any of the events listed in Section 9.3.3.1 occur, enrollment into the trial will be halted to complete an extensive safety analysis. Notification of the study enrollment halt will be sent by the Sponsor to the participating sites via telephone and email immediately after becoming aware of a safety concern. This will ensure no additional subjects are dosed until the signal has been completely evaluated. If, following safety review by the DRB and the Sponsor, it is deemed appropriate to restart dosing, a request to restart dosing with pertinent data will be submitted to the health authority.

A summary of events and assessments are provided by visit in Table 9.1.1 for Screening, Baseline and BMN 270 Infusion, in Table 9.1.2 for Post-Infusion Follow-up, and in Table 9.1.3 and Table 9.1.4 for Safety Follow-up.

Table 9.1.5, dealing with the apeutic corticosteroid use in the event of elevated LFTs, is discussed in Section 9.4.8.2.

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Table 9.1.1: Schedule of Events – Screening and Infusion

	Prior to BMN 270 Infusion			BMN 270
Assessment	Screening ⁱ (Day -28 to Day -1)	Smart Rescreening ⁱ (Day -28 to Day -1)	Baseline (Day -7 to Day -1) ^h	Infusion Visit (Day 1) ^k
Informed consent	X	, , , , , , , , , , , , , , , , , , ,	• / /	
Medical History	Х			
Physical Examination ^a	X		Х	X
Height and Weight ^a	X			
Vital Signs	X	Х		Х
Assessment of Adverse Events and Concomitant Medications	X	Х	Х	Х
Documentation of bleeding episodes and FVIII usage (by either subject or clinical information)	X	X	Х	
Distribution of subject diaries and training in their use			Х	
Electrocardiogram	X			
Chest X-ray	X			
Liver Ultrasound	X			
hFVIII Assays ^b	X	Xj		
AAV5 Assays ^c	Х	X		X
Screen for Hepatitis B, Hepatitis C, HIV ^d	X			
Blood chemistry, haematology, coagulation screen, and CRPe	Х	X	X	
Urine Tests ^e	Х	X	X	
Liver Function Tests ^e	Х	X	X	
PBMC collection for CTL baseline			X	
Von Willebrand Factor Antigen (VWF:Ag)	Х			
Direct Thrombin Test			X	
PCR of vector DNA in blood, saliva, urine, semen, and stools			X	
Biomarker testing ^f	Х			
Exploratory biomarker assessments ^g			X	
Haemo-QoL-A Quality of Life (QoL) assessment			Х	
BMN 270 Infusion				Х

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^a Complete physical examination should be done at Screening. Brief physical examination may be done at Baseline and at the BMN 270 Infusion Visit. Height will be recorded at Screening only. Weight will be recorded at Screening and then every 6 months thereafter.

- ^b Includes baseline hFVIII activity (chromogenic FXa and one-stage APTT assays), hFVIII coagulation activity exploratory assay, hFVIII inhibitor level (Bethesda assay with Nijmegen modification), hFVIII total antibody titer, and hFVIII antigen (ELISA).
- ^c Screening (done during Screening) and testing (at Infusion Visit) of AAV5 pre-existing immunity may include plasma samples for 3 assays (in vivo transduction inhibition, in vitro transduction inhibition and AAV5 total antibody assays). Sample collection on the day of the infusion visit must be performed before the BMN 270 infusion is given.
- ^d Patients with documented negative results within the last 30 days do not need to be retested.
- ^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 function tests.
- $^{\rm f}$ Includes HLA genotyping, FVIII genotyping, TNF α and IL10a single nucleotide polymorphisms.
- ^g Blood samples will be collected from subjects to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to Haemophilia A disease. The exploratory genetic/genomic testing on these samples is optional.
- ^h Should the screening visit occur within 7 days of the drug infusion, physical examination, blood chemistry, LFTs, haematology, urine tests, coagulation screen, and CRP do not need to be repeated at Baseline.
- ⁱ Smart rescreening should only be performed if a patient has been determined to be eligible for the study and is unable to complete the Baseline assessments and Infusion prior to the closing of the original Screening window. Subjects who undergo smart rescreening must complete the rescreening assessments and receive the infusion within 90 days of signing the original consent. Subjects who do not complete dosing within 90 days will be required to re-consent and undergo all screening procedures. Subjects may not undergo smart rescreening more than once.
- ^j Only the hFVIII inhibitor level (Bethesda assay with Nijmegen modification) assay must be done at smart rescreening.
- ^k Assessments on the day of infusion must be performed prior to the infusion. 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), following the infusion hourly (± 5 minutes) for 6 hours and then every 2 hours (± 15 minutes) for 6 hours and then at 4 hour intervals (± 15 minutes).

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

					F	'ollow-	Up Af	iter BN	AN 27	0 Adm	inistra	ntion –	Week	s*					
		Week	1																
Assessment	D2	D4	D8	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
Physical examination ^a			X	X	X	X	X	X	X	X	X	X	X	X	X	X	Х	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	Х	X	X	Х	X	X	Х	Х	
Vital Signs			X	X	X	X	X	X	X	X	X	X	X	X	X	X	Х	K X	
Blood chemistry, haematology, coagulation screen, and CRP ^b				X		X		X		X		X		Х				X	
Urine Tests ^b						Х				X				Х				Х	
Liver Function Tests (local) ^b		Х	X	Х	X	Х	Х	X	Х	X	X	X	X	Х	Х	X	Х	X	
FVIII assays (local) ^c		Х	X	X	X	Х	Х	X	Х	X	X	X	X	Х	Х	X	Х	X	
Liver Function Tests (central) ^b		Х	X	X	X	Х	Х	X	Х	X	X	X	X	Х	Х	X	Х	X	
FVIII assays (central) ^d		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Х	X	
FVIII antibody titer						X				X				X				X	
PCR of vector DNA in blood, saliva, urine, semen, and stools ^e	X	X	X			X		X		X		X		X		X		Х	
Exploratory biomarker assessments ^f						Х				X				Х				Х	
Haemo-QoL-A QoL assessment			X	X	X	Х												X	
AAV5 antibody titer										X								X	
Testing for reactivation of hepatitis B and hepatitis C																		Xg	
PBMC collection			X	Х	X	Х	Х	X	Х	X	Х	Х	X	Х	Х	Х	Х	Х	
Von Willebrand Factor Antigen (VWF:Ag)						Х				X				Х				X	
Direct Thrombin test			X												Х				

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

^a Brief physical examination should be done at all weekly visits except Week 16, where a complete physical examination should be performed. Refer to Section 9.7.8.5.
 ^b Refer to Table 9.7.8.2.1 for laboratory assessments to be included, and to Table 9.7.8.3.1 for liver function tests. LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data. Patients with ALT > 1.5 ULN during the study may undergo additional evaluations (e.g., imaging studies including MRI or ultrasound, additional blood tests, and/or liver biopsy) at the discretion of the investigator.

^c Includes hFVIII activity level (one-stage APTT and FXa chromogenic 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. 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 Includes hFVIII activity level (one-stage APTT and FXa chromogenic assay), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, hFVIII coagulation activity exploratory assay, and hFVIII antigen (ELISA). 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. 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 Collection to occur on Day 2 and 4 following BMN 270 infusion, and then until at least 3 consecutive negative results are obtained. Collection and testing of semen samples must continue through Week 12, even if 3 consecutive negative samples in that compartment have already been recorded.
- ^f Blood samples will be collected from subjects to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to Haemophilia A disease. The exploratory genetic/genomic testing on these samples is optional.
- ^g Testing for reactivation of hepatitis B and hepatitis C at Week 16 should be performed only in subjects who have not received therapeutic corticosteroids prior to Week 16; subjects who have received therapeutic corticosteroids will have hepatitis B and hepatitis C testing at the time points indicated in Table 9.1.5.

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

					Follow	v-Up A	fter BN	AN 270) Admi	nistrat	ion – V	Veeks*				
Assessment	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
Physical examination ^a	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight										X						
Assessment of Adverse Events and Concomitant	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medications (including review of subject diary for																
bleeding and FVIII use)																
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood chemistry, haematology, coagulation screen,				X				X				X				X
and CRP ^b																
Urine Tests ^b				X				X				X				X
Liver Function Tests (local) ^b	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FVIII assays (local) ^c	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Liver Function Tests (central) ^b	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FVIII assays (central) ^d	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FVIII antibody titer				X								X				
PCR of vector DNA in blood, saliva, urine, semen,				X				X				X				X
and stools ^e																
Exploratory biomarker assessments ^f				X				X								
Haemo-QoL-A QoL assessment												X				
AAV5 antibody titer				X				X				X				X
PBMC collection	X	X	X	X		X		X		X		X		X		X
Von Willebrand Factor Antigen (VWF:Ag)				X				X				X				X
Direct Thrombin test										Х						

* Visit windows are \pm 48 hours

^a Brief physical examination should be done at all weekly visits. Refer to Section 9.7.8.5.

^b Refer to Table 9.7.8.2.1 for laboratory assessments to be included, and to Table 9.7.8.3.1 for liver function tests. LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data. Patients with ALT > 1.5 ULN during the study may undergo additional evaluations (e.g., imaging studies including MRI or ultrasound, additional blood tests, and/or liver biopsy) at the discretion of the investigator.

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^c Includes hFVIII activity level (one-stage APTT and FXa chromogenic 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. 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 Includes hFVIII activity level (one-stage APTT and FXa chromogenic assay), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, hFVIII coagulation activity exploratory assay, and hFVIII antigen (ELISA). 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. 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 Collection to occur until at least 3 consecutive negative results are obtained.

^f Blood samples will be collected from subjects to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to Haemophilia A disease. The exploratory genetic/genomic testing on these samples is optional.

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Table 9.1.4: Schedule of Events – Safety Follow-Up

					Ye	ear 1 –	Week	ks*					Years 2-5	ETV
Assessment	33	34	35	36	38	40	42	44	46	48	50	52	Q3M	LIV
Physical examination ^a	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight ^a												X	Xa	
Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)	X	X	X	Х	Х	Х	Х	Х	Х	X	X	X	Х	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood chemistry, haematology, coagulation screen, and CRP ^b				X		X		X		X		X	X	X
Urine Tests ^b				X		Х		Х		X		X	X	X
Liver Function Tests (local) ^b	X	Х	Х	Х	Х	Х	Х	Х	Х	X	X	Х	X	X
FVIII assays (local) ^c	X	Х	Х	Х	Х	Х	Х	Х	Х	X	X	Х	X	X
Liver Function Tests (central) ^b	X	X	X	Х	Х	Х	Х	Х	Х	X	X	X	X	X
FVIII assays (central) ^d	X	X	X	X	X	Х	X	X	Х	X	X	X	X	X
AAV5 antibody titer				Х		Х		X		X		X	X	X
FVIII antibody titer				X				X				X	X	X
PBMC Collection (for determination of FVIII and Capsid specific CTL activity)		X		Х				X				X	X	X
Von Willebrand Factor Antigen (VWF:Ag)				X		X		X		X		X	X	X
Direct Thrombin Test					Х							Х	X	X
PCR of vector DNA in blood, saliva, urine, semen, and stools ^e				Х		Х		Х		X		X		X
Haemo-QoL-A QoL assessment												Х	Xf	Х

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* Visit windows are ± 48 hours through Week 36, then ± 1 week until Week 52 and ± 2 weeks for visits in Years 2-5.

- ^a Complete physical examination should be performed at Week 52 and every 52 weeks thereafter; brief physical examination may be performed at other study visits. Refer to Section 9.7.8.5. During Years 2-5, weight should be performed every 6 months.
- ^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 function tests. LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data. Patients with ALT > 1.5 ULN during the study may undergo additional evaluations (e.g., imaging studies including MRI or ultrasound, additional blood tests, and/or liver biopsy) at the discretion of the investigator.
- ^c Includes hFVIII activity level (one-stage APTT and chromogenic FXa 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. 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 Includes hFVIII activity level (one-stage APTT and chromogenic FXa assay), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, hFVIII coagulation activity exploratory assay, and hFVIII antigen (ELISA). 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. 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 Sample testing during Safety Follow-Up is not required if at least 3 consecutive samples are cleared during the Post-Infusion Follow-Up period. Subjects who have not had 3 consecutive negative samples by Week 52 should continue to have PCR testing every 4 weeks until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor).
- ^fHaemo-QoL-A QoL assessment during Years 2-5 of Safety Follow-up should be performed at every other visit (every 6 months) starting with the Week 78 visit (ie, 26 weeks after the Week 52 visit at the end of Year 1 of the Safety Follow-up period).

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					Steroid T	reatment	Period ^d					Post-Steroid Period ^c							
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11 ^b	Week 1	Week 2	Week 3	Week 4	Week 13			
Therapeutic corticosteroids (dose in mg/day) ^a	60 mg	60 mg	40 mg	40 mg	30 mg	30 mg	20 mg	20 mg	15 mg	10 mg	5 mg								
FVIII activity testing												X	Х	Х	Х				
Liver function testing												X	Х	Х	Х				
Hepatitis B testing						X						X				Х			
HCV Viral Load						Х						Х				Х			

Table 9.1.5: Schedule of Events – Therapeutic Corticosteroids

^a Therapeutic corticosteroids may be initiated when a subject's ALT value is $\geq 1.5x$ ULN or based on review of FVIII and liver enzyme data after consultation between the Investigator and the Medical Monitor.

^b Following initiation or completion of steroid regimen, if ALT elevation $\geq 1.5x$ ULN is reported, steroid management decisions will based on discussions between the Investigator and Medical Monitor. Modification of the steroid regimen may take into consideration possible confounders for the ALT elevation and impact on FVIII expression.

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

^d Regardless of the assessments listed in the Schedule of Assessments (Table 9.1.2, Table 9.1.3, or Table 9.1.4), subjects initiated on corticosteroids will only be required to have laboratory evaluations on a weekly basis.

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9.2 Discussion of Study Design, Including Choice of Control Group

Study 270-201 is designed to be a first-in-man, phase 1/2 open-label, dose escalation study in patients with severe haemophilia A. Four doses of BMN 270 will be evaluated and the dose escalation decision tree for Cohorts 1-3 is summarized in Figure 9.1.1.

The decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and the DRB.

There will be no control group. Parameters for each subject will be compared to a pre-treatment assessment of safety (liver function) and efficacy (number of bleeds, use of replacement therapy).

As AAV based treatment always leads to anti-capsid immune response, no true control group (for example with an empty AAV) is possible.

9.3 Selection of Study Population

Up to 15 severe haemophilia A patients may enroll into the study; the actual number of patients will depend on the criteria for dose escalation.

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 criteria:

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

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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 immunity to the AAV5 capsid as measured by AAV5 transduction inhibition or AAV5 total antibodies
- 2. Any evidence of active infection or any immunosuppressive disorder.
- 3. HIV positive
- 4. Significant liver dysfunction as defined by abnormal elevation of:
 - ALT (alanine transaminase) to 3 times the upper limit of normal;
 - Bilirubin above 3 times the upper limit of normal;
 - Alkaline phosphatase above 3 times the upper limit of normal; or
 - INR (international normalized ratio) \geq 1.4.
- 5. Potential participants who have had a liver biopsy in the past 3 years are excluded if they had significant fibrosis of 3 or 4 as rated on a scale of 0-4
- 6. Evidence of any bleeding disorder not related to Haemophilia A
- 7. Platelet count of $< 100 \times 10^9/L$
- 8. Creatinine $\geq 1.5 \text{ mg/dL}$
- 9. Liver cirrhosis of any etiology as assessed by liver ultrasound
- 10. Hepatitis B if surface antigen is positive
- 11. Hepatitis C if RNA is positive
- 12. Treatment with any IP within 30 days prior to the end of the screening period
- 13. Any disease or condition at the physician's discretion that would prevent the patient from fully complying with the requirements of the study including possible corticosteroid treatment outlined in the protocol. The physician may exclude patients unwilling or unable to agree on not using alcohol for the 16-week period following the viral infusion.
- 14. Prior treatment with any gene transfer agent
- 15. Major surgery planned in the 16-week period following the viral infusion
- 16. Use of immunosuppressive agents or live vaccines within 30 days before the viral infusion

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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. A subject's participation in the study may be discontinued at any time at the discretion 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.

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 admitted into the study or does not meet entry criteria
- Subject is lost to follow-up

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

The Investigator or designee must explain to each subject, before enrollment into the study, that for evaluation of study results, the subject's protected health information obtained during the study may be shared with the study Sponsor, regulatory agencies, and IRB/IEC/REB. It is the Investigator's (or designee's) responsibility to obtain written permission to use protected health information per country-specific regulations, such as the Health Insurance Portability and Accountability Act (HIPAA) in the US, from each subject. If permission to use protected health information is withdrawn, it is the Investigator's responsibility to obtain a written request, to ensure that no further data will be collected from the subject and the subject will be removed from the study.

9.3.3.1 Study Safety Evaluation Criteria

If any of the following events occur in a subject in the study who has received BMN 270 infusion, enrollment into the trial will be put on halt to complete an extensive safety analysis per Section 9.1.

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- Any ALT elevation > 5x ULN for at least 2 consecutive weeks after administration of BMN 270, in the absence of a definitive alternate etiology for the increase
- The occurrence of Grade 3 or higher adverse events (excluding ALT elevation) assessed as related to study drug, including liver failure and clinical hepatitis
- The detection of neutralizing antibodies to hFVIII following BMN 270 infusion
- The detection of AAV vector DNA in the semen of a participant in 3 consecutive samples (which are at least 2 weeks apart) more than 52 weeks after BMN 270 infusion, as discussed in Section 9.7.8.6
- The occurrence of a malignancy excluding skin cancers at any point after BMN 270 infusion

If the following event occurs in a subject in the study who has received BMN 270 infusion, a DRB review and analysis of safety data will be undertaken to determine whether the enrollment into the trial will be put on halt:

• Grade 2 adverse event assessed as related to study drug that persists for at least 7 days

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 CRF pages. In legal jurisdictions where use of initials is not permitted, a substitute identifier will be used.

Subjects who withdraw from the study will not be replaced.

9.3.5 Duration of Subject Participation

The duration of this study will be approximately 264 weeks. This includes 4 weeks of screening, 1 day of BMN 270 infusion, 16 weeks of Post-Infusion Follow-Up, and 244 weeks of Safety Follow-Up. A primary endpoint analysis on safety and efficacy will be performed at 16 weeks.

9.4 Treatments

BioMarin or its designee will provide the study site with study drug sufficient for study completion. BioMarin is responsible for shipping study drug to clinical sites.

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.

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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 2 mL polypropylene cryovial. Each vial contains 1.1 mL of AAV5-hFVIII-SQ at a concentration of 2E13 vector genomes per mL in a pH 7.4 phosphate buffer.

The study drug label includes the following information: lot number, required storage conditions, a precautionary statement, expiry date, study number, and BioMarin name and address. Labelling will be done according to country specific requirements.

9.4.3 Storage

At the study site, all IP must be stored under the conditions specified in the IB 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

After a physical examination performed by the PI or designee, participants will be admitted on the day of BMN 270 infusion. An IV catheter will be inserted into a suitable peripheral vein (e.g. 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. An electric syringe pump will be used to infuse through an in-line, low protein binding 0.22 micron filter. BMN 270 will be infused through the catheter using an appropriate infusion pump at a constant rate of 4 ml/min while monitoring the vital signs (pulse, blood pressure, respiration rate and temperature) at 15 minute (\pm 5 minutes) intervals. The anticipated maximum interval from initiation of thawing of BMN 270 to completion of the infusion is 4 hours, although the IP has been shown to be stable at room temperature for 6 hours.

Following completion of the infusion, vital signs will be monitored hourly (\pm 5 minutes) for 6 hours and then every 2 hours (\pm 15 minutes) for 6 hours and then at 4 hour intervals. If the vital signs are stable the catheter will be removed 20-24 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 24 hours to observe for any immediate toxicity of the procedure. After 24 hours, participants will be

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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.

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 Sponsor will be required prior to enrollment of each study subject. Upon their enrollment into the study, subjects will be assigned a unique subject number and dose level by the Sponsor.

Cohorts 1 to 3 are enrolled serially and their dose is defined in Section 9.4.6.2 below. Escalation is based on FVIII activity 3 weeks after injection. Cohorts may receive the next higher dose if subjects in the previous cohort does not meet the activity criteria, or the same dose if subjects in the previous cohort meets the activity criteria. Subjects in Cohort 4 will all be enrolled at a single dose.

9.4.6 Selection of Doses Used in the Study

The starting dose was based on the expression of hFVIII observed in nonclinical studies of mice and monkeys. The starting dose has a significant safety margin (10-fold) from NOAEL in mice. The dose escalation is half-logs based.

9.4.6.1 Selection of Timing of Dose for Each Subject

A minimum of three weeks are required between subjects, to allow for evaluation of safety and expression of hFVIII. After three weeks, depending on the activity level, the choice of the dose for the next subject will be made as described below.

9.4.6.2 Selection of Dose for Each Subject

The starting dose was determined by expression of hFVIII observed in mice and monkeys and a scale up factor based on previous experience, an improved purification process over previous trials (thus potentially decreasing the risk of immune response), and a new evaluation of the titer (PCR performed after hairpin removal).

For Cohorts 1 to 3, approximately three weeks after an injection, the decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and the DRB.

Subject 1 (Cohort 1) will be dosed by intravenous infusion with 6E12 vg/kg of body weight. If the FVIII activity level does not reach 5 IU/dL or greater (expressed as % in Figure 9.1.1)

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at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 1 and enrollment into Cohort 2 will initiate with Subject 2 at the next dose (2E13 vg/kg).

If the FVIII activity level in the first subject treated in Cohort 2 does not reach \geq 5 IU/dL at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 2 and enrollment into Cohort 3 (6E13) will initiate with the next subject.

If the FVIII activity level in the first subject treated in Cohort 3 does not reach \geq 5 IU/dL at the Week 3 visit in both assays, then the DRB will recommend whether to continue to add subjects to the cohort and/or whether to continue the study.

For the first subject treated in each of the first 3 cohorts, if the activity level reaches ≥ 5 IU/dL and no safety issue is found, then up to four subjects will be enrolled in that cohort, though the adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

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

There will be an ongoing review of individual patient safety and efficacy data by the medical monitor and the DRB. The adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

Refer to Figure 9.1.1 for a visual representation of the study design for Cohorts 1-3

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 CRF. The Investigator may prescribe additional medications 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 CRF.

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The following medications are prohibited starting 30 days before Screening:

- Live vaccines
- Systemic immunosuppressive agents

Medications which are predominately metabolized by the liver (e.g., acetaminophen) and alcohol should, whenever possible, be avoided for the first 52 weeks of the study, and particularly within 48 hours prior to lab work.

9.4.8.1 Concomitant Haemophilia Treatments

Subjects on "on demand" therapy for FVIII will continue their treatment at will. Subjects on prophylactic FVIII therapy will discontinue their treatment starting the day of infusion and switch to an "on demand" schedule. FVIII can always be taken as needed by the subject, who will carefully record his treatment and bleeding episodes in his diary. In addition, information on FVIII usage by medical history will be collected (if available) from subjects for the 6 month period immediately preceding study enrollment.

9.4.8.2 Glucocorticoid Treatment of Elevated Hepatic Transaminases

During the Post-Infusion Follow-up Period and the Safety Follow-Up Period, each subject will have comprehensive surveillance plan monitoring of LFTs (at local labs, once per week for Weeks 1-36, then once every 2 weeks from Week 37-52). LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.

9.4.8.2.1 Therapeutic Corticosteroids

In general, therapeutic corticosteroids may be initiated when a subject's ALT value is $\geq 1.5x$ ULN, or based on review of FVIII and liver enzyme data after consultation between the Medical Monitor and the Investigator.

Reports of raised LFTs (defined as $ALT \ge 1.5x$ ULN) should be made to the BioMarin medical monitor within 30 minutes of the lab value being available. Local laboratory results of LFTs will be used to trigger corticosteroid treatment as needed. In case of discrepant results between local and central laboratories, the Investigator and Medical Monitor will decide further action.

Following initiation or completion of therapeutic corticosteroids, if ALT elevation $\geq 1.5x$ ULN is reported, steroid management decisions will based on discussions between the Investigator and Medical Monitor. Modification of the steroid regimen may take into consideration possible confounders for the ALT elevation and impact on FVIII expression.

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Treatment with prednisolone will be initiated at a dose of 60 mg per day and then gradually tapered (60 mg daily for the first 2 weeks, then 40 mg the next 2 weeks, then 30 mg the next two weeks, then 20 mg the next two weeks, then 15 mg for the next week, then 10 mg for the next week, then 5 mg for the next week, then stop, for a total treatment of 11 weeks) (refer to Table 9.1.5).

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

Management and monitoring of reactions to corticosteroids should be determined by the Investigator's clinical judgment in consultation with the Sponsor's Medical Monitor. This includes the contraindicated use of NSAIDs during corticosteroid treatment, and specific monitoring not already covered by the schedule of events. Hepatitis B status and HCV viral load will be rechecked 6 weeks after the start of corticosteroid treatment, and then 1 week and 13 weeks after the completion of corticosteroid treatment. All adverse events should be reported as outlined in Section 10 of the protocol.

9.4.9 Treatment Compliance

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

9.5 Investigational Product Accountability

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

9.5.1 Return and Disposition of Clinical Supplies

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

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

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appropriately, the site can return unused study drug to BioMarin upon request. The return of study drug or study drug materials must be accounted for on a Study Drug Return Form provided by BioMarin.

All study drug and related materials should be stored, inventoried, reconciled, and destroyed or returned according to applicable state and federal regulations and study procedures.

9.6 Dietary or Other Protocol Restrictions

There are no dietary or other protocol restrictions for this study.

9.7 Safety and Efficacy Variables

As this is a first-in-man study, the primary endpoint of safety will be assessed as explained in Section 9.7.8.

The primary efficacy measure will be to assess plasma FVIII activity. The efficacy goal of the study is to establish the dose relationship to FVIII activity \geq 5 IU/dL at 16 weeks post BMN 270 administration.

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

The primary efficacy measure will be the plasma FVIII activity monitored on a regular basis after BMN 270 dose. The efficacy goal of the protocol is to ascertain the dose range of BMN 270 required to convert severe HA patients to expression of FVIII at 5 IU/dL or above, i.e., a mild severity. This is associated in natural history studies with clinically superior long term outcomes (Den Ujil, 2011, Haemophilia).

The following assays (assessed by the central laboratory) will be used to measure the primary efficacy variable:

- FVIII activity (chromogenic FXa assay)
- FVIII activity by one-stage APTT (Activated Partial Thromboplastin Time)

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 FVIII activity level in both assays and the number of subjects with FVIII activity ≥ 5 IU/dL in at least one of the two assays will be summarized.

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FVIII activity assays will also be performed at the local laboratory at the time points indicated in Table 9.1.2, Table 9.1.3, and Table 9.1.4, but will be used in conjunction with local lab LFT assessments to monitor subject safety and need for initiation of therapeutic corticosteroid dosing; local laboratory FVIII activity assessments will not be used to assess efficacy or to measure the primary efficacy outcome of the study.

Timing of assessment by these assays is provided in Table 9.1.2, Table 9.1.3, and Table 9.1.4. Details on performing the assays are included in the Laboratory Manual.

9.7.3 Secondary Efficacy Variables

Secondary efficacy measures will be the reduction in the frequency of factor replacement therapy, and reduction in the number of bleeding episodes. 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.

9.7.4 Immunogenicity

Immunogenicity assays will be performed on plasma. The assays will include detection of anti-capsid, and anti-FVIII total antibody, and determination of neutralizing antibodies against FVIII. Any increase in total antibody level, especially during the time period of 5-12 weeks, will be compared with FVIII activity measurements. Any abnormality of the liver parameters will lead to a retrospective immunogenicity assessment to determine anti-FVIII and capsid specific CTL. Anti-FVIII and capsid specific CTL assays will be performed on collected PBMCs.

Timing of assessment by these assays is provided in Table 9.1.2, Table 9.1.3, and Table 9.1.4.

9.7.5 Pharmacodynamics

The hFVIII antigen and activity level will be measured by an ELISA (antigen) and by one-stage APTT and/or chromogenic FXa assay (activity). Individual antigen and activity plasma plots will be prepared to assess changes over 16 weeks. FVIII activity measurements will be used to determine PD parameters.

If supported by FVIII activity data, non-compartmental analysis and observation will be used to estimate individual values of C_b (baseline concentration), C_{ss} (steady state concentration), T_{ss} (time to steady state), C(t) and AUC(0-t) where t is 16 weeks. Other parameters that may be used to describe individual FVIII protein and activity plasma profiles are C_{max} (maximum

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concentration) and C_{avg} (average concentration, AUC(0-t)/t). The PD parameters and dose will be used to assess clinical pharmacology.

Sample collection times are indicated in Table 9.1.2, Table 9.1.3, and Table 9.1.4.

9.7.6 Exploratory Assessments

Blood samples will be collected from subjects at the time points indicated in Table 9.1.1, Table 9.1.2, Table 9.1.3, and Table 9.1.4 to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to Haemophilia A disease. The exploratory genetic/genomic testing is optional.

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 may be used for exploratory use once the primary use has been completed.

On an exploratory basis, samples may be fractionated prior to shedding analysis in order to better characterize the presence and location of vector DNA and/or vector capsid within each matrix. The fractionation may be performed with samples collected specifically for shedding analysis (saliva, blood, semen, urine, faeces), or by using exploratory samples, such as plasma, PBMCs, and red blood cells, collected under the study protocol.

9.7.7 Haemo-QoL-A Quality of Life Assessment

The Haemo-QoL-A is a patient-reported outcome (PRO) questionnaire which will be used to assess subject quality of life (QoL) during the study. Assessments will occur at the time points listed in the Schedules of Assessments.

Details regarding the QoL assessment will be included in the Study Reference Manual.

9.7.8 Safety Variables

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

9.7.8.1 Adverse Events

The occurrence of AEs will be assessed continuously from the time the subject signs the ICF. The determination, evaluation and reporting of AEs will be performed as outlined in Section 10. Assessments of AEs will occur at the time points shown in Table 9.1.1, Table 9.1.2, Table 9.1.3, and Table 9.1.4.

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9.7.8.2 Clinical Laboratory Assessments

Specific visits for obtaining clinical laboratory assessment samples are provided in Table 9.1.1, Table 9.1.2, Table 9.1.3, and Table 9.1.4. The scheduled clinical laboratory tests are listed in Table 9.7.8.2.1. Refer to the Study Reference Manual 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 the cause of the abnormality is determined, the value returns to baseline or to within normal limits, or 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 CRF.

Blood Chemistry	Haematology	Urine Tests	Other
Albumin	Haemoglobin	Appearance	CRP
BUN	Haematocrit	Color	
Calcium	WBC count	pН	Coagulation Screen
			including:
Chloride	RBC count	Specific gravity	APTT
Total cholesterol	Platelet count	Ketones	PT/INR
CO ₂	Differential cell count	Protein	TT
СРК		Glucose	
Creatinine		Bilirubin	
Glucose		Nitrite	
Phosphorus		Urobilinogen	
Potassium		Haemoglobin	
Total protein			
Sodium			
Uric Acid			

 Table 9.7.8.2.1:
 Clinical Laboratory Tests

BUN, blood urea nitrogen; CO₂, carbon dioxide; 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.

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9.7.8.3 Liver Function and Hepatitis Testing

Subjects will be screened for evidence of previous hepatitis B or hepatitis C infection at Screening. Subjects with documented results showing an absence of active Hepatitis B or Hepatitis C infection (as measured by positive surface antigen for hepatitis B or positive RNA testing for hepatitis C) 30 days prior to providing signed informed consent do not need to be screened again.

Evidence of ongoing Hepatitis B or Hepatitis C infection is exclusionary. Subjects who have cleared a Hepatitis B infection or are seronegative do not need to receive the Hepatitis B vaccination.

Subjects will be tested for hepatitis B and hepatitis C reactivation at Week 16. Subjects who receive therapeutic corticosteroids prior to Week 16 do not need to complete the Week 16 reactivation assessment; instead, they will be tested for hepatitis B and hepatitis C reactivation at the time points listed in Table 9.1.5.

A liver ultrasound and liver function testing at Screening will identify any significant hepatic dysfunction, which is defined as:

- More than 3x the normal ALT level
- More than 3x the normal bilirubin level
- More than 3x the normal Alkaline phosphatase level.
- INR \geq 1.4.
- Thrombocytopoenia under $100 \ge 10^9/L$
- Liver ultrasound results indicative of a liver cirrhosis

Liver function tests will be monitored on a regular basis, at the time points indicated in Table 9.1.1, Table 9.1.2, Table 9.1.3, and Table 9.1.4. At each time point, the following LFTs should be assessed:

 Table 9.7.8.3.1: Liver Function Tests

Liver Function Tests			
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

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Patients with ALT > 1.5 ULN during the study may undergo additional evaluations (e.g., imaging studies including MRI or ultrasound, additional blood tests, and/or liver biopsy) at the discretion of the investigator.

9.7.8.4 HIV Testing

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

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

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

Systolic blood pressure, diastolic blood pressure, heart rate, respiration rate, and temperature will be assessed at Screening, Baseline, and at the beginning of each visit during the Post-Infusion Follow-Up and Safety Follow-Up periods. On the day of the BMN 270 Infusion, vital signs will be monitored prior to infusion, during the infusion every 15 minutes (\pm 5 minutes), following the infusion hourly (\pm 5 minutes) for 6 hours and then every 2 hours (\pm 15 minutes) for 6 hours and then at 4 hour intervals (\pm 15 minutes).

A complete physical examination is necessary during Screening/Baseline, at Week 16 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, respiratory, neurologic, and gastrointestinal assessments.

Height will be recorded at Screening only. Weight will be recorded at Screening and then every 6 months thereafter.

9.7.8.6 Vector Shedding

Vector shedding has been extensively studied in all similar clinical trials performed to date. (Nathwani, 2014, N.Engl.J.Med.); (Manno, 2006, Nat.Med.); (Schenk-Braat, 2007, J.Gene Med.); (Croteau, 2004, Ann.Occup.Hyg.). In the literature referenced above, including Haemophilia B clinical studies utilizing AAV2 and AAV8, vector was no longer detectable

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after 40 days in blood, saliva, urine or stool, but in one study was detected in the seminal fluid but not in motile sperm (Manno, 2006, Nat.Med.). In these studies, the amount of vector present in these bodily fluids involved an extremely small fraction of the infused dose. More recent data from an ongoing AAV-FIX study demonstrates persistence of the vector in both the blood and the semen for at least 39 weeks (Miesbach, 2016, Haemophilia).

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 PCR at the time points indicated in Table 9.1.2, Table 9.1.3, and Table 9.1.4. Fluids tested will include:

- Blood
- Saliva
- Semen
- Urine
- Stool

Vector shedding will also be extensively studied in the present clinical trial, every other week between Weeks 4-16, then every 4 weeks to Week 52 until at least 3 consecutive negative results are obtained. Testing of semen will continue through Week 12, even if 3 consecutive negative results have been recorded in that compartment prior to that timepoint. Subjects who have not had 3 consecutive negative samples by Week 52 should continue to have PCR testing every 4 weeks until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor).

Contraception use may need to be extended beyond 26 weeks in individual subjects based on observed vector shedding in semen. After 6 months, subjects may stop contraception use only if they have had 3 consecutive negative semen samples.

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

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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 haematology, 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, a reportable adverse event (AE) is any untoward medical occurrence (e.g., sign, symptom, illness, disease or injury) in a subject administered the study-drug or other protocol-imposed intervention, regardless of attribution. This includes the following:

- AEs not previously observed in the subject that emerge during the course of the study.
- Pre-existing medical conditions judged by the Investigator to have worsened in severity or frequency or changed in character during the study.
- Complications that occur as a result of non-drug protocol-imposed interventions (eg, AEs related to screening procedures).

An adverse drug reaction is any AE for which there is a reasonable possibility that the study-drug caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the study-drug and the AE.

Bleeding events that are normal events of haemophilia (ie, bleeding events which occur only because the subject is a haemophiliac) should not be recorded as AEs but will instead be captured in subject diaries. Bleeding events that occur where a normal (ie, non-haemophiliac) patient would bleed, such as bleeding as a result of major trauma, should be recorded as adverse events. All bleeding events which meet criteria for being serious should be reported as serious adverse events (SAEs) whether or not they are bleeding events that are normal sequelae of haemophilia.

Whenever possible, it is preferable to record a diagnosis as the AE term rather than a series of terms relating to a diagnosis.

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10.2 Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that at any dose meets 1 or more of the following criteria:

- Is fatal
- Is life threatening

Note: Life-threatening refers to an event that places the subject at immediate risk of death. This definition does not include a reaction that, had it occurred in a more severe form, might have caused death.

- Requires or prolongs inpatient hospitalization.
- 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 intervention to prevent one of the above consequences (e.g. anaphylaxis)

All adverse events that do not meet any of the criteria for SAEs should be regarded as nonserious AEs.

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 liver enzymes (ALT) that triggers an initiation or modification of corticosteroid treatment

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 treatment, only SAEs associated with any protocol-imposed interventions will be reported. After informed consent is obtained and the first administration of study drug, the reporting period for all non-serious AEs and SAEs begins and continues for approximately 5 years or until study discontinuation/termination, whichever is longer. The criteria for determining, and the reporting of SAEs is provided in Section 10.2.

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10.3.2 Eliciting Adverse Events

Investigators will seek information on AEs, SAEs, and EOSI at each subject contact by specific questioning and, as appropriate, by examination. Information on all AEs and SAEs and EOSI, should be recorded in the subject's medical record and on the 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 severity of each will be assessed using the defined categories in Table 10.3.3.2.1.

The Investigator will determine the severity of each AE and SAE and EOSI using the NCI CTCAE v4. 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 as stated below.

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Grade	Description		
1	Mild: asymptomatic or mild symptoms; clinical or diagnostic observati indicated	ons only; intervention not	
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 or debilitating: consequences; urgent intervention indicated	Grade 4 and 5 AEs should always be	
5	Death related to AE	reported as SAEs	

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

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

10.3.3.3 Causality

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

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

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

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

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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

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 haemorrhage 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.

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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.

10.4.1.4 Abnormal Laboratory Values

Laboratory test results will be recorded on the laboratory results pages of the AE 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 should be reported as such, in addition to being recorded as an AE in the AE eCRF.

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

- Accompanied by clinical symptoms
- Leading to a change in study medication (e.g. dose modification, interruption or permanent discontinuation)
- Requiring a change in concomitant therapy (e.g. 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 hFVIII activity should not be reported as adverse events unless signs of worsening are observed.

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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 document 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 changed
- Hospitalization solely for the purpose of insertion of an in-dwelling IV catheter (such as a Port-a-Cath or other brand) for administration of study drug will not be considered an SAE.
- 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

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is unknown and cannot be ascertained at the time of reporting, record "Unexplained Death" or "Death of Unknown Cause" on the AE eCRF.

10.4.1.9 Pregnancy

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

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

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

If the EDC is unavailable, all SAEs should be reported to BPV by completing the SAE Report Form and faxing or emailing the completed form to BPV within 24 hours of the site

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becoming aware of the event. Once the EDC is available, the information should be entered in the AE eCRF.

10.5.2 Ethics Committee Reporting Requirements

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

10.6 Follow-up of Subjects after Adverse Events

The Investigator should follow all unresolved AEs and SAEs until the events are resolved or have stabilized, the subject is lost to follow-up, or it has been determined that the study treatment or participation is not the cause of the AE/SAE. Resolution of AEs and SAEs (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, 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 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 treatment.

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 treatment. 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

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investigational medicinal product where that new event is likely to affect the safety of the patients, the Sponsor and the Investigator shall take appropriate urgent safety measures to protect the patients against any immediate hazard. The Sponsor shall forthwith inform the competent authorities of those new events and the measures taken and shall ensure that the IRB/IEC/REB is notified at the same time."

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

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

- Immediate need to revise the IP administration (eg, modified dose amount or frequency not defined in protocol)
- 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	
Address:	105 Dig	gital Drive	
	Novato	, CA 94949 USA	
Phone:	PI		
E-mail:	PI		

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

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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 will be performed within 28 days (\pm 14 days) of BMN 270 infusion while baseline assessments will take place within 7 days of BMN 270 infusion (Day 1). Should the screening visit occur within 7 days of the drug infusion, physical examination, vital signs, blood chemistry, LFTs, haematology, urine tests, coagulation screen, and CRP do not need to be repeated at Baseline.

The following procedures will be performed during the Screening Period:

- Full medical history, including haemophilia A history, Hepatitis B, Hepatitis C, and HIV.
- 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)
- Electrocardiogram
- Chest X-ray
- Liver Ultrasound
- Samples for hFVIII Assays
 - Baseline hFVIII activity chromogenic FXa (plasma)
 - Baseline hFVIII activity level one-stage APTT assay
 - o hFVIII coagulation activity exploratory assay
 - o hFVIII inhibitor level (Bethesda assay with Nijmegen modification)
 - hFVIII total antibody assay
 - hFVIII antigen (ELISA)

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- Blood sample for AAV5 Assays
 - o AAV5 antibody titer
 - AAV5 transduction inhibition assay
- Screen for Hepatitis B, Hepatitis C, and HIV if required (subjects with documented negative results 30 days prior to informed consent being obtained do not need to be retested)
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- Urine Tests (refer to Table 9.7.8.2.1)
- Liver Function Tests (refer to Table 9.7.8.3.1)
- Von Willebrand Factor Antigen (VWF:Ag)
- Blood samples for Biomarker testing (including HLA genotyping, FVIII genotyping status, TNFα and IL10a single nucleotide polymorphisms)

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 sample for AAV5 Assays
 - AAV5 antibody titer
 - AAV5 transduction inhibition assay
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.8.2.1)

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

12.3 Baseline Visit

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

- Physical examination
- Assessment of Adverse Events and Concomitant Medications
- Documentation of bleeding episodes and FVIII usage (by either subject or clinical information)
- Distribution of subject diaries and training in diary completion
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- Urine Tests (refer to Table 9.7.8.2.1)
- Liver Function Tests (refer to Table 9.7.8.3.1)
- PBMC collection for CTL baseline
- Direct Thrombin test
- PCR of vector DNA in blood, saliva, urine, semen, and stools
- Exploratory biomarker assessments
- Haemo-QoL-A QoL assessment

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 24 hours for the BMN 270 Infusion Visit. The following procedures will be performed during the BMN 270 Infusion Visit:

- Physical examination
- Assessment of Adverse Events and Concomitant Medications
- Blood sample for AAV5 Assays (must be performed before the BMN 270 infusion)
 - o AAV5 antibody titer
 - AAV5 transduction inhibition assay
- BMN 270 Infusion
- Vital Signs

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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 the first 6 hours, every 2 hours (± 15 minutes) for the next 6 hours, and then at 4 hour (± 15 minutes) intervals for the remainder of the subject's stay in the clinic.

12.5 BMN 270 Infusion Follow-Up Visits

After BMN 270 has been infused, subjects will return to the study site every week $(\pm 48 \text{ hours})$ for 16 weeks, when the following procedures will be completed:

12.5.1 Once per week (Weeks 1 through 16)

The following procedures will be performed at one visit per week from Weeks 1 through 16:

- Physical examination
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Vital Signs
- Liver Function Tests (refer to Table 9.7.8.3.1) central laboratory assessment
 - LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- Samples for FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage APTT)
 - FVIII activity level (chromogenic FXa assay)
 - FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level
 - FVIII antigen (ELISA)

Note: 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.

- Central assessment of FVIII activity level should be performed 1x/week from Week 1 through Week 16
- Liver Function Tests (refer to Table 9.7.8.3.1) local laboratory assessment
 - LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.

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- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage APTT)
 - FVIII activity level (chromogenic FXa assay)
- PBMC collection

12.5.2 Week 1 – Day 2 and Day 4

On Day 2 and Day 4 of Week 1, the following procedures will be performed:

- PCR of vector DNA in blood, saliva, urine, semen, and stools (Day 2 and Day 4)
- Samples for FVIII Assays (Day 4 only) central laboratory assessment
 - FVIII activity level (one-stage APTT)
 - FVIII activity level (chromogenic FXa assay)
 - FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level
 - FVIII antigen (ELISA)

Note: 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.

- Liver Function Tests (refer to Table 9.7.8.3.1) (Day 4 only) central laboratory assessment
- Liver Function Tests (refer to Table 9.7.8.3.1) (Day 4 only) local laboratory assessment
- FVIII activity level (Day 4 only) local laboratory assessment
 - FVIII activity level (one-stage APTT)
 - FVIII activity level (chromogenic FXa assay)

12.5.3 Week 1 – Day 8

On Day 8, the following procedures will be performed:

- PCR of vector DNA in blood, saliva, urine, semen, and stools
- Direct Thrombin test
- Haemo-QoL-A QoL assessment

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12.5.4 Every 2 Weeks

Every 2 weeks (Weeks 2, 4, 6, 8, 10, 12, 14 and 16), the following procedures will be performed:

- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.8.2.1) (not assessed at Week 14)
- PCR of vector DNA in blood, saliva, urine, semen, and stools (not collected at Week 2)
 - Collection to occur until at least 3 consecutive negative results are obtained. Semen samples should continue to be collected and tested through Week 12, even if 3 consecutive negative results in that compartment have been recorded prior to that timepoint.

12.5.5 Weeks 4, 8, 12, and 16

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

- Urine Tests (refer to Table 9.7.8.2.1)
- VWF:Ag
- FVIII antibody titer
- Exploratory biomarker assessments

12.5.6 Week 16

At Week 16, the following procedures will be performed:

- Test for Hepatitis B and Hepatitis C reactivation
 - Subjects will be tested for hepatitis B and hepatitis C reactivation at Week 16. Subjects who receive therapeutic corticosteroids prior to Week 16 do not need to complete the Week 16 reactivation assessment; instead, they will be tested for hepatitis B and hepatitis C reactivation at the time points listed in Table 9.1.5.

12.5.7 Weeks 8 and 16

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

• AAV5 antibody titer

12.5.8 Weeks 2, 3, 4, and 16

At Weeks 2, 3, 4, and 16, the following procedure will be performed:

• Haemo-QoL-A QoL assessment

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12.5.9 Week 13

At Week 13, the following procedure will be performed:

• Direct Thrombin test

12.6 Safety Follow-Up – Weeks 17-36

After the Post-Infusion Follow-Up visits are complete, subjects will return to the study site for Safety Follow-Up visits from Weeks 17 through Week 36 (\pm 48 hours), when the following procedures will be completed:

12.6.1 Once per week (Weeks 17 through 36)

Once per week from Week 17 through Week 36, the following procedures will be performed:

- Physical examination
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Vital Signs
- Liver Function Tests (refer to Table 9.7.8.3.1) central laboratory assessment
 - LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage APTT)
 - FVIII activity level (chromogenic FXa assay)
 - FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - FVIII antigen (ELISA)

Note: 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.

- Liver Function Tests (refer to Table 9.7.8.3.1) local laboratory assessment
 - LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage APTT)

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• FVIII activity level (chromogenic FXa assay)

12.6.2 Once per week (Weeks 17 through 20)

Once per week from Week 17 through Week 20, the following procedures will be performed:

• PBMC collection

12.6.3 Every 2 weeks (Weeks 21 through 36)

Every 2 weeks (Weeks 22, 24, 26, 28, 30, 32, 34, and 36), the following procedures will be performed:

• PBMC collection

12.6.4 Every 4 Weeks

Every 4 weeks (Weeks 20, 24, 28, 32, and 36), the following procedures will be performed:

- Exploratory biomarker assessments (Weeks 20 and 24 only)
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- Urine Tests (refer to Table 9.7.8.2.1)
- VWF:Ag
- AAV5 antibody titer
- PCR of vector DNA in blood, saliva, urine, semen, and stools
 - Sample testing during Safety Follow-Up is not required if at least
 3 consecutive samples are clear during the Post-Infusion Follow-Up period.

12.6.5 Every 8 Weeks

Every 8 weeks (Weeks 20, 28, and 36), the following procedure will be performed:

• FVIII antibody titer

12.6.6 Week 26

At Week 26, the following procedure will be performed:

- Direct Thrombin test
- Weight

12.6.7 Week 28

At Week 28, the following procedure will be performed:

• Haemo-QoL-A QoL assessment

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12.7 Safety Follow-Up – Weeks 37-52

Subjects will return every 2 weeks (Week 38, 40, 42, 44, 46, 48, 50, and 52) from Week 37-52 (± 1 week), when the following procedures will be completed:

12.7.1 Once per visit

At Weeks 38, 40, 42, 44, 46, 48, 50, and 52, the following procedures will be performed:

- Physical examination
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Vital Signs
- Liver Function Tests (refer to Table 9.7.8.3.1) local laboratory assessment
 - LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage APTT)
 - FVIII activity level (chromogenic FXa assay)
- Liver Function Tests (refer to Table 9.7.8.3.1) central laboratory assessment
 - LFTs may be monitored more or less frequently based (and in particular when ALT values are >1.5x ULN) on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage APTT)
 - FVIII activity level (chromogenic FXa assay)
 - FVIII coagulation activity exploratory assay
 - Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - FVIII antigen (ELISA)

Note: 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.

12.7.2 Every 4 Weeks

Every 4 weeks (Weeks 40, 44, 48, and 52), the following procedures will be performed:

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- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- Urine Tests (refer to Table 9.7.8.2.1)
- AAV5 antibody titer
- VWF:Ag
- PCR of vector DNA in blood, saliva, urine, semen, and stools
 - Sample testing during Safety Follow-Up is not required if at least 3 consecutive samples are clear during the Post-Infusion Follow-Up period. Subjects who have not had 3 consecutive negative samples by Week 52 should continue to have PCR testing every 4 weeks until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor).

12.7.3 Every 8 Weeks

Every 8 weeks (Weeks 44 and 52), the following procedure will be performed:

- PBMC collection
- FVIII antibody titer

12.7.4 Week 38 and 52

At Week 38 and Week 52, the following procedure will be performed:

• Direct Thrombin test

12.7.5 Week 52

At Week 52, the following procedure will be performed:

- Haemo-QoL-A QoL assessment
- Weight

12.8 Safety Follow-Up – Years 2-5

During Years 2-5 of Safety Follow-up, subjects will be assessed every 3 months (\pm 2 weeks). At these times, the following procedures will be completed:

12.8.1 Every Visit

Every 3 months (\pm 2 weeks), the following procedures will be performed:

- Physical examination
 - Complete Physical Examination will be performed every 52 weeks; Brief Physical Examinations may be performed at other visits.

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- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Vital Signs
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- Urine Tests (refer to Table 9.7.8.2.1)
- Liver Function Tests (refer to Table 9.7.8.3.1) local laboratory assessment
 - LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage APTT)
 - FVIII activity level (chromogenic FXa assay)
- Liver Function Tests (refer to Table 9.7.8.3.1) central laboratory assessment
 - LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage APTT)
 - FVIII activity level (FXa chromogenic assay)
 - FVIII coagulation activity exploratory assay
 - Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - FVIII antigen (ELISA)

Note: 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.

- AAV5 antibody titer
- FVIII antibody titer
- PBMC collection
- VWF:Ag
- Direct Thrombin test

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12.8.2 Every Other Visit (Every 6 Months)

Every six months starting at the Week 78 visit (ie, 26 weeks after the Week 52 visit at the end of Year 1 of the Safety Follow-up period), the following procedure will be performed:

- Haemo-QoL-A QOL assessment
- Weight

12.9 Early Termination Visit

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

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

- Physical examination
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Vital Signs
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- Urine Tests (refer to Table 9.7.8.2.1)
- Liver Function Tests (refer to Table 9.7.8.3.1) local laboratory assessment
- FVIII activity level local laboratory assessment
 - FVIII activity level (one-stage APTT)
 - FVIII activity level (chromogenic FXa assay)
- Liver Function Tests (refer to Table 9.7.8.3.1) central laboratory assessment
- FVIII Assays central laboratory assessment
 - FVIII activity level (one-stage APTT)
 - FVIII activity level (chromogenic FXa assay)
 - FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - FVIII antigen (ELISA)

Note: 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.

- AAV5 antibody titer
- FVIII antibody titer
- PBMC collection
- VWF:Ag
- Direct Thrombin test
- PCR of vector DNA in blood, saliva, urine, semen, and stools
 - Sample testing at the ETV is not required if at least 3 consecutive samples are clear during the Post-Infusion Follow-Up period.
- Haemo-QoL-A QOL assessment

12.10 End of Study

The study will end after the last subject completes the last Safety Follow-Up visit (Week 260). 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.

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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, any applicable randomization procedures, source document requirements, eCRFs, monitoring requirements, and procedures for reporting AEs, including SAEs.

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

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

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14 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

14.1 Statistical and Analytical Plans

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

14.1.1 Interim Analyses

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

14.1.2 Procedures for Accounting for Missing, Unused and Spurious Data

Missing data will not be imputed.

14.2 Primary and Secondary Efficacy Analysis

The subjects will be followed in a longitudinal manner and all the relevant information will be collected. The analysis of the data will be descriptive in nature. Descriptive statistics include the number of subjects, mean, median, standard deviation, minimum, and maximum for continuous variables and count and percent for categorical variables. Efficacy variables will be summarized by dose cohort at each time point. Relationship between dose and efficacy results will be examined.

Data collected in a longitudinal manner may be analyzed using longitudinal methods such as mixed effect model which takes into account the correlation among the observation taken at various time points within a participant. Efficacy is a secondary endpoint, defined as biologically active hFVIII at ≥ 5 IU/dL by chromogenic FXa and/or one-stage APTT assay as measured by the central laboratory at 16 weeks following study treatment. hFVIII activity will be assessed weekly during the study period. We can only assess the true steady state of hFVIII protein produced from BMN 270 after a minimum of 72 hours has elapsed since the last infusion of FVIII protein concentrates.

14.3 Immunogenicity

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

14.4 Pharmacodynamic Analyses

The FVIII antigen and activity level as measured by an Elisa (antigen level) and by a one-stage APTT and/or chromogenic FXa assay (activity level), will be used for plasma

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profiles; FVIII activity will be used to determine PD parameters. Traditional PK analysis is not applicable.

If supported by FVIII activity data, non-compartmental analysis and observation will be used to estimate individual PD parameter values of C_b (baseline), C_{ss} (steady state), T_{ss} (time to steady state), C(t) and AUC(0-t) where t is 16 weeks. Other parameters that may be used to describe individual FVIII protein and activity plasma profiles are C_{max} (maximum concentration) and C_{avg} (average concentration, AUC(0-t)/t). The parameters will be summarized using descriptive statistics.

14.5 Safety Analysis

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

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

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.

14.6 Determination of Sample Size

No formal sample size calculations based on statistical power were performed.

The sample size is determined based upon clinical consideration and could detect a strong clinical efficacy signal. Up to 15 subjects may be dosed in the study; the actual number of subjects will depend on the criteria for dose escalation.

14.7 Analysis Populations

The Safety analysis population is defined as all enrolled subjects who receive any study drug. The analysis of safety data will be performed on Safety Set.

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The Full Analysis Set (FAS) is defined as all enrolled subjects who receive study drug and have at least one Baseline and post-Baseline assessment. The FAS will be used for efficacy analysis.

14.8 Changes in the Conduct of the Study or Planned Analyses

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

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

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

Note: If discrepancies exist between the text of the statistical analysis as planned in the protocol, and the final SAP, a protocol amendment will not be issued and the SAP will prevail.

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15 DATA REVIEW BOARD

There will be no formal DMC for this study, however a safety and efficacy evaluation board (the Data Review Board [DRB]) composed of the investigator representatives and the Sponsor will be established.

The DRB will review safety and efficacy on an ongoing basis. The DRB will meet prior to dose escalation or dose expansion to assess available subject safety and efficacy data and make recommendations with regards to the conduct of study. Should a safety signal arise, including one which may warrant a halt of study enrollment, the DRB will promptly convene for further assessment of subject safety. Notification of all DRB meetings and meeting outcomes will be sent to participating sites.

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16 COMPENSATION, INSURANCE AND INDEMNITY

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

The Investigator should contact BioMarin immediately upon notification that a study subject has been injured by the IP 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 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 subject has followed the Investigator's instructions, BioMarin will pay for reasonable and necessary medical services to treat the injuries caused by the IP or study procedures, if these costs are not covered by health insurance or another third party that usually pays these costs. In some jurisdictions, BioMarin is obligated by law to pay for study-related injuries without prior recourse to third party payer billing. If this is the case, BioMarin will comply with the law.

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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 CRF casebook to verify its accuracy.

CRFs 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 CRF instructions, blank data fields are not acceptable.

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

BioMarin's policy is that study data on the CRFs 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 an Investigator or institution refuses to allow access to subject records because of confidentiality, arrangements must be made to allow an "interview" style of data verification.

A CRA designated by BioMarin will compare the CRFs 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 CRA, 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 CRA 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 CRF 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 CRFs 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

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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.

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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.

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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.

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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 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).

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22 INVESTIGATOR RESPONSIBILITIES

22.1 Conduct of Study and Protection of Human Patients

In accordance with FDA Form 1572, 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 patients.
- He or she will personally conduct or supervise the study.
- He or she will inform any potential patients, 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 IRB review and approval in 21 CFR Part 56 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.
- 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
- He or she will ensure that adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.
- He or she will ensure that the IRB/IEC/REB complies with the requirements of 21 CFR Part 56, 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 patients or others are reported to the IRB/IEC/REB. Additionally, he or she will not make any changes in the research without IRB/IEC/REB approval, except where necessary to eliminate apparent immediate hazards to human patients.
- 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.

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23 SIGNATURE PAGE

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

Protocol Number: 270-201, Amendment 5

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 E6 ICH, as stated in the protocol, and other information supplied to me.

Investigator Signature	Date
Printed name:	
Accepted for the Sponsor:	
DocuSigned by:	
PI	14-Feb-2017 8:34 AM F
Medical Monitor Signature Signer Name: Pl Signing Reason: Lapprove this document Signing Time: Pl	Date
50FE2C0CB1C24F7C96F74CC498E3FB2F	
Printed name: PI , MD, PI , Clinical Sciences	

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24 PROTOCOL AMENDMENT TEXT REVISIONS

The following table summarizes the revisions made to the protocol and relates the changes to the appropriate rationale (See pages 2-3). Text that has been added or inserted is indicated by <u>underlined</u> font, and deleted text is indicated by strikethrough font.

Section No./Title	Text Revisions	<u>Rationale</u>
2/Synopsis (Criteria for Evaluation)	No major toxicity is expected based on preclinical studies in mice and monkeys. Each subject will have comprehensive surveillance monitoring of LFTs (at local labs, twice-once per week for Weeks 1-2036, then once per week from Week 21-36, and then once every 2 weeks from Week 37-52) during Year 1. LFTs will be monitored every three months for up to 5 years post-dose in the safety extension; the frequency and duration of LFT testing may be changed based on discussion between the Medical Monitor and the Investigator and review of subject data.	1
7/Introduction	Gene therapy offers the potential of a cure through disease-modifying therapy by continuous endogenous production of human FVIII following a single administration of vector.	5
Tables 9.1.1, 9.1.2, 9.1.3, 9.1.4	Schedules of Assessments and footnotes were updated to be consistent with other changes made elsewhere in the protocol.	1, 2, 3, 5
9.4.8.2/Glucocorticoid Treatment of Elevated Hepatic Transaminases	During the Post-Infusion Follow-up Period and the Safety Follow-Up Period, each subject will have comprehensive surveillance plan monitoring of LFTs (at local labs, twice once per week for Weeks 1- <u>3620</u> , then once per week from Week 21- 36, and then once every 2 weeks from Week 37-52). LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.	1
9.7.6/Exploratory Biomarker Assessments	On an exploratory basis, samples may be fractionated prior to shedding analysis in order to better characterize the presence and location of vector DNA and/or vector capsid within each matrix. The fractionation may be performed with samples collected specifically for shedding analysis (saliva, blood, semen, urine, faeces), or by using exploratory samples, such as plasma, PBMCs, and red blood cells, collected under the study protocol.	4
9.7.8.3/Liver Function and Hepatitis Testing	Patients with persistent-ALT > 1.5 ULN during the study and no other etiology identified may undergo additional evaluations (e.g., imaging studies including MRI or ultrasound, additional blood tests, and/or liver biopsy) at the discretion of the investigator.	5

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Section No./Title	Text Revisions	<u>Rationale</u>
9.7.8.6/Vector Shedding	Vector shedding will also be extensively studied in the present clinical trial, every other week between Weeks 4-16, then every 4 weeks to Week 52 until at least 3 consecutive negative results are obtained. <u>Testing of semen will continue through Week 12</u> , even if 3 consecutive negative results have been recorded in that compartment prior to that timepoint.	3
10.4.1.1/Diagnosis versus Signs and Symptoms	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.	5
10.4.1.9/Pregnancy	Pregnancy in a partner should be reported within 24 hours of the site becoming aware of the pregnancy by entering the information on the Pregnancy eCRF and submitting to BPV within 24 hours of the site becoming aware of the event. The Investigator must make every effort to follow the subject's partner (with that partner's consent) through resolution of the pregnancy (delivery or termination) and to report the resolution on the Pregnancy Follow-up Form in the study reference materials.	5
12.5.1/Once per Week (Weeks 1-16)	 The following procedures will be performed at one visit per week from Weeks 1 through 16: Liver Function Tests (refer to Table 9.7.8.3.1) – local laboratory assessment LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data. FVIII activity level – local laboratory assessment FVIII activity level (one-stage APTT) FVIII activity level (chromogenic FXa assay) PMBC collection 	1, 2
12.5.2/Twice per Week (Weeks 1-16)	The following procedures will be performed twice per week from Weeks 1 through 16: • Liver Function Tests (refer to Table 9.7.8.3.1) local laboratory assessment • Local assessment of liver function tests should be performed on Day 8 during Week 1, and then 2x/week from Week 2 through Week 16 • LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.	1

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Section No./Title	Text Revisions	<u>Rationale</u>
	FVIII activity level local laboratory assessment	
	○ FVIII activity level (chromogenic FXa assay)	
	 Local assessment of FVIII activity level should be performed on Day 8 during Week 1, and then 2x/week from Week 2 through Week 16 	
12.5.4/Every 2 Weeks	Every 2 weeks (Weeks 2, 4, 6, 8, 10, 12, 14 and 16), the following procedures will be performed:	3
	• PCR of vector DNA in blood, saliva, urine, semen, and stools (not collected at Week 2)	
	 Collection to occur until at least 3 consecutive negative results are obtained. Semen samples should continue to be collected and tested through Week 12, even if 3 consecutive negative results in that compartment have been recorded prior to that timepoint. 	
12.5.5/Weeks 4, 8, 12, and 16	At Weeks 4, 8, 12, and 16, the following procedures will be performed:	2
12.6.1/Once per week (Weeks 17 through 36)	Once per week from Week 17 through Week 36, the following procedures will be performed: • Liver Function Tests (refer to Table 9.7.8.3.1) – local laboratory assessment • LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data. • FVIII activity level – local laboratory assessment • FVIII activity level (one-stage APTT) • FVIII activity level (chromogenic FXa assay)	1
12.6.2/ Twice <u>Once</u> per Week (Weeks 17 through 20)	Twice Once per week from Week 17 through Week 20, the following procedures will be performed: • PBMC collection • Liver Function Tests (refer to Table 9.7.8.3.1)	1, 2

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Section No./Title	Text Revisions	<u>Rationale</u>
	 LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data. 	
	FVIII activity level local laboratory assessment	
	↔ FVIII activity level (APTT)	
12.6.3/ Once per week Every Two Weeks (Weeks 21 through	Once per week from Week 21 through Week 36-Every two weeks (Weeks 22, 24, 26, 28, 30, 32, 34, and 36), the following procedures will be performed:	1,2
(Weeks 21 through 36)	Liver Function Tests (refer to Table 9.7.8.3.1) — local laboratory assessment	
	 LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data. 	
	FVIII activity level local laboratory assessment	
	↔ FVIII activity level (APTT)	
	↔ FVIII activity level (chromogenic FXa assay)	
	<u>PBMC collection</u>	
12.6.4/Every 4 Weeks	Every 4 weeks (Weeks 20, 24, 28, 32, and 36), the following procedures will be performed:	2
	PBMC collection	
References	Heller CG & Clermont Y. Kinetics of the germinal epithelium in man. Recent Prog Horm Res. 1964;20:545-571.	3
	Heller CG, Heller GV, Rowley MJ. Human spermatogenesis: an estimate of the duration of each cell association and each cell type. Excerpta Med Int Congr Ser. 1969;184:1012-1018.	

CLINICAL STUDY PROTOCOL

Study Title: Protocol Number: Active Investigational Product: IND/European Union Drug Regulating Authorities Clinical Trials (EudraCT) Number:	A Phase 1/2, Dose-Escalation, Safety, Tolerability and Efficacy Study of BMN 270, an Adenovirus-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII in Patients with Severe Haemophilia A 270-201 AAV5-hFVIII-SQ 2014-003880-38
Indication:	Haemophilia A
Sponsor:	BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949
Development Phase:	Phase 1/2
Sponsor's Responsible Medical Monitor:	PI , MD PI BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949
Duration of Subject Participation:	Approximately 264 weeks
Dose:	Varied
Study Population:	Males aged 18 or older
Date of Original Protocol:	10 February 2015
Date of Amendment 1:	06 March 2015
Date of Amendment 2:	26 May 2015
Date of Amendment 3:	06 November 2015
Date of Amendment 4:	02 September 2016

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This study will be conducted according to the principles of Good Clinical Practice as described in the U.S. Code of Federal Regulations and the International Conference on Harmonisation Guidelines, including the archiving of essential documents



CLINICAL STUDY PROTOCOL AMENDMENT SUMMARY

Amendment: 4

Date: 2 September 2016

RATIONALE AND SUMMARY OF MAJOR CHANGES

A summary of major changes covered by Amendment 4 to the BMN 270-201 protocol is provided below.

 The requirement for prophylactic corticosteroids has been removed and the threshold for starting therapeutic corticosteroids has been changed from alanine aminotransferase (ALT) ≥ 1.5x baseline value to ≥ 1.5x upper limit of normal (ULN).

Rationale: Previous FIX gene-therapy clinical studies have demonstrated an association between increases in ALT and declines in FIX expression, which are thought to be due to a cell-mediated immune response to transduced hepatocytes (Manno, 2006, Nat.Med.) Mingozzi, 2013, Blood; (Nathwani, 2014, N.Engl.J.Med.); (Nathwani, 2011, Mol.Ther.). In one study (Nathwani, 2014, N.Engl.J.Med.); (Nathwani, 2011, Mol.Ther.), partial rescue of FIX expression was observed with the initiation of corticosteroids. Based on these results, as a conservative measure to preserve FVIII activity, the BMN 270-201 protocol set the threshold for initiating a therapeutic course of corticosteroids at $\geq 1.5x$ baseline. Further, following this event in the first subject, all subsequent subjects were to receive prophylactic corticosteroid therapy. To date, however, in clinical study 270-201, mild asymptomatic elevations in ALT largely near or slightly above the ULN have been observed following dosing, but in general, have not been associated with a concomitant drop in FVIII expression. These observations are consistent with preliminary clinical trial data reported from recent AAV-FIX gene therapy studies (George, 2016, Haemophilia; Miesbach, 2016, Haemophilia), which demonstrate that subjects with mild elevations in ALT did not have associated concomitant loss in FIX activity; in one study (George, 2016, Haemophilia), subjects did not require corticosteroid dosing (no hepatic transaminases >1.5x ULN). Given the fact that elevations in ALT values of 1.5x baseline could represent normal fluctuations in liver enzymes (Watkins, 2006, JAMA), the threshold for initiating corticosteroids is being amended to $\geq 1.5x$ the ULN. Adjusting the threshold to $\geq 1.5x$ ULN will avoid unnecessary prolonged exposure to corticosteroids at lower levels of ALT elevation. Given the lack of association between changes in liver enzymes and FVIII activity, the 270-201 protocol has been amended to provide increased flexibility and clinical discretion and to recommend initiation of corticosteroids if there is a rise in ALT greater than 1.5x ULN or in consultation

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between the investigator and the medical monitor based on the pattern of FVIII activity and/or changes in liver enzymes as well as an ongoing review of efficacy and safety data from subjects on-study to date.

To maintain adequate surveillance of hepatocyte injury and FVIII expression, liver enzymes and FVIII levels will be monitored at regular intervals (at local labs, twice per week for Weeks 1-20, then once per week from Week 21-36, and then once every 2 weeks from Week 37-52) to ensure that any elevations in ALT and decreases in FVIII are observed early which may support intervention with corticosteroids. The monitoring schedule and corticosteroid regimen may be adjusted as needed based on individual subject data upon discussion between the investigator and the medical monitor.

 An additional cohort of subjects has been added. For Cohort 4, 3 subjects will be enrolled at the dose of 4E13 vector genomes (vg) per kilogram. If FVIII activity in these 3 subjects is ≥ 5% at 8 weeks and no safety issue is found, an additional 3 subjects may be enrolled in this cohort.

Rationale: In order to fully understand the dose-response relationship of BMN 270, an additional cohort of subjects will be enrolled at a dose of 4E13 vg/kg, a dose level which is intermediate between the high (6E13 vg/kg) and mid (2E13 vg/kg) dose levels. A dose level of 4E13 vg/kg was chosen in order to target FVIII levels within the normal range, which is expected to prevent the need for exogenous FVIII administration under most circumstances, such as peri-surgically or following serious trauma (White, 2001, Thromb Haemost). The current dose of 6E13 vg/kg has resulted in FVIII levels above the upper limit of normal in 2 of 7 treated patients, which suggests that a lower dose could provide more optimal FVIII expression and activity levels. The 4E13 dose is expected to be effective based on clinical experience to date in 270-201 as improvements in FVIII activity and an acceptable safety profile were observed in both Cohort 2 (2E13) and Cohort 3 (6E13).

3. The enrollment stopping criterion related to serum ALT levels has been changed from a 5-fold increase from baseline after BMN 270 administration to:

ALT elevation > 5x ULN for at least 2 consecutive weeks after administration of BMN 270 in the absence of a definitive alternate etiology for the increase.

Rationale: Given that 270-201 is a first in human study, a 5-fold ALT increase from baseline was considered, at study initiation, to be an appropriately conservative approach to enhancing patient safety. Clinical experience to date with BMN 270 demonstrates mild asymptomatic increases in ALT from baseline values, which have not to date exceeded Common Terminology Criteria for Adverse Events (CTCAE) grade 1 toxicity level (up to 3x ULN). Most ALT increases from baseline were within the normal range or slightly

greater than the ULN. Given that the fluctuations in liver enzymes observed above baseline values in treated subjects are potentially in-line with normal variations found in healthy volunteers (Watkins, 2006, JAMA) and as safety data to date generated with AAV vectors with tropism to the liver (Nathwani, 2014, N.Engl.J.Med.); Pasi, 2016, Haemophilia; Monahan, 2015, J. Thromb Haemostasis; George, 2016, Haemophilia; Miesbach, 2016, Haemophilia; (Manno, 2006, Nat.Med.); (Nathwani, 2011, Mol.Ther.), have found reversible and, in most cases, mild elevations in ALT without signs of significant hepatic injury, the ALT enrollment stopping criteria has been modified to 5x the ULN with a duration of at least 2 consecutive weeks. This criterion is in line with FDA guidance on drug-induced liver injury. To support patient safety, monitoring of liver enzymes will be performed frequently and at regular intervals (at local labs, twice per week for Weeks 1-20, then once per week from Week 21-36, and then once every 2 weeks from Week 37-52) to ensure that any elevations in ALT are observed early, with repeat testing to confirm the abnormality. In addition, when considering whether to dose subsequent subjects following an elevation in ALT in any treated subject, other factors that may have directly caused the rise in ALT (eg, excessive alcohol use or ALT rise from non-liver origin such as from excessive physical strain) will be considered to fully evaluate the etiology of the increase.

4. Frequency of monitoring of vector shedding assessment (by polymerase chain reaction [PCR]) during the Post-Infusion Follow-Up period (Weeks 1 to 16) has been reduced to every other week between Week 4 and Week 16.

Rationale: In the Post-Infusion Follow-Up period, collection every 2 weeks after Week 4 is sufficient, as clinical study data generated to date demonstrates that the earliest biofluid to clear is urine, but not earlier than Week 4. A visit every week presents an unnecessary burden on subjects given the slow clearance in most fluids.

 Frequency of monitoring of the vector shedding assessment (by PCR) in the Safety Follow-Up period (after Week 16) has been changed to include assessments every 4 weeks between Weeks 20 and 52.

Rationale: More frequent testing after week 20 is needed in order to better characterize the time point at which vector shedding has ceased. Per protocol, testing of vector shedding in any fluid compartment can be stopped after 3 consecutive negative tests. In the case of vector shedding in the semen, more frequent testing will avoid prolonged and unnecessary contraception use.

6. The enrollment stopping criterion around vector shedding has been modified. Enrollment in the study will be put on halt if there is persistent detection (defined as 3 consecutive positive samples) of AAV vector DNA in the semen of a participant more than 52 weeks after BMN 270 administration.

Rationale: The original enrollment stopping criterion related to vector shedding had set a threshold of 26 weeks if detected in the semen, based on expected clearance from AAV clinical studies (Nathwani, 2014, N.Engl.J.Med.); (Manno, 2006, Nat.Med.); (Schenk-Braat, 2007, J.Gene Med.); (Croteau, 2004, Ann.Occup.Hyg.). In the literature referenced above, including Haemophilia B clinical studies utilizing AAV2 and AAV8, vector was no longer detectable after 40 days in blood, saliva, urine or stool, but in one study was detected in the seminal fluid for 16 weeks, but not in motile sperm (Manno, 2006, Nat.Med.). In these studies, the amount of vector present in these bodily fluids involved an extremely small fraction of the infused dose. More recent data from an ongoing AAV5-FIX study demonstrates persistence of the vector in both the blood and the semen for at least 39 weeks (Miesbach, 2016, Haemophilia). Similarly, clinical study data from 270-201 has demonstrated that subjects show a residual, but progressively declining level of vector DNA in the semen with very low copies identified past week 26 in one subject to date (2 copies/5µL qPCR sample at week 28 with 2 prior negative values). The slow clearance from the semen mirrors clearance from the blood compartment and as the semen values are declining with a very low copy level at week 28, shedding in semen is expected to clear by week 40. The modified enrollment stopping criterion is deemed appropriate to allow for complete clearance from the semen while controlling the potential risk to patient safety that may be posed by the continued persistence of the vector DNA in semen. Subjects will continue effective contraception use until at least 3 consecutive semen samples are negative for vector DNA.

7. Stopping criterion regarding Grade 2 related events has been changed. The occurrence of a Grade 2 related adverse event persisting for at least 7 days will now trigger a Data Review Board (DRB) review of safety data to determine whether an enrollment halt is warranted, rather than triggering an automatic enrollment halt.

Rationale: The original stopping criterion was set very conservatively, in the absence of any clinical data for BMN 270 at the start of the first-in-human study. Given the safety profile observed to date in 9 subjects dosed with BMN 270, an automatic enrollment halt based on a related Grade 2 event of 7 days duration is not warranted. To date, no subject has experienced a Grade 2 related event lasting 7 days or more. As such, a prolonged Grade 2 event assessed by the investigator as related to BMN 270 will trigger a DRB review of study

safety; the DRB will be consulted to evaluate the event as well as the totality of safety data and may choose to halt enrollment or not based upon the results of that review.

8. Testing of von Willebrand factor Antigen (VWF:Ag) has been added as an assessment (at Screening and the same time points that FVIII activity is measured during the study).

Rationale: As fluctuations in FVIII levels are commonly observed and may be related to changes in VWF levels (e.g. increase in VWF secondary to exercise), following VWF levels at regular intervals over the course of the study will enable a more complete assessment of any on-study changes in FVIII levels.

9. Testing of creatine phosphokinase (CPK) has been added to routine blood chemistry assessments during the study. CPK testing may be performed at other intervals based on PI assessment.

Rationale: CPK will allow for a more complete assessment of elevations in ALT and/or alanine aminotransferase (AST) by potentially differentiating between muscle and liver as the source of the enzymes. An elevation of CPK may indicate muscle injury and not hepatic injury.

10. An exploratory Direct Thrombin assay has been added at Baseline, Week 1, and every 3 months thereafter.

Rationale: To better understand the relationship between FVIII levels and the downstream clotting cascade following administration of BMN 270, a direct thrombin assay will be performed.

11. The identity of the medical monitor has been changed.

12. Minor edits for clarity and consistency have been incorporated.

Specific changes included in this amendment, including the Synopsis, since Amendment 3 (approved 6 November 2015) are outlined in Section 24.

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2 SYNOPSIS

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TITLE OF STUDY:		

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

PROTOCOL NUMBER:

270-201

STUDY SITES:

Approximately 6-10 sites worldwide.

PHASE OF DEVELOPMENT:

Phase 1/2

STUDY RATIONALE:

Haemophilia 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 cascade. This disorder can be either inherited, due to a new mutation 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 is largely governed by the level of residual expression. Severe HA is classified as FVIII activity less than 1% of wild type (< 1 IU/dL), moderate disease comprises 1-5% of wild type activity and the mild form is 5-40% activity. The clinical manifestations of severe HA remain frequent spontaneous bleeding episodes, predominantly in joints and soft tissues, with a substantially increased risk of death from haemorrhage when the brain is involved.

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 treatment (mean of 1 to 7 episodes/year with prophylaxis and up to 30 to 50 episodes/year for on demand treatment). The consequence of multiple bleeding events is the development of an underlying pathology that contributes to debilitating multiple-joint arthropathy and substantially increased risk of death. Chemical modification (e.g. direct conjugation of polyethylene glycol (PEG) polymers) and bioengineering of FVIII (e.g. FVIII-Fc fusion proteins) improve half-life

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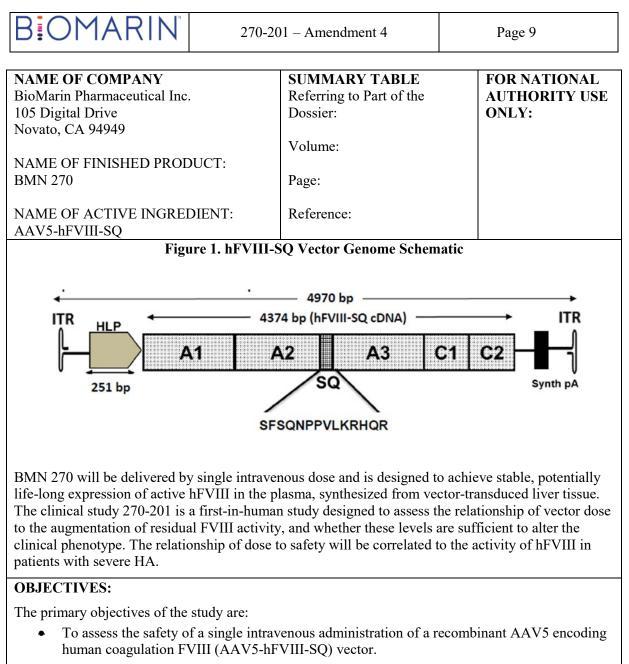
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by approximately 50%, and thus, show promi	se in reduced dosing and maintain	ning activity levels
above 1% trough. However, these longer actin	ng FVIIIs remain dependent on m	ultiple infusions to

above 1% trough. However, these longer acting FVIIIs remain dependent on multiple infusions to maintain critical levels of FVIII activity in severe HA patients. There is therefore a strong unmet need for a fully preventive treatment of HA to give patients a FVIII level compatible with a normal and haemorrhage-free life.

Gene therapy offers the potential of disease-modifying therapy by continuous endogenous production of active FVIII following a single intravenous administration of a vector with the appropriate gene sequence. Haemophilia 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 modest increases in the level of FVIII (any increase of the plasma level by 2 ng/ml induces an increase in activity of 1%) can ameliorate the severe form of the disease. Thus, relatively small changes in endogenous FVIII activity results in clinically relevant improvements in disease phenotype. Finally, the 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 for specific tissues such as the liver (for serotypes 2, 5 and 8 among others). Indeed, an on-going gene therapy clinical trial for a related disorder, haemophilia B, has established that stable (>36 months) expression of human factor IX at levels that are sufficient for conversion of their bleeding phenotype from severe to moderate or mild is achievable following a single peripheral vein administration of AAV-8 vector. Several participants in this trial have been able to discontinue factor prophylaxis without suffering spontaneous haemorrhages, 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 liver-selective promoter (Figure 1).



• To determine the dose of AAV5-hFVIII-SQ required to achieve FVIII at or above 5% of normal activity (≥5 IU/dL) at 16 weeks after infusion. The kinetics, duration and magnitude of AAV-mediated FVIII activity in individuals with haemophilia A will be determined and correlated to an appropriate BMN 270 dose.

The secondary objectives of the study are:

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

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STUDY DESIGN AND PLAN:

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

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

Cohort 1: 6E12 vector genomes [vg] per kilogram of body weight, given as a single intravenous dose (iv)

Cohort 2: 2E13 vg per kilogram, iv

Cohort 3: 6E13 vg per kilogram, iv

Cohort 4: 4E13 vg per kilogram, iv

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

Cohorts 1-3

The first 3 cohorts will be enrolled sequentially, allowing a period of 3 weeks or more between cohorts. Dose escalation may occur after a single subject has been safely dosed if the resulting FVIII activity at the Week 3 visit is < 5 IU/dL in both the aPTT and chromogenic assays. Three weeks is expected to be the time the expression will be close to the maximum. This escalation paradigm is intended to minimize the subject numbers exposed to subtherapeutic doses.

Approximately three weeks after an injection, the decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and a panel of investigators participating in the study, the Data Review Board (DRB).

If the FVIII activity reaches \geq 5 IU/dL at the Week 3 visit, then the remaining subjects in the cohort will be enrolled without the need to wait for 3 weeks between subjects.

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Subject 1 will be dosed by intravenous infusion with 6E12 vector genomes [vg] per kilogram of body weight. If the FVIII activity level does not reach ≥ 5 IU/dL at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 1 and enrollment into Cohort 2 will initiate with Subject 2 at the next dose (2E13 vg/kg).

If the FVIII activity level in the first subject treated in Cohort 2 does not reach ≥ 5 IU/dL at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 2 and enrollment into Cohort 3 (6E13) will initiate with the next subject. If the FVIII activity level in the first subject treated in Cohort 3 does not reach ≥ 5 IU/dL at the Week 3 visit in both assays, then the Data Review Board (DRB) will recommend whether to continue to add subjects to the cohort and/or whether to continue the study.

For the first subject treated in each of the first 3 cohorts, if the activity level reaches \geq 5 IU/dL and no safety issue is found, then up to four subjects will be enrolled in the Cohort, though, the adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

<u>Cohort 4</u>

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

There will be an ongoing review of individual patient safety and efficacy data by the medical monitor and the DRB. The adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

Because subjects develop neutralizing immunity upon exposure to the capsid, re-challenge of vector is not a likely treatment option and these subjects have effectively a single opportunity for therapy using this AAV capsid. Efficacy will be determined by FVIII activity at 16 weeks post dose. Safety will be evaluated for approximately 5 years after dosing. Any safety signal may trigger a review of the data and possible additional immunogenicity studies that include an assessment of cellular immune responses using collected peripheral blood mononuclear cells (PBMC).

NUMBER OF SUBJECTS PLANNED:

Up to 15 subjects may enroll into the study; the actual number of subjects will depend on the FVIII activity levels seen in each Cohort.

DIAGNOSIS AND ALL CRITERIA FOR INCLUSION AND EXCLUSION:

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

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 NAME OF ACTIVE INGREDIENT: AAV5-hFVIII-SQ 1. Males that are 18 years or older win medical history. Patients will be complete the second se		
 Treated/exposed to FVIII concentra (EDs) 		
3. Greater or equal to 12 bleeding epi 12 months. Does not apply to patie	ents on prophylaxis	
4. Able to sign informed consent and	comply with requirements of the t	rial
 No history of inhibitor, and results 0.6 Bethesda Units (BU) on 2 cons 12 months 		•
 Sexually active patients must be windouble barrier, including hormonal 6 months, subjects may stop contrasemen samples. 	contraception for at least 6 month	s post-treatment. After
Individuals who meet any of the follow study:	ving exclusion criteria will not be e	ligible to participate in the
1. Detectable pre-existing immunity tr inhibition or AAV5 total antibodies	1	y AAV5 transduction
2. Any evidence of active infection or	any immunosuppressive disorder	
3. HIV positive		
4. Significant liver dysfunction as def	ined by abnormal elevation of:	
• ALT (alanine transaminase	e) to 3 times the upper limit of nor	mal;
• Bilirubin above 3 times the	e upper limit of normal;	
• Alkaline phosphatase abov	e 3 times the upper limit of norma	l; or
• INR (international normali	zed ratio) ≥ 1.4	
5. Potential participants who have have significant fibrosis of 3 or 4 as rate		are excluded if they had
6. Evidence of any bleeding disorder	not related to Haemonhilia A	

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7. Platelet count of $< 100 \times 10^{9/2}$	L	
8. Creatinine $\geq 1.5 \text{ mg/dL}$		
9. Liver cirrhosis of any etiolog	y as assessed by liver ultrasound	
10. Hepatitis B if surface antigen	is positive	
11. Hepatitis C if RNA is positiv	e	
12. Treatment with any IP within	30 days prior to the end of the screening	ng period
complying with the requirem in the protocol. The physicia	ne physician's discretion that would pre ents of the study including possible cort n may exclude patients unwilling or una od following the viral infusion.	ticosteroid treatment outlined
14. Prior treatment with any vect	or or gene transfer agent	
15. Major surgery planned in the	16-week period following the viral infu	ision
16. Use of systemic immunosupp infusion	pressive agents or live vaccines within 3	0 days before the viral
INVESTIGATIONAL PRODU	CT(S), DOSE, ROUTE AND REGIN	1EN:
Each subject will receive a single infusion will depend on the dose	injection of BMN 270 as an intravenou level.	is infusion. The volume of
REFERENCE THERAPY(IES), DOSE, ROUTE AND REGIMEN:	
The study is open label with com	parison of FVIII activity to baseline val	ues. No reference therapy

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

CRITERIA FOR EVALUATION:

Safety:

The following safety outcome measurements will be assessed:

- Incidence of adverse events (AEs), including serious AEs (SAEs)
- Change in clinical laboratory tests (serum chemistry and haematology)

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- Change in vital signs
- Change in physical examination
- Vector shedding
- Liver function tests (LFTs, including ALT, AST, GGT, LDH, bilirubin, alkaline phosphatase)
- Immune response to FVIII transgene and AAV capsid proteins

No major toxicity is expected based on preclinical studies in mice and monkeys. Each subject will have comprehensive surveillance monitoring of LFTs (at local labs, twice per week for Weeks 1-20, then once per week from Week 21-36, and then once every 2 weeks from Week 37-52) during Year 1. LFTs will be monitored every three months for up to 5 years post-dose in the safety extension; the frequency and duration of LFT testing may be changed based on discussion between the Medical Monitor and the Investigator and review of subject data.

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

Efficacy:

The primary efficacy measure will be to assess plasma FVIII activity. The efficacy goal of the study is to establish the dose relationship to FVIII activity \geq 5 IU/dL at 16 weeks post BMN 270 administration.

Secondary efficacy measures include assessing the impact of BMN 270 on the frequency of FVIII replacement therapy and on the number of bleeding episodes during the study. Subjects will be asked to keep a subject diary to record the details in these areas.

Pharmacodynamics:

The FVIII antigen and activity level as measured by an ELISA (antigen level) and by one-stage APTT and/or chromogenic FXa assay (activity level), will be used for plasma profiles; FVIII activity will be used to determine PD parameters. Traditional PK analysis is not applicable.

If supported by the FVIII activity data, non-compartmental analysis and observation will be used to estimate individual values of Cb (baseline concentration), Css (steady state concentration), Tss (time to steady state), C(t) and AUC(0-t) where t is 16 weeks.

STATISTICAL METHODS:

The sample size is based upon clinical considerations and could detect a strong clinical efficacy signal. Up to 15 subjects may be dosed in the study. The subjects will be followed in a longitudinal manner and all the relevant information will be collected. The analysis of the data will be descriptive

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in nature but data collected in a	longitudinal r	nanner may be analyzed us	ng longitudinal m	ethods
such as mixed effect model wh				
various time points within a participant. Efficacy is a secondary endpoint, defined as biologically				
active FVIII at ≥ 5 IU/dL by chromogenic FXa assay and/or one-stage APTT assay at 16 weeks				
following study treatment. FVIII activity will be assessed weekly during the study period. We can				
only assess the true steady state of FVIII protein produced from BMN 270 after a minimum of				

72 hours has elapsed since the last infusion of FVIII protein concentrates.

Analysis of neutralizing antibody response and other immunological parameters as well as vector shedding will be primarily descriptive and involve both inter-participant and intra-participant comparisons across doses.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

AAV	adeno-associated virus
ADL	activities of daily living
ADR	adverse drug reaction
AE	adverse event
ALT	alanine transaminase
APTT	activated partial thromboplastin time
BPV	BioMarin Pharmacovigilance
BU	Bethesda Unit
CFR	Code of Federal Regulations
CRA	clinical research associate
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DRB	Data Review Board
eCRF	electronic case report form
ED	exposure days
EOSI	events of special interest
ETV	early termination visit
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIH	first-in-human
FVIII	coagulation factor VIII
FXa	coagulation factor Xa
GCP	Good Clinical Practice
HA	Haemophilia A
hFVIII	human coagulation factor VIII
HIPAA	Health Insurance Portability and Accountability Act
IB	investigator brochure
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for
	Registration of Pharmaceuticals for Human Use
ICH E6	ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6
IEC	independent ethics committee
IND	Investigational New Drug (application)

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INR	international normalized ratio	
IP	investigational product	
IRB	institutional review board	
IV	intravenous	
LFT	liver function test	
MedDRA	Medical Dictionary for Regulatory Activities	
NOAEL	no-observed-adverse-effect level	
PBMC	peripheral blood mononuclear cells	
PD	pharmacodynamics	
PEG	polyethylene glycol	
РК	Pharmacokinetics	
PRO	patient-reported outcome	
rhFVIII	recombinant human FVIII protein	
REB	research ethics board	
SAE	serious adverse event	
SAP	statistical analysis plan	
SDV	source data verification	
ULN	upper limit of normal	
vg	vector genomes	
VWF:Ag	von Willebrand factor Antigen	

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]).

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

5 ETHICS

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

5.1 Institutional Review Board or Independent Ethics Committee

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

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

5.2 Ethical Conduct of Study

It is expected that Investigators understand and comply with the protocol. This includes, but is not limited to: establishing and meeting enrollment commitments, including providing

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eligible subjects for study enrollment; adhering to 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)

Specifically, this study is based on adequately performed laboratory and animal experimentation. The study will be conducted under a protocol reviewed and approved by an IRB/IEC/REB and will be conducted by scientifically and medically qualified persons. The benefits of the study are in proportion to the 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), United States Code of Federal Regulations (CFR) 21 CFR §50, European Clinical Trial Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC, and other applicable local regulations, will be obtained for each subject prior to entering the subject into the study. The Investigator will prepare the ICF and provide the documents to BioMarin for approval prior to submission to the IRB/IEC/REB approval. BioMarin and the IRB/IEC/REB must approve the documents before they are implemented. A copy of the approved ICF, and if applicable, a copy of the approved subject information sheet and all ICFs translated to a language other than the native language of the clinical site must also be received by BioMarin or designee prior to any study-specific procedures being performed.

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

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

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

Prior to beginning the study, the Investigator at each site must provide to BioMarin or designee, a fully executed and signed US Food and Drug Administration (FDA) Form FDA 1572 and a Financial Disclosure Form. All sub-Investigators must be listed on Form FDA 1572. Financial Disclosure Forms must also be completed for all sub-Investigators listed on the Form FDA 1572 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.

Liver function tests (LFTs) will be performed at the local laboratories associated with the study sites. Local laboratory results of LFTs will be used to trigger corticosteroid treatment as needed (refer to Section 9.4.8.2). In case of discrepant results between local and central laboratories, the Investigator and Medical Monitor will decide further action. Safety labs evaluations (including LFTs) will be performed at the central lab, while bioanalytical samples will be performed at the appropriate specialty lab. Refer to the Laboratory Manual for more details.

7 INTRODUCTION

Haemophilia A (HA) is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males (Nathwani, 1992, Baillieres Clin.Haematol.). It is caused by mutations in the factor VIII (FVIII) gene that codes for FVIII protein, an essential cofactor in the coagulation cascade. 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 haemorrhage. Treatment in Western (Berntorp, 2012, Haemophilia.) countries consists of intravenous injection of plasma derived or recombinant FVIII protein concentrates at the time of a bleed, 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 haemophilia A patients. These individuals develop debilitating arthropathy and have a substantially increased risk of death from haemorrhage in life (Stonebraker, 2010, Haemophilia.). Chemical modification or bioengineering of FVIII may improve half-life to 18-19 hours (Kaufman, 2013, Blood). However, these long acting FVIII variants do not eliminate the need for lifelong FVIII protein administration (Hay, 2012, Blood).

Gene therapy offers the potential of a cure through continuous endogenous production of human FVIII following a single administration of vector. Haemophilia 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, Haemophilia.); thus the therapeutic goal for gene therapy is a modest increase in hFVIII. Finally, the consequences of gene transfer can be assessed using simple quantitative rather than qualitative endpoints that can be easily assayed in most clinical laboratories.

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

7.1 Nonclinical Studies

The nonclinical program supports a single IV administration of BMN 270, the planned clinical route of administration, for the treatment of Haemophilia A in male patients. This

nonclinical program took into account the guidelines and reflection papers for gene therapy medicinal products under EMA Advanced Therapies. 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 (normal CD-1 mouse, B and T cell deficient mouse model of haemophilia 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.

The primary PD of BMN 270 was assessed in a series of non-GLP single dose studies in a FVIII KO x Rag2 mouse model of severe Haemophilia A that recapitulates the change in coagulation observed in the human severe disease population without interfering cross species immunogenicity. PD activity and expression of hFVIII was assessed for durations up to 13-weeks in the FVIII KO x Rag2 mouse given dose range of 2E11 through 2E14 vector genomes (vg)/kg. Low levels of plasma hFVIII were observed in mice given 2E12 vg/kg after eight-weeks, post dose. Plasma hFVIII activity using bleeding time as an endpoint was evaluated in the FVIII KO x Rag2 mouse given up to 2E13 and 1E14 vg/kg BMN 270 at 8 weeks, post dose. BMN 270 related correction of bleeding times showed a dose relationship that was similar to that observed in FVIII KO x Rag2 mice given matched IU levels of Refacto[®].

All cynomolgus monkeys used in this program were screened for neutralizing anti-AAV5 activity prior to study enrollment. PD activity and plasma hFVIII concentrations were evaluated in the cynomolgus monkey given up to 6E13 vg/kg BMN 270 for eight weeks. Peak expression of hFVIII was observed three to six weeks post administration with a subsequent decrease in expression presumably due to immunogenicity though not necessarily correlated to antibody titer.

The normal mouse was utilized in the GLP toxicology study to assess the safety profile of BMN 270 without the background of disease progression and in sufficient number per parameter. The GLP single dose toxicity study in normal CD-1 mice given 6E12 and 6E13 vg/kg with a 4 and 13-week follow up period monitored clinical pathology, defined potential target organs, immunogenicity, gene expression and activity. No changes in liver function were observed. In a single dose PD study in monkey given BMN 270, formation of anti-AAV5 total antibodies was observed at Week 8 with relatively low formation of anti-hFVIII total antibodies. No changes in liver function was observed.

The overall nonclinical safety profile includes formation of anti-AAV5 total antibodies with relatively lower formation of anti-hFVIII total antibodies. Immunogenicity against the AAV capsid and hFVIII is an anticipated finding for BMN 270 treatment and will be monitored in

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the nonclinical and clinical programs. Though not observed in the nonclinical species, liver toxicity utilizing clinical pathology parameters will be monitored in the clinical program based on previous literature. Cellular immune response will also be monitored.

Additionally, the BMN 270 transgene product has a final sequence closely matching that of the protein replacement treatment, Refacto[®] and therefore the safety profile of the BMN 270 transgene product is anticipated to be similar to Refacto® and have no unique FVIII-specific target organs of toxicity. The AAV5 capsid has not been modified and therefore no unique capsid-specific safety findings are anticipated. Because the biodistribution pattern of AAV5 after IV administration is consistent across species, BioMarin will confirm the nonclinical distribution pattern of BMN 270 during clinical development. Biodistribution of the AAV5 capsid has been documented to predominately target the liver with relatively lower levels of transduction observed in the lung, kidney, spleen, testes and blood compartment depending on the species and timing of administration. Liver targeted distribution of a similar AAV5 Factor IX gene therapy product was observed in the rhesus macaque monkey with low levels of vector genomes detected in spleen, kidney and testis (Nathwani, 2006, Blood). Despite distribution to non-liver organs, no expression of Factor IX was detected in these tissues. Additionally, distribution to the testis was observed in another study in monkeys given an AAV5-codon-optimized human porphobilinogen deaminase; however, vector genomes in the semen were only transiently observed within one week but not thereafter (Paneda, 2013, Hum.Gene Ther.).

Both normal and disease model mice and a limited number of monkeys were utilized to establish proof of concept, species scaling and dose response in order to select the first-in-human (FIH) dose of 6E12 vg/kg. This dose represents 10-fold safety factor from the no observed adverse effect level (NOAEL) in the GLP enabling nonclinical toxicology study in mice.

7.2 Previous Clinical Studies

This is the first clinical study for BMN 270.

BioMarin's program for haemophilia A builds on previous clinical trials of AAV-mediated gene transfer for a related condition, haemophilia B, that were conducted with an AAV2 vector (Manno, 2003, Blood) and an AAV8 vector (Nathwani, 2011, N.Engl.J.Med.), (Nathwani, 2014, N.Engl.J.Med.). The large size of the FVIII cDNA was shortened and a preclinical validation of this approach was performed with an AAV8 vector (McIntosh, 2013, Blood).

AAV serotype 5 is being tested in other clinical trials and was reportedly well tolerated without treatment-related serious adverse events in a recent phase 1 study for treatment of Acute Intermittent Porphyria (D'Avola, 2014, J.Hepatol.). In addition, AAV using other serotypes have been used in 105 clinical studies to date and no safety issue specific to the vector was ever reported.

7.3 Study Rationale

Haemophilia A (HA) is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males (Mannucci, 2001, N.Engl.J.Med.). It is caused by deficiency in the activity of coagulation factor VIII (FVIII), an essential cofactor in the intrinsic coagulation cascade. This disorder can be either inherited, due to a new mutation 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 is largely governed by the level of residual expression. Severe HA is classified as FVIII activity less than 1% of wild type (< 1 IU/dL), moderate disease comprises 1-5% of wild type activity and the mild form is 5-40% activity. The clinical manifestations of severe HA remain frequent spontaneous bleeding episodes, predominantly in joints and soft tissues, with a substantially increased risk of death from haemorrhage when the brain is involved.

Treatment of severe HA presently consists of intravenous injection of plasma derived or recombinant human FVIII protein (rhFVIII) concentrates both as prophylaxis 2-4 times per week, and at the time of a bleed, to prevent or control bleeding episodes, respectively. The half-life for FVIII (12-18 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 treatment (mean of 1 to 7 episodes/year with prophylaxis and up to 30 to 50 episodes/year for on demand treatment) (Nagel, 2011, Haemophilia.). The consequence of multiple bleeding events is the development of an underlying pathology that contributes to debilitating multiple-joint arthropathy and substantially increased risk of death (Nagel, 2011, Haemophilia). Chemical modification (e.g. direct conjugation of polyethylene glycol (PEG) polymers) and bioengineering of FVIII (e.g. FVIII-Fc fusion proteins) improve half-life by approximately 50%, and thus, show promise in reduced dosing and maintaining activity levels above 1%trough (Stonebraker, 2010, Haemophilia.), (Mahlangu, 2014, Blood). However, these longer acting FVIIIs remain dependent on multiple infusions to maintain critical levels of FVIII activity in severe HA patients. There is therefore a strong unmet need for a fully preventive treatment of HA to give patients a FVIII level compatible with a normal and haemorrhage-free life.

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Gene therapy offers the potential of disease-modifying therapy by continuous endogenous production of active FVIII following a single intravenous administration of a vector with the appropriate gene sequence. Haemophilia 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 modest increases in the level of FVIII (any increase of the plasma level by 2 ng/ml induces an increase in activity of 1%) can ameliorate the severe form of the disease. Thus, relatively small changes in endogenous FVIII activity results in clinically relevant improvements in disease phenotype. Finally, the 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 (Mannucci, 2001, N.Engl.J.Med.). They have an excellent and well defined safety profile, and can direct long term transgene expression with tropism for specific tissues such as the liver (Nathwani, 2005, Curr.Hematol.Rep.) for serotypes 2, 5 and 8 among others). Indeed, an on-going gene therapy clinical trial for a related disorder, haemophilia B, has established that stable (>36 months) expression of human factor IX at levels that are sufficient for conversion of their bleeding phenotype from severe to moderate or mild is achievable following a single peripheral vein administration of AAV-8 vector (Nathwani, 2014, N.Engl.J.Med.). Several participants in this trial have been able to discontinue factor prophylaxis without suffering spontaneous haemorrhages, 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, 2011, Mol.Ther.), (Bainbridge, 2008, N.Engl.J.Med.), (Maguire, 2009, Lancet); (Simonelli, 2010, Mol.Ther.).

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

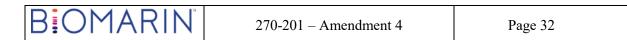
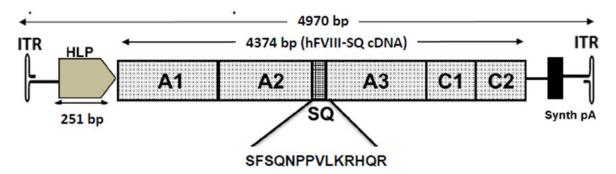


Figure 7.3.1: hFVIII-SQ Vector Genome Schematic



BMN 270 will be delivered by single intravenous dose and is designed to achieve stable, potentially life-long expression of active FVIII in the plasma, synthesized from vector-transduced liver tissue. The clinical study BMN 270-201 is a first-in-human study designed to assess the relationship of vector dose to the augmentation of residual FVIII activity, and whether these levels are sufficient to alter the clinical phenotype. The relationship of dose to safety will be correlated to the activity of FVIII in patients with severe HA.

7.4 Summary of Overall Risks and Benefits

Safety will be assessed by adverse event reporting and clinical laboratory assessment. Based on prior human studies with peripheral injections of AAV vectors, there is no known safety risk of AAV gene therapy. However, a mild asymptomatic transaminitis was observed at week 7-12 after administration in humans with an AAV8-FIX, providing the rationale for the following surveillance plan (Nathwani, 2011, Mol.Ther.). Each subject will have a comprehensive surveillance plan that monitors LFTs during the study.

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

Dose selection: The benefit of this study can only be enhanced by selecting a starting dose that maximizes the opportunity of observing a therapeutic effect, and therefore, reducing the possibility of a sub-therapeutic effect. With this consideration in mind, the starting dose 6E12 vg/kg was selected using overall data from the pre-clinical studies conducted in mice (normal and disease model, Rag2 -/- x FVIII -/-) and monkey. A detectable pharmacological response based on activity was observed at 6E12 vg/kg. A 10-fold safety margin based upon the NOAEL was observed in the GLP 13-week study in normal mouse at the highest dose administered. A 30-fold safety margin in an 8-week dose response study in disease model mice based on histology was observed at the highest dose administered. No BMN 270-related

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changes in clinical observations or chemistry was observed in the monkey at doses up to 6E13 vg/kg, a 10-fold safety margin after 8-weeks. Overall, no BMN 270-related findings, except expected formation of anti-AAV5 antibodies, were observed at the highest administered doses of 6E13, 2E14 and 6E13 vg/kg in the normal mouse, disease model mouse and monkey, respectively.

Based on these key pre-clinical findings it can be suggested that the proposed starting dose of 6E12 vg/kg should not pose any risk or safety concerns to subjects with the best chance of benefiting the subject therapeutically.

8 STUDY OBJECTIVES

The primary objectives of the study are:

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

The secondary objectives of the study are:

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

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

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

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

- Cohort 1: 6E12 vector genomes [vg] per kilogram of body weight, given as a single intravenous dose (iv)
- Cohort 2: 2E13 vg per kilogram, iv
- Cohort 3: 6E13 vg per kilogram, iv
- Cohort 4: 4E13 vg per kilogram, iv

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

Cohorts 1-3

The first three cohorts will be enrolled sequentially, allowing a period of 3 weeks or more between cohorts. Dose escalation may occur after a single subject in a cohort has been safely dosed if the resulting FVIII activity at the Week 3 visit is < 5 IU/dL in both assays. Three weeks is expected to be the time the expression will be close to the maximum. This escalation paradigm is intended to minimize the subject numbers exposed to subtherapeutic doses. The decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and a panel of investigators participating in the study.

If the FVIII activity reaches ≥ 5 IU/dL at the Week 3 visit, then the remaining subjects in the cohort will be enrolled without the need to wait for 3 weeks between subjects.

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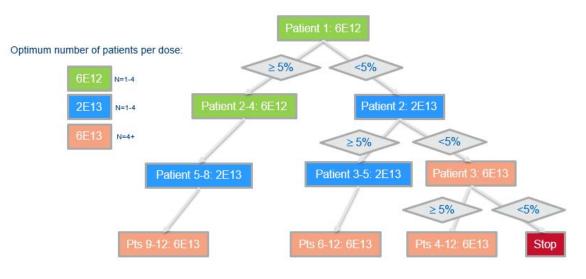


Figure 9.1.1: Flow Chart of Dose Escalation Scheme for Cohorts 1 to 3

Subject 1 (Cohort 1) will be dosed by intravenous infusion with 6E12 vg/kg of body weight. If the FVIII activity level does not reach 5 IU/dL or greater (expressed as % in Figure 9.1.1) at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 1 and enrollment into Cohort 2 will initiate with Subject 2 at the next dose (2E13 vg/kg).

If the FVIII activity level in the first subject treated in Cohort 2 does not reach \geq 5 IU/dL at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 2 and enrollment into Cohort 3 (6E13) will initiate with the next subject.

If the FVIII activity level in the first subject treated in Cohort 3 does not reach \geq 5 IU/dL at the Week 3 visit in both assays, then the DRB will recommend whether to continue to add subjects to the cohort and/or whether to continue the study.

For the first subject treated in each of the first 3 cohorts, if the activity level reaches \geq 5 IU/dL and no safety issue is found, then up to four subjects will be enrolled in the Cohort, though the adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

<u>Cohort 4</u>

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

There will be an ongoing review of individual patient safety and efficacy data by the medical monitor and the DRB. The adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

Because subjects develop neutralizing immunity upon exposure to the capsid, re-challenge of vector is not a likely treatment option and these subjects have effectively a single opportunity for therapy using this AAV capsid. Efficacy will be determined by FVIII activity at 16 weeks post dose. Safety will be evaluated for approximately 5 years after dosing. Any safety signal may trigger a review of the data and possible additional immunogenicity studies that include an assessment of cellular immune responses using collected peripheral blood mononuclear cells (PBMC). Additionally, if any of the events listed in Section 9.3.3.1 occur, enrollment into the trial will be halted to complete an extensive safety analysis. Notification of the study enrollment halt will be sent by the Sponsor to the participating sites via telephone and email immediately after becoming aware of a safety concern. This will ensure no additional subjects are dosed until the signal has been completely evaluated. If, following safety review by the Data Review Board (DRB) and the Sponsor, it is deemed appropriate to restart dosing, a request to restart dosing with pertinent data will be submitted to the health authority.

A summary of events and assessments are provided by visit in Table 9.1.1 for Screening, Baseline and BMN 270 Infusion, in Table 9.1.2 for Post-Infusion Follow-up, and in Table 9.1.3 and Table 9.1.4 for Safety Follow-up.

Table 9.1.5, dealing with the apeutic corticosteroid use in the event of elevated LFTs, is discussed in Section 9.4.8.2.

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Table 9.1.1: Schedule of Events – Screening and Infusion

	Prie	BMN 270		
Assessment	Screening ⁱ (Day -28 to Day -1)	Smart Rescreening ⁱ (Day -28 to Day -1)	Baseline (Day -7 to Day -1) ^h	Infusion Visit (Day 1) ^k
Informed consent	X			
Medical History	X			
Physical Exam ^a	Х		Х	X
Height and Weight ^a	Х			
Vital Signs	Х	X		X
Assessment of Adverse Events and Concomitant Medications	X	X	Х	X
Documentation of bleeding episodes and FVIII usage (by either subject or clinical information)	X	Х	Х	
Distribution of subject diaries and training in their use			Х	
Electrocardiogram	Х			
Chest X-ray	Х			
Liver Ultrasound	X			
hFVIII Assays ^b	X	X ^j		
AAV5 Assays ^c	Х	X		X
Screen for Hepatitis B, Hepatitis C, HIV ^d	Х			
Blood chemistry, haematology, coagulation screen, and CRP ^e	Х	X	Х	
Urine Tests ^e	X	Х	Х	
Liver Function Tests ^e	X	X	Х	
PBMC collection for CTL baseline			Х	
Von Willebrand Factor Antigen (VWF:Ag)	Х			
Direct Thrombin Test			Х	
PCR of vector DNA in blood, saliva, urine, semen, and stools			Х	

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	Pric	BMN 270		
Assessment	Screening ⁱ (Day -28 to Day -1)	Smart Rescreening ⁱ (Day -28 to Day -1)	Baseline (Day -7 to Day -1) ^h	Infusion Visit $(Day 1)^k$
Biomarker testing ^f	X			
Exploratory biomarker assessments ^g			Х	
Haemo-QoL-A Quality of Life (QoL) assessment			Х	
BMN 270 Infusion				Х

^a Complete physical examination should be done at Screening. Brief physical examination may be done at Baseline and at the BMN 270 Infusion Visit. Height will be recorded at Screening only. Weight will be recorded at Screening and then every 6 months thereafter.

^b Includes baseline hFVIII activity (chromogenic FXa and one-stage APTT assays), hFVIII coagulation activity exploratory assay, hFVIII inhibitor level (Bethesda assay with Nijmegen modification), hFVIII total antibody titer, and hFVIII antigen (ELISA).

^c Screening (done during Screening) and testing (at Infusion Visit) of AAV5 pre-existing immunity may include plasma samples for 3 assays (in vivo transduction inhibition, in vitro transduction inhibition and AAV5 total antibody assays). The assessment on the day of the infusion visit must be performed before the BMN 270 infusion is given.

^d Patients with documented negative results within the last 30 days do not need to be retested.

^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 function tests.

^f Includes HLA genotyping, FVIII genotyping, TNFα and IL10a single nucleotide polymorphisms.

^g Blood samples will be collected from subjects to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to Haemophilia A disease. The exploratory genetic/genomic testing on these samples is optional.

^h Should the screening visit occur within 7 days of the drug infusion, physical examination, blood chemistry, LFTs, haematology, urine tests, coagulation screen, and CRP do not need to be repeated at Baseline.

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

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

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^k Assessments on the day of infusion must be performed prior to the infusion. 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), following the infusion hourly (± 5 minutes) for 6 hours and then every 2 hours (± 15 minutes) for 6 hours and then at 4 hour intervals (± 15 minutes).

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

					F	ollow-l	Up Aft	er BM	IN 270	Admi	nistrat	tion – `	Weeks	*				
	,	Week	1															
Assessment	D2	D4	D8	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Physical exam ^a			Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)			Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Vital Signs			Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Blood chemistry, haematology, coagulation screen, and CRP^b				Х		Х		Х		Х		Х		Х				Х
Urine Tests ^b						Х				Х				Х				Х
Liver Function Tests (local) ^b		Х	Х	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX
FVIII assays (local) ^c		Х	Х	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX
Liver Function Tests (central) ^b		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
FVIII assays (central) ^d		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
FVIII antibody titer						X				Х				Х				Х
PCR of vector DNA in blood, saliva, urine, semen, and stools ^e	Х	Х	Х			X		Х		Х		Х		Х		Х		Х
Exploratory biomarker assessments ^f						Х				Х				Х				Х
Haemo-QoL-A QoL assessment			Х	Х	Х	Х												Х
AAV5 antibody titer										Х								Х
Testing for reactivation of hepatitis B and hepatitis C																		X ^g
PBMC collection						Х				Х				Х				Х
Von Willebrand Factor Antigen (VWF:Ag)						Х				Х				Х				Х
Direct Thrombin test			Х												Х			

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* Visit windows are \pm 48 hours (and include the Day 4 visit)

^a Brief physical examination should be done at all weekly visits except Week 16, where a complete physical examination should be performed. Refer to Section 9.7.8.5.
 ^b Refer to Table 9.7.8.2.1 for laboratory assessments to be included, and to Table 9.7.8.3.1 for liver function tests. LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data. Patients with persistent ALT > 1.5 ULN during the study and no other etiology identified may undergo additional evaluations (e.g., imaging studies including MRI or ultrasound, additional blood tests, and/or liver biopsy) at the discretion of the investigator.

^c Includes hFVIII activity level (APTT and FXa chromogenic 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. 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 Includes hFVIII activity level (APTT and FXa chromogenic assay), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, hFVIII coagulation activity exploratory assay, and hFVIII antigen (ELISA). 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. 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 Collection to occur on Day 2 and 4 following BMN 270 infusion, and then until at least 3 consecutive negative results are obtained.

- ^f Blood samples will be collected from subjects to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to Haemophilia A disease. The exploratory genetic/genomic testing on these samples is optional.
- ^g Testing for reactivation of hepatitis B and hepatitis C at Week 16 should be performed only in subjects who have not received therapeutic corticosteroids prior to Week 16; subjects who have received therapeutic corticosteroids will have hepatitis B and hepatitis C testing at the time points indicated in Table 9.1.5.



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

	Follow-Up After BMN 270 Administration – Weeks*															
Assessment	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
Physical exam ^a	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Weight										Х						
Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)	Х	X	Х	X	Х	Х	X	Х	Х	Х	Х	Х	Х	Х	Х	Х
Vital Signs	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Blood chemistry, haematology, coagulation screen, and CRP^b				X				Х				X				X
Urine Tests ^b				Х				Х				Х				Х
Liver Function Tests (local) ^b	XX	XX	XX	XX	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
FVIII assays (local) ^c	XX	XX	XX	XX	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Liver Function Tests (central) ^b	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
FVIII assays (central) ^d	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
FVIII antibody titer				Х								Х				
PCR of vector DNA in blood, saliva, urine, semen, and stools ^e				X				Х				X				X
Exploratory biomarker assessments ^f				Х				Х								
Haemo-QoL-A QoL assessment												Х				
AAV5 antibody titer				Х				Х				Х				Х
PBMC collection				Х				Х				Х				Х
Von Willebrand Factor Antigen (VWF:Ag)				Х				Х				Х				Х
Direct Thrombin test										Х						

* Visit windows are ± 48 hours

^a Brief physical examination should be done at all weekly visits. Refer to Section 9.7.8.5.

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^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 function tests. LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data. Patients with persistent ALT > 1.5 ULN during the study and no other etiology identified may undergo additional evaluations (e.g., imaging studies including MRI or ultrasound, additional blood tests, and/or liver biopsy) at the discretion of the investigator.

^c Includes hFVIII activity level (APTT and FXa chromogenic 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. 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 Includes hFVIII activity level (APTT and FXa chromogenic assay), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, hFVIII coagulation activity exploratory assay, and hFVIII antigen (ELISA). 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. 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.

^eCollection to occur until at least 3 consecutive negative results are obtained.

^f Blood samples will be collected from subjects to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to Haemophilia A disease. The exploratory genetic/genomic testing on these samples is optional.

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Table 9.1.4: Schedule of Events – Safety Follow-Up	
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		Year 1 – Weeks*						Years 2-5	ETV					
Assessment		34	35	36	38	40	42	44	46	48	50	52	Q3M	
Physical exam ^a	X	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Weight ^a												Х	X ^a	
Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)	X	Х	Х	Х	Х	X	X	X	X	Х	Х	Х	Х	Х
Vital Signs	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Blood chemistry, haematology, coagulation screen, and $CRP^{\rm b}$				Х		X		Х		Х		Х	Х	X
Urine Tests ^b				Х		Х		Х		Х		Х	Х	X
Liver Function Tests (local) ^b	X	Х	Х	Х	Х	X	X	X	Х	Х	Х	Х	Х	Х
FVIII assays (local) ^c	X	Х	Х	Х	Х	Х	Х	Х	X	Х	Х	Х	Х	Х
Liver Function Tests (central) ^b	X	Х	Х	Х	Х	X	Х	X	Х	Х	Х	Х	Х	Х
FVIII assays (central) ^d	X	Х	Х	Х	Х	X	Х	X	Х	Х	Х	Х	Х	Х
AAV5 antibody titer				Х		Х		Х		Х		Х	Х	X
FVIII antibody titer				Х				Х				Х	Х	X
PBMC Collection (for determination of FVIII and Capsid specific CTL activity)				Х				X				Х	Х	Х
Von Willebrand Factor Antigen (VWF:Ag)				Х		Х		Х		Х		Х	Х	X
Direct Thrombin Test					Х							Х	Х	X
PCR of vector DNA in blood, saliva, urine, semen, and stools ^e				Х		Х		Х		Х		Х		X

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	Haemo-QoL-A QoL assessment												Х	\mathbf{X}^{f}	Х
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^{*} Visit windows are \pm 48 hours through Week 36, then \pm 1 week until Week 52 and \pm 2 weeks for visits in Years 2-5.

^a Complete physical examination should be performed at Week 52 and every 52 weeks thereafter; brief physical exam may be performed at other study visits. Refer to Section 9.7.8.5. During Years 2-5, weight should be performed every 6 months.

^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 function tests. LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data. Patients with persistent ALT > 1.5 ULN during the study and no other etiology identified may undergo additional evaluations (e.g., imaging studies including MRI or ultrasound, additional blood tests, and/or liver biopsy) at the discretion of the investigator.

^c Includes hFVIII activity level (one-stage APTT and chromogenic FXa 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. 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 Includes hFVIII activity level (one-stage APTT and chromogenic FXa assay), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, hFVIII coagulation activity exploratory assay, and hFVIII antigen (ELISA). 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. 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 Sample testing during Safety Follow-Up is not required if at least 3 consecutive samples are cleared during the Post-Infusion Follow-Up period. Subjects who have not had 3 consecutive negative samples by Week 52 should continue to have PCR testing every 4 weeks until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor).

^f Haemo-QoL-A QoL assessment during Years 2-5 of Safety Follow-up should be performed at every other visit (every 6 months) starting with the Week 78 visit (ie, 26 weeks after the Week 52 visit at the end of Year 1 of the Safety Follow-up period).

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	Steroid Treatment Period ^d									Post-Steroid Period ^c						
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11 ^b	Week 1	Week 2	Week 3	Week 4	Week 13
Therapeutic corticosteroids (dose in mg/day) ^a	60 mg	60 mg	40 mg	40 mg	30 mg	30 mg	20 mg	20 mg	15 mg	10 mg	5 mg					
FVIII activity testing												Х	Х	Х	Х	
Liver function testing												Х	Х	Х	Х	
Hepatitis B testing						Х						Х				Х
HCV Viral Load						Х						Х				Х

Table 9.1.5: Schedule of Events – Therapeutic Corticosteroids

^a Therapeutic corticosteroids may be initiated when a subject's ALT value is≥ 1.5x ULN or based on review of FVIII and liver enzyme data after consultation between the Investigator and the Medical Monitor.

^b Following initiation or completion of steroid regimen, if ALT elevation $\geq 1.5x$ ULN is reported, steroid management decisions will based on discussions between the Investigator and Medical Monitor. Modification of the steroid regimen may take into consideration possible confounders for the ALT elevation and impact on FVIII expression.

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

^d Regardless of the assessments listed in the Schedule of Assessments (Table 9.1.2, Table 9.1.3, or Table 9.1.4), subjects initiated on corticosteroids will only be required to have laboratory evaluations on a weekly basis.

9.2 Discussion of Study Design, Including Choice of Control Group

Study 270-201 is designed to be a first-in-man, phase 1/2 open-label, dose escalation study in patients with severe haemophilia A. Four doses of BMN 270 will be evaluated and the dose escalation decision tree for Cohorts 1-3 is summarized in Figure 9.1.1.

The decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and the DRB.

There will be no control group. Parameters for each subject will be compared to a pre-treatment assessment of safety (liver function) and efficacy (number of bleeds, use of replacement therapy).

As AAV based treatment always leads to anti-capsid immune response, no true control group (for example with an empty AAV) is possible.

9.3 Selection of Study Population

Up to 15 severe haemophilia A patients may enroll into the study; the actual number of patients will depend on the criteria for dose escalation.

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 criteria:

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

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 immunity to the AAV5 capsid as measured by AAV5 transduction inhibition or AAV5 total antibodies
- 2. Any evidence of active infection or any immunosuppressive disorder.
- 3. HIV positive
- 4. Significant liver dysfunction as defined by abnormal elevation of:
 - ALT (alanine transaminase) to 3 times the upper limit of normal;
 - Bilirubin above 3 times the upper limit of normal;
 - Alkaline phosphatase above 3 times the upper limit of normal; or
 - INR (international normalized ratio) \geq 1.4.
- 5. Potential participants who have had a liver biopsy in the past 3 years are excluded if they had significant fibrosis of 3 or 4 as rated on a scale of 0-4
- 6. Evidence of any bleeding disorder not related to Haemophilia A
- 7. Platelet count of $< 100 \times 10^9/L$
- 8. Creatinine $\geq 1.5 \text{ mg/dL}$
- 9. Liver cirrhosis of any etiology as assessed by liver ultrasound
- 10. Hepatitis B if surface antigen is positive
- 11. Hepatitis C if RNA is positive
- 12. Treatment with any IP within 30 days prior to the end of the screening period
- 13. Any disease or condition at the physician's discretion that would prevent the patient from fully complying with the requirements of the study including possible corticosteroid treatment outlined in the protocol. The physician may exclude patients unwilling or unable to agree on not using alcohol for the 16-week period following the viral infusion.
- 14. Prior treatment with any gene transfer agent
- 15. Major surgery planned in the 16-week period following the viral infusion
- 16. Use of immunosuppressive agents or live vaccines within 30 days before the viral infusion

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.

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A subject's participation in the study may be discontinued at any time at the discretion 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.

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 admitted into the study or does not meet entry criteria
- Subject is lost to follow-up

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

The Investigator or designee must explain to each subject, before enrollment into the study, that for evaluation of study results, the subject's protected health information obtained during the study may be shared with the study Sponsor, regulatory agencies, and IRB/IEC/REB. It is the Investigator's (or designee's) responsibility to obtain written permission to use protected health information per country-specific regulations, such as the Health Insurance Portability and Accountability Act (HIPAA) in the US, from each subject. If permission to use protected health information is withdrawn, it is the Investigator's responsibility to obtain a written request, to ensure that no further data will be collected from the subject and the subject will be removed from the study.

9.3.3.1 Study Safety Evaluation Criteria

If any of the following events occur in a subject in the study who has received BMN 270 infusion, enrollment into the trial will be put on halt to complete an extensive safety analysis per Section 9.1.

• Any ALT elevation > 5x ULN for at least 2 consecutive weeks after administration of BMN 270, in the absence of a definitive alternate etiology for the increase

- The occurrence of Grade 3 or higher adverse events (excluding ALT elevation) assessed as related to study drug, including liver failure and clinical hepatitis
- The detection of neutralizing antibodies to hFVIII following BMN 270 infusion
- The detection of AAV vector DNA in the semen of a participant in 3 consecutive samples (which are at least 2 weeks apart) more than 52 weeks after BMN 270 infusion, as discussed in Section 9.7.8.5
- The occurrence of a malignancy excluding skin cancers at any point after BMN 270 infusion

If the following event occurs in a subject in the study who has received BMN 270 infusion, a DRB review and analysis of safety data will be undertaken to determine whether the enrollment into the trial will be put on halt:

• Grade 2 adverse event assessed as related to study drug that persists for at least 7 days

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 CRF pages. In legal jurisdictions where use of initials is not permitted, a substitute identifier will be used.

Subjects who withdraw from the study will not be replaced.

9.3.5 Duration of Subject Participation

The duration of this study will be approximately 264 weeks. This includes 4 weeks of screening, 1 day of BMN 270 infusion, 16 weeks of Post-Infusion Follow-Up, and 244 weeks of Safety Follow-Up. A primary endpoint analysis on safety and efficacy will be performed at 16 weeks.

9.4 Treatments

BioMarin or its designee will provide the study site with study drug sufficient for study completion. BioMarin is responsible for shipping study drug to clinical sites.

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.

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 2 mL polypropylene cryovial. Each vial contains 1.1 mL of AAV5-hFVIII-SQ at a concentration of 2E13 vector genomes per mL in a pH 7.4 phosphate buffer.

The study drug label includes the following information: lot number, required storage conditions, a precautionary statement, expiry date, study number, and BioMarin name and address. Labelling will be done according to country specific requirements.

9.4.3 Storage

At the study site, all IP must be stored under the conditions specified in the IB 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

After a physical exam performed by the PI or designee, participants will be admitted on the day of BMN 270 infusion. An IV catheter will be inserted into a suitable peripheral vein (e.g. 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. An electric syringe pump will be used to infuse through an in-line, low protein binding 0.22 micron filter. BMN 270 will be infused through the catheter using an appropriate infusion pump at a constant rate of 4 ml/min while monitoring the vital signs (pulse, blood pressure, respiration rate and temperature) at 15 minute (\pm 5 minutes) intervals. The anticipated maximum interval from initiation of thawing of BMN 270 to completion of the infusion is 4 hours, although the IP has been shown to be stable at room temperature for 6 hours.

Following completion of the infusion, vital signs will be monitored hourly (\pm 5 minutes) for 6 hours and then every 2 hours (\pm 15 minutes) for 6 hours and then at 4 hour intervals. If the vital signs are stable the catheter will be removed 20-24 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 24 hours to observe for any immediate toxicity of the procedure. After 24 hours, participants 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.

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 Sponsor will be required prior to enrollment of each study subject. Upon their enrollment into the study, subjects will be assigned a unique subject number and dose level by the Sponsor.

Cohorts 1 to 3 are enrolled serially and their dose is defined in Section 9.4.6.2 below. Escalation is based on FVIII activity 3 weeks after injection. Cohorts may receive the next higher dose if subjects in the previous cohort does not meet the activity criteria, or the same dose if subjects in the previous cohort meets the activity criteria. Subjects in Cohort 4 will all be enrolled at a single dose.

9.4.6 Selection of Doses Used in the Study

The starting dose was based on the expression of hFVIII observed in nonclinical studies of mice and monkeys. The starting dose has a significant safety margin (10-fold) from NOAEL in mice. The dose escalation is half-logs based.

9.4.6.1 Selection of Timing of Dose for Each Subject

A minimum of three weeks are required between subjects, to allow for evaluation of safety and expression of hFVIII. After three weeks, depending on the activity level, the choice of the dose for the next subject will be made as described below.

9.4.6.2 Selection of Dose for Each Subject

The starting dose was determined by expression of hFVIII observed in mice and monkeys and a scale up factor based on previous experience, an improved purification process over previous trials (thus potentially decreasing the risk of immune response), and a new evaluation of the titer (PCR performed after hairpin removal).

For Cohorts 1 to 3, approximately three weeks after an injection, the decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and the DRB.

Subject 1 (Cohort 1) will be dosed by intravenous infusion with 6E12 vg/kg of body weight. If the FVIII activity level does not reach 5 IU/dL or greater (expressed as % in Figure 9.1.1)

at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 1 and enrollment into Cohort 2 will initiate with Subject 2 at the next dose (2E13 vg/kg).

If the FVIII activity level in the first subject treated in Cohort 2 does not reach \geq 5 IU/dL at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 2 and enrollment into Cohort 3 (6E13) will initiate with the next subject.

If the FVIII activity level in the first subject treated in Cohort 3 does not reach \geq 5 IU/dL at the Week 3 visit in both assays, then the DRB will recommend whether to continue to add subjects to the cohort and/or whether to continue the study.

For the first subject treated in each of the first 3 cohorts, if the activity level reaches \geq 5 IU/dL and no safety issue is found, then up to four subjects will be enrolled in that cohort, though the adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

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

There will be an ongoing review of individual patient safety and efficacy data by the medical monitor and the DRB. The adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

Refer to Figure 9.1.1 for a visual representation of the study design for Cohorts 1-3

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 CRF. The Investigator may prescribe additional medications 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 CRF.

The following medications are prohibited starting 30 days before Screening:

- Live vaccines
- Systemic immunosuppressive agents

Medications which are predominately metabolized by the liver (e.g., acetaminophen) and alcohol should, whenever possible, be avoided for the first 52 weeks of the study, and particularly within 48 hours prior to lab work.

9.4.8.1 Concomitant Haemophilia Treatments

Subjects on "on demand" therapy for FVIII will continue their treatment at will. Subjects on prophylactic FVIII therapy will discontinue their treatment starting the day of infusion and switch to an "on demand" schedule. FVIII can always be taken as needed by the subject, who will carefully record his treatment and bleeding episodes in his diary. In addition, information on FVIII usage by medical history will be collected (if available) from subjects for the 6 month period immediately preceding study enrollment.

9.4.8.2 Glucocorticoid Treatment of Elevated Hepatic Transaminases

During the Post-Infusion Follow-up Period and the Safety Follow-Up Period, each subject will have comprehensive surveillance plan monitoring of LFTs (at local labs, twice per week for Weeks 1-20, then once per week from Week 21-36, and then once every 2 weeks from Week 37-52). LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.

9.4.8.2.1 Therapeutic Corticosteroids

In general, therapeutic corticosteroids may be initiated when a subject's ALT value is $\geq 1.5x$ ULN, or based on review of FVIII and liver enzyme data after consultation between the Medical Monitor and the Investigator.

Reports of raised LFTs (defined as $ALT \ge 1.5x$ ULN) should be made to the BioMarin medical monitor within 30 minutes of the lab value being available. Local laboratory results of LFTs will be used to trigger corticosteroid treatment as needed. In case of discrepant results between local and central laboratories, the Investigator and Medical Monitor will decide further action.

Following initiation or completion of the rapeutic corticosteroids, if ALT elevation $\geq 1.5x$ ULN is reported, steroid management decisions will based on discussions between the

Investigator and Medical Monitor. Modification of the steroid regimen may take into consideration possible confounders for the ALT elevation and impact on FVIII expression.

Treatment with prednisolone will be initiated at a dose of 60 mg per day and then gradually tapered (60 mg daily for the first 2 weeks, then 40 mg the next 2 weeks, then 30 mg the next two weeks, then 20 mg the next two weeks, then 15 mg for the next week, then 10 mg for the next week, then 5 mg for the next week, then stop, for a total treatment of 11 weeks) (refer to Table 9.1.5).

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

Management and monitoring of reactions to corticosteroids should be determined by the Investigator's clinical judgment in consultation with the Sponsor's Medical Monitor. This includes the contraindicated use of NSAIDs during corticosteroid treatment, and specific monitoring not already covered by the schedule of events. Hepatitis B status and HCV viral load will be rechecked 6 weeks after the start of corticosteroid treatment, and then 1 week and 13 weeks after the completion of corticosteroid treatment. All adverse events should be reported as outlined in Section 10 of the protocol.

9.4.9 Treatment Compliance

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

9.5 Investigational Product Accountability

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

9.5.1 Return and Disposition of Clinical Supplies

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

Unused study drug may be destroyed on site, per the site's standard operating procedures, but only after BioMarin has granted approval for drug destruction. The monitor must account for all study drug in a formal reconciliation process prior to study drug destruction. All study

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drug destroyed on site must be documented. Documentation must be provided to BioMarin and retained in the Investigator study files. If a site is unable to destroy study drug appropriately, the site can return unused study drug to BioMarin upon request. The return of study drug or study drug materials must be accounted for on a Study Drug Return Form provided by BioMarin.

All study drug and related materials should be stored, inventoried, reconciled, and destroyed or returned according to applicable state and federal regulations and study procedures.

9.6 Dietary or Other Protocol Restrictions

There are no dietary or other protocol restrictions for this study.

9.7 Safety and Efficacy Variables

As this is a first-in-man study, the primary endpoint of safety will be assessed as explained in Section 9.7.8.

The primary efficacy measure will be to assess plasma FVIII activity. The efficacy goal of the study is to establish the dose relationship to FVIII activity \geq 5 IU/dL at 16 weeks post BMN 270 administration.

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

The primary efficacy measure will be the plasma FVIII activity monitored on a regular basis after BMN 270 dose. The efficacy goal of the protocol is to ascertain the dose range of BMN 270 required to convert severe HA patients to expression of FVIII at 5 IU/dL or above, i.e., a mild severity. This is associated in natural history studies with clinically superior long term outcomes (Den Ujil, 2011, Haemophilia).

The following assays (assessed by the central laboratory) will be used to measure the primary efficacy variable:

- FVIII activity (chromogenic FXa assay)
- FVIII activity by one-stage APTT (Activated Partial Thromboplastin Time)

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 FVIII activity level in both assays and the number of subjects with FVIII activity ≥ 5 IU/dL in at least one of the two assays will be summarized.

FVIII activity assays will also be performed at the local laboratory at the time points indicated in Table 9.1.2, Table 9.1.3, and Table 9.1.4, but will be used in conjunction with local lab LFT assessments to monitor subject safety and need for initiation of therapeutic corticosteroid dosing; local laboratory FVIII activity assessments will not be used to assess efficacy or to measure the primary efficacy outcome of the study.

Timing of assessment by these assays is provided in Table 9.1.2, Table 9.1.3, and Table 9.1.4. Details on performing the assays are included in the Laboratory Manual.

9.7.3 Secondary Efficacy Variables

Secondary efficacy measures will be the reduction in the frequency of factor replacement therapy, and reduction in the number of bleeding episodes. 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.

9.7.4 Immunogenicity

Immunogenicity assays will be performed on plasma. The assays will include detection of anti-capsid, and anti-FVIII total antibody, and determination of neutralizing antibodies against FVIII. Any increase in total antibody level, especially during the time period of 5-12 weeks, will be compared with FVIII activity measurements. Any abnormality of the liver parameters will lead to a retrospective immunogenicity assessment to determine anti-FVIII and capsid specific CTL. Anti-FVIII and capsid specific CTL assays will be performed on collected PBMCs.

Timing of assessment by these assays is provided in Table 9.1.2, Table 9.1.3, and Table 9.1.4.

9.7.5 Pharmacodynamics

The hFVIII antigen and activity level will be measured by an ELISA (antigen) and by one-stage APTT and/or chromogenic FXa assay (activity). Individual antigen and activity plasma plots will be prepared to assess changes over 16 weeks. FVIII activity measurements will be used to determine PD parameters.

If supported by FVIII activity data, non-compartmental analysis and observation will be used to estimate individual values of C_b (baseline concentration), C_{ss} (steady state concentration), T_{ss} (time to steady state), C(t) and AUC(0-t) where t is 16 weeks. Other parameters that may Proprietary and Confidential 2 September 2016

be used to describe individual FVIII protein and activity plasma profiles are C_{max} (maximum concentration) and C_{avg} (average concentration, AUC(0-t)/t). The PD parameters and dose will be used to assess clinical pharmacology.

Sample collection times are indicated in Table 9.1.2, Table 9.1.3, and Table 9.1.4.

9.7.6 Exploratory Biomarker Assessments

Blood samples will be collected from subjects at the time points indicated in Table 9.1.1, Table 9.1.2, Table 9.1.3, and Table 9.1.4 to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to Haemophilia A disease. The exploratory genetic/genomic testing is optional.

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 may be used for exploratory use once the primary use has been completed.

9.7.7 Haemo-QoL-A Quality of Life Assessment

The Haemo-QoL-A is a patient-reported outcome (PRO) questionnaire which will be used to assess subject quality of life (QoL) during the study. Assessments will occur at the time points listed in the Schedules of Assessments.

Details regarding the QoL assessment will be included in the Study Reference Manual.

9.7.8 Safety Variables

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

9.7.8.1 Adverse Events

The occurrence of AEs will be assessed continuously from the time the subject signs the ICF. The determination, evaluation and reporting of AEs will be performed as outlined in Section 10. Assessments of AEs will occur at the time points shown in Table 9.1.1, Table 9.1.2, Table 9.1.3, and Table 9.1.4.

9.7.8.2 Clinical Laboratory Assessments

Specific visits for obtaining clinical laboratory assessment samples are provided in Table 9.1.1, Table 9.1.2, Table 9.1.3, and Table 9.1.4. The scheduled clinical laboratory tests

are listed in Table 9.7.8.2.1. Refer to the Study Reference Manual 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 the cause of the abnormality is determined, the value returns to baseline or to within normal limits, or 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 CRF.

Blood Chemistry	Haematology	Urine Tests	Other
Albumin	Haemoglobin	Appearance	CRP
BUN	Haematocrit	Color	
Calcium	WBC count	pН	Coagulation Screen including:
Chloride	RBC count	Specific gravity	APTT
Total cholesterol	Platelet count	Ketones	PT/INR
CO ₂	Differential cell count	Protein	TT
СРК		Glucose	
Creatinine		Bilirubin	
Glucose		Nitrite	
Phosphorus		Urobilinogen	
Potassium		Haemoglobin	
Total protein			
Sodium			
Uric Acid			

 Table 9.7.8.2.1: Clinical Laboratory Tests

BUN, blood urea nitrogen; CO₂, carbon dioxide; 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.

9.7.8.3 Liver Function and Hepatitis Testing

Subjects will be screened for evidence of previous hepatitis B or hepatitis C infection at Screening. Subjects with documented results showing an absence of active Hepatitis B or Hepatitis C infection (as measured by positive surface antigen for hepatitis B or positive RNA testing for hepatitis C) 30 days prior to providing signed informed consent do not need to be screened again.

Evidence of ongoing Hepatitis B or Hepatitis C infection is exclusionary. Subjects who have cleared a Hepatitis B infection or are seronegative do not need to receive the Hepatitis B vaccination.

Subjects will be tested for hepatitis B and hepatitis C reactivation at Week 16. Subjects who receive therapeutic corticosteroids prior to Week 16 do not need to complete the Week 16 reactivation assessment; instead, they will be tested for hepatitis B and hepatitis C reactivation at the time points listed in Table 9.1.5.

A liver ultrasound and liver function testing at Screening will identify any significant hepatic dysfunction, which is defined as:

- More than 3x the normal ALT level
- More than 3x the normal bilirubin level
- More than 3x the normal Alkaline phosphatase level.
- INR \geq 1.4.
- Thrombocytopoenia under $100 \ge 10^9/L$
- Liver ultrasound results indicative of a liver cirrhosis

Liver function tests will be monitored on a regular basis, at the time points indicated in Table 9.1.1, Table 9.1.2, Table 9.1.3, and Table 9.1.4. At each time point, the following LFTs should be assessed:

 Table 9.7.8.3.1: Liver Function Tests

Liver Function Tests								
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

Patients with persistent ALT > 1.5 ULN during the study and no other etiology identified may undergo additional evaluations (e.g., imaging studies including MRI or ultrasound, additional blood tests, and/or liver biopsy) at the discretion of the investigator.

9.7.8.4 HIV Testing

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

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

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

Systolic blood pressure, diastolic blood pressure, heart rate, respiration rate, and temperature will be assessed at Screening, Baseline, and at the beginning of each visit during the Post-Infusion Follow-Up and Safety Follow-Up periods. On the day of the BMN 270 Infusion, vital signs will be monitored prior to infusion, during the infusion every 15 minutes (\pm 5 minutes), following the infusion hourly (\pm 5 minutes) for 6 hours and then every 2 hours (\pm 15 minutes) for 6 hours and then at 4 hour intervals (\pm 15 minutes).

A complete physical examination is necessary during Screening/Baseline, at Week 16 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, respiratory, neurologic, and gastrointestinal assessments.

Height will be recorded at Screening only. Weight will be recorded at Screening and then every 6 months thereafter.

9.7.8.6 Vector Shedding

Vector shedding has been extensively studied in all similar clinical trials performed to date. (Nathwani, 2014, N.Engl.J.Med.); (Manno, 2006, Nat.Med.); (Schenk-Braat, 2007, J.Gene Med.); (Croteau, 2004, Ann.Occup.Hyg.). In the literature referenced above, including Haemophilia B clinical studies utilizing AAV2 and AAV8, vector was no longer detectable

after 40 days in blood, saliva, urine or stool, but in one study was detected in the seminal fluid but not in motile sperm (Manno, 2006, Nat.Med.). In these studies, the amount of vector present in these bodily fluids involved an extremely small fraction of the infused dose. More recent data from an ongoing AAV-FIX study demonstrates persistence of the vector in both the blood and the semen for at least 39 weeks (Miesbach, 2016, Haemophilia).

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 PCR at the time points indicated in Table 9.1.2, Table 9.1.3, and Table 9.1.4. Fluids tested will include:

- Blood
- Saliva
- Semen
- Urine
- Stool

Vector shedding will also be extensively studied in the present clinical trial, every other week between Weeks 4-16, then every 4 weeks to Week 52 until at least 3 consecutive negative results are obtained. Subjects who have not had 3 consecutive negative samples by Week 52 should continue to have PCR testing every 4 weeks until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor).

Contraception use may need to be extended beyond 26 weeks in individual subjects based on observed vector shedding in semen. After 6 months, subjects may stop contraception use only if they have had 3 consecutive negative semen samples.

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 haematology, 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, a reportable adverse event (AE) is any untoward medical occurrence (e.g., sign, symptom, illness, disease or injury) in a subject administered the study-drug or other protocol-imposed intervention, regardless of attribution. This includes the following:

- AEs not previously observed in the subject that emerge during the course of the study.
- Pre-existing medical conditions judged by the Investigator to have worsened in severity or frequency or changed in character during the study.
- Complications that occur as a result of non-drug protocol-imposed interventions (eg, AEs related to screening procedures).

An adverse drug reaction is any AE for which there is a reasonable possibility that the study-drug caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the study-drug and the AE.

Bleeding events that are normal events of haemophilia (ie, bleeding events which occur only because the subject is a haemophiliac) should not be recorded as AEs but will instead be captured in subject diaries. Bleeding events that occur where a normal (ie, non-haemophiliac) patient would bleed, such as bleeding as a result of major trauma, should be recorded as adverse events. All bleeding events which meet criteria for being serious should be reported as serious adverse events (SAEs) whether or not they are bleeding events that are normal sequelae of haemophilia.

Whenever possible, it is preferable to record a diagnosis as the AE term rather than a series of terms relating to a diagnosis.

10.2 Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that at any dose meets 1 or more of the following criteria:

- Is fatal
- Is life threatening

Note: Life-threatening refers to an event that places the subject at immediate risk of death. This definition does not include a reaction that, had it occurred in a more severe form, might have caused death.

- Requires or prolongs inpatient hospitalization.
- 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 intervention to prevent one of the above consequences (e.g. anaphylaxis)

All adverse events that do not meet any of the criteria for SAEs should be regarded as nonserious AEs.

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 liver enzymes (ALT) that triggers an initiation or modification of corticosteroid treatment

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 treatment, only SAEs associated with any protocol-imposed interventions will be reported. After informed consent is obtained and the first administration of study drug, the reporting period for all non-serious AEs and SAEs begins and continues for approximately 5 years or until study discontinuation/termination, whichever is longer. The criteria for determining, and the reporting of SAEs is provided in Section 10.2.

10.3.2 Eliciting Adverse Events

Investigators will seek information on AEs, SAEs, and EOSI at each subject contact by specific questioning and, as appropriate, by examination. Information on all AEs and SAEs and EOSI, should be recorded in the subject's medical record and on the 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 severity of each will be assessed using the defined categories in Table 10.3.3.2.1.

The Investigator will determine the severity of each AE and SAE and EOSI using the NCI CTCAE v4. 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 as stated below.

Table 10.3.3.2.1: Adverse Event Grading (Severity) Scale

Grade	Description	
1	Mild: asymptomatic or mild symptoms; clinical or diagnostic observation indicated	ns only; intervention not
2	Moderate: minimal, local or noninvasive intervention indicated; limiting instrumental activities of daily living (ADL) ^a	age-appropriate
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 or debilitating: consequences; urgent intervention indicated	Grade 4 and 5 AEs should always be
5	Death related to AE	reported as SAEs

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

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

10.3.3.3 Causality

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



Table 10.3.3.3.1: Causality Attribution Guidance

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

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

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

The investigator's assessment of causality for individual AE reports is part of the study documentation process. Regardless of the Investigator's assessment of causality for individual AE reports, the Sponsor will promptly evaluate all reported SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators and applicable regulatory authorities.

10.4 Procedures for Recording Adverse Events

10.4.1 Recording Adverse Events on a eCRF

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

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

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

10.4.1.1 Diagnosis versus Signs and Symptoms

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 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 haemorrhage 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.

10.4.1.4 Abnormal Laboratory Values

Laboratory test results will be recorded on the laboratory results pages of the AE 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 should be reported as such, in addition to being recorded as an AE in the AE eCRF.

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

- Accompanied by clinical symptoms
- Leading to a change in study medication (e.g. dose modification, interruption or permanent discontinuation)
- Requiring a change in concomitant therapy (e.g. 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 hFVIII activity should not be reported as adverse events unless signs of worsening are observed.

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 document 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 changed
- Hospitalization solely for the purpose of insertion of an in-dwelling IV catheter (such as a Port-a-Cath or other brand) for administration of study drug will not be considered an SAE.
- 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 partner should be reported within 24 hours of the site becoming aware of the pregnancy by entering the information on the Pregnancy eCRF and submitting to BPV within 24 hours of the site becoming aware of the event. The Investigator must make every effort to follow the subject's partner through resolution of the pregnancy (delivery or termination) and to report the resolution on the Pregnancy Follow-up Form in the study reference materials. 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.

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

If the EDC is unavailable, all SAEs should be reported to BPV by completing the SAE Report Form and faxing or emailing the completed form to BPV within 24 hours of the site

becoming aware of the event. Once the EDC is available, the information should be entered in the AE eCRF.

10.5.2 Ethics Committee Reporting Requirements

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

10.6 Follow-up of Subjects after Adverse Events

The Investigator should follow all unresolved AEs and SAEs until the events are resolved or have stabilized, the subject is lost to follow-up, or it has been determined that the study treatment or participation is not the cause of the AE/SAE. Resolution of AEs and SAEs (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, 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 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 treatment.

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 treatment. 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

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investigational medicinal product where that new event is likely to affect the safety of the patients, the Sponsor and the Investigator shall take appropriate urgent safety measures to protect the patients against any immediate hazard. The Sponsor shall forthwith inform the competent authorities of those new events and the measures taken and shall ensure that the IRB/IEC/REB is notified at the same time."

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

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

- Immediate need to revise the IP administration (eg, modified dose amount or frequency not defined in protocol)
- 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	
Address:	105 Dig	ital 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 FXa assay and the APTT assays 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 will be performed within 28 days (\pm 14 days) of BMN 270 infusion while baseline assessments will take place within 7 days of BMN 270 infusion (Day 1). Should the screening visit occur within 7 days of the drug infusion, physical examination, vital signs, blood chemistry, LFTs, haematology, urine tests, coagulation screen, and CRP do not need to be repeated at Baseline.

The following procedures will be performed during the Screening Period:

- Full medical history, including haemophilia A history, Hepatitis B, Hepatitis C, and HIV.
- Complete Physical Exam
- 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)
- Electrocardiogram
- Chest X-ray
- Liver Ultrasound
- Samples for hFVIII Assays
 - Baseline hFVIII activity chromogenic FXa (plasma)
 - Baseline hFVIII activity level one-stage APTT assay
 - o hFVIII coagulation activity exploratory assay
 - o hFVIII inhibitor level (Bethesda assay with Nijmegen modification)
 - hFVIII total antibody assay
 - hFVIII antigen (ELISA)



- Blood sample for AAV5 Assays
 - o AAV5 antibody titer
 - AAV5 transduction inhibition assay
- Screen for Hepatitis B, Hepatitis C, and HIV if required (subjects with documented negative results 30 days prior to informed consent being obtained do not need to be retested)
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- Urine Tests (refer to Table 9.7.8.2.1)
- Liver Function Tests (refer to Table 9.7.8.3.1)
- Von Willebrand Factor Antigen (VWF:Ag)
- Blood samples for Biomarker testing (including HLA genotyping, FVIII genotyping status, TNFα and IL10a single nucleotide polymorphisms)

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 sample for AAV5 Assays
 - AAV5 antibody titer
 - AAV5 transduction inhibition assay
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.8.2.1)

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

12.3 Baseline Visit

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

- Physical exam
- Assessment of Adverse Events and Concomitant Medications
- Documentation of bleeding episodes and FVIII usage (by either subject or clinical information)
- Distribution of subject diaries and training in diary completion
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- Urine Tests (refer to Table 9.7.8.2.1)
- Liver Function Tests (refer to Table 9.7.8.3.1)
- PBMC collection for CTL baseline
- Direct Thrombin test
- PCR of vector DNA in blood, saliva, urine, semen, and stools
- Exploratory biomarker assessments
- Haemo-QoL-A QoL assessment

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 24 hours for the BMN 270 Infusion Visit. The following procedures will be performed during the BMN 270 Infusion Visit:

- Physical exam
- Assessment of Adverse Events and Concomitant Medications
- Blood sample for AAV5 Assays (must be performed before the BMN 270 infusion)
 - o AAV5 antibody titer
 - AAV5 transduction inhibition assay
- BMN 270 Infusion
- Vital Signs

Vital signs will be recorded prior to BMN 270 infusion and then every 15 minutes (± 5 minutes) during BMN 270 infusion. Following infusion, vital signs will be monitored every 1 hour (± 5 minutes) for the first 6 hours, every 2 hours (± 15 minutes) for the next 6 hours, and then at 4 hour (± 15 minutes) intervals for the remainder of the subject's stay in the clinic.

12.5 BMN 270 Infusion Follow-Up Visits

After BMN 270 has been infused, subjects will return to the study site every week $(\pm 48 \text{ hours})$ for 16 weeks, when the following procedures will be completed:

12.5.1 Once per week (Weeks 1 through 16)

The following procedures will be performed at one visit per week from Weeks 1 through 16:

- Physical exam
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Vital Signs
- Liver Function Tests (refer to Table 9.7.8.3.1) central laboratory assessment
 - LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- Samples for FVIII Assays central laboratory assessment
 - FVIII activity level (APTT)
 - FVIII activity level (chromogenic FXa assay)
 - FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level
 - o FVIII antigen (ELISA)

Note: 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.

• Central assessment of FVIII activity level should be performed 1x/week from Week 1 through Week 16

12.5.2 Twice per week (Weeks 1 through 16)

The following procedures will be performed twice per week from Weeks 1 through 16:

- Liver Function Tests (refer to Table 9.7.8.3.1) local laboratory assessment
 - Local assessment of liver function tests should be performed on Day 8 during Week 1, and then 2x/week from Week 2 through Week 16
 - LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII activity level local laboratory assessment
 - FVIII activity level (APTT)
 - FVIII activity level (chromogenic FXa assay)
 - Local assessment of FVIII activity level should be performed on Day 8 during Week 1, and then 2x/week from Week 2 through Week 16

12.5.3 Week 1 – Day 2 and Day 4

On Day 2 and Day 4 of Week 1, the following procedures will be performed:

- PCR of vector DNA in blood, saliva, urine, semen, and stools (Day 2 and Day 4)
- Samples for FVIII Assays (Day 4 only) central laboratory assessment
 - FVIII activity level (APTT)
 - FVIII activity level (chromogenic FXa assay)
 - FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level
 - FVIII antigen (ELISA)

Note: 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.

- Liver Function Tests (refer to Table 9.7.8.3.1) (Day 4 only) central laboratory assessment
- Liver Function Tests (refer to Table 9.7.8.3.1) (Day 4 only) local laboratory assessment
- FVIII activity level (Day 4 only) local laboratory assessment
 - FVIII activity level (APTT)

• FVIII activity level (chromogenic FXa assay)

12.5.4 Week 1 – Day 8

On Day 8, the following procedures will be performed:

- PCR of vector DNA in blood, saliva, urine, semen, and stools
- Direct Thrombin test
- Haemo-QoL-A QoL assessment

12.5.5 Every 2 Weeks

Every 2 weeks (Weeks 2, 4, 6, 8, 10, 12, 14 and 16), the following procedures will be performed:

- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.8.2.1) (not assessed at Week 14)
- PCR of vector DNA in blood, saliva, urine, semen, and stools (not collected at Week 2)
 - Collection to occur until at least 3 consecutive negative results are obtained

12.5.6 Weeks 4, 8, 12, and 16

At Weeks 4, 8, 12, and 16, the following procedure will be performed:

- PBMC collection
- Urine Tests (refer to Table 9.7.8.2.1)
- VWF:Ag
- FVIII antibody titer
- Exploratory biomarker assessments

12.5.7 Week 16

At Week 16, the following procedure will be performed:

- Test for Hepatitis B and Hepatitis C reactivation
 - Subjects will be tested for hepatitis B and hepatitis C reactivation at Week 16. Subjects who receive therapeutic corticosteroids prior to Week 16 do not need to complete the Week 16 reactivation assessment; instead, they will be tested for hepatitis B and hepatitis C reactivation at the time points listed in Table 9.1.5.

12.5.8 Weeks 8 and 16

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

• AAV5 antibody titer

12.5.9 Weeks 2, 3, 4, and 16

At Weeks 2, 3, 4, and 16, the following procedure will be performed:

• Haemo-QoL-A QoL assessment

12.5.10Week 13

At Week 13, the following procedure will be performed:

• Direct Thrombin test

12.6 Safety Follow-Up – Weeks 17-36

After the Post-Infusion Follow-Up visits are complete, subjects will return to the study site for Safety Follow-Up visits from Weeks 17 through Week 36 (\pm 48 hours), when the following procedures will be completed:

12.6.1 Once per week (Weeks 17 through 36)

Once per week from Week 17 through Week 36, the following procedures will be performed:

- Physical exam
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Vital Signs
- Liver Function Tests (refer to Table 9.7.8.3.1) central laboratory assessment
 - LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII Assays central laboratory assessment
 - FVIII activity level (APTT)
 - FVIII activity level (chromogenic FXa assay)
 - FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - FVIII antigen (ELISA)

Note: 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.

12.6.2 Twice per week (Weeks 17 through 20)

Twice per week from Week 17 through Week 20, the following procedures will be performed:

- Liver Function Tests (refer to Table 9.7.8.3.1) local laboratory assessment
 - LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII activity level local laboratory assessment
 - FVIII activity level (APTT)
 - FVIII activity level (chromogenic FXa assay)

12.6.3 Once per week (Weeks 21 through 36)

Once per week from Week 21 through Week 36, the following procedures will be performed:

- Liver Function Tests (refer to Table 9.7.8.3.1) local laboratory assessment
 - LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII activity level local laboratory assessment
 - FVIII activity level (APTT)
 - FVIII activity level (chromogenic FXa assay)

12.6.4 Every 4 Weeks

Every 4 weeks (Weeks 20, 24, 28, 32, and 36), the following procedures will be performed:

- Exploratory biomarker assessments (Weeks 20 and 24 only)
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- Urine Tests (refer to Table 9.7.8.2.1)
- VWF:Ag
- AAV5 antibody titer
- PBMC collection
- PCR of vector DNA in blood, saliva, urine, semen, and stools

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Sample testing during Safety Follow-Up is not required if at least
 3 consecutive samples are clear during the Post-Infusion Follow-Up period.

12.6.5 Every 8 Weeks

Every 8 weeks (Weeks 20, 28, and 36), the following procedure will be performed:

• FVIII antibody titer

12.6.6 Week 26

At Week 26, the following procedure will be performed:

- Direct Thrombin test
- Weight

12.6.7 Weeks 28

At Week 28, the following procedure will be performed:

• Haemo-QoL-A QoL assessment

12.7 Safety Follow-Up – Weeks 37-52

Subjects will return every 2 weeks (Week 38, 40, 42, 44, 46, 48, 50, and 52) from Week $37-52 (\pm 1 \text{ week})$, when the following procedures will be completed:

12.7.1 Once per visit

At Weeks 38, 40, 42, 44, 46, 48, 50, and 52, the following procedures will be performed:

- Physical exam
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Vital Signs
- Liver Function Tests (refer to Table 9.7.8.3.1) local laboratory assessment
 - LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII activity level local laboratory assessment
 - FVIII activity level (APTT)
 - FVIII activity level (chromogenic FXa assay)
- Liver Function Tests (refer to Table 9.7.8.3.1) central laboratory assessment

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- LFTs may be monitored more or less frequently based (and in particular when ALT values are >1.5x ULN) on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII Assays central laboratory assessment
 - FVIII activity level (APTT)
 - FVIII activity level (chromogenic FXa assay)
 - o FVIII coagulation activity exploratory assay
 - Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - FVIII antigen (ELISA)

Note: 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.

12.7.2 Every 4 Weeks

Every 4 weeks (Weeks 40, 44, 48, and 52), the following procedures will be performed:

- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- Urine Tests (refer to Table 9.7.8.2.1)
- AAV5 antibody titer
- VWF:Ag
- PCR of vector DNA in blood, saliva, urine, semen, and stools
 - Sample testing during Safety Follow-Up is not required if at least 3 consecutive samples are clear during the Post-Infusion Follow-Up period. Subjects who have not had 3 consecutive negative samples by Week 52 should continue to have PCR testing every 4 weeks until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor).

12.7.3 Every 8 Weeks

Every 8 weeks (Weeks 44 and 52), the following procedure will be performed:

- PBMC collection
- FVIII antibody titer

12.7.4 Week 38 and 52

At Week 38 and Week 52, the following procedure will be performed:

• Direct Thrombin test

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12.7.5 Week 52

At Week 52, the following procedure will be performed:

- Haemo-QoL-A QoL assessment
- Weight

12.8 Safety Follow-Up – Years 2-5

During Years 2-5 of Safety Follow-up, subjects will be assessed every 3 months (\pm 2 weeks). At these times, the following procedures will be completed:

12.8.1 Every Visit

Every 3 months (\pm 2 weeks), the following procedures will be performed:

- Physical exam
 - Complete Physical Exam will be performed every 52 weeks; Brief Physical Exams may be performed at other visits.
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Vital Signs
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- Urine Tests (refer to Table 9.7.8.2.1)
- Liver Function Tests (refer to Table 9.7.8.3.1) local laboratory assessment
 - LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII activity level local laboratory assessment
 - FVIII activity level (APTT)
 - FVIII activity level (chromogenic FXa assay)
- Liver Function Tests (refer to Table 9.7.8.3.1) central laboratory assessment
 - LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.
- FVIII Assays central laboratory assessment
 - FVIII activity level (APTT)
 - FVIII activity level (FXa chromogenic assay)

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- o FVIII coagulation activity exploratory assay
- Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
- FVIII antigen (ELISA)

Note: 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.

- AAV5 antibody titer
- FVIII antibody titer
- PBMC collection
- VWF:Ag
- Direct Thrombin test

12.8.2 Every Other Visit (Every 6 Months)

Every six months starting at the Week 78 visit (ie, 26 weeks after the Week 52 visit at the end of Year 1 of the Safety Follow-up period), the following procedure will be performed:

- Haemo-QoL-A QOL assessment
- Weight

12.9 Early Termination Visit

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

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

- Physical exam
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Vital Signs
- Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- Urine Tests (refer to Table 9.7.8.2.1)
- Liver Function Tests (refer to Table 9.7.8.3.1) local laboratory assessment
- FVIII activity level local laboratory assessment

- FVIII activity level (APTT)
- FVIII activity level (chromogenic FXa assay)
- Liver Function Tests (refer to Table 9.7.8.3.1) central laboratory assessment
- FVIII Assays central laboratory assessment
 - FVIII activity level (APTT)
 - FVIII activity level (chromogenic FXa assay)
 - FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - FVIII antigen (ELISA)

Note: 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.

- AAV5 antibody titer
- FVIII antibody titer
- PBMC collection
- VWF:Ag
- Direct Thrombin test
- PCR of vector DNA in blood, saliva, urine, semen, and stools
 - Sample testing at the ETV is not required if at least 3 consecutive samples are clear during the Post-Infusion Follow-Up period.
- Haemo-QoL-A QOL assessment

12.10 End of Study

The study will end after the last subject completes the last Safety Follow-Up visit (Week 260). 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, any applicable randomization procedures, source document requirements, eCRFs, monitoring requirements, and procedures for reporting AEs, including SAEs.

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

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

14 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

14.1 Statistical and Analytical Plans

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

14.1.1 Interim Analyses

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

14.1.2 Procedures for Accounting for Missing, Unused and Spurious Data

Missing data will not be imputed.

14.2 Primary and Secondary Efficacy Analysis

The subjects will be followed in a longitudinal manner and all the relevant information will be collected. The analysis of the data will be descriptive in nature. Descriptive statistics include the number of subjects, mean, median, standard deviation, minimum, and maximum for continuous variables and count and percent for categorical variables. Efficacy variables will be summarized by dose cohort at each time point. Relationship between dose and efficacy results will be examined.

Data collected in a longitudinal manner may be analyzed using longitudinal methods such as mixed effect model which takes into account the correlation among the observation taken at various time points within a participant. Efficacy is a secondary endpoint, defined as biologically active hFVIII at ≥ 5 IU/dL by chromogenic FXa and/or one-stage APTT assay as measured by the central laboratory at 16 weeks following study treatment. hFVIII activity will be assessed weekly during the study period. We can only assess the true steady state of hFVIII protein produced from BMN 270 after a minimum of 72 hours has elapsed since the last infusion of FVIII protein concentrates.

14.3 Immunogenicity

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

14.4 Pharmacodynamic Analyses

The FVIII antigen and activity level as measured by an Elisa (antigen level) and by a one-stage APTT and/or chromogenic FXa assay (activity level), will be used for plasma

profiles; FVIII activity will be used to determine PD parameters. Traditional PK analysis is not applicable.

If supported by FVIII activity data, non-compartmental analysis and observation will be used to estimate individual PD parameter values of C_b (baseline), C_{ss} (steady state), T_{ss} (time to steady state), C(t) and AUC(0-t) where t is 16 weeks. Other parameters that may be used to describe individual FVIII protein and activity plasma profiles are C_{max} (maximum concentration) and C_{avg} (average concentration, AUC(0-t)/t). The parameters will be summarized using descriptive statistics.

14.5 Safety Analysis

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

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

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.

14.6 Determination of Sample Size

No formal sample size calculations based on statistical power were performed.

The sample size is determined based upon clinical consideration and could detect a strong clinical efficacy signal. Up to 15 subjects may be dosed in the study; the actual number of subjects will depend on the criteria for dose escalation.

14.7 Analysis Populations

The Safety analysis population is defined as all enrolled subjects who receive any study drug. The analysis of safety data will be performed on Safety Set.

The Full Analysis Set (FAS) is defined as all enrolled subjects who receive study drug and have at least one Baseline and post-Baseline assessment. The FAS will be used for efficacy analysis.

14.8 Changes in the Conduct of the Study or Planned Analyses

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

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

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

Note: If discrepancies exist between the text of the statistical analysis as planned in the protocol, and the final SAP, a protocol amendment will not be issued and the SAP will prevail.

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15 DATA REVIEW BOARD

There will be no formal DMC for this study, however a safety and efficacy evaluation board (the Data Review Board [DRB]) composed of the investigator representatives and the Sponsor will be established.

The DRB will review safety and efficacy on an ongoing basis. The DRB will meet prior to dose escalation or dose expansion to assess available subject safety and efficacy data and make recommendations with regards to the conduct of study. Should a safety signal arise, including one which may warrant a halt of study enrollment, the DRB will promptly convene for further assessment of subject safety. Notification of all DRB meetings and meeting outcomes will be sent to participating sites.

16 COMPENSATION, INSURANCE AND INDEMNITY

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

The Investigator should contact BioMarin immediately upon notification that a study subject has been injured by the IP 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 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 subject has followed the Investigator's instructions, BioMarin will pay for reasonable and necessary medical services to treat the injuries caused by the IP or study procedures, if these costs are not covered by health insurance or another third party that usually pays these costs. In some jurisdictions, BioMarin is obligated by law to pay for study-related injuries without prior recourse to third party payer billing. 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 CRF casebook to verify its accuracy.

CRFs 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 CRF instructions, blank data fields are not acceptable.

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

BioMarin's policy is that study data on the CRFs 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 an Investigator or institution refuses to allow access to subject records because of confidentiality, arrangements must be made to allow an "interview" style of data verification.

A CRA designated by BioMarin will compare the CRFs 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 CRA, 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 CRA 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 CRF 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 CRFs 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

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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 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).

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22 INVESTIGATOR RESPONSIBILITIES

22.1 Conduct of Study and Protection of Human Patients

In accordance with FDA Form 1572, 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 patients.
- He or she will personally conduct or supervise the study.
- He or she will inform any potential patients, 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 IRB review and approval in 21 CFR Part 56 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.
- 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
- He or she will ensure that adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.
- He or she will ensure that the IRB/IEC/REB complies with the requirements of 21 CFR Part 56, 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 patients or others are reported to the IRB/IEC/REB. Additionally, he or she will not make any changes in the research without IRB/IEC/REB approval, except where necessary to eliminate apparent immediate hazards to human patients.
- 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.

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23 SIGNATURE PAGE

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

Protocol Number: 270-201, Amendment 4

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

Date

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24 PROTOCOL AMENDMENT TEXT REVISIONS

The following table summarizes the revisions made to the protocol and relates the changes to the appropriate rationale (See pages 2-3). Text that has been added or inserted is indicated by <u>underlined</u> font, and deleted text is indicated by <u>strikethrough</u> font.

Section No./Title	Text Revisions	<u>Rationale</u>
2/Synopsis/Study	Figure 1. BMN 270 transgene construct, ~ 5.0 kbph FVIII-SQ Vector Genome Schematic	12
Rationale	[an updated version of Figure 1 was provided in this protocol amendment]	
2/Synopsis/Objectives	The primary objectives of the study are:	12
	• To determine the dose of AAV5-hFVIII-SQ required to achieve expression of FVIII at or above 5% of normal activity (≥5 IU/dL) at 16 weeks after infusion. The kinetics, duration and magnitude of AAV-mediated FVIII activity in individuals with haemophilia A will be determined and correlated to an appropriate BMN 270 dose.	
2/Synopsis/Study Design & Plan	Patients who provide written informed consent, meet the entry criteria definition of severe HA, and do not have transduction inhibition activity to AAV5 will be eligible to enroll in the study. Participants will be enrolled into one of up to three four cohorts according to dose level:	2
	Cohort 1: 6E12 vector genomes [vg] per kilogram of body weight, given as a single intravenous dose (iv)	
	<u>Cohort 2:</u> 2E13 vg per kilogram, iv	
	Cohort 3: 6E13 vg per kilogram, iv	
	Cohort 4: 4E13 vg per kilogram, iv	
	The starting dose was based on the expression and safety of FVIII observed in nonclinical studies of mice and monkeys. The starting dose has a significant safety margin (10-fold) from no observed adverse effect level (NOAEL) in non-human primates.	
	Cohorts 1-3	
	<u>The first 3</u> cohorts will be enrolled sequentially, allowing a period of 3 weeks or more between cohorts. Dose escalation may occur after a single subject has been safely dosed if the resulting FVIII activity at the Week 3 visit is < 5 IU/dL in both the aPTT and chromogenic assays. Three weeks is expected to be the time the expression will be close to the maximum. This escalation paradigm is intended to minimize the subject numbers exposed to subtherapeutic doses.	
	The starting dose was based on the expression and safety of FVIII observed in nonclinical studies of mice and monkeys. The starting dose has a significant safety margin (10 fold) from no observed adverse effect level (NOAEL) in non human primates.	

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Section No./Title	Text Revisions	Rationale
	 For the first subject treated in each <u>Cohortof the first 3 cohorts</u> , if the activity level reaches \geq 5 IU/dL and no safety issue is found, then up to four subjects will be enrolled in the Cohort. <u>Although the optimum design of this study is three cohorts of 4 subjects</u> , <u>though</u> , the adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals. <u>Cohort 4</u>	
	For Cohort 4, 3 subjects will be enrolled at 4E13 vg/kg. If FVIII activity in these 3 subjects is ≥ 5% at 8 weeks and if no safety issue is found, an additional 3 subjects may be enrolled in this cohort. There will be an ongoing review of individual patient safety and efficacy data by the medical monitor and the DRB. The adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.	
2/Synopsis/Number of Subjects Planned	Up to <u>1215</u> subjects may enroll into the study; the actual number of subjects will depend on the FVIII activity levels seen in each Cohort.	2
2/Synopsis/Diagnosis and All Criteria for Inclusion and Exclusion	 Individuals eligible to participate in this study must meet all of the following criteria: 6. Sexually active patients must be willing to use an acceptable method of contraception such as double barrier, including hormonal contraception for at least 6 months post-treatment. After 6 months, subjects may stop contraception use only if they have had 3 consecutive negative semen samples. 	6
2/Synopsis/Criteria for Evaluation	<u>Safety:</u> No major toxicity is expected based on preclinical studies in mice and monkeys. An asymptomatic transaminitis was observed at week 7 12 after administration in humans with an AAV8 FIX, providing the rationale for the following surveillance plan. Each subject will have comprehensive surveillance monitoring <u>LFTs of LFTs (at local labs, twice per week for Weeks 1-20, then once a per week from dose to completion of Week 6, 3 times per week from Weeks 7 to 1221-36, and then once a week from Weeks 13 to 16. If a subject's ALT is found to be greater than 1.5x his baseline every 2 weeks from Week 37-52) during these periods, then <u>Year 1.</u> LFTs will be monitored three times per week or until the ALT returns to baseline. LFTs will be monitored every other month for the first year and then every three months for up to 5 years post-dose in the safety extension; the frequency and duration of LFT testing may be changed if dictated by ongoing safety evaluations based on discussion between the Medical Monitor and the Investigator and review of subject data.</u>	1, 3, 12

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Section No./Title	Text Revisions	<u>Rationale</u>
2/Synopsis/Statistical Methods	The sample size is based upon clinical considerations and could detect a strong clinical efficacy signal. Up to $\frac{1215}{12}$ subjects may be dosed in the study	2
Figure 7.3.1	BMN 270 Transgene Construct, ~ 5.0 kbph-FVIII-SQ Vector Genome Schematic	12
	[An updated version of Figure 7.3.1 has been provided in this protocol amendment]	
7.4/Summary of Overall Risks and Benefits	Safety will be assessed by adverse event reporting and clinical laboratory assessment. Based on prior human studies with peripheral injections of AAV vectors, there is no known safety risk of AAV gene therapy. However, a mild asymptomatic transaminitis was observed at week 7-12 after administration in humans with an AAV8-FIX, providing the rationale for the following surveillance plan (Nathwani, 2011, Mol.Ther.). Each subject will have a comprehensive surveillance plan that monitors LFTs once a week from dose to completion of Week 6, 3 times per week from Weeks 7 to 12, and once a week from Weeks 13 to 16. If a subject's ALT is found to be greater than 1.5x baseline during these periods, then LFTs will be monitored three times per week or until the ALT returns to baseline. LFTs will be monitored every other month for the first year and then every three months for up to 5 years post-dose in the safety extension. study.	1, 3, 12
	For additional information on safety findings in 270-201, refer to current version of the Investigator's Brochure.	
9.1/Overall Study Design and Plan	Patients who provide written informed consent, meet the entry criteria definition of severe HA, and do not have transduction inhibition activity to AAV5 will be eligible to enroll in the study. Participants will be enrolled into one of up to three four cohorts according to dose level:	1, 2, 12
	• <u>Cohort 1: 6E12 vector genomes [vg/kg] per kilogram</u> of body weight, given as a single intravenous dose (iv)	
	• <u>Cohort 2:</u> 2E13 vg/ kg per kilogram, iv	
	• <u>Cohort 3:</u> 6E13 vg/ kg per kilogram, iv	
	• <u>Cohort 4: 4E13 vg per kilogram, iv</u>	
	<u>Cohort 4</u>	
	For Cohort 4, 3 subjects will be enrolled at 4E13 vg/kg. If FVIII activity in these 3 subjects is \geq 5% at 8 weeks and if no safety issue is found, an additional 3 subjects may be enrolled in this cohort.	
	There will be an ongoing review of individual patient safety and efficacy data by the medical monitor and the DRB. The adaptive	

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Section No./Title	Text Revisions	<u>Rationale</u>
	nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.	
	Because subjects develop neutralizing immunity upon exposure to the capsid, re-challenge of vector is not a likely treatment option and these subjects have effectively a single opportunity for therapy using this AAV capsid. Efficacy will be determined by FVIII activity at 16 weeks post dose. Safety will be evaluated for approximately 5 years after dosing. Any safety signal may trigger a review of the data and possible additional immunogenicity studies that include an assessment of cellular immune responses using collected peripheral blood mononuclear cells (PBMC). Additionally, if any of the events listed in Section 9.3.3.1 occur, enrollment into the trial will be halted to complete an extensive safety analysis. Notification of the study <u>enrollment</u> halt will be sent by the Sponsor to the participating sites via telephone and email immediately after becoming aware of a safety concern. This will ensure no additional subjects are dosed until the signal has been completely evaluated. If, following safety review by the Data Review Board (DRB) and the Sponsor, it is deemed appropriate to restart dosing, a request to restart dosing with pertinent data will be submitted to the health authority.	
	A summary of events and assessments are provided by visit in Table 9.1.1 for Screening, Baseline and BMN 270 Infusion, in Table 9.1.2 for Post-Infusion Follow-up, and in Table 9.1.3 and Table 9.1.4 for Safety Follow-up.	
	Table 9.1.5, dealing with steroid prophylaxis therapeutic corticosteroid use in the event of elevated LFTs, is discussed in Section 9.4.8.2.	
Figure 9.1.1	The figure title was updated.	12
Tables 9.1.1, 9.1.2, 9.1.3, 9.1.4, and 9.1.5	All tables and footnotes were updates to reflect the changes in the protocol amendment. These changes are also reflected as changes in Section 12 and are detailed below.	1, 4, 5, 6, 7, 8, 9, 10, 12
9.2/Discussion of Study Design, Including Choice of Control Group	Study 270-201 is designed to be a first-in-man, phase 1/2 open-label, dose escalation study in patients with severe haemophilia A. <u>ThreeFour</u> doses of BMN 270 will be evaluated and the dose escalation decision tree <u>for Cohorts 1-3</u> is summarized in Figure 9.1.1.	2
9.3/Selection of Study Population	Up to <u>1215</u> severe haemophilia A patients may enroll into the study; the actual number of patients will depend on the criteria for dose escalation.	2

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Section No./Title	Text Revisions	<u>Rationale</u>
9.3.1/Inclusion Criteria	 Individuals eligible to participate in this study must meet all of the following criteria: 6. Sexually active patients must be willing to use an acceptable method of contraception such as double barrier, including hormonal contraception for at least 6 months post-treatment. <u>After 6 months, subjects may stop contraception use only if they have had 3 consecutive negative semen samples.</u> 	6
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, enrollment into the trial will be put on halt to complete an extensive safety analysis per Section 9.1. A 5-fold increase from baseline in Any ALT elevation > 5x ULN for at least 2 consecutive weeks after BMN 270 administration of BMN 270, in the absence of a definitive alternate etiology for the increase The occurrence of Grade 3 or higher adverse events (excluding ALT elevation) assessed as related to study drug, including liver failure and clinical hepatitis Grade 2 adverse event assessed as related to study drug that persists for at least 7 days The persistent detection of the AAV vector genomeDNA in the semen of a participant in 3 consecutive samples (which are at least 2 weeks apart) more than 2652 weeks after BMN 270 infusion, a DRB review and analysis of safety data will be undertaken to determine whether the enrollment into the trial will be put on halt: Grade 2 adverse event assessed as related to study drug that persists for at least 7 days 	3, 6, 7, 12
9.4.5/Method of Assigning Subjects to Treatment Groups9.4.6.2/Selection of Dose for Each Subject	Cohorts 1 to 3are enrolled serially and their dose is defined in Section 9.4.6.2 below. Escalation is based on FVIII activity 3weeks after injection. Cohorts may receive the next higher dose if subjects in the previous cohort does not meet the activitycriteria, or the same dose if subjects in the previous cohort meets the activity criteria. Subjects in Cohort 4 will all be enrolled at asingle dose.For Cohort 4, 3 subjects will be enrolled at 4E13 vg/kg. If FVIII activity in these 3 subjects is \geq 5% at 8 weeks and if no safetyissue is found, an additional 3 subjects may be enrolled in this cohort.There will be an ongoing review of individual patient safety and efficacy data by the medical monitor and the DRB. The adaptive	2 2,12
	nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals. Refer to Figure 9.1.1 for a visual representation of the study design- <u>for Cohorts 1-3</u>	

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Section No./Title	Text Revisions	<u>Rationale</u>
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 CRF	12
	Medications which are predominately metabolized by the liver (e.g., acetaminophen) and alcohol should, whenever possible, be avoided for the first 52 weeks of the study, and particularly within 48 hours prior to lab work.	
9.4.8.1/Concomitant Haemophilia Treatments	Subjects on "on demand" therapy for FVIII will continue their treatment at will. Subjects on prophylactic FVIII therapy will discontinue their treatment starting the day of infusion and switch to an "on demand" schedule. FVIII can always be taken as needed by the subject, who will carefully record his treatment and bleeding episodes in his diary. In addition, information on FVIII usage by medical history will be collected (if available) from subjects for the 6 month period immediately preceding study enrollment.	12
9.4.8.2/Glucocorticoid Treatment of Elevated Hepatic Transaminases	During the Post-Infusion Follow-up Period and the Safety Follow-Up Period, each subject will have comprehensive surveillance plan monitoring LFTs once a week from dose to completion of Week 6, 3 times of LFTs (at local labs, twice per week from for Weeks 7 to 121-20, then once per week from Week 21-36, and then once a week from Weeks 13 to 16. If every 2 weeks from Week 37-52). LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.	1, 3
9.4.8.2.1/Therapeutic Corticosteroids	In general, therapeutic corticosteroids may be initiated when a subject's ALT value is found to be greater than 1.5x his baseline during these periods, then LFTs will be monitored three times per week until the ALT returns to baseline.≥ 1.5x ULN, or based on review of FVIII and liver enzyme data after consultation between the Medical Monitor and the Investigator. Reports of abnormalraised LFTs (defined as 1.5x the subject's baseline ALT level≥ 1.5x ULN) should be made to the BioMarin medical monitor within 30 minutes of the lab value being available, and. Local laboratory results of LFTs will be used to trigger corticosteroid treatment as needed. In case of discrepant results between local and central laboratories, the Investigator and Medical Monitor will decide further action.	1, 3, 12
	Following initiation or completion of therapeutic corticosteroids, if ALT elevation $\geq 1.5x$ ULN is reported, steroid managementdecisions will based on discussions between the Investigator and Medical Monitor. Modification of the steroid regimen may takeinto consideration possible confounders for the ALT elevation and impact on FVIII expression.Treatment with prednisolone will be initiated immediately at a dose of 60 mg per day and then gradually tapered (60 mg daily forthe first 2 weeks, then 40 mg the next 2 weeks, then 30 mg the next two weeks, then 20 mg the next two weeks, then 15 mg for thenext week, then 10 mg for the next week, then 5 mg for the next week, then stop, for a total treatment of $\$11$ weeks). Local	

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Section No./Title	Text Revisions	<u>Rationale</u>
	laboratory results of LFTs will be used) (refer to Table 9.1.5 trigger corticosteroid treatment as needed. In case of discrepant	
	results between local and central laboratories, the Investigator and Medical Monitor will decide further action.).	
	 If a glucocorticoid treatment is started<u>After discontinuation of corticosteroids</u>, weekly labs for a subject at any point of the study, the following steps<u>ALT and FVIII levels</u> will be taken: 	
	 A prophylactic glucocorticoid treatment will be started for subsequent subjects scheduled to be dosed. Subjects will receive prednisolone 40 mg per day starting at measured once a week 3, for a duration of 4 weeks, then tapered by 5 mg every two weeks for 8 weeks (until 20 mg/day is reached), then tapered 5 mg per week for 3 weeks, for a total duration of 15 weeks (refer to). 	
	Subjects already dosed who have not yet reached Week 17 to ensure stability in the study will be evaluated for the use of prophylactic steroids after discussion between the Investigator and the Medical Monitor.	
	Once prophylactic glucocorticoid treatments have been initiated, then all subjects (who have not already passed that period in the	
	study) will have 3x/week LFT assessments during the 6 week period when a liver response is expected based on the liver response	
	in the original subject, if this period is different from the 3x/weekly LFT assessments already planned for Weeks 7-12.	
	Subjects who have already passed that 6 week period in the study will continue to have the regularly scheduled LFT assessments as planned in the protocolvalues.	
	Management and monitoring of reactions to corticosteroids should be determined by the Investigator's clinical judgment in consultation with the Sponsor's Medical Monitor. This includes the contraindicated use of NSAIDs during corticosteroid treatment, and specific monitoring not already covered by the schedule of events. Hepatitis B status and HCV viral load will be	
	rechecked at <u>6 weeks after</u> the <u>end-start</u> of <u>corticosteroid treatment</u> , and then 1 week and 13 weeks after the <u>completion of</u> corticosteroid treatment. All adverse events should be reported as outlined in Section 10 of the protocol.	
9.7.2/Primary Efficacy Variables	The primary efficacy measure will be the plasma FVIII activity monitored on a regular basis after BMN 270 dose. The efficacy goal of the protocol is to ascertain the dose range of BMN 270 required to convert severe HA patients to stable expression of FVIII at 5 IU/dL or above, i.e., a mild severity. This is associated in natural history studies with clinically superior long term outcomes, (Den Ujil, 2011, Haemophilia).	1, 12
	The following assays (assessed by the central laboratory) will be used to measure the primary efficacy variable:	
	• FVIII activity (chromogenic FXa assay)	

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Section No./Title	Text Revisions	Rationale
	 FVIII activity by one-stage APTT (Activated Partial Thromboplastin Time) <u>FVIII activity assays will also be performed at the local laboratory at the time points indicated in Table 9.1.2.</u> Table 9.1.3. and Table 9.1.4. but will be used in conjunction with local lab LFT assessments to monitor subject safety and need for initiation of therapeutic corticosteroid dosing; local laboratory FVIII activity assessments will not be used to assess efficacy or to measure the primary efficacy outcome of the study. 	
9.7.6/Exploratory Biomarker Assessments	Blood samples will be collected from subjects at the time points indicated in Table 9.1.1, Table 9.1.2, Table 9.1.3, and Table 9.1.4 to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to Haemophilia A disease. The <u>exploratory</u> genetic/genomic testing-on these exploratory samples is optional. 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 may be used for exploratory use once the primary use has been completed. No additional genetic or genomic testing will be conducted on any sample (other	12
Table 9.7.8.2.1/Clinical Laboratory Tests	than testing specified in the protocol). This table has been updated as part of this protocol amendment.	1, 3, 9, 12
9.7.8.3/Liver Function and Hepatitis Testing	 9.7.8.3 Liver Function and Hepatitis Testing at Screening Subjects will be tested for hepatitis B and hepatitis C reactivation at Week 16. Subjects who receive therapeutic corticosteroids prior to Week 16 do not need to complete the Week 16 reactivation assessment; instead, they will be tested for hepatitis B and hepatitis C reactivation at the time points listed in Table 9.1.5. Liver function tests will be monitored on a regular basis, at the time points indicated in Table 9.1.1, Table 9.1.2, Table 9.1.3, and Table 9.1.4. At each time point, the following LFTs should be assessed: 	1, 3, 12
	<u>Table 9.7.8.3.1: Liver Function Tests</u> [this table has been added as part of this protocol amendment]	

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Section No./Title	Text Revisions	<u>Rationale</u>
	Patients with persistent $ALT > 1.5$ ULN during the study and no other etiology identified may undergo additional evaluations (e.g., imaging studies including MRI or ultrasound, additional blood tests, and/or liver biopsy) at the discretion of the investigator.	
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.	12
9.7.8.5/Vital Signs, Physical Examinations and Other Observations Related to Safety	A complete physical examination is necessary during Screening/Baseline, <u>at Week 16 and 52 and every 52 weeks</u> thereafter; <u>at</u> <u>other visits</u> , 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 Weight and hHeight will be recorded at Screening only. Weight will be recorded at Screening and then every 6 months thereafter.	
9.7.8.6/Vector Shedding	 9.7.8.6 ViralVector Shedding ViralVector shedding has been extensively studied in all similar clinical trials performed to date. (Nathwani, 2014, N.Engl.J.Med.); (Manno, 2006, Nat.Med.); (Schenk-Braat, 2007, J.Gene Med.); (Croteau, 2004, Ann.Occup.Hyg.). In the literature referenced above, including Haemophilia B clinical studies utilizing AAV2 and AAV8, vector was no longer detectable after 40 days in blood, saliva, urine or stool. However, vector persisted, but in semen for 16 weeksone study was detected in the seminal fluid but not in motile sperm (Manno, 2006, Nat.Med.). In all easesthese studies, the amount of vector present in these bodily fluids involved an extremely small fraction of the infused dose. More recent data from an ongoing AAV-FIX study demonstrates persistence of the vector in both the blood and the semen for at least 39 weeks (Miesbach, 2016, Haemophilia). Viral shedding will also be extensively studied in the present clinical trial, every week up to 16 weeks, then every 4 weeks to one year, then every three months, until at least 3 consecutive negative results are obtainedDuring the Post-Infusion Follow-Up period, subjects will undergo testing of various bodily samples to look for evidence of viralvector shedding for possible viral transmission. Bodily fluids will be tested by PCR at the time points indicated in Table 9.1.2, Table 9.1.3, and Table 9.1.4 Vector shedding will also be extensively studied in the present clinical trial, every other week between Weeks 4-16, then every 4 weeks to Week 52 until at least 3 consecutive negative results are obtained. Subjects who have not had 3 consecutive negative samples by Week 52 should continue to have PCR testing every 4 weeks until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor). Contraception use may need to be extended beyond 26 weeks in individual subjects based on observed vector shedding in semen. 	4, 5, 6, 12

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Section No./Title	Text Revisions	<u>Rationale</u>
	After 6 months, subjects may stop contraception use only if they have had 3 consecutive negative semen samples.	
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:	12
10.4.1.3/Persistent or Recurrent Adverse Events	Elevation of liver enzymes (ALT) that triggers a <u>an initiation or modification of</u> corticosteroid treatment A persistent AE (duration of adverse event > 7 days) is one that extends continuously, without resolution, between subject evaluation time points. SuchEvents that change in severity necessitate the recording of an event additional AE. AEs that do not have a change in severity should be recorded only once on the AE-eCRF-unless its severity increases or decreases (in which case it should be recorded again on the AE eCRF).	7, 12
10.4.1.4/Abnormal Laboratory Values	A clinical laboratory abnormality is considered clinically significant and should be documented as <u>AE if anyan AE if not refuted</u> by a repeat test to confirm the abnormality and any one or more of the following conditions is met: • <u>The laboratory abnormality persists upon repeat confirmatory testing.</u>	12
10.9/BioMarin Pharmacovigilance Contact Inforamtion	Contact information for the medical monitor is as follows: Name: PI Address: 105 Digital Drive Novato, CA 94949 USA Phone: PI E-mail: PI	11
12.2/Screening Visit	Screening assessments will be performed within 28 days (± 14 days) of BMN 270 infusion while baseline assessments will take place within 7 days of BMN 270 infusion (Day 1). Should the screening visit occur within 7 days of the drug infusion, physical examination, vital signs, blood chemistry, LFTs, haematology, urine tests, coagulation screen, and CRP do not need to be repeated at Baseline. The following procedures will be performed during the Screening Period: • Complete Physical Exam (including height and weight) • Height and weight	1, 3, 8, 12

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Section No./Title	Text Revisions	<u>Rationale</u>
	Blood chemistry, haematology, urine tests, coagulation screen, and CRP (refer to Table 9.7.8.2.1)	
	• <u>Urine Tests (refer to Table 9.7.8.2.1)</u>	
	• <u>Liver Function Tests (refer to Table 9.7.8.3.1)</u>	
	<u>Von Willebrand Factor Antigen (VWF:Ag)</u>	
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: Blood chemistry, haematology, urine tests, coagulation screen, and CRP (refer to Table 9.7.8.2.1) Urine Tests (refer to Table 9.7.8.2.1) 	1, 3, 12
	 <u>Office Tests (refer to Table 9.7.8.2.1)</u> <u>Liver Function Tests (refer to Table 9.7.8.3.1)</u> 	
12.3/Baseline Visit	The following procedures will be performed during the Baseline Period:	1, 3, 10, 12
	• Blood chemistry, haematology, urine tests, coagulation screen, and CRP (refer to Table 9.7.8.2.1)	
	• <u>Urine Tests (refer to Table 9.7.8.2.1)</u>	
	• Liver Function Tests (refer to Table 9.7.8.3.1)	
	<u>Direct Thrombin test</u>	
	• PCR of vector <u>genomesDNA</u> in blood, saliva, urine, semen, and stools	
12.5.1/BMN 270 Infusion Follow-Up Visits/Once per Week	 The following procedures will be performed at one visit per week from Weeks 1 through 16: Blood chemistry, haematology, urine tests, coagulation screen, and CRP 	1, 3
	 <u>Liver Function Tests</u> (refer to Table 9.7.8.3.1) – central laboratory assessment <u>Each subject will have comprehensive surveillance plan monitoring LFTs once a week from dose to completion of Week 6, 3 times per week (every other day excluding weekends) from Weeks 7 to 12, and once a week from Weeks 13 to 16. If a subject's ALT is found to be greater than 1.5x baseline during these periods, then LFTs will be monitored three times per week or until the ALT returns to baseline.</u> 	

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Section No./Title	Text Revisions	<u>Rationale</u>
	 LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data. 	
	Samples for FVIII Assays – central laboratory assessment	
	• FVIII activity level (APTT)	
	 FVIII activity level (chromogenic FXa assay) 	
	 FVIII coagulation activity exploratory assay 	
	 Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level 	
	• FVIII antigen (ELISA)	
	Note: 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.	
	Central assessment of FVIII activity level should be performed 1x/week from Week 1 through Week 16	
<u>12.5.2/Twice per week</u>	The following procedures will be performed twice per week from Weeks 1 through 16:	1, 3
(Weeks 1 through 16)	• Liver Function Tests (refer to Table 9.7.8.3.1) – local laboratory assessment	
	 Local assessment of liver function tests should be performed on Day 8 during Week 1, and then 2x/week from Week 2 through Week 16 	
	 <u>LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based</u> on discussion between the Medical Monitor and the Investigator and review of subject data. 	
	<u>FVIII activity level – local laboratory assessment</u>	
	• <u>FVIII activity level (APTT)</u>	
	• <u>FVIII activity level (chromogenic FXa assay)</u>	
	 Local assessment of FVIII activity level should be performed on Day 8 during Week 1, and then 2x/week from Week 2 through Week 16 	
12.5.3/Week 1 – Day	On Day 2 and Day 4 of Week 1, the following procedures will be performed:	1, 3, 12
2 and Day 4	• PCR of vector <u>genomesDNA</u> in blood, saliva, urine, semen, and stools (Day 2 and Day 4)	

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Section No./Title	Text Revisions	<u>Rationale</u>
	Samples for FVIII Assays (Day 4 only) – central laboratory assessment	
	• FVIII activity level (APTT)	
	 FVIII activity level (chromogenic FXa assay) 	
	 FVIII coagulation activity exploratory assay 	
	 Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level 	
	• FVIII antigen (ELISA)	
	Note: 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.	
	• Liver Function Tests (refer to Table 9.7.8.3.1) (Day 4 only) – central laboratory assessment	
	• Liver Function Tests (refer to Table 9.7.8.3.1) (Day 4 only) – local laboratory assessment	
	• <u>FVIII activity level (Day 4 only) – local laboratory assessment</u>	
	• <u>FVIII activity level (APTT)</u>	
	• FVIII activity level (chromogenic FXa assay)	
12.5.4/Week 1 – Day	On Day 8, the following procedures will be performed:	4, 10, 12
8	• <u>PCR of vector DNA in blood, saliva, urine, semen, and stools</u>	
	<u>Direct Thrombin test</u>	
	<u>Haemo-QoL-A QoL assessment</u>	
12.5.5/Every 2 Weeks	Every 2 weeks (Weeks 2, 4, 6, 8, 10, 12, 14 and 16), the following procedure procedures will be performed:	4, 9
	• Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.8.2.1) (not assessed at Week 14)	
	Exploratory biomarker assessments	
	• PCR of vector DNA in blood, saliva, urine, semen, and stools (not collected at Week 2)	
	• Collection to occur until at least 3 consecutive negative results are obtained	

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Section No./Title	Text Revisions	<u>Rationale</u>
12.5.5/Weeks 1, 3, and	At Weeks 1, 3, and 6, the following procedure will be performed:	1, 3, 12
6	• Test for Hepatitis B and Hepatitis C reactivation	
12.5.6/Weeks 4, 8, 12,	At Weeks 4, 8, 12, and 16, the following procedure will be performed:	8, 12
and 16	PBMC collection	
	• <u>Urine Tests (refer to Table 9.7.8.2.1</u>)	
	• <u>VWF:Ag</u>	
	• <u>FVIII antibody titer</u>	
	• Exploratory biomarker assessments	
12.5.7/Week 16	At Week 16, the following procedure will be performed:	1, 3, 12
	• Test for Hepatitis B and Hepatitis C reactivation	
	Subjects will be tested for hepatitis B and hepatitis C reactivation at Week 16. Subjects who receive therapeutic	
	corticosteroids prior to Week 16 do not need to complete the Week 16 reactivation assessment; instead, they will	
	be tested for hepatitis B and hepatitis C reactivation at the time points listed in Table 9.1.5.	
12.5.10/Weeks 1, 2, 3,	At Weeks 1, 2, 3, 4, and 16, the following procedure will be performed:	12
4 and 16	Haemo-QoL-A QoL assessment	
12.5.11/Week 13	At Week 13, the following procedure will be performed:	10
	• <u>Direct Thrombin test</u>	
12.6/Safety Follow-	Section 12.6 and its subsections (describing assessments to be performed during the Week 17-52 Safety Follow-Up Period) have	12
Up Year 1	been deleted and replaced with the new Section 12.6 (for Weeks 17-36) and Section 12.7 (for Weeks 37-52).	12
12.6/Safety Follow-	After the 16 weekly Post-Infusion Follow-Up visits are complete, subjects will return to the study site at for Safety Follow-Up	12
<u>Up – Weeks 17-36</u>	visits from Weeks $\frac{20, 28, 17}{20, 28, 17}$ through Week $36, 44, and 52$ (± 1 week (± 48 hours), when the following procedures will be	
	<u>completed:</u>	

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Section No./Title	Text Revisions	<u>Rationale</u>
12.6.1/Once per week	Once per week from Week 17 through Week 36, the following procedures will be performed:	3, 12
<u>(Weeks 17 through</u> <u>36)</u>	• <u>Physical exam</u>	
	 <u>Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII</u> use) 	
	• <u>Vital Signs</u>	
	 <u>Blood chemistry, haematology, urine tests, coagulation screen, and CRP</u>Liver Function Tests (refer to Table 9.7.8.3.1) – central laboratory assessment 	
	 LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data. 	
	• <u>FVIII Assays – central laboratory assessment</u>	
	• <u>FVIII activity level (APTT)</u>	
	• FVIII activity level (chromogenic FXa assay)	
	• FVIII coagulation activity exploratory assay	
	o Bethesda assay (with Nijmegen modification) for FVIII inhibitor level	
	o <u>FVIII antigen (ELISA)</u>	
	Note: 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.	
<u>12.6.2/Twice per week</u>	Twice per week from Week 17 through Week 20, the following procedures will be performed:	3
(Weeks 17 through 20)	• <u>Liver Function Tests (refer to Table 9.7.8.3.1) – local laboratory assessment</u>	
	 LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data. 	
	<u>FVIII activity level – local laboratory assessment</u>	
	• <u>FVIII activity level (APTT)</u>	
	• FVIII activity level (chromogenic FXa assay)	

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Section No./Title	Text Revisions	<u>Rationale</u>
12.6.3/Once per week (Weeks 21 through 36)	Once per week from Week 21 through Week 36, the following procedures will be performed: • Liver Function Tests (refer to Table 9.7.8.3.1) – local laboratory assessment • LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data. • FVIII activity level – local laboratory assessment • FVIII activity level (APTT) • FVIII activity level (chromogenic FXa assay)	3
12.6.4/Every 4 Weeks	 Every 4 weeks (Weeks 20, 24, 28, 32, and 36), the following procedures will be performed: Exploratory biomarker assessments (Weeks 20 and 24 only) Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.8.2.1) Urine Tests (refer to Table 9.7.8.2.1) VWF:Ag AAV5 antibody titer PBMC collection PCR of vector DNA in blood, saliva, urine, semen, and stools Sample testing during Safety Follow-Up is not required if at least 3 consecutive samples are clear during the Post-Infusion Follow-Up period. 	5, 8, 9
<u>12.6.5/Every 8 Weeks</u>	 <u>Every 8 weeks (Weeks 20, 28, and 36), the following procedure will be performed:</u> <u>FVIII antibody titer</u> 	12
12.6.6/Week 26	At Week 26, the following procedure will be performed: • Direct Thrombin test	10

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Section No./Title	Text Revisions	<u>Rationale</u>
	• <u>Weight</u>	
10 (7/11 1 - 00		12
<u>12.6.7/Weeks 28</u>	At Week 28, the following procedure will be performed:	12
	<u>Haemo-QoL-A QoL assessment</u>	
12.7/Safety Follow-up	Subjects will return every 2 weeks (Week 38, 40, 42, 44, 46, 48, 50, and 52) from Week 37-52 (± 1 week), when the following	12
<u>– Weeks 37-52</u>	procedures will be completed:	
12.7.1/Once per visit	At Weeks 38, 40, 42, 44, 46, 48, 50, and 52, the following procedures will be performed:	3, 12
	• <u>Physical exam</u>	
	 <u>Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII</u> use) 	
	Vital Signs	
	 Liver Function Tests (refer to Table 9.7.8.3.1) – local laboratory assessment 	
	\circ LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based	
	on discussion between the Medical Monitor and the Investigator and review of subject data.	
	<u>FVIII activity level – local laboratory assessment</u>	
	• <u>FVIII activity level (APTT)</u>	
	 <u>FVIII activity level (chromogenic FXa assay)</u> 	
	• <u>Liver Function Tests (refer to Table 9.7.8.3.1) – central laboratory assessment</u>	
	 <u>LFTs may be monitored more or less frequently based (and in particular when ALT values are >1.5x ULN) on</u> discussion between the Medical Monitor and the Investigator and review of subject data. 	
	• <u>FVIII Assays – central laboratory assessment</u>	
	• <u>FVIII activity level (APTT)</u>	

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Section No./Title	Text Revisions	<u>Rationale</u>
	 <u>FVIII activity level (chromogenic FXa assay)</u> 	
	• FVIII coagulation activity exploratory assay	
	• Bethesda assay (with Nijmegen modification) for FVIII inhibitor level	
	• <u>FVIII antigen (ELISA)</u>	
	Note: 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	
12.7.2/Every 4 Weeks	Every 4 weeks (Weeks 40, 44, 48, and 52), the following procedures will be performed:	5, 8, 9, 12
	Blood chemistry, haematology, coagulation screen, and CRP (refer to Table 9.7.8.2.1)	
	• <u>Urine Tests (refer to Table 9.7.8.2.1)</u>	
	• <u>AAV5 antibody titer</u>	
	• <u>VWF:Ag</u>	
	• <u>PCR of vector genomesDNA in blood, saliva, urine, semen, and stools</u>	
	Sample testing during Safety Follow-Up is not required if at least 3 consecutive samples are clear during the	
	Post-Infusion Follow-Up period. Subjects who have not had 3 consecutive negative samples by Week 52 should	
	continue to have PCR testing every 4 weeks until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor).	
12.7.3/Every 8 Weeks	Every 8 weeks (Weeks 44 and 52), the following procedure will be performed:	12
	<u>PBMC collection</u>	
	• <u>FVIII antibody titer</u>	
12.7.4/Week 38 and	At Weeks 28 and Week 38 and Week 52, the following procedure will be performed:	10
<u>52</u>	• <u>Direct Thrombin test</u>	
12.7.5/Week 52	At Week 52, the following procedure will be performed:	12
	Haemo-QoL-A QoL assessment	

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Section No./Title	Text Revisions	<u>Rationale</u>
	• <u>Weight</u>	
12.8.1/Safety Follow- Up (Years 2-5): Every Visit	 Weight Every 3 months (± 2 weeks), the following procedures will be performed: <u>Vital Signs</u> Blood chemistry, haematology, urine tests, coagulation screen, and CRP (refer to Table 9.7.8.2.1) <u>Urine Tests (refer to</u> Table 9.7.8.2.1) <u>Liver Function Tests (refer to</u> Table 9.7.8.3.1) – local laboratory assessment <u>LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.</u> <u>FVIII activity level – local laboratory assessment</u> <u>FVIII activity level (APTT)</u> <u>FVIII activity level (chromogenic FXa assay)</u> <u>Liver Function Tests (refer to</u> Table 9.7.8.3.1) – central laboratory assessment <u>LFTs may be monitored more or less frequently (and in particular when ALT values are >1.5x ULN) based on discussion between the Medical Monitor and the Investigator and review of subject data.</u> FVIII activity level (APTT) <u>FVIII activity level (APTT)</u> <u>FVIII activity level (APTT)</u> <u>Liver Function Tests (refer to</u> Table 9.7.8.3.1) – central laboratory assessment <u>Liver Function Tests (refer to</u> Table 9.7.8.3.1) – central laboratory assessment <u>FVIII activity level (APTT)</u> <u>FVIII activity level (APTT)</u> FVIII activity level (APTT) FVIII activity level (FXa chromogenic assay) FVIII activity level (FXa chromogenic assay) FVIII activity level (FXa chromogenic assay) FVIII activity level (EISA) Note: 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. 	1, 3, 8, 10, 12

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Section No./Title	Text Revisions	<u>Rationale</u>
	<u>Direct Thrombin test</u>	
	 PCR of vector genomes in blood, saliva, urine, semen, and stools 	
	 Sample testing during Safety Follow Up is not required if at least 3 consecutive samples are clear during the Post Infusion Follow Up period. 	
	Vital Signs	
12.8.2/Every Other Visit (Every 6 Months)	• Weight	
12.9/Early	At the Early Termination visit, as many of the following assessments as possible should be done:	1, 3, 5, 6,
Termination Visit	• <u>Vital Signs</u>	8, 10, 12
	• Blood chemistry, haematology, urine tests, coagulation screen, and CRP (refer to Table 9.7.8.2.1)	
	• <u>Urine Tests (refer to Table 9.7.8.2.1)</u>	
	• <u>Liver Function Tests (refer to Table 9.7.8.3.1) – local laboratory assessment</u>	
	• <u>FVIII activity level – local laboratory assessment</u>	
	• <u>FVIII activity level (APTT)</u>	
	• FVIII activity level (chromogenic FXa assay)	
	• <u>Liver Function Tests (refer to Table 9.7.8.3.1) – central laboratory assessment</u>	
	• FVIII Assays <u>– central laboratory assessment</u>	
	• FVIII activity level (APTT)	
	 FVIII activity level (chromogenic FXa assay) 	
	 FVIII coagulation activity exploratory assay 	
	 Bethesda assay (with Nijmegen modification) for FVIII inhibitor level 	
	• FVIII antigen (ELISA)	
	Note: If a subject has used FVIII within 72 hours of a measurement day, all efforts should be made to obtain FVIII	

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Section No./Title	Text Revisions	<u>Rationale</u>
	activity measurements when a 72-hour interval without FVIII use is achieved.	
	• <u>VWF:Ag</u>	
	• Direct Thrombin test	
	• PCR of vector <u>genomesDNA</u> in blood, saliva, urine, semen, and stools	
	 Sample testing at the ETV is not required if at least 3 consecutive samples are clear during the Post-Infusion Follow-Up period. 	
	Vital Signs	
14.2/Primary and Secondary Efficacy Analysis	Data collected in a longitudinal manner may be analyzed using longitudinal methods such as mixed effect model which takes into account the correlation among the observation taken at various time points within a participant. Efficacy is a secondary endpoint, defined as biologically active hFVIII at ≥ 5 IU/dL by chromogenic FXa and/or one-stage APTT assay <u>as measured by the central laboratory</u> at 16 weeks following study treatment. hFVIII activity will be assessed weekly during the study period. We can only assess the true steady state of hFVIII protein produced from BMN 270 after a minimum of 72 hours has elapsed since the last infusion of FVIII protein concentrates.	1, 3, 12
14.6/Determination of Sample Size	The sample size is determined based upon clinical consideration and could detect a strong clinical efficacy signal. Up to $\frac{1215}{12}$ subjects may be dosed in the study; the actual number of subjects will depend on the criteria for dose escalation.	2

CLINICAL STUDY PROTOCOL

Study Title: Protocol Number: Active Investigational Product: IND/European Union Drug Regulating Authorities Clinical Trials (EudraCT) Number:	A Phase 1/2, Dose-Escalation Safety, Tolerability and Efficacy Study of BMN 270, an Adenovirus-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII in Patients with Severe Haemophilia A 270-201 AAV5-hFVIII-SQ 2014-003880-38
Indication:	Haemophilia A
Sponsor:	BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949
Development Phase:	Phase 1/2
Sponsor's Responsible Medical Monitor:	PI , MD, PhD PI BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949
Duration of Subject Participation:	Approximately 264 weeks
Dose:	Varied
Study Population:	Males aged 18 or older
Date of Original Protocol:	10 February 2015
Date of Amendment 1:	06 March 2015
Date of Amendment 2:	26 May 2015
Date of Amendment 3:	06 November 2015

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May not be divulged, published, or otherwise disclosed to others without prior written approval from BioMarin.

This study will be conducted according to the principles of Good Clinical Practice as described in the U.S. Code of Federal Regulations and the International Conference on Harmonisation Guidelines, including the archiving of essential documents



CLINICAL STUDY PROTOCOL AMENDMENT SUMMARY

Amendment: 3

Date: 06 November 2015

RATIONALE AND SUMMARY OF MAJOR CHANGES

A summary of major changes covered by Amendment 3 to the BMN 270-201 protocol is provided below.

1. If a subject develops hepatic transaminases elevated 1.5x above his baseline during the study, changes to subject management, including the use of prophylactic glucocorticoids and a change to the frequency of liver function testing, will be adopted.

Rationale: Previous clinical trials using AAV2-FIX and AAV8-FIX have shown some occurrences of elevation of liver enzymes 5-12 weeks after dosing. Such elevation was correlated with a loss of transgene expression in these clinical trials. As the present trial is a First-in-Human (FIH) for the combination of this vector serotype and Factor VIII, the occurrence of such a liver response is unknown as well as the possible consequences on gene expression. Occurrences of liver enzyme elevation in previous clinical trial were readily managed by a tapered regimen of low dose steroids. By including prophylactic corticosteroids for all subsequent subjects as well as shifting the surveillance monitoring period to coincide with the initial liver response, reductions in transgene expression may be avoided.

2. Added as an exclusion criterion any subject with major surgery planned during the 16-week period following viral infusion.

Rationale: A major surgery, such as hip replacement, planned during the initial 16-week follow up period would jeopardize the subject's safety, as it is unknown what his expression level of factor VIII would be at this time.

3. Added a "smart rescreening" option for subjects who are successfully screened but do not undergo Baseline assessments and Infusion within the 28 + 14 day window required by the protocol.

Rationale: Reducing the number of screening assessments for a smart rescreen poses minimal risk to the subject and keeps the subject below the statutory 12 week blood volume threshold. 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.

4. Clarified that subjects who have cleared a Hepatitis B infection or are seronegative will not be required to receive the hepatitis vaccination as a requirement for enrolling in the study.

Rationale: Subjects who have cleared the infection or are seronegative have a very low chance of becoming seropositive during the trial. Most Haemophilia A patients are already vaccinated, and the risk is too low to mandate the vaccination.

5. Minor edits for clarity and consistency have been incorporated.

Specific changes included in this amendment, including the Synopsis, since Amendment 2 (approved 26 May 2015) are outlined in Section 24.

2 SYNOPSIS

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AAV5-hFVIII-SQ		
TITLE OF STUDY:		

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

PROTOCOL NUMBER:

270-201

STUDY SITES:

Approximately 6-10 sites worldwide.

PHASE OF DEVELOPMENT:

Phase 1/2

STUDY RATIONALE:

Haemophilia 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 cascade. This disorder can be either inherited, due to a new mutation 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 is largely governed by the level of residual expression. Severe HA is classified as FVIII activity less than 1% of wild type (< 1 IU/dL), moderate disease comprises 1-5% of wild type activity and the mild form is 5-40% activity. The clinical manifestations of severe HA remain frequent spontaneous bleeding episodes, predominantly in joints and soft tissues, with a substantially increased risk of death from haemorrhage when the brain is involved.

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 treatment (mean of 1 to 7 episodes/year with prophylaxis and up to 30 to 50 episodes/year for on demand treatment). The consequence of multiple bleeding events is the development of an underlying pathology that contributes to debilitating multiple-joint arthropathy and substantially increased risk of death. Chemical modification (e.g. direct conjugation of polyethylene glycol (PEG) polymers) and bioengineering of FVIII (e.g. FVIII-Fc fusion proteins) improve half-life by

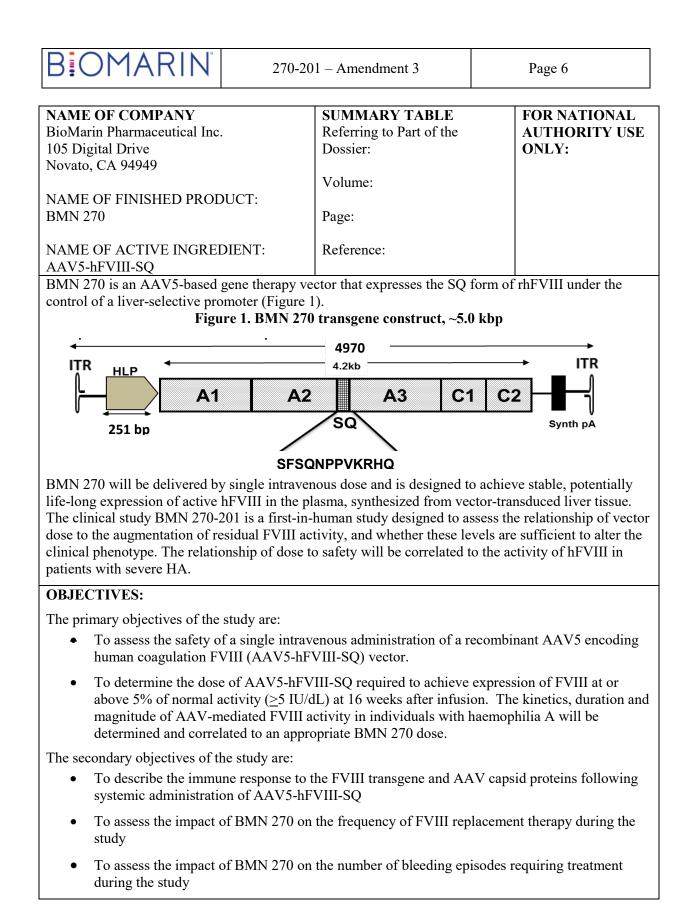
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approximately 50%, and thus, show promise in reduced dosing and maintaining activity levels above 1% trough. However, these longer acting FVIIIs remain dependent on multiple infusions to maintain critical levels of FVIII activity in severe HA patients. There is therefore a strong unmet need for a fully preventive treatment of HA to give patients a FVIII level compatible with a normal and haemorrhage-free life.

Gene therapy offers the potential of disease-modifying therapy by continuous endogenous production of active FVIII following a single intravenous administration of a vector with the appropriate gene sequence. Haemophilia 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 modest increases in the level of FVIII (any increase of the plasma level by 2 ng/ml induces an increase in activity of 1%) can ameliorate the severe form of the disease. Thus, relatively small changes in endogenous FVIII activity results in clinically relevant improvements in disease phenotype. Finally, the 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 for specific tissues such as the liver (for serotypes 2, 5 and 8 among others). Indeed, an on-going gene therapy clinical trial for a related disorder, haemophilia B, has established that stable (>36 months) expression of human factor IX at levels that are sufficient for conversion of their bleeding phenotype from severe to moderate or mild is achievable following a single peripheral vein administration of AAV-8 vector. Several participants in this trial have been able to discontinue factor prophylaxis without suffering spontaneous haemorrhages, 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.



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NAME OF ACTIVE INGREDIENT: AAV5-hFVIII-SQ

Reference: STUDY DESIGN AND PLAN:

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

Patients who provide written informed consent, meet the entry criteria definition of severe HA, and do not have transduction inhibition activity to AAV5 will be eligible to enroll in the study. Participants will be enrolled into one of up to three cohorts according to dose level:

- 1. 6E12 vector genomes [vg] per kilogram of body weight, given as a single intravenous dose (iv)
- 2. 2E13 vg per kilogram, iv
- 3. 6E13 vg per kilogram, iv

Cohorts will be enrolled sequentially, allowing a period of 3 weeks or more between cohorts. Dose escalation may occur after a single subject has been safely dosed if the resulting FVIII activity at the Week 3 visit is < 5 IU/dL in both the aPTT and chromogenic assays. Three weeks is expected to be the time the expression will be close to the maximum. This escalation paradigm is intended to minimize the subject numbers exposed to subtherapeutic doses.

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

Approximately three weeks after an injection, the decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and a panel of investigators participating in the study, the Data Review Board (DRB).

If the FVIII activity reaches > 5 IU/dL at the Week 3 visit, then the remaining subjects in the cohort will be enrolled without the need to wait for 3 weeks between subjects.

Subject 1 will be dosed by intravenous infusion with 6E12 vector genomes [vg] per kilogram of body weight. If the FVIII activity level does not reach $\geq 5 \text{ IU/dL}$ at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 1 and enrollment into Cohort 2 will initiate with Subject 2 at the next dose (2E13 vg/kg).

If the FVIII activity level in the first subject treated in Cohort 2 does not reach \geq 5 IU/dL at the Week

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BMN 270

3 visit in both assays, then no further subjects will be dosed in Cohort 2 and enrollment into Cohort 3 (6E13) will initiate with the next subject. If the FVIII activity level in the first subject treated in Cohort 3 does not reach \geq 5 IU/dL at the Week 3 visit in both assays, then the Data Review Board (DRB) will recommend whether to continue to add subjects to the cohort and/or whether to continue the study.

Reference:

For the first subject treated in each Cohort, if the activity level reaches ≥ 5 IU/dL and no safety issue is found, then up to four subjects will be enrolled in the Cohort. Although the optimum design of this study is three cohorts of 4 subjects, the adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

Because subjects develop neutralizing immunity upon exposure to the capsid, re-challenge of vector is not a likely treatment option and these subjects have effectively a single opportunity for therapy using this AAV capsid. Efficacy will be determined by FVIII activity at 16 weeks post dose. Safety will be evaluated for approximately 5 years after dosing. Any safety signal may trigger a review of the data and possible additional immunogenicity studies that include an assessment of cellular immune responses using collected peripheral blood mononuclear cells (PBMC).

NUMBER OF SUBJECTS PLANNED:

Up to 12 subjects may enroll into the study; the actual number of subjects will depend on the FVIII activity levels seen in each Cohort.

DIAGNOSIS AND ALL CRITERIA FOR INCLUSION AND EXCLUSION:

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

- 1. Males that are 18 years or older with established severe haemophilia A as evidenced by their medical history. Patients will be considered as severe if their base FVIII level is 1 IU/dL or less
- 2. Treated/exposed to FVIII concentrates or cryoprecipitate for a minimum of 150 exposure days (EDs)
- 3. Greater or equal to 12 bleeding episodes only if receiving on-demand therapy over the previous 12 months. Does not apply to patients on prophylaxis
- 4. Able to sign informed consent and comply with requirements of the trial
- 5. No history of inhibitor, and results from a modified Nijmegen Bethesda assay of less than 0.6 Bethesda Units (BU) on 2 consecutive occasions at least one week apart within the past 12 months

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NAME OF ACTIVE INGREDIENT: AAV5-hFVIII-SQ	Reference:	
6. Sexually active patients must be w double barrier, including hormona		
Individuals who meet any of the following	exclusion criteria will not be eli	gible to participate in the
study:		
1. Detectable pre-existing immunity inhibition or AAV5 total antibodie		by AAV5 transduction
2. Any evidence of active infection o	r any immunosuppressive disord	er.
3. HIV positive		
4. Significant liver dysfunction as de	fined by abnormal elevation of:	
	3 times the upper limit of norma	al·
 Bilirubin above 3 times the up 	**	,
	· ·	
* *	times the upper limit of normal;	or
• INR (international normalized	<i>,</i>	
5. Potential participants who have ha significant fibrosis of 3 or 4 as rate		rs are excluded if they had
6. Evidence of any bleeding disorder	not related to Haemophilia A	
7. Platelet count of $< 100 \text{ x } 10^9/\text{L}$		

- 9. Liver cirrhosis of any etiology as assessed by liver ultrasound
- 10. Hepatitis B if surface antigen is positive
- 11. Hepatitis C if RNA is positive
- 12. Treatment with any IP within 30 days prior to the end of the screening period
- 13. Any disease or condition at the physician's discretion that would prevent the patient from fully complying with the requirements of the study including possible corticosteroid treatment outlined in the protocol. The physician may exclude patients unwilling or unable to agree on not using alcohol for the 16-week period following the viral infusion.
- 14. Prior treatment with any vector or gene transfer agent

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15. Major surgery planned in the 16-week period following the viral infusion

16. Use of systemic immunosuppressive agents or live vaccines within 30 days before the viral infusion

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

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

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

The study is open label with comparison of FVIII activity to baseline values. 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:

Safety:

The following safety outcome measurements will be assessed:

- Incidence of adverse events (AEs), including serious AEs (SAEs)
- Change in clinical laboratory tests (serum chemistry and haematology)
- Change in vital signs
- Change in physical examination
- Vector shedding
- Liver function tests (LFTs, including ALT, AST, GGT, LDH, bilirubin, alkaline phosphatase)
- Immune response to FVIII transgene and AAV capsid proteins

No major toxicity is expected based on preclinical studies in mice and monkeys. An asymptomatic transaminitis was observed at week 7-12 after administration in humans with an AAV8-FIX, providing the rationale for the following surveillance plan. Each subject will have comprehensive surveillance monitoring LFTs once a week from dose to completion of Week 6, 3 times per week from Weeks 7 to 12, and once a week from Weeks 13 to 16. If a subject's ALT is found to be greater than 1.5x his baseline during these periods, then LFTs will be monitored three times per week or until the ALT returns to baseline. LFTs will be monitored every other month for the first year and then every three months for up to 5 years post-dose in the safety extension; the frequency and duration of LFT testing

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may be changed if dictated by ongoing safety evaluations.

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

Efficacy:

The primary efficacy measure will be to assess plasma FVIII activity. The efficacy goal of the study is to establish the dose relationship to FVIII activity ≥ 5 IU/dL at 16 weeks post BMN 270 administration.

Secondary efficacy measures include assessing the impact of BMN 270 on the frequency of FVIII replacement therapy and on the number of bleeding episodes during the study. Subjects will be asked to keep a subject diary to record the details in these areas.

Pharmacodynamics:

The FVIII antigen and activity level as measured by an ELISA (antigen level) and by one-stage APTT and/or chromogenic FXa assay (activity level), will be used for plasma profiles; FVIII activity will be used to determine PD parameters. Traditional PK analysis is not applicable.

If supported by the FVIII activity data, non-compartmental analysis and observation will be used to estimate individual values of Cb (baseline concentration), Css (steady state concentration), Tss (time to steady state), C(t) and AUC(0-t) where t is 16 weeks.

STATISTICAL METHODS:

The sample size is based upon clinical considerations and could detect a strong clinical efficacy signal. Up to 12 subjects may be dosed in the study. The subjects will be followed in a longitudinal manner and all the relevant information will be collected. The analysis of the data will be descriptive in nature but data collected in a longitudinal manner may be analyzed using longitudinal methods such as mixed effect model which takes into account the correlation among the observation taken at various time points within a participant. Efficacy is a secondary endpoint, defined as biologically active FVIII at ≥ 5 IU/dL by chromogenic FXa assay and/or one-stage APTT assay at 16 weeks following study treatment. FVIII activity will be assessed weekly during the study period. We can only assess the true steady state of FVIII protein produced from BMN 270 after a minimum of 72 hours has elapsed since the last infusion of FVIII protein concentrates.

Analysis of neutralizing antibody response and other immunological parameters as well as viral shedding will be primarily descriptive and involve both inter-participant and intra-participant comparisons across doses.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

AAV	adeno-associated virus
ADL	activities of daily living
ADR	adverse drug reaction
AE	adverse event
ALT	alanine transaminase
APTT	activated partial thromboplastin time
BPV	BioMarin Pharmacovigilance
BU	Bethesda Unit
CFR	Code of Federal Regulations
CRA	clinical research associate
CRF	case report form
CSR	clinical study report
DMC	Data Monitoring Committee
DRB	Data Review Board
eCRF	electronic case report form
ED	exposure days
EOSI	events of special interest
ETV	early termination visit
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIH	first-in-human
FVIII	coagulation factor VIII
FXa	coagulation factor Xa
GCP	Good Clinical Practice
HA	Haemophilia A
hFVIII	human coagulation factor VIII
HIPAA	Health Insurance Portability and Accountability Act
IB	investigator brochure
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for
	Registration of Pharmaceuticals for Human Use
ICH E6	ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6
IEC	independent ethics committee
	independent ethics committee
IND	Investigational New Drug (application)
IND INR	-

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IP	investigat	ional product	
IRB		al review board	
IV	intraveno	us	
LFT	liver func	tion test	
MedDRA	Medical I	Dictionary for Regulatory Activities	
NOAEL	no-observ	red-adverse-effect level	
PBMC	peripheral	l blood mononuclear cells	
PD	pharmaco	dynamics	
PEG	polyethyle	ene glycol	
РК	Pharmaco	kinetics	
PRO	patient-re	ported outcome	
rhFVIII	recombina	ant human FVIII protein	
REB	research e	thics board	
SAE	serious ad	lverse event	
SAP	statistical	analysis plan	
SDV	source dat	ta verification	
vg	vector ger	nomes	

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]).

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

5 ETHICS

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

5.1 Institutional Review Board or Independent Ethics Committee

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

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

5.2 Ethical Conduct of Study

It is expected that Investigators understand and comply with the protocol. This includes, but is not limited to: establishing and meeting enrollment commitments, including providing

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eligible subjects for study enrollment; adhering to 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)

Specifically, this study is based on adequately performed laboratory and animal experimentation. The study will be conducted under a protocol reviewed and approved by an IRB/IEC/REB and will be conducted by scientifically and medically qualified persons. The benefits of the study are in proportion to the 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), United States Code of Federal Regulations (CFR) 21 CFR §50, European Clinical Trial Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC, and other applicable local regulations, will be obtained for each subject prior to entering the subject into the study. The Investigator will prepare the ICF and provide the documents to BioMarin for approval prior to submission to the IRB/IEC/REB approval. BioMarin and the IRB/IEC/REB must approve the documents before they are implemented. A copy of the approved ICF , and if applicable, a copy of the approved subject information sheet and all ICFs translated to a language other than the native language of the clinical site must also be received by BioMarin or designee prior to any study-specific procedures being performed.

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

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

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

Prior to beginning the study, the Investigator at each site must provide to BioMarin or designee, a fully executed and signed US Food and Drug Administration (FDA) Form FDA 1572 and a Financial Disclosure Form. All sub-Investigators must be listed on Form FDA 1572. Financial Disclosure Forms must also be completed for all sub-Investigators listed on the Form FDA 1572 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.

Liver function tests (LFTs) will be performed at the local laboratories associated with the study sites. Local laboratory results of LFTs will be used to trigger corticosteroid treatment as needed (refer to Section 9.4.8.2). In case of discrepant results between local and central laboratories, the Investigator and Medical Monitor will decide further action. Safety labs evaluations (including LFTs) will be performed at the central lab, while bioanalytical samples will be performed at the appropriate specialty lab. Refer to the Laboratory Manual for more details.

7 INTRODUCTION

Haemophilia A (HA) is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males (Nathwani, 1992, Baillieres Clin.Haematol.). It is caused by mutations in the factor VIII (FVIII) gene that codes for FVIII protein, an essential cofactor in the coagulation cascade. 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 haemorrhage. Treatment in Western (Berntorp, 2012, Haemophilia.) countries consists of intravenous injection of plasma derived or recombinant FVIII protein concentrates at the time of a bleed, 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 haemophilia A patients. These individuals develop debilitating arthropathy and have a substantially increased risk of death from haemorrhage in life (Stonebraker, 2010, Haemophilia.). Chemical modification or bioengineering of FVIII may improve half-life to 18-19 hours (Kaufman, 2013, Blood). However, these long acting FVIII variants do not eliminate the need for lifelong FVIII protein administration (Hay, 2012, Blood).

Gene therapy offers the potential of a cure through continuous endogenous production of human FVIII following a single administration of vector. Haemophilia 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 2ng/ml protein leads to a 1% expression) can ameliorate the severe phenotype (Srivastava, 2013, Haemophilia.); thus the therapeutic goal for gene therapy is a modest increase in hFVIII. Finally, the consequences of gene transfer can be assessed using simple quantitative rather than qualitative endpoints that can be easily assayed in most clinical laboratories.

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

7.1 Nonclinical Studies

The nonclinical program supports a single IV administration of BMN 270, the planned clinical route of administration, for the treatment of Haemophilia A in male patients. This

nonclinical program took into account the guidelines and reflection papers for gene therapy medicinal products under EMA Advanced Therapies. 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 (normal CD-1 mouse, B and T cell deficient mouse model of haemophilia 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.

The primary PD of BMN 270 was assessed in a series of non-GLP single dose studies in a FVIII KO x Rag2 mouse model of severe Haemophilia A that recapitulates the change in coagulation observed in the human severe disease population without interfering cross species immunogenicity. PD activity and expression of hFVIII was assessed for durations up to 13-weeks in the FVIII KO x Rag2 mouse given dose range of 2E11 through 2E14 vector genomes (vg)/kg. Low levels of plasma hFVIII were observed in mice given 2E12 vg/kg after eight-weeks, post dose. Plasma hFVIII activity using bleeding time as an endpoint was evaluated in the FVIII KO x Rag2 mouse given up to 2E13 and 1E14 vg/kg BMN 270 at 8 weeks, post dose. BMN 270 related correction of bleeding times showed a dose relationship that was similar to that observed in FVIII KO x Rag2 mice given matched IU levels of Refacto[®].

All cynomolgus monkeys used in this program were screened for neutralizing anti-AAV5 activity prior to study enrollment. PD activity and plasma hFVIII concentrations were evaluated in the cynomolgus monkey given up to 6E13 vg/kg BMN 270 for eight weeks. Peak expression of hFVIII was observed three to six weeks post administration with a subsequent decrease in expression presumably due to immunogenicity though not necessarily correlated to antibody titer.

The normal mouse was utilized in the GLP toxicology study to assess the safety profile of BMN 270 without the background of disease progression and in sufficient number per parameter. The GLP single dose toxicity study in normal CD-1 mice given 6E12 and 6E13 vg/kg with a 4 and 13-week follow up period monitored clinical pathology, defined potential target organs, immunogenicity, gene expression and activity. No changes in liver function were observed. In a single dose PD study in monkey given BMN 270, formation of anti-AAV5 total antibodies was observed at Week 8 with relatively low formation of anti-hFVIII total antibodies. No changes in liver function was observed.

The overall nonclinical safety profile includes formation of anti-AAV5 total antibodies with relatively lower formation of anti-hFVIII total antibodies. Immunogenicity against the AAV capsid and hFVIII is an anticipated finding for BMN 270 treatment and will be monitored in

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the nonclinical and clinical programs. Though not observed in the nonclinical species, liver toxicity utilizing clinical pathology parameters will be monitored in the clinical program based on previous literature. Cellular immune response will also be monitored.

Additionally, the BMN 270 transgene product has a final sequence closely matching that of the protein replacement treatment, Refacto[®] and therefore the safety profile of the BMN 270 transgene product is anticipated to be similar to Refacto® and have no unique FVIII-specific target organs of toxicity. The AAV5 capsid has not been modified and therefore no unique capsid-specific safety findings are anticipated. Because the biodistribution pattern of AAV5 after IV administration is consistent across species, BioMarin will confirm the nonclinical distribution pattern of BMN 270 during clinical development. Biodistribution of the AAV5 capsid has been documented to predominately target the liver with relatively lower levels of transduction observed in the lung, kidney, spleen, testes and blood compartment depending on the species and timing of administration. Liver targeted distribution of a similar AAV5 Factor IX gene therapy product was observed in the rhesus macaque monkey with low levels of vector genomes detected in spleen, kidney and testis (Nathwani, 2006, Blood). Despite distribution to non-liver organs, no expression of Factor IX was detected in these tissues. Additionally, distribution to the testis was observed in another study in monkeys given an AAV5-codon-optimized human porphobilinogen deaminase; however, vector genomes in the semen were only transiently observed within one week but not thereafter (Paneda, 2013, Hum.Gene Ther.).

Both normal and disease model mice and a limited number of monkeys were utilized to establish proof of concept, species scaling and dose response in order to select the first-in-human (FIH) dose of 6E12 vg/kg. This dose represents 10-fold safety factor from the no observed adverse effect level (NOAEL) in the GLP enabling nonclinical toxicology study in mice.

7.2 Previous Clinical Studies

This is the first clinical study for BMN 270.

BioMarin's program for haemophilia A builds on previous clinical trials of AAV-mediated gene transfer for a related condition, haemophilia B, that were conducted with an AAV2 vector (Manno, 2003, Blood) and an AAV8 vector (Nathwani, 2011, N.Engl.J.Med.), (Nathwani, 2014, N.Engl.J.Med.). The large size of the FVIII cDNA was shortened and a preclinical validation of this approach was performed with an AAV8 vector (McIntosh, 2013, Blood).

AAV serotype 5 is being tested in other clinical trials and was reportedly well tolerated without treatment-related serious adverse events in a recent phase 1 study for treatment of Acute Intermittent Porphyria (D'Avola, 2014, J.Hepatol.). In addition, AAV using other serotypes have been used in 105 clinical studies to date and no safety issue specific to the vector was ever reported.

7.3 Study Rationale

Haemophilia A (HA) is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males (Mannucci, 2001, N.Engl.J.Med.). It is caused by deficiency in the activity of coagulation factor VIII (FVIII), an essential cofactor in the intrinsic coagulation cascade. This disorder can be either inherited, due to a new mutation 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 is largely governed by the level of residual expression. Severe HA is classified as FVIII activity less than 1% of wild type (< 1 IU/dL), moderate disease comprises 1-5% of wild type activity and the mild form is 5-40% activity. The clinical manifestations of severe HA remain frequent spontaneous bleeding episodes, predominantly in joints and soft tissues, with a substantially increased risk of death from haemorrhage when the brain is involved.

Treatment of severe HA presently consists of intravenous injection of plasma derived or recombinant human FVIII protein (rhFVIII) concentrates both as prophylaxis 2-4 times per week, and at the time of a bleed, to prevent or control bleeding episodes, respectively. The half-life for FVIII (12-18 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 treatment (mean of 1 to 7 episodes/year with prophylaxis and up to 30 to 50 episodes/year for on demand treatment) (Nagel, 2011, Haemophilia.). The consequence of multiple bleeding events is the development of an underlying pathology that contributes to debilitating multiple-joint arthropathy and substantially increased risk of death (Nagel, 2011, Haemophilia). Chemical modification (e.g. direct conjugation of polyethylene glycol (PEG) polymers) and bioengineering of FVIII (e.g. FVIII-Fc fusion proteins) improve half-life by approximately 50%, and thus, show promise in reduced dosing and maintaining activity levels above 1%trough (Stonebraker, 2010, Haemophilia.), (Mahlangu, 2014, Blood). However, these longer acting FVIIIs remain dependent on multiple infusions to maintain critical levels of FVIII activity in severe HA patients. There is therefore a strong unmet need for a fully preventive treatment of HA to give patients a FVIII level compatible with a normal and haemorrhage-free life.

Gene therapy offers the potential of disease-modifying therapy by continuous endogenous production of active FVIII following a single intravenous administration of a vector with the appropriate gene sequence. Haemophilia 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 modest increases in the level of FVIII (any increase of the plasma level by 2 ng/ml induces an increase in activity of 1%) can ameliorate the severe form of the disease. Thus, relatively small changes in endogenous FVIII activity results in clinically relevant improvements in disease phenotype. Finally, the 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 (Mannucci, 2001, N.Engl.J.Med.). They have an excellent and well defined safety profile, and can direct long term transgene expression with tropism for specific tissues such as the liver (Nathwani, 2005, Curr.Hematol.Rep.) for serotypes 2, 5 and 8 among others). Indeed, an on-going gene therapy clinical trial for a related disorder, haemophilia B, has established that stable (>36 months) expression of human factor IX at levels that are sufficient for conversion of their bleeding phenotype from severe to moderate or mild is achievable following a single peripheral vein administration of AAV-8 vector (Nathwani, 2014, N.Engl.J.Med.). Several participants in this trial have been able to discontinue factor prophylaxis without suffering spontaneous haemorrhages, 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, 2011, Mol.Ther.), (Bainbridge, 2008, N.Engl.J.Med.), (Maguire, 2009, Lancet); (Simonelli, 2010, Mol.Ther.).

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

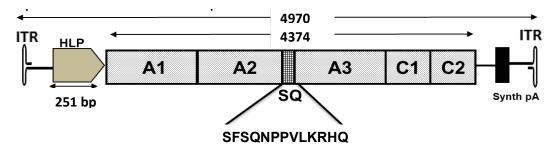


Figure 7.3.1: BMN 270 Transgene Construct, ~5.0 kbp

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BMN 270 will be delivered by single intravenous dose and is designed to achieve stable, potentially life-long expression of active FVIII in the plasma, synthesized from vector-transduced liver tissue. The clinical study BMN 270-201 is a first-in-human study designed to assess the relationship of vector dose to the augmentation of residual FVIII activity, and whether these levels are sufficient to alter the clinical phenotype. The relationship of dose to safety will be correlated to the activity of FVIII in patients with severe HA.

7.4 Summary of Overall Risks and Benefits

Safety will be assessed by adverse event reporting and clinical laboratory assessment. Based on prior human studies with peripheral injections of AAV vectors, there is no known safety risk of AAV gene therapy. However, a mild asymptomatic transaminitis was observed at week 7-12 after administration in humans with an AAV8-FIX, providing the rationale for the following surveillance plan (Nathwani, 2011, Mol.Ther.). Each subject will have a comprehensive surveillance plan that monitors LFTs once a week from dose to completion of Week 6, 3 times per week from Weeks 7 to 12, and once a week from Weeks 13 to 16. If a subject's ALT is found to be greater than 1.5x baseline during these periods, then LFTs will be monitored three times per week or until the ALT returns to baseline. LFTs will be monitored every other month for the first year and then every three months for up to 5 years post-dose in the safety extension.

Dose selection: The benefit of this study can only be enhanced by selecting a starting dose that maximizes the opportunity of observing a therapeutic effect, and therefore, reducing the possibility of a sub-therapeutic effect. With this consideration in mind, the starting dose 6E12 vg/kg was selected using overall data from the pre-clinical studies conducted in mice (normal and disease model, Rag2 -/- x FVIII -/-) and monkey. A detectable pharmacological response based on activity was observed at 6E12 vg/kg. A 10-fold safety margin based upon the NOAEL was observed in the GLP 13-week study in normal mouse at the highest dose administered. A 30-fold safety margin in an 8-week dose response study in disease model mice based on histology was observed at the highest dose administered. No BMN 270-related changes in clinical observations or chemistry was observed in the monkey at doses up to 6E13 vg/kg, a 10-fold safety margin after 8-weeks. Overall, no BMN 270-related findings, except expected formation of anti-AAV5 antibodies, were observed at the highest administered doses of 6E13, 2E14 and 6E13 vg/kg in the normal mouse, disease model mouse and monkey, respectively.

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Based on these key pre-clinical findings it can be suggested that the proposed starting dose of 6E12 vg/kg should not pose any risk or safety concerns to subjects with the best chance of benefiting the subject therapeutically.

8 STUDY OBJECTIVES

The primary objectives of the study are:

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

The secondary objectives of the study are:

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

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

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

Patients who provide written informed consent, meet the entry criteria definition of severe HA, and do not have transduction inhibition activity to AAV5 will be eligible to enroll in the study. Participants will be enrolled into one of up to three cohorts according to dose level:

- 1. 6E12 vg/kg of body weight, given as a single intravenous dose (iv)
- 2. 2E13 vg/kg, iv
- 3. 6E13 vg/kg, iv

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

Cohorts will be enrolled sequentially, allowing a period of 3 weeks or more between cohorts. Dose escalation may occur after a single subject in a cohort has been safely dosed if the resulting FVIII activity at the Week 3 visit is < 5 IU/dL in both assays. Three weeks is expected to be the time the expression will be close to the maximum. This escalation paradigm is intended to minimize the subject numbers exposed to subtherapeutic doses. The decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and a panel of investigators participating in the study.

If the FVIII activity reaches ≥ 5 IU/dL at the Week 3 visit, then the remaining subjects in the cohort will be enrolled without the need to wait for 3 weeks between subjects.

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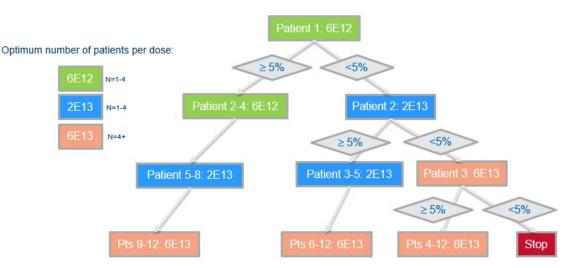


Figure 9.1.1: Flow Chart of Dose Escalation Scheme

Subject 1 (Cohort 1) will be dosed by intravenous infusion with 6E12 vg/kg of body weight. If the FVIII activity level does not reach 5 IU/dL or greater (expressed as % in Figure 9.1.1) at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 1 and enrollment into Cohort 2 will initiate with Subject 2 at the next dose (2E13 vg/kg).

If the FVIII activity level in the first subject treated in Cohort 2 does not reach \geq 5 IU/dL at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 2 and enrollment into Cohort 3 (6E13) will initiate with the next subject.

If the FVIII activity level in the first subject treated in Cohort 3 does not reach \geq 5 IU/dL at the Week 3 visit in both assays, then the DRB will recommend whether to continue to add subjects to the cohort and/or whether to continue the study.

For the first subject treated in each Cohort, if the activity level reaches ≥ 5 IU/dL and no safety issue is found, then up to four subjects will be enrolled in the Cohort. Although the optimum design of this study is three cohorts of 4 subjects, the adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals. Because subjects develop neutralizing immunity upon exposure to the capsid, re-challenge of vector is not a likely treatment option and these subjects have effectively a single opportunity for therapy using this AAV capsid. Efficacy will be determined by FVIII activity at 16 weeks post dose. Safety will be evaluated for approximately 5 years after dosing. Any safety signal may trigger a review of the data and possible additional immunogenicity studies that include an assessment of cellular immune responses using collected peripheral blood mononuclear cells (PBMC). Additionally, if any of the events listed in Section 9.3.3.1 occur, enrollment into the trial will be halted to

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complete an extensive safety analysis. Notification of the study halt will be sent by the Sponsor to the participating sites via telephone and email immediately after becoming aware of a safety concern. This will ensure no additional subjects are dosed until the signal has been completely evaluated. If, following safety review by the Data Review Board (DRB) and the Sponsor, it is deemed appropriate to restart dosing, a request to restart dosing with pertinent data will be submitted to the health authority.

A summary of events and assessments are provided by visit in Table 9.1.1 for Screening, Baseline and BMN 270 Infusion, in Table 9.1.2 for Post-Infusion Follow-up, and in Table 9.1.3 for Safety Follow-up.

Table 9.1.4, dealing with steroid prophylaxis in the event of elevated LFTs, is discussed in Section 9.4.8.2.

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Table 9.1.1: Schedule of Events – Screening and Infusion

	Prio	r to BMN 270 Infusion		BMN 270	
Assessment	Screening ⁱ (Day -28 to Day -1)	Smart Rescreening ⁱ (Day -28 to Day -1)	Baseline (Day -7 to Day -1) ^h	Infusion Visit $(Day 1)^k$	
Informed consent	Х				
Medical History	Х				
Physical Exam ^a	X		Х	X	
Vital Signs	Х	X		X	
Assessment of Adverse Events and Concomitant Medications	X	X	Х	X	
Documentation of bleeding episodes and FVIII usage (by either subject or clinical information)	X	Х	Х		
Distribution of subject diaries and training in their use			Х		
Electrocardiogram	Х				
Chest X-ray	Х				
Liver Ultrasound	Х				
hFVIII Assays ^b	X	X ^j			
AAV5 Assays ^c	X	X		X	
Screen for Hepatitis B, Hepatitis C, HIV ^d	Х				
Blood chemistry, haematology, urine tests, coagulation screen, and CRP ^e	Х	X	Х		
PBMC collection for CTL baseline			Х		
PCR of vector genomes in blood, saliva, urine, semen, and stools			Х		
Biomarker testing ^f	X				
Exploratory biomarker assessments ^g			Х		
Haemo-QoL-A Quality of Life (QoL) assessment			Х		
BMN 270 Infusion				X	

|--|

^a Complete physical examination should be done at Screening. Brief physical examination may be done at Baseline and at the BMN 270 Infusion Visit. Height and weight will be recorded at Screening only.

^b Includes baseline hFVIII activity (chromogenic FXa and one-stage APTT assays), hFVIII coagulation activity exploratory assay, hFVIII inhibitor level (Bethesda assay with Nijmegen modification), hFVIII total antibody titer, and hFVIII antigen (ELISA).

^c Screening (done during Screening) and testing (at Infusion Visit) of AAV5 pre-existing immunity may include plasma samples for 3 assays (in vivo transduction inhibition, in vitro transduction inhibition and AAV5 total antibody assays). The assessment on the day of the infusion visit must be performed before the BMN 270 infusion is given.

^d Patients with documented negative results within the last 30 days do not need to be retested.

^e Refer to Table 9.7.8.2.1 for laboratory assessments to be included.

 $^{\rm f}$ Includes HLA genotyping, FVIII genotyping, TNF α and IL10a single nucleotide polymorphisms.

^g Blood samples will be collected from subjects to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to Haemophilia A disease. The genetic/genomic testing on these exploratory samples is optional.

^h Should the screening visit occur within 7 days of the drug infusion, physical examination, blood chemistry, haematology, urine tests, coagulation screen, and CRP do not need to be repeated at Baseline.

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

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

^k Assessments on the day of infusion should be performed prior to the infusion. 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), following the infusion hourly (± 5 minutes) for 6 hours and then every 2 hours (± 15 minutes) for 6 hours and then at 4 hour intervals (± 15 minutes).

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		Follow-Up After BMN 270 Administr										istration - Weeks [*]								
		Week 1																		
Assessment		1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16		
	D2	D4	D8																	
Physical exam ^a			Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х		
Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)			Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х		
Vital Signs			Х	X	Х	X	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х		
Blood chemistry, haematology, urine tests, coagulation screen, and CRP ^b			Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х		
FVIII assays ^c		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х		
FVIII antibody titer			Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х		
PCR of vector genomes in blood, saliva, urine, semen, and stools ^d	Х	Х	Х	X	Х	X	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х		
Exploratory biomarker assessments ^e				Х		Х		Х		Х		Х		Х		Х		Х		
Haemo-QoL-A QoL assessment			X	Х	Х	Х												Х		
AAV5 antibody titer										Х								Х		
Testing for reactivation of hepatitis B and hepatitis C			Х		Х			Х												
PBMC collection						Х				Х				Х				Х		

Table 9.1.2: Schedule of Events – Post-Infusion Follow-Up

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

^a Brief physical examination should be done at all weekly visits except Week 16, where a complete physical examination should be performed. Refer to Section 9.7.8.4.

^b Refer to Table 9.7.8.2.1 for laboratory assessments to be included. Each subject will have comprehensive surveillance plan monitoring LFTs once a week from dose to completion of Week 6, 3 times per week (every other day excluding weekends) from Weeks 7 to 12, and once a week from Weeks 13 to 16. If a subject's ALT is found to be greater than 1.5x baseline during these periods, then LFTs will be monitored three times per week or until the ALT returns to baseline.

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^c Includes hFVIII activity level (APTT and FXa chromogenic assay), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, hFVIII coagulation activity exploratory assay, and hFVIII antigen (ELISA). 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.

^d Collection to occur on Day 2 and 4 following BMN 270 infusion, and then weekly until at least 3 consecutive negative results are obtained.

^e Blood samples will be collected from subjects to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to Haemophilia A disease. The genetic/genomic testing on these exploratory samples is optional.

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		Yea	r 1 - W	eeks [*]		Years 2- 5 [*]	ETV (early		
Assessment	20	28	36	44	52	Q3M	termination visit)		
Physical exam ^a	Х	Х	X	Х	Х	Х	Х		
Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)	Х	Х	Х	Х	Х	Х	Х		
Vital Signs	Х	Х	Х	Х	Х	Х	Х		
Blood chemistry, haematology, urine tests, coagulation screen, and CRP ^b	Х	Х	Х	Х	Х	Х	Х		
FVIII assays ^c	Х	Х	Х	Х	Х	Х	Х		
AAV5 antibody titer	Х	Х	Х	Х	Х	Х	Х		
FVIII antibody titer	Х	Х	Х	Х	Х	Х	Х		
PBMC Collection (for determination of FVIII and Capsid specific CTL activity)	Х	X	X	X	X	Х	Х		
PCR of vector genomes in blood, saliva, urine, semen, and stools ^d	Х	Х	Х	Х	Х	Х	Х		
Haemo-QoL-A QoL assessment		Х			Х	X ^e	Х		

Table 9.1.3: Schedule of Events – Safety Follow-Up

* Visit windows are ± 1 week for visits in Year 1, and $\pm \overline{2}$ weeks for visits in Years 2-5.

^a Complete physical examination should be performed at Weeks 52 and every 52 weeks thereafter; brief physical exam may be performed at other study visits. Refer to Section 9.7.8.4.

^bRefer to Table 9.7.8.2.1 for laboratory assessments to be included.

^c Includes hFVIII activity level (one-stage APTT and chromogenic FXa assay), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, hFVIII coagulation activity exploratory assay, and hFVIII antigen (ELISA). 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.

^d Sample testing during Safety Follow-Up is not required if at least 3 consecutive samples are cleared during the Post-Infusion Follow-Up period.

^e Haemo-QoL-A QoL assessment during Years 2-5 of Safety Follow-up should be performed at every other visit (every 6 months) starting with the Week 78 visit (ie, 26 weeks after the Week 52 visit at the end of Year 1 of the Safety Follow-up period).

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Table 9.1.4: Schedule of Events – Steroid Prophylaxis

	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12	Week 13	Week 14	Week 15	Week 16	Week 17	Week 23-25
Prophylactic steroids (dose in mg/day) ^a	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	
Hepatitis B testing ^b																X
Liver function testing ^c	Week	Weekly, then 3x/week during the 6-week period when a liver response is expected based on the liver response in the original subject														

^a Steroid prophylaxis will be started in all subjects <u>not yet dosed</u> following the first subject who develops elevated liver function tests (defined as 1.5x baseline ALT) during the study. Subjects already dosed who have not yet reached Week 17 in the study will be evaluated for the use of prophylactic steroids after discussion between the Investigator and the Medical Monitor. Deviations from this prophylactic steroid dosing regimen must be approved by the Medical Monitor.

^b The subject's hepatitis B status should be rechecked 6-8 weeks after the end of corticosteroid treatment, using the same tests performed for hepatitis B status at Screening.

^c Reports of abnormal LFTs (defined as 1.5x the subject's baseline ALT) should be made to the BioMarin medical monitor within 30 minutes of the lab value being available.

9.2 Discussion of Study Design, Including Choice of Control Group

Study 270-201 is designed to be a first-in-man, phase 1/2 open-label, dose escalation study in patients with severe haemophilia A. Three doses of BMN 270 will be evaluated and the dose escalation decision tree is summarized in Figure 9.1.1.

The decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and the DRB.

There will be no control group. Parameters for each subject will be compared to a pre-treatment assessment of safety (liver function) and efficacy (number of bleeds, use of replacement therapy).

As AAV based treatment always leads to anti-capsid immune response, no true control group (for example with an empty AAV) is possible.

9.3 Selection of Study Population

Up to 12 severe haemophilia A patients may enroll into the study; the actual number of patients will depend on the criteria for dose escalation.

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 criteria:

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

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 immunity to the AAV5 capsid as measured by AAV5 transduction inhibition or AAV5 total antibodies
- 2. Any evidence of active infection or any immunosuppressive disorder.
- 3. HIV positive
- 4. Significant liver dysfunction as defined by abnormal elevation of:
 - ALT (alanine transaminase) to 3 times the upper limit of normal;
 - Bilirubin above 3 times the upper limit of normal;
 - Alkaline phosphatase above 3 times the upper limit of normal; or
 - INR (international normalized ratio) \geq 1.4.
- 5. Potential participants who have had a liver biopsy in the past 3 years are excluded if they had significant fibrosis of 3 or 4 as rated on a scale of 0-4
- 6. Evidence of any bleeding disorder not related to Haemophilia A
- 7. Platelet count of $< 100 \times 10^9/L$
- 8. Creatinine $\geq 1.5 \text{ mg/dL}$
- 9. Liver cirrhosis of any etiology as assessed by liver ultrasound
- 10. Hepatitis B if surface antigen is positive
- 11. Hepatitis C if RNA is positive
- 12. Treatment with any IP within 30 days prior to the end of the screening period
- 13. Any disease or condition at the physician's discretion that would prevent the patient from fully complying with the requirements of the study including possible corticosteroid treatment outlined in the protocol. The physician may exclude patients unwilling or unable to agree on not using alcohol for the 16-week period following the viral infusion.
- 14. Prior treatment with any gene transfer agent
- 15. Major surgery planned in the 16-week period following the viral infusion
- 16. Use of immunosuppressive agents or live vaccines within 30 days before the viral infusion

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. A subject's participation in the study may be discontinued at any time at the discretion 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.

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 admitted into the study or does not meet entry criteria
- Subject is lost to follow-up

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

The Investigator or designee must explain to each subject, before enrollment into the study, that for evaluation of study results, the subject's protected health information obtained during the study may be shared with the study Sponsor, regulatory agencies, and IRB/IEC/REB. It is the Investigator's (or designee's) responsibility to obtain written permission to use protected health information per country-specific regulations, such as the Health Insurance Portability and Accountability Act (HIPAA) in the US, from each subject. If permission to use protected health information is withdrawn, it is the Investigator's responsibility to obtain a written request, to ensure that no further data will be collected from the subject and the subject will be removed from the study.

9.3.3.1 Study Safety Evaluation Criteria

If any of the following events occur in a subject in the study who has received BMN 270 infusion, enrollment into the trial will be put on halt to complete an extensive safety analysis per Section 9.1.

- A 5-fold increase from baseline in ALT after BMN 270 administration
- The occurrence of Grade 3 or higher adverse events assessed as related to study drug, including liver failure and clinical hepatitis
- Grade 2 adverse event assessed as related to study drug that persists for at least 7 days
- The detection of neutralizing antibodies to hFVIII following BMN 270 infusion
- The persistent detection of the AAV vector genome in the semen of a participant more than 26 weeks after BMN 270 infusion, as discussed in Section 9.7.8.5
- The occurrence of a malignancy excluding skin cancers at any point after BMN 270 infusion

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 CRF pages. In legal jurisdictions where use of initials is not permitted, a substitute identifier will be used.

Subjects who withdraw from the study will not be replaced.

9.3.5 Duration of Subject Participation

The duration of this study will be approximately 264 weeks. This includes 4 weeks of screening, 1 day of BMN 270 infusion, 16 weeks of Post-Infusion Follow-Up, and 244 weeks of Safety Follow-Up. A primary endpoint analysis on safety and efficacy will be performed at 16 weeks.

9.4 Treatments

BioMarin or its designee will provide the study site with study drug sufficient for study completion. BioMarin is responsible for shipping study drug to clinical sites.

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.

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 2 mL polypropylene cryovial. Each vial contains 1.1 mL of AAV5-hFVIII-SQ at a concentration of 2E13 vector genomes per mL in a pH 7.4 phosphate buffer.

The study drug label includes the following information: lot number, required storage conditions, a precautionary statement, expiry date, study number, and BioMarin name and address. Labelling will be done according to country specific requirements.

9.4.3 Storage

At the study site, all IP must be stored under the conditions specified in the IB 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

After a physical exam performed by the PI or designee, participants will be admitted on the day of BMN 270 infusion. An IV catheter will be inserted into a suitable peripheral vein (e.g. 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. An electric syringe pump will be used to infuse through an in-line, low protein binding 0.22 micron filter. BMN 270 will be infused through the catheter using an appropriate infusion pump at a constant rate of 4 ml/min while monitoring the vital signs (pulse, blood pressure, respiration rate and temperature) at 15 minute (\pm 5 minutes) intervals. The anticipated maximum interval from initiation of thawing of BMN 270 to completion of the infusion is 4 hours, although the IP has been shown to be stable at room temperature for 6 hours.

Following completion of the infusion, vital signs will be monitored hourly (± 5 minutes) for 6 hours and then every 2 hours (± 15 minutes) for 6 hours and then at 4 hour intervals. If the vital signs are stable the catheter will be removed 20-24 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 24 hours to observe for any immediate toxicity of the procedure. After 24 hours, participants 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.

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 Sponsor will be required prior to enrollment of each study subject. Upon their enrollment into the study, subjects will be assigned a unique subject number and dose level by the Sponsor.

Cohorts are enrolled serially and their dose is defined in Section 9.4.6.2 below. Escalation is based on FVIII activity 3 weeks after injection. Cohorts may receive the next higher dose if subjects in the previous cohort does not meet the activity criteria, or the same dose if subjects in the previous cohort meets the activity criteria.

9.4.6 Selection of Doses Used in the Study

The starting dose was based on the expression of hFVIII observed in nonclinical studies of mice and monkeys. The starting dose has a significant safety margin (10-fold) from NOAEL in mice. The dose escalation is half-logs based.

9.4.6.1 Selection of Timing of Dose for Each Subject

A minimum of three weeks are required between subjects, to allow for evaluation of safety and expression of hFVIII. After three weeks, depending on the activity level, the choice of the dose for the next subject will be made as described below.

9.4.6.2 Selection of Dose for Each Subject

The starting dose was determined by expression of hFVIII observed in mice and monkeys and a scale up factor based on previous experience, an improved purification process over previous trials (thus potentially decreasing the risk of immune response), and a new evaluation of the titer (PCR performed after hairpin removal).

Approximately three weeks after an injection, the decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and the DRB.

Subject 1 (Cohort 1) will be dosed by intravenous infusion with 6E12 vg/kg of body weight. If the FVIII activity level does not reach 5 IU/dL or greater (expressed as % in Figure 9.1.1) at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 1 and enrollment into Cohort 2 will initiate with Subject 2 at the next dose (2E13 vg/kg).

If the FVIII activity level in the first subject treated in Cohort 2 does not reach \geq 5 IU/dL at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 2 and enrollment into Cohort 3 (6E13) will initiate with the next subject.

If the FVIII activity level in the first subject treated in Cohort 3 does not reach \geq 5 IU/dL at the Week 3 visit in both assays, then the DRB will recommend whether to continue to add subjects to the cohort and/or whether to continue the study.

For the first subject treated in each Cohort, if the activity level reaches \geq 5 IU/dL and no safety issue is found, then up to four subjects will be enrolled in the Cohort. Although the optimum design of this study is three cohorts of 4 subjects, the adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

Refer to Figure 9.1.1 for a visual representation of the study design.

9.4.7 Blinding

This is an open-label study.

9.4.8 Prior and Concomitant Medications

All prescription and over-the-counter medications taken by a subject for 30 days before Screening will be recorded on the designated CRF. The Investigator may prescribe additional medications 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 CRF.

The following medications are prohibited starting 30 days before Screening:

- Live vaccines
- Systemic immunosuppressive agents

9.4.8.1 Concomitant Haemophilia Treatments

Subjects on "on demand" therapy for FVIII will continue their treatment at will. Subjects on prophylactic FVIII therapy will discontinue their treatment starting the day of infusion and switch to an "on demand" schedule. FVIII can always be taken as needed by the subject, who will carefully record his treatment and bleeding episodes in his diary.

9.4.8.2 Glucocorticoid Treatment of Elevated Hepatic Transaminases

During the Post-Infusion Follow-up Period, each subject will have comprehensive surveillance plan monitoring LFTs once a week from dose to completion of Week 6, 3 times per week from Weeks 7 to 12, and once a week from Weeks 13 to 16. If a subject's ALT is

found to be greater than 1.5x his baseline during these periods, then LFTs will be monitored three times per week until the ALT returns to baseline.

Reports of abnormal LFTs (defined as 1.5x the subject's baseline ALT level) should be made to the BioMarin medical monitor within 30 minutes of the lab value being available, and treatment with prednisolone will be initiated immediately at a dose of 60 mg per day and then gradually tapered (60 mg daily for the first 2 weeks, then 40 mg the next 2 weeks, then 30 mg the next two weeks, then 20 mg the next two weeks, then stop, for a total treatment of 8 weeks). Local laboratory results of LFTs will be used to trigger corticosteroid treatment as needed. In case of discrepant results between local and central laboratories, the Investigator and Medical Monitor will decide further action.

If a glucocorticoid treatment is started for a subject at any point of the study, the following steps will be taken:

- A prophylactic glucocorticoid treatment will be started for subsequent subjects scheduled to be dosed. Subjects will receive prednisolone 40 mg per day starting at week 3, for a duration of 4 weeks, then tapered by 5 mg every two weeks for 8 weeks (until 20 mg/day is reached), then tapered 5 mg per week for 3 weeks, for a total duration of 15 weeks (refer to 4).
 - Subjects already dosed who have not yet reached Week 17 in the study will be evaluated for the use of prophylactic steroids after discussion between the Investigator and the Medical Monitor.
- Once prophylactic glucocorticoid treatments have been initiated, then all subjects (who have not already passed that period in the study) will have 3x/week LFT assessments during the 6-week period when a liver response is expected based on the liver response in the original subject, if this period is different from the 3x/weekly LFT assessments already planned for Weeks 7-12.
 - Subjects who have already passed that 6-week period in the study will continue to have the regularly scheduled LFT assessments as planned in the protocol.
- Management and monitoring of reactions to corticosteroids should be determined by the Investigator's clinical judgment in consultation with the Sponsor's Medical Monitor. This includes the contraindicated use of NSAIDs during corticosteroid treatment, and specific monitoring not already covered by the schedule of events. Hepatitis B status will be rechecked at the end of the corticosteroid treatment. All adverse events should be reported as outlined in Section 10 of the protocol.

9.4.9 Treatment Compliance

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

9.5 Investigational Product Accountability

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

9.5.1 Return and Disposition of Clinical Supplies

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

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

All study drug and related materials should be stored, inventoried, reconciled, and destroyed or returned according to applicable state and federal regulations and study procedures.

9.6 Dietary or Other Protocol Restrictions

There are no dietary or other protocol restrictions for this study.

9.7 Safety and Efficacy Variables

As this is a first-in-man study, the primary endpoint of safety will be assessed as explained in Section 9.7.8.

The primary efficacy measure will be to assess plasma FVIII activity. The efficacy goal of the study is to establish the dose relationship to FVIII activity ≥ 5 IU/dL at 16 weeks post BMN 270 administration.

Proprietary and Confidential

9.7.1 Safety and Efficacy Measurements Assessed

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

9.7.2 Primary Efficacy Variables

The primary efficacy measure will be the plasma FVIII activity monitored on a regular basis after BMN 270 dose. The efficacy goal of the protocol is to ascertain the dose range of BMN 270 required to convert severe HA patients to stable expression of FVIII at 5 IU/dL or above, i.e., a mild severity. This is associated in natural history studies with clinically superior long term outcomes, (Den Ujil, 2011, Haemophilia).

The following assays will be used to measure the primary efficacy variable:

- FVIII activity (chromogenic FXa assay)
- FVIII activity by one-stage APTT (Activated Partial Thromboplastin Time)

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 FVIII activity level in both assays and the number of subjects with FVIII activity ≥ 5 IU/dL in at least one of the two assays will be summarized.

Timing of assessment by these assays is provided in Table 9.1.2 and Table 9.1.3. Details on performing the assays are included in the Laboratory Manual.

9.7.3 Secondary Efficacy Variables

Secondary efficacy measures will be the reduction in the frequency of factor replacement therapy, and reduction in the number of bleeding episodes. 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.

9.7.4 Immunogenicity

Immunogenicity assays will be performed on plasma. The assays will include detection of anti-capsid, and anti-FVIII total antibody, and determination of neutralizing antibodies against FVIII. Any increase in total antibody level, especially during the time period of 5-12 weeks, will be compared with FVIII activity measurements. Any abnormality of the liver parameters will lead to a retrospective immunogenicity assessment to determine anti-FVIII and capsid specific CTL. Anti-FVIII and capsid specific CTL assays will be performed on collected PBMCs.

Timing of assessment by these assays is provided in Table 9.1.2 and Table 9.1.3.

9.7.5 Pharmacodynamics

The hFVIII antigen and activity level will be measured by an ELISA (antigen) and by one-stage APTT and/or chromogenic FXa assay (activity). Individual antigen and activity plasma plots will be prepared to assess changes over 16 weeks. FVIII activity measurements will be used to determine PD parameters.

If supported by FVIII activity data, non-compartmental analysis and observation will be used to estimate individual values of C_b (baseline concentration), C_{ss} (steady state concentration), T_{ss} (time to steady state), C(t) and AUC(0-t) where t is 16 weeks. Other parameters that may be used to describe individual FVIII protein and activity plasma profiles are C_{max} (maximum concentration) and C_{avg} (average concentration, AUC(0-t)/t). The PD parameters and dose will be used to assess clinical pharmacology.

Sample collection times are indicated in Table 9.1.2 and Table 9.1.3.

9.7.6 Exploratory Biomarker Assessments

Blood samples will be collected from subjects at the time points indicated in Table 9.1.1 and Table 9.1.2 to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to Haemophilia A disease. The genetic/genomic testing on these exploratory samples is optional.

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 may be used for exploratory use once the primary use has been completed. No additional genetic or genomic testing will be conducted on any sample (other than testing specified in the protocol).

9.7.7 Haemo-QoL-A Quality of Life Assessment

The Haemo-QoL-A is a patient-reported outcome (PRO) questionnaire which will be used to assess subject quality of life (QoL) during the study. Assessments will occur at the time points listed in the Schedules of Assessments.

Details regarding the QoL assessment will be included in the Study Reference Manual.

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.

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9.7.8.1 Adverse Events

The occurrence of AEs will be assessed continuously from the time the subject signs the ICF. The determination, evaluation and reporting of AEs will be performed as outlined in Section 10. Assessments of AEs will occur at the time points shown in Table 9.1.1.

9.7.8.2 Clinical Laboratory Assessments

Specific visits for obtaining clinical laboratory assessment samples are provided in Table 9.1.1. The scheduled clinical laboratory tests are listed in Table 9.7.8.2.1. Refer to the Study Reference Manual 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 the cause of the abnormality is determined, the value returns to baseline or to within normal limits, or 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 CRF.



Table 9.7.8.2.1:	Clinical Laboratory Tests
------------------	----------------------------------

Blood Chemistry	Haematology	Urine Tests	Other
Albumin	Haemoglobin	Appearance	CRP
Alkaline phosphatase	Haematocrit	Color	
ALT (SGPT)	WBC count	рН	Coagulation Screen including:
AST (SGOT)	RBC count	Specific gravity	APTT
Direct bilirubin	Platelet count	Ketones	PT/INR
Total bilirubin	Differential cell count	Protein	ТТ
BUN		Glucose	
Calcium		Bilirubin	
Chloride		Nitrite	
Total cholesterol		Urobilinogen	
CO ₂		Haemoglobin	
Creatinine			
Glucose			
GGT			
LDH			
Phosphorus			
Potassium			
Total protein			
Sodium			
Uric acid			

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CO₂, carbon dioxide; GGT, gamma-glutamyltransferase; LDH, lactate dehydrogenase; PT, prothrombin time; APTT, activated partial thromboplastin time; RBC, red blood cell; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; WBC, white blood cell; TT, thrombin time; INR, international normalized ratio.

9.7.8.3 Liver function and Hepatitis Testing at Screening

Subjects will be screened for evidence of previous hepatitis B or hepatitis C infection at Screening. Subjects with documented results showing an absence of active Hepatitis B or Hepatitis C infection (as measured by positive surface antigen for hepatitis B or positive RNA testing for hepatitis C) 30 days prior to providing signed informed consent do not need to be screened again.

Evidence of ongoing Hepatitis B or Hepatitis C infection is exclusionary. Subjects who have cleared a Hepatitis B infection or are seronegative do not need to receive the Hepatitis B vaccination.

A liver ultrasound and liver function testing at Screening will identify any significant hepatic dysfunction, which is defined as:

- More than 3x the normal ALT level
- More than 3x the normal bilirubin level
- More than 3x the normal Alkaline phosphatase level.
- INR \geq 1.4.
- Thrombocytopoenia under $100 \ge 10^9/L$
- Liver ultrasound results indicative of a liver cirrhosis

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

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

Systolic blood pressure, diastolic blood pressure, heart rate, respiration rate, and temperature will be assessed at Screening, Baseline, and at the beginning of each visit during the Post-Infusion Follow-Up and Safety Follow-Up periods. On the day of the BMN 270 Infusion, vital signs will be monitored prior to infusion, during the infusion every 15 minutes (\pm 5 minutes), following the infusion hourly (\pm 5 minutes) for 6 hours and then every 2 hours (\pm 15 minutes) for 6 hours and then at 4 hour intervals (\pm 15 minutes).

A complete physical examination is necessary during Screening/Baseline; thereafter, 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, respiratory, neurologic, and gastrointestinal assessments.

Weight and height will be recorded at Screening only.

9.7.8.5 Viral Shedding

Viral shedding has been extensively studied in all similar clinical trials performed to date. (Nathwani, 2014, N.Engl.J.Med.); (Manno, 2006, Nat.Med.); (Schenk-Braat, 2007, J.Gene Med.); (Croteau, 2004, Ann.Occup.Hyg.). In the literature referenced above, vector was no longer detectable after 40 days in blood, saliva, urine or stool. However, vector persisted in semen for 16 weeks in the seminal fluid but not in motile sperm (Manno, 2006, Nat.Med.). In all cases, the amount of vector present in these bodily fluids involved an extremely small fraction of the infused dose.

Viral shedding will also be extensively studied in the present clinical trial, every week up to 16 weeks, then every 4 weeks to one year, then every three months, until at least 3 consecutive negative results are obtained. During the Post-Infusion Follow-Up period, subjects will undergo testing of various bodily samples to look for evidence of viral shedding for possible viral transmission. Bodily fluids will be tested by PCR at the time points indicated in Table 9.1.2 and Table 9.1.3. Fluids tested will include:

- Blood
- Saliva
- Semen
- Urine
- Stool

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 haematology, 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, a reportable adverse event (AE) is any untoward medical occurrence (e.g., sign, symptom, illness, disease or injury) in a subject administered the study-drug or other protocol-imposed intervention, regardless of attribution. This includes the following:

- AEs not previously observed in the subject that emerge during the course of the study.
- Pre-existing medical conditions judged by the Investigator to have worsened in severity or frequency or changed in character during the study.
- Complications that occur as a result of non-drug protocol-imposed interventions (eg, AEs related to screening procedures).

An adverse drug reaction is any AE for which there is a reasonable possibility that the study-drug caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the study-drug and the AE.

Bleeding events that are normal events of haemophilia (ie, bleeding events which occur only because the subject is a haemophiliac) should not be recorded as AEs but will instead be captured in subject diaries. Bleeding events that occur where a normal (ie, non-haemophiliac) patient would bleed, such as bleeding as a result of major trauma, should be recorded as adverse events. All bleeding events which meet criteria for being serious should be reported as serious adverse events (SAEs) whether or not they are bleeding events that are normal sequelae of haemophilia.

Whenever possible, it is preferable to record a diagnosis as the AE term rather than a series of terms relating to a diagnosis.

10.2 Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that at any dose meets 1 or more of the following criteria:

- Is fatal
- Is life threatening

Note: Life-threatening refers to an event that places the subject at immediate risk of death. This definition does not include a reaction that, had it occurred in a more severe form, might have caused death.

- Requires or prolongs inpatient hospitalization.
- 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 intervention to prevent one of the above consequences (e.g. anaphylaxis)

All adverse events that do not meet any of the criteria for SAEs should be regarded as nonserious AEs.

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 liver enzymes (ALT) that triggers a corticosteroid treatment

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 treatment, only SAEs associated with any protocol-imposed interventions will be reported. After informed consent is obtained and the first administration of study drug, the reporting period for all non-serious AEs and SAEs begins and continues for approximately 5 years or until study discontinuation/termination, whichever is longer. The criteria for determining, and the reporting of SAEs is provided in Section 10.2.

10.3.2 Eliciting Adverse Events

Investigators will seek information on AEs, SAEs, and EOSI at each subject contact by specific questioning and, as appropriate, by examination. Information on all AEs and SAEs

and EOSI, should be recorded in the subject's medical record and on the 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 severity of each will be assessed using the defined categories in Table 10.3.3.2.1.

The Investigator will determine the severity of each AE and SAE and EOSI using the NCI CTCAE v4. 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 as stated below.

Grade	Description	
1	Mild: asymptomatic or mild symptoms; clinical or diagnostic observatio indicated	ns only; intervention not
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 or debilitating: consequences; urgent intervention indicated	Grade 4 and 5 AEs should always be
5	Death related to AE	reported as SAEs

 Table 10.3.3.2.1: Adverse Event Grading (Severity) Scale

^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.

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10.3.3.3 Causality

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

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

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

- Plausible temporal relationship
- Absence of alternative explanations
- Rarity of event in a given patient or disease state
- Absence of event prior to study drug exposure
- Consistency with study product pharmacology

- Known relationship to underlying mechanism of study drug action
- Similarity to adverse reactions seen with related drug products
- Abatement of AE with discontinuation of study drug, and/or recurrence of AE with reintroduction of study drug

The investigator's assessment of causality for individual AE reports is part of the study documentation process. Regardless of the Investigator's assessment of causality for individual AE reports, the Sponsor will promptly evaluate all reported SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators and applicable regulatory authorities.

10.4 Procedures for Recording Adverse Events

10.4.1 Recording Adverse Events on a eCRF

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

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

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

10.4.1.1 Diagnosis versus Signs and Symptoms

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 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 haemorrhage 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 is one that extends continuously, without resolution, between subject evaluation time points. Such an event should be recorded only once on the AE eCRF unless its severity increases or decreases (in which case it should be recorded again on the AE 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.

10.4.1.4 Abnormal Laboratory Values

Laboratory test results will be recorded on the laboratory results pages of the AE 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 should be reported as such, in addition to being recorded as an AE in the AE eCRF.

A clinical laboratory abnormality is considered clinically significant and should be documented as AE if **any** of the following conditions is met:

- Accompanied by clinical symptoms
- Leading to a change in study medication (e.g. dose modification, interruption or permanent discontinuation)
- Requiring a change in concomitant therapy (e.g. addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment).
- The laboratory abnormality persists upon repeat confirmatory testing.
- 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 hFVIII activity should not be reported as adverse events unless signs of worsening are observed.

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 document 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 changed
- Hospitalization solely for the purpose of insertion of an in-dwelling IV catheter (such as a Port-a-Cath or other brand) for administration of study drug will not be considered an SAE.
- 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 partner should be reported within 24 hours of the site becoming aware of the pregnancy by entering the information on the Pregnancy eCRF and submitting to BPV within 24 hours of the site becoming aware of the event. The Investigator must make every effort to follow the subject's partner through resolution of the pregnancy (delivery or termination) and to report the resolution on the Pregnancy Follow-up Form in the study reference materials. 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.

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

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

10.5.2 Ethics Committee Reporting Requirements

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

10.6 Follow-up of Subjects after Adverse Events

The Investigator should follow all unresolved AEs and SAEs until the events are resolved or have stabilized, the subject is lost to follow-up, or it has been determined that the study treatment or participation is not the cause of the AE/SAE. Resolution of AEs and SAEs (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, 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 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 treatment.

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 treatment. The Sponsor should also be notified if the Investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that participated in this study.

10.8 Urgent Safety Measures

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

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

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

- Immediate need to revise the IP administration (eg, modified dose amount or frequency not defined in protocol)
- 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

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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, PhD
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 FXa assay and the APTT assays 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 will be performed within 28 days (\pm 14 days) of BMN 270 infusion while baseline assessments will take place within 7 days of BMN 270 infusion (Day 1). Should the screening visit occur within 7 days of the drug infusion, physical examination, vital signs, blood chemistry, haematology, urine tests, coagulation screen, and CRP do not need to be repeated at Baseline.

The following procedures will be performed during the Screening Period:

- Full medical history, including haemophilia A history, Hepatitis B, Hepatitis C, and HIV.
- Complete Physical Exam (including 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)
- Electrocardiogram
- Chest X-ray
- Liver Ultrasound
- Samples for hFVIII Assays
 - Baseline hFVIII activity chromogenic FXa (plasma)
 - o Baseline hFVIII activity level one-stage APTT assay
 - o hFVIII coagulation activity exploratory assay
 - o hFVIII inhibitor level (Bethesda assay with Nijmegen modification)
 - hFVIII total antibody assay
 - hFVIII antigen (ELISA)



- Blood sample for AAV5 Assays
 - o AAV5 antibody titer
 - AAV5 transduction inhibition assay
- Screen for Hepatitis B, Hepatitis C, and HIV if required (subjects with documented negative results 30 days prior to informed consent being obtained do not need to be retested)
- Blood chemistry, haematology, urine tests, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- Blood samples for Biomarker testing (including HLA genotyping, FVIII genotyping status, TNFα and IL10a single nucleotide polymorphisms)

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 sample for AAV5 Assays
 - AAV5 antibody titer
 - AAV5 transduction inhibition assay
- Blood chemistry, haematology, urine tests, coagulation screen, and CRP (refer to Table 9.7.8.2.1)

12.3 Baseline Visit

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

- Physical exam
- Assessment of Adverse Events and Concomitant Medications
- Documentation of bleeding episodes and FVIII usage (by either subject or clinical information)
- Distribution of subject diaries and training in diary completion
- Blood chemistry, haematology, urine tests, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- PBMC collection for CTL baseline
- PCR of vector genomes in blood, saliva, urine, semen, and stools
- Exploratory biomarker assessments
- Haemo-QoL-A QoL assessment

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 24 hours for the BMN 270 Infusion Visit. The following procedures will be performed during the BMN 270 Infusion Visit:

- Physical exam
- Assessment of Adverse Events and Concomitant Medications
- Blood sample for AAV5 Assays (must be performed before the BMN 270 infusion)
 - o AAV5 antibody titer
 - o AAV5 transduction inhibition assay
- BMN 270 Infusion
- Vital Signs
 - Vital signs will be recorded prior to BMN 270 infusion and then every 15 minutes (± 5 minutes) during BMN 270 infusion. Following infusion, vital signs will be monitored every 1 hour (± 5 minutes) for the first 6 hours, every 2 hours (± 15 minutes) for the next 6 hours, and then at 4 hour (± 15 minutes) intervals for the remainder of the subject's stay in the clinic.

12.5 BMN 270 Infusion Follow-Up Visits

After BMN 270 has been infused, subjects will return to the study site every week $(\pm 48 \text{ hours})$ for 16 weeks, when the following procedures will be completed:

12.5.1 Every Visit

Every week (Weeks 1 through 16), the following procedures will be performed:

- Physical exam
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Vital Signs
- Blood chemistry, haematology, urine tests, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
 - Each subject will have comprehensive surveillance plan monitoring LFTs once a week from dose to completion of Week 6, 3 times per week (every other day excluding weekends) from Weeks 7 to 12, and once a week from Weeks 13 to 16. If a subject's ALT is found to be greater than 1.5x baseline during these periods, then LFTs will be monitored three times per week or until the ALT returns to baseline.
- Samples for FVIII Assays
 - FVIII activity level (APTT)
 - FVIII activity level (chromogenic FXa assay)
 - FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level
 - FVIII antigen (ELISA)

Note: 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.

- FVIII antibody titer
- PCR of vector genomes in blood, saliva, urine, semen, and stools
 - Collection to occur weekly until at least 3 consecutive negative results are obtained

12.5.2 Week 1 – Day 2 and Day 4

On Day 2 and Day 4 of Week 1, the following procedures will be performed:

- PCR of vector genomes in blood, saliva, urine, semen, and stools (Day 2 and Day 4)
- Samples for FVIII Assays (Day 4 only)
 - FVIII activity level (APTT)
 - FVIII activity level (chromogenic FXa assay)
 - FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level
 - FVIII antigen (ELISA)

Note: 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.

12.5.3 Every 2 Weeks

Every 2 weeks (Weeks 2, 4, 6, 8, 10, 12, 14 and 16), the following procedure will be performed:

• Exploratory biomarker assessments

12.5.4 Weeks 4, 8, 12, and 16

At Weeks 4, 8, 12, and 16, the following procedure will be performed:

• PBMC collection

12.5.5 Weeks 1, 3, and 6

At Weeks 1, 3, and 6, the following procedure will be performed:

• Test for Hepatitis B and Hepatitis C reactivation

12.5.6 Weeks 8 and 16

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

• AAV5 antibody titer

12.5.7 Weeks 1, 2, 3, 4, and 16

At Weeks 1, 2, 3, 4, and 16, the following procedure will be performed:

• Haemo-QoL-A QoL assessment

12.6 Safety Follow-Up – Year 1

After the 16 weekly infusion follow-up visits are complete, subjects will return to the study site at Weeks 20, 28, 36, 44, and 52 (\pm 1 week), when the following procedures will be completed:

12.6.1 Every Visit

At Weeks 20, 28, 36, 44, and 52, the following procedures will be performed:

- Physical exam
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Vital Signs
- Blood chemistry, haematology, urine tests, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- FVIII Assays
 - FVIII activity level (APTT)
 - FVIII activity level (chromogenic FXa assay)
 - FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - FVIII antigen (ELISA)

Note: 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.

- AAV5 antibody titer
- FVIII antibody titer
- PBMC collection
- PCR of vector genomes in blood, saliva, urine, semen, and stools
 - Sample testing during Safety Follow-Up is not required if at least 3 consecutive samples are clear during the Post-Infusion Follow-Up period.

12.6.2 Weeks 28 and 52

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

• Haemo-QoL-A QoL assessment

12.7 Safety Follow-Up – Years 2-5

During Years 2-5 of Safety Follow-up, subjects will be assessed every 3 months (\pm 2 weeks). At these times, the following procedures will be completed:

12.7.1 Every Visit

Every 3 months (\pm 2 weeks), the following procedures will be performed:

- Physical exam
 - Complete Physical Exam will be performed every 52 weeks; Brief Physical Exams may be performed at other visits.
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Blood chemistry, haematology, urine tests, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- FVIII Assays
 - FVIII activity level (APTT)
 - FVIII activity level (FXa chromogenic assay)
 - FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - o FVIII antigen (ELISA)

Note: 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.

- AAV5 antibody titer
- FVIII antibody titer
- PBMC collection
- PCR of vector genomes in blood, saliva, urine, semen, and stools
 - Sample testing during Safety Follow-Up is not required if at least 3 consecutive samples are clear during the Post-Infusion Follow-Up period.
- Vital Signs

12.7.2 Every Other Visit (Every 6 Months)

Every six months starting at the Week 78 visit (ie, 26 weeks after the Week 52 visit at the end of Year 1 of the Safety Follow-up period), the following procedure will be performed:

• Haemo-QoL-A QOL assessment

12.8 Early Termination Visit

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

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

- Physical exam
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Blood chemistry, haematology, urine tests, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- FVIII Assays
 - FVIII activity level (APTT)
 - FVIII activity level (chromogenic FXa assay)
 - o FVIII coagulation activity exploratory assay
 - o Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - FVIII antigen (ELISA)

Note: 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.

- AAV5 antibody titer
- FVIII antibody titer
- PBMC collection
- PCR of vector genomes in blood, saliva, urine, semen, and stools
 - Sample testing at the ETV is not required if at least 3 consecutive samples are clear during the Post-Infusion Follow-Up period.
- Vital Signs

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• Haemo-QoL-A QOL assessment

12.9 End of Study

The study will end after the last subject completes the last Safety Follow-Up visit (Week 260). 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, any applicable randomization procedures, source document requirements, eCRFs, monitoring requirements, and procedures for reporting AEs, including SAEs.

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

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

14 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

14.1 Statistical and Analytical Plans

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

14.1.1 Interim Analyses

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

14.1.2 Procedures for Accounting for Missing, Unused and Spurious Data

Missing data will not be imputed.

14.2 Primary and Secondary Efficacy Analysis

The subjects will be followed in a longitudinal manner and all the relevant information will be collected. The analysis of the data will be descriptive in nature. Descriptive statistics include the number of subjects, mean, median, standard deviation, minimum, and maximum for continuous variables and count and percent for categorical variables. Efficacy variables will be summarized by dose cohort at each time point. Relationship between dose and efficacy results will be examined.

Data collected in a longitudinal manner may be analyzed using longitudinal methods such as mixed effect model which takes into account the correlation among the observation taken at various time points within a participant. Efficacy is a secondary endpoint, defined as biologically active hFVIII at ≥ 5 IU/dL by chromogenic FXa and/or one-stage APTT assay at 16 weeks following study treatment. hFVIII activity will be assessed weekly during the study period. We can only assess the true steady state of hFVIII protein produced from BMN 270 after a minimum of 72 hours has elapsed since the last infusion of FVIII protein concentrates.

14.3 Immunogenicity

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

14.4 Pharmacodynamic Analyses

The FVIII antigen and activity level as measured by an Elisa (antigen level) and by a one-stage APTT and/or chromogenic FXa assay (activity level), will be used for plasma

profiles; FVIII activity will be used to determine PD parameters. Traditional PK analysis is not applicable.

If supported by FVIII activity data, non-compartmental analysis and observation will be used to estimate individual PD parameter values of C_b (baseline), C_{ss} (steady state), T_{ss} (time to steady state), C(t) and AUC(0-t) where t is 16 weeks. Other parameters that may be used to describe individual FVIII protein and activity plasma profiles are C_{max} (maximum concentration) and C_{avg} (average concentration, AUC(0-t)/t). The parameters will be summarized using descriptive statistics.

14.5 Safety Analysis

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

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

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.

14.6 Determination of Sample Size

No formal sample size calculations based on statistical power were performed.

The sample size is determined based upon clinical consideration and could detect a strong clinical efficacy signal. Up to 12 subjects may be dosed in the study; the actual number of subjects will depend on the criteria for dose escalation.

14.7 Analysis Populations

The Safety analysis population is defined as all enrolled subjects who receive any study drug. The analysis of safety data will be performed on Safety Set.

The Full Analysis Set (FAS) is defined as all enrolled subjects who receive study drug and have at least one Baseline and post-Baseline assessment. The FAS will be used for efficacy analysis.

14.8 Changes in the Conduct of the Study or Planned Analyses

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

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

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

Note: If discrepancies exist between the text of the statistical analysis as planned in the protocol, and the final SAP, a protocol amendment will not be issued and the SAP will prevail.

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15 DATA REVIEW BOARD

There will be no formal DMC for this study, however a safety and efficacy evaluation board (the Data Review Board [DRB]) composed of the investigator representatives and the Sponsor will be established.

The DRB will review safety and efficacy on an ongoing basis. The DRB will meet prior to dose escalation or dose expansion to assess available subject safety and efficacy data and make recommendations with regards to the conduct of study. Should a safety signal arise, including one which may warrant a halt of study enrollment, the DRB will promptly convene for further assessment of subject safety. Notification of all DRB meetings and meeting outcomes will be sent to participating sites.

16 COMPENSATION, INSURANCE AND INDEMNITY

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

The Investigator should contact BioMarin immediately upon notification that a study subject has been injured by the IP 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 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 subject has followed the Investigator's instructions, BioMarin will pay for reasonable and necessary medical services to treat the injuries caused by the IP or study procedures, if these costs are not covered by health insurance or another third party that usually pays these costs. In some jurisdictions, BioMarin is obligated by law to pay for study-related injuries without prior recourse to third party payer billing. 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 CRF casebook to verify its accuracy.

CRFs 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 CRF instructions, blank data fields are not acceptable.

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

BioMarin's policy is that study data on the CRFs 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 an Investigator or institution refuses to allow access to subject records because of confidentiality, arrangements must be made to allow an "interview" style of data verification.

A CRA designated by BioMarin will compare the CRFs 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 CRA, 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 CRA 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 CRF 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 CRFs 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

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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 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).

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22 INVESTIGATOR RESPONSIBILITIES

22.1 Conduct of Study and Protection of Human Patients

In accordance with FDA Form 1572, 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 patients.
- He or she will personally conduct or supervise the study.
- He or she will inform any potential patients, 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 IRB review and approval in 21 CFR Part 56 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.
- 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
- He or she will ensure that adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.
- He or she will ensure that the IRB/IEC/REB complies with the requirements of 21 CFR Part 56, 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 patients or others are reported to the IRB/IEC/REB. Additionally, he or she will not make any changes in the research without IRB/IEC/REB approval, except where necessary to eliminate apparent immediate hazards to human patients.
- 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.

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23 SIGNATURE PAGE

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

Protocol Number: 270-201, Amendment 3

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 E6 ICH, as stated in the protocol, and other information supplied to me.

Investigator Signatur	re	Date
Printed name:		
Accepted for the Sp	oonsor:	
וכ		
Printed name: PI	, MD, PhD, <mark>Pl</mark>	, Clinical Sciences

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24 PROTOCOL AMENDMENT TEXT REVISIONS

The following table summarizes the revisions made to the protocol and relates the changes to the appropriate rationale (See pages 2-3). Text that has been added or inserted is indicated by <u>underlined</u> font, and deleted text is indicated by <u>strikethrough</u> font.

Section No./Title	Text Revisions	<u>Rationale</u>
2/Synopsis/Study Rationale	Treatment of severe HA presently consists of intravenous injection of plasma derived or recombinant <u>human FVIII</u> 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 rhFVIII (under 24 <u>FVIII (12 to 18</u> 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 treatment (mean of 1 to 7 episodes/year with prophylaxis <u>and</u> up to 30 to 50 <u>episodes/year</u> for on demand treatment).	1, 5
2/Synopsis/Study Design and Plan	PatientsCohorts will be enrolled sequentially every, allowing a period of 3 weeks or more between cohorts. Dose escalation may occur after a single patientsubject has been safely dosed if the resulting FVIII activity at the Week 3 visit is < 5 IU/dL in both the aPTT and chromogenic assays. Three weeks is expected to be the time the expression will be close to the maximum. This escalation paradigm is intended to minimize the patientsubject numbers exposed to subtherapeutic doses.	5
	Approximately three weeks after an injection, the decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and a panel of investigators participating in the study-, the Data Review Board (DRB).	
	If the FVIII activity $isreaches \ge 5$ IU/dL at the Week 3 visit, then the other patients of remaining subjects in the dose group cohort will be enrolled without waiting the need to wait for 3 weeks between patients subjects.	
	Patient Subject 1 will be dosed by intravenous perfusion infusionwith 6E12 vector genomes [vg] per kilogram of body weight.If the FVIII activity level does not reach ≥ 5 IU/dL at $\frac{21 \text{ days the Week 3 visit in both assays}}{21 \text{ days the Meek 3 visit in both assays}}$, then a higher no further subjectswill be dosed in Cohort 1 and enrollment into Cohort 2 will initiate with Subject 2 at the next dose (2E13 vg per kilogram) willbe used for the next patient./kg).	
	If the activity level does not reach \geq 5 IU/dL after Patient 2, then the highest dose (6E13 vg per kilogram) will be used for the next patient. FVIII activity level in the first subject treated in Cohort 2 does not reach \geq 5 IU/dL at the Week 3 visit in both assays, then no further subjects will be dosed in Cohort 2 and enrollment into Cohort 3 (6E13) will initiate with the next subject. If the FVIII activity level in the first subject treated in Cohort 3 does not reach \geq 5 IU/dL at the Week 3 visit in both assays, then the Data Review Board (DRB) will recommend whether to continue to add subjects to the cohort and/or whether to continue the study.	

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Section No./Title	Text Revisions	<u>Rationale</u>
	For <u>the first subject treated in each dose <u>Cohort</u>, if the activity level reaches ≥5 IU/dL and no safety issue is found, then up to four patients will receive subjects will be enrolled in the Cohort. Although the optimum design of this dose. If at any time study is three cohorts of 4 subjects, the adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts <u>based on</u> activity levels reach 10 IU/dL or higher, no further dose escalation will take place, but additional patients will then be dosed at this dose level for a total of 6 patients per dose. Of FVIII and safety signals. Because patients<u>subjects</u> develop neutralizing immunity upon exposure to the capsid, re-challenge of vector is not a <u>likely</u> treatment option and these patients<u>subjects</u> have effectively a single opportunity for therapy using this AAV capsid. Efficacy will be determined by FVIII activity at 16 weeks post dose. Safety will be evaluated for approximately 5 years after dose<u>dosing</u>. Any safety signal will may trigger a review of the data and possible additional analysis including immunogenicity studies that include an assessment of cellular immune responses using collected peripheral blood</u> mononuclear collection . <u>Cells (PBMC)</u> .	
2/Synopsis/Number of Subjects Planned	Up to 12 patientssubjects may enroll into the study; the actual number of patientssubjects will depend on the eriteria for dose escalation. A total of 6 patients may be enrolled at a single dose level VIII activity levels seen in each Cohort.	5
2/Synopsis/Diagnosis and All Criteria for Inclusion and Exclusion	 Individuals eligible to participate in this study must meet all of the following criteria: Males that are 18 years or older with established severe haemophilia A as evidenced by their medical history. Patients will be considered as severe if their <u>base</u> FVIII-<u>baseline</u> level is 1 IU/dL or less Treated/exposed to FVIII concentrates or eryoprecipitates <u>cryoprecipitate</u> for a minimum of 150 exposure days (EDs) No history of inhibitor, or no inhibitor on 2 consecutive occasions within the past 12 months using and results from a modified Nijmegen Bethesda assay higher of less than 0.6 Bethesda Unit <u>Units</u> (BU) on 2 consecutive occasions at least one week apart within the past 12 months Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study: Detectable pre-existing immunity to the AAV5 capsid as measured by AAV5 transduction inhibition andora AAV5 total antibodies Patients that are HIV positive are excluded. Significant liver dysfunction as defined by abnormal elevation of: 	1, 2, 5

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Section No./Title	Text Revisions	<u>Rationale</u>
	• ALT (alanine transaminase) to 3 times the upper limit of normal, bilirubin, <u>;</u>	
	• Bilirubin above 3 times the upper limit of normal;	
	• Alkaline phosphatase, above 3 times the upper limit of normal; or	
	• an-INR (international normalized ratio) of ≥ 1.4	
	• Treatment with any IP within 30 days prior to the <u>end of the screening visit period</u>	
	• Any disease or condition at the physician's discretion that would prevent the patient from fully complying with the requirements of the study- <u>including possible corticosteroid treatment outlined in the protocol.</u> The physician may exclude patients unwilling or unable to agree on not using alcohol for the 16-week period following the viral infusion.	
	• Receipt of Prior treatment with any vector or gene transfer agent	
	• Major surgery planned in the 16-week period following the viral infusion	
	• Use of systemic immunosuppressive agents or live vaccines within 30 days before the viral infusion	
2/Synopsis/Duration of Treatment	BMN 270 is given as a single dose by intravenous perfusion infusion.	5
2/Synopsis/Criteria for	Safety:	1, 5
Evaluation	The following safety outcome measurements will be assessed:	
	• Incidence of adverse events (AEs), including serious AEs (SAEs)	
	Change in clinical laboratory tests (serum chemistry and haematology)	
	Change in vital signs	
	Change in physical examination	
	Vector shedding	
	 Liver function tests (<u>LFTLFTs, including ALT, AST, GGT, LDH, bilirubin, alkaline phosphatase</u>) 	
	Immune response to FVIII transgene and AAV capsid proteins	
	No major toxicity is expected based on preclinical studies in mice and monkeys. An asymptomatic transaminitis was observed at	

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Section No./Title	Text Revisions	<u>Rationale</u>
	week <u>8-107-12</u> after administration <u>in humans</u> with an AAV8-FIX, providing the rationale for the following surveillance plan. Each <u>patient_subject</u> will have comprehensive surveillance- <u>plan</u> monitoring LFTs once a week from dose to completion of Week 6, 3 times per week from Weeks 7 to 12, and once a week from Weeks 13 to 16. If a <u>patient's subject's</u> ALT is found to be greater than 1.5x <u>his</u> baseline during these periods, then LFTs will be monitored three times per week or until the ALT returns to baseline. LFTs will be monitored every other month for the first year and then every three months for up to 5 years post-dose in the safety extension; the frequency and duration of LFT testing may be changed if dictated by ongoing safety evaluations. There will be a detailed-monitoring plan for assessment of cellular and humoral responses to AAV5 capsid and FVIII protein.	
2/Synopsis/Statistical Methods	Efficacy is a secondary endpoint, defined as biologically active FVIII at ≥ 5 IU/dL by chromogenic FXa assay and/or one-stage APTT assay between 1 to at 16 weeks following study treatment.	5
4/List of Abbreviations	eCRF-CSR - electronic case clinical study report-form eCRF - electronic case report form PBMC - peripheral blood mononuclear cells	5
6/Investigators and Study Administrative Structure	Liver function tests (LFTs) will be performed at the local laboratories associated with the study sites. Local laboratory results of LFTs will be used to trigger corticosteroid treatment as needed (refer to Section 9.4.8.2Laboratory evaluations will be performed at the local laboratories associated with the study sites.). In case of discrepant results between local and central laboratories, the Investigator and Medical Monitor will decide further action. Safety labs evaluations (including LFTs) will be performed at the central lab, while bioanalytical samples will be performed at the appropriate specialty lab. Refer to the Laboratory Manual for more details.	1
7/Introduction	Chemical modification or bioengineering of FVIII may improve half-life to around 2018-19 hours (Pipe, 2010, Blood), Kaufman, 2013, Blood). However, these long acting FVIII variants do not eliminate the need for lifelong FVIII protein administration or problems of FVIII inhibitor formation, which occurs in 30% of patients on standard FVIII replacement therapy (Nathwani, 1992, Baillieres Clin.Haematol.).(Hay, 2012, Blood).	5
7.1/Nonclinical Studies	BMN 270 related correction of bleeding times showed a dose relationship that was similar to that observed in <u>FVIII KO x Rag2</u> mice given matched IU levels of Refacto®.Additionally, the BMN 270 transgene product has a final sequence <u>closely</u> matching that of the protein replacement treatment, Refacto® and therefore the safety profile of the BMN 270 transgene product is anticipated to be similar to Refacto® and have no	5

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Section No./Title	Text Revisions	<u>Rationale</u>
	unique FVIII-specific target organs of toxicity.	
	Liver targeted distribution of a similar AAV5 Factor IX gene therapy product was observed in the rhesus macaque monkey with low levels of vector genomes detected in spleen, kidney and testis (Paneda, 2009, Hum.Gene Ther.). Nathwani 2006, Blood).	
	This dose represents > 3010 -fold safety factor from the no observed adverse effect level (NOAEL) in <u>the GLP</u> enabling nonclinical studies toxicology study in mice.	
7.2/Previous Clinical Studies	AAV serotype 5 is also used being tested in other clinical trials and has shown good safety was reportedly well tolerated without treatment-related serious adverse events in a recent phase 1 study for treatment of Acute Intermittent Porphyria (D'Avola. 2014, J Hepatology). In addition, AAV using other serotypes have been used in 105 clinical studies to date and no safety issue specific to the vector was ever reported.	5
7.3/Study Rationale	Haemophilia A (HA) is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males (Nathwani, 1992, Baillieres Clin. Haematol Mannucci, 2001, NEJM).	1, 5
	Treatment of severe HA presently consists of intravenous injection of plasma derived or recombinant <u>human FVIII</u> protein (rhFVIII) concentrates both as prophylaxis 2- <u>34</u> times per week, and at the time of a bleed, to prevent or control bleeding episodes, respectively. The half-life for rhFVIII (under 24<u>FVIII (12-18</u> 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 treatment (mean of 1 to 7 episodes/year with prophylaxis <u>and up to 30 to 50 episodes/year</u> for on demand treatment) (Nagel, 2011, Haemophilia).	
	Several different gene transfer strategies for FVIII replacement have been evaluated, but adeno-associated viral (AAV) vectors show the greatest promise (Pipe, 2010, Blood). Mannucci, 2001, NEJM).	
	Indeed, an on-going gene therapy clinical trial for a related disorder, haemophilia B, has established that stable (>36 months) expression of human factor IX at levels that are sufficient for conversion of their bleeding phenotype from severe to moderate or mild is achievable following a single peripheral vein administration of AAV-8 vector (Nathwani, 20112014, NEJM).	
	BMN 270 will be delivered by single intravenous dose and is designed to achieve stable, potentially life-long expression of active hFVIII FVIII in the plasma, synthesized from vector-transduced liver tissue. The clinical study BMN 270-201 is a first-in-human study designed to assess the relationship of vector dose to the augmentation of residual FVIII activity, and whether these	

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Section No./Title	Text Revisions	<u>Rationale</u>
	levels are sufficient to alter the clinical phenotype. The relationship of dose to safety will be correlated to the activity of hFVIII FVIII in patients with severe HA.	
7.4/Summary of Overall Risks and Benefits	Safety will be assessed by adverse event reporting and clinical laboratory assessment. Based on prior human studies with peripheral injections of AAV vectors, there is no known safety risk of AAV gene therapy. However, a mild asymptomatic transaminitis was observed at week 8 <u>107-12</u> after administration <u>in humans</u> with an AAV8-FIX, providing the rationale for the following surveillance plan (Manno, 2006, Nature Med.). <u>Nathwani, 2011, Mol.Ther.</u>). Each <u>patientsubject</u> will have <u>a</u> comprehensive surveillance plan <u>monitoring that monitors</u> LFTs once a week from dose to completion of Week 6, 3 times per week from Weeks 7 to 12, and once a week from Weeks 13 to 16. If a <u>patient's subject's</u> ALT is found to be greater than 1.5x baseline during these periods, then LFTs will be monitored three times per week or until the ALT returns to baseline. Dose selection: The benefit of this study can only be enhanced by selecting a starting dose that potentially could contribute to a	1, 5
	better maximizes the opportunity of observing a therapeutic effect, and therefore, reducing the possibility of a sub-therapeutic effect. Overall, no BMN 270-related findings, except expected formation of anti-AAV5 antibodies, were observed at the highest administered doses of 6E13, 2E14 and <u>6E13</u> vg/kg in the normal mouse, disease model mouse and monkey, respectively.	
	Based on these key pre-clinical findings it can be suggested that the proposed starting dose of 6E12 vg/kg should not pose any risk or safety concerns to patients but may potentially benefit the patient subjects with the best chance of benefiting the subject therapeutically.	
9/Investigational Plan	 Patients who provide written informed consent, meet the entry criteria definition of severe HA, and do not have transduction inhibition activity to AAV5 will be eligible to enroll in the study. Participants will be enrolled sequentially into one of up to three cohorts according to dose level: 6E12 vector genomes [vg] per kilogram/kg of body weight, given as a single intravenous dose (iv) 2E13 vg per kilogram/kg, iv 	5
	 2E13 vg-per-kilogram/kg, iv 6E13 vg-per-kilogram/kg, iv 	
	Patients will be enrolled sequentially every 3 weeks or more between cohorts. Dose escalation may occur after a single patient has been safely dosed if the resulting FVIII activity at Week 3 is < 5 IU/dL. Three weeks is expected to be the time the	

Section No./Title	Text Revisions	Rationale
	expression will be close to the maximum. This escalation paradigm is intended to minimize the patient numbers exposed to subtherapeutic doses.	
	The starting dose was based on the expression and safety of FVIII observed in nonclinical studies of mice and monkeys. The starting dose has a significant safety margin (10-fold) from no observed adverse effect level (NOAEL) in non-human primates mice.	
	Approximately three weeks after an injection, Cohorts will be enrolled sequentially, allowing a period of 3 weeks or more between cohorts. Dose escalation may occur after a single subject in a cohort has been safely dosed if the resulting FVIII activity at the Week 3 visit is < 5 IU/dL in both assays. Three weeks is expected to be the time the expression will be close to the maximum. This escalation paradigm is intended to minimize the subject numbers exposed to subtherapeutic doses. The decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and a panel of investigators participating in the study.	
	If the FVIII activity $\frac{1}{1}$ is reaches $\geq 5 \text{ IU/dL}$ at the Week 3 visit, then the other patients of remaining subjects in the dose group cohort will be enrolled without waiting the need to wait for 3 weeks between patients subjects.	
	<u>Subject 1 (Cohort 1)</u> will be dosed by intravenous <u>perfusion infusion</u> with 6E12 <u>vector genomes [vg] per kilogram/kg</u> of body weight. If the <u>FVIII</u> activity level does not reach \geq 5 IU/dL <u>or greater (expressed as % in Figure 9.1.1) at 21 days the Week 3 visit in both assays, then a higher no further subjects will be dosed in Cohort 1 and enrollment into Cohort 2 will initiate with Subject 2 at the next dose (2E13 vg-per kilogram) will be used for the next patient./kg).</u>	
	If the <u>FVIII</u> activity level <u>in the first subject treated in Cohort 2</u> does not reach \geq 5 IU/dL after Patient 2 <u>at the Week 3 visit in</u> <u>both assays</u> , then the highest dose (6E13 vg per kilogram) <u>no further subjects</u> will be <u>used for dosed in Cohort 2 and enrollment</u> <u>into Cohort 3 (6E13) will initiate with</u> the next patient. <u>Subject.</u>	
	If the FVIII activity level in the first subject treated in Cohort 3 does not reach \geq 5 IU/dL at the Week 3 visit in both assays, then the DRB will recommend whether to continue to add subjects to the cohort and/or whether to continue the study.	
	For <u>the first subject treated in each dose Cohort</u> , if the activity level reaches ≥ 5 IU/dL and if no safety issue is found, then up to four patients will receive subjects will be enrolled in the Cohort. Although the optimum design of this <u>dose</u> . If at any time study is three cohorts of 4 subjects, the adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels reach 10 IU/dL or higher, no further dose escalation will take place, but additional patients will then be	

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Section No./Title	Text Revisions	<u>Rationale</u>
	dosed at this dose level for a total of 6 patients per dose.of FVIII and safety signals.Because patientsBecause patientsBe	
Table 9.1.1/Schedule of Events/Screening and Infusion/Assessment	Distribution of subject diaries and training in their use Mononuclear cell PBMC Mononuclear cell PBMC Haemo-QoL-A Quality of Life (QoL) assessment	5
Table 9.1.1/Schedule ofEvents/Screening andInfusion/Rescreening	Added this new column	3
Table 9.1.1/Schedule of Events/Screening and Infusion/Footnotes	 ^f Includes HLA typing genotyping, FVIII mutation status genotyping, TNFα and IL10a single nucleotide polymorphisms. ^h Should the screening visit occur within 7 days of the drug infusion, physical examination, vital signs, blood chemistry, haematology, urine tests, coagulation screen, and CRP do not need to be repeated at Baseline. ⁱ Smart rescreening should only be performed if a patient has been determined to be eligible for the study and is unable to complete the Baseline assessments and Infusion prior to the closing of the original Screening window. Subjects who undergo smart rescreening must complete the rescreening assessments and receive the infusion within 90 days of signing the original consent. Subjects who do not complete dosing within 90 days will be required to re-consent and undergo all screening procedures. Subjects may not undergo smart rescreening more than once. ^j Only the hFVIII inhibitor level (Bethesda assay with Nijmegen modification) assay must be done at smart rescreening. ^k Assessments on the day of infusion should be performed prior to the infusion. 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), following the infusion hourly (± 5 	3

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Section No./Title	Text Revisions	<u>Rationale</u>
	minutes) for 6 hours and then every 2 hours (\pm 15 minutes) for 6 hours and then at 4 hour intervals (\pm 15 minutes).	
Table 9.1.2/Schedule of	Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)	5
Events/Post-Infusion Follow-Up/Assessment	hFVIII activity FVIII assays ^c	
	hFVIII FVIII antibody titer	
	Haemo-QoL-A QoL assessment	
	Mononuclear cell <u>PBMC</u> collection	
Table 9.1.2/Schedule of Events/Post-Infusion Follow-Up/Follow-Up After BMN270 Administration - Weeks	Expanded Week 1 column to include D2, D4, and D8.	5
Table 9.1.2/Schedule of	* Visit windows are ±48 hours (and include the Day 4 visit)	1, 5
Events/Post-Infusion Follow-Up/Footnotes	^c Includes hFVIII activity level (APTT and FXa chromogenic assay), hFVIII activity confirmation (frozen plasma), Bethesda	
	assay (with Nijmegen modification) for hFVIII inhibitor level, hFVIII coagulation activity exploratory assay, and hFVIII	
	antigen (ELISA). 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.	
	^d Collection to occur on Day 1, 3, 72 and 4 following BMN 270 infusion, and then weekly until at least 3 consecutive negative results are obtained.	
Table 9.1.3/Schedule of	Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)	5
Events/Safety Follow- Up/Assessment	hFVIII activity FVIII assays ^c	
	hFVIII FVIII antibody titer	
	Mononuclear Cell-PBMC Collection (for determination of FVIII and Capsid specific CTL activity)	
	Haemo-QoL-A QoL assessment	
Table 9.1.3/Schedule of Events/Safety Follow-	* Visit windows are ± 72 hours 1 week for visits in Year 1, and ± 2 weeks for visits in Years 2-5.	5

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Section No./Title	Text Revisions	<u>Rationale</u>
Up/Footnotes	 ^c Includes hFVIII activity level (one-stage APTT and chromogenic FXa assay), hFVIII activity confirmation (frozen plasma), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, hFVIII coagulation activity exploratory assay, and hFVIII antigen (ELISA). 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. ^e Haemo-QoL-A QoL assessment during Years 2-5 of Safety Follow-up should be performed at every other visit (every 	
	6 months) starting with the Week 78 visit (ie, 26 weeks after the Week 52 visit at the end of Year 1 of the Safety Follow-up period).	
Table 9.1.4/Schedule of Events/Steroid Prophylaxis	This table was added as part of this amendment.	1
9.2/Discussion of Study Design, Including Choice of Control Group	The decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and a panel of investigators participating in the study. the DRB. There will be no control group. Parameters for each patientsubject will be compared to a pre-treatment assessment of safety (liver function) and efficacy (number of bleeds, use of replacement therapy).	5
9.3/Selection of Study Population	Up to 12 severe haemophilia A patients may enroll into the study; the actual number of patients will depend on the criteria for dose escalation. A total of 6 patients may be enrolled at a single dose level.	5
9.3.1/Inclusion Criteria	 Males that are 18 years or older with established severe Haemophilia A as evidenced by their medical history. Patients will be considered as severe if their <u>base</u> FVIII-<u>baseline</u> level is 1 IU/dL or less Treated/exposed to FVIII concentrates or cryoprecipitates cryoprecipitate for a minimum of 150 exposure days (EDs) No history of inhibitor, or no inhibitor on 2 consecutive occasions within the past 12 months using and results from a modified Nijmegen Bethesda assay higher of less than 0.6 Bethesda Unit <u>Units</u> (BU) <u>2 consecutive occasions at least one week apart within the past 12 months</u> 	5
9.3.1/Exclusion Criteria	 Detectable pre-existing immunity to the AAV5 capsid as measured by AAV5 transduction inhibition and or AAV5 total antibodies Patients that are HIV positive are excluded. Significant liver dysfunction as defined by abnormal elevation of: 	1, 2, 5

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Section No./Title	Text Revisions	<u>Rationale</u>
	• ALT (alanine transaminase) to 3 times the upper limit of normal, bilirubin, <u>;</u>	
	• Bilirubin above 3 times the upper limit of normal;	
	• Alkaline phosphatase, above 3 times the upper limit of normal; or	
	• -an-INR (international normalized ratio) of \geq 1.4.	
	• Treatment with any IP within 30 days prior to the <u>end of the screening visit period</u>	
	• Any disease or condition at the physician's discretion that would prevent the patient from fully complying with the requirements of the study- <u>including possible corticosteroid treatment outlined in the protocol</u> . The physician may exclude patients unwilling or unable to agree on not using alcohol for the 16-week period following the viral infusion.	
	• Receipt of Prior treatment with any vector or gene transfer agent	
	Major surgery planned in the 16-week period following the viral infusion	
	• Use of immunosuppressive agents or live vaccines within 30 days before the viral infusion	
9.3.3.1/Study Safety Evaluation Criteria	If any of the following events occur (except the persistence of AAV5) in a patient <u>subject</u> in the study who has received BMN 270 infusion, enrollment into the trial will be put on halt to complete an extensive safety analysis per Section 9.1.	5
	• A 5-fold increase from baseline in ALT after BMN 270 administration	
	• The occurrence of other drug-Grade 3 or higher adverse events assessed as related Grade III-IV toxicity to study drug, including liver failure and clinical hepatitis	
	• Drug-Grade 2 adverse event assessed as related Grade II toxicity to study drug that persists for at least 7 days	
	• The occurrence detection of neutralizing antibodies to hFVIII following BMN 270 infusion	
	The occurrence of a malignancy <u>excluding skin cancers</u> at any point after BMN 270 infusion- that is assessed as possibly, probably, or definitely related to the study agent	
9.3.5/Subject Identification and Replacement of Subjects	Patients Subjects who withdraw from the study after Week 16-will not be replaced.	5
9.4.2.1/Product Characteristics and	BMN 270 is a sterile, clear, colorless-to-pale yellow solution for IV infusion and is supplied in a 2 mL polypropylene cryovial.	5

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Section No./Title	Text Revisions	<u>Rationale</u>
Labeling	Each vial contains 1.1 mL of AAV5-hFVIII-SQ at a concentration of 2E13 vector genomes per mL in a pH 7.4 phosphate buffer.	
9.4.4/Directions for Administration	FVIII protein concentrate replacement therapy will not be given since venipuncture is a minimally invasive procedure in these individuals under ordinary conditions.	5
	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. An electric syringe <u>pump</u> will be used to infuse through an in-line, low protein binding 0.22 micron filter. BMN 270 will be infused through the catheter using an appropriate infusion pump <u>at a constant rate of 4</u> <u>ml/min</u> while monitoring the vital signs (pulse, blood pressure, respiration rate and temperature) at 15 minute (\pm 5 minutes) intervals. The anticipated maximum interval from initiation of thawing of BMN 270 to completion of the infusion is 4 hours- <u>a</u> <u>although the IP has been shown to be stable at room temperature for 6 hours.</u>	
	Patients Subjects will remain hospitalized in the clinic for 24 hours to observe for any immediate toxicity of the procedure. After 24 hours of hospitalization, participants will be discharged from the clinic unless toxicity has been observed in which case hospitalization the stay in the clinic may be extended or the subject may transfer to an outpatient a separate facility may occur based on the evaluation and judgment of the Principal Investigator after consultation with the Medical Monitor.	
9.4.5/Method of Assigning Subjects to Treatment Groups	Cts to Approval by the Sponsor will be required prior to enrollment of each study patientsubject. Upon their enrollment into the study,	
9.4.6/Selection of Doses Used in the Study	The starting dose was based on the expression of hFVIII observed in nonclinical studies of mice and monkeys. The starting dose has a significant safety margin (10-fold) from NOAEL in non-human primates. Mice. The dose escalation is half-logs based.	5
9.4.6.2/Selection of Dose for Each Subject	The starting dose was determined by expression of hFVIII observed in mice and monkeys and a scale up factor based on previous experience, an improved purification process over previous trials (thus <u>potentially</u> decreasing the risk of immune response), and a new evaluation of the titer (PCR performed after hairpin removal).	

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Section No./Title	Text Revisions	<u>Rationale</u>
	Approximately three weeks after an injection, the decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and a panel of investigators participating in the study the DRB .	
	Patient Subject 1 (Cohort 1) will be dosed by intravenous infusion with 6E12 vector genomes [vg] per kilogram/kg of body weight. If the <u>FVIII</u> activity level does not reach \geq 5 IU/dL or greater (expressed as % in Figure 9.1.1) at 21 days the Week 3 visit in both assays, then a higher no further subjects will be dosed in Cohort 1 and enrollment into Cohort 2 will initiate with Subject 2 at the next dose (2E13 vg-per kilogram) will be used for the next patient./kg).	
	If the <u>FVIII</u> activity level in the first subject treated in Cohort 2 does not reach ≥ 5 IU/dL after Patient 2at the Week 3 visit in <u>both assays</u> , then the highest dose (6E13 vg per kilogram)no further subjects will be used for dosed in Cohort 2 and enrollment into Cohort 3 (6E13) will initiate with the next patient. Subject.	
	<u>If the FVIII activity level in the first subject treated in Cohort 3 does not reach \geq 5 IU/dL at the Week 3 visit in both assays, then</u> <u>the DRB will recommend whether to continue to add subjects to the cohort and/or whether to continue the study.</u>	
	For the first subject treated in each dose <u>Cohort</u> , if the activity level reaches \geq 5 IU/dL and if no safety issue is found, then up to four patients will receive subjects will be enrolled in the Cohort. Although the optimum design of this dose. If at any time study is three cohorts of 4 subjects, the adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels reach 10 IU/dL or higher, no further dose escalation will take place, but additional patients will then be dosed at this dose level for a total of 6 patients per dose of FVIII and safety signals.	
9.4.8/Prior and Concomitant Medications	The following medications are prohibited starting 30 days before Screening: • Systemic immunosuppressive agents	5
9.4.8.2/Glucocorticoid Treatment of Elevated Hepatic Transaminases	Reports of abnormal LFTs (defined as 1.5x the patient's subject's baseline <u>ALT</u> level) should be made to the BioMarin medical <u>monitor</u> within 24 hours 30 minutes of the lab value being available. If the LFTs are abnormal, and treatment with prednisolone <u>will be</u> initiated <u>immediately</u> at a dose of 60 mg per day and then gradually tapered (60 mg daily for the first week2 weeks, then 40 mg the second week next 2 weeks, then 30 mg the third week next two weeks, then 20 mg the fourth week next two weeks, then stop) will be, for a total treatment of 8 weeks). Local laboratory results of LFTs will be used to trigger corticosteroid treatment as needed. In case of discrepant results between local and central laboratories, the Investigator and Medical Monitor will decide further action.	1, 4

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Section No./Title	Text Revisions	<u>Rationale</u>
	If a glucocorticoid treatment is started for a subject at any point of the study, the following steps will be taken: • A prophylactic glucocorticoid treatment will be started for subsequent subjects scheduled to be dosed. Subjects will receive prednisolone 40 mg per day starting at week 3, for a duration of 4 weeks, then tapered by 5 mg every two weeks for 8 weeks (until 20 mg/day is reached), then tapered 5 mg per week for 3 weeks, for a total duration of 15 weeks (refer to Table 9.1.4immediately). • Subjects already dosed who have not yet reached Week 17 in the study will be evaluated for the use of prophylactic steroids after discussion between the Investigator and the Medical Monitor • Once prophylactic glucocorticoid treatments have been initiated, then all subjects (who have not already passed that period in the study) will have 3x/week LFT assessments during the 6-week period when a liver response is expected based on the liver response in the original subject, if this period is different from the 3x/weekly LFT assessments already planned for Weeks 7-12. • Subjects who have already passed that 6-week period in the study will continue to have the regularly scheduled LFT assessments as planned in the protocol. 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. All adverse events should be reported as outlined in section 10 of the protocol.	
9.4.9/Treatment Compliance	Study drug will be administered to <u>patients subjects</u> at the study site by a qualified professional. The quantity dispensed, returned, used, lost, etc. must be recorded on the dispensing log provided for the study. Sites will be instructed to return <u>or</u> <u>destroy</u> all used and unused study drug containers.	5
9.5/Investigational Product Accountability	The Investigator or designee is responsible for maintaining accurate records (including dates and quantities) of IP(s) received, patients to whom IP is dispensed (patient-by-patient dose specific accounting), 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.	5
9.7.2/Primary Efficacy	The primary efficacy measure will be the plasma FVIII activity monitored on a regular basis after BMN 270 dose. The efficacy	5

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Section No./Title	Text Revisions	<u>Rationale</u>
Variables	goal of the protocol is to ascertain the dose range of BMN 270 required to convert severe HA patients to stable expression of FVIII at 5 IU/dL or above, i.e., a mild severity. This is associated in natural history studies with clinically superior long term outcomes (Nathwani, 1992, Baillieres Clin.Haematol.).Den Uijl, 2011, Haemophilia).	
	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 FVIII activity level <u>in both assays</u> and the number of <u>patients</u> with FVIII activity ≥ 5 IU/dL <u>in at least one of the two</u> <u>assays</u> will be summarized.	
9.7.3/Secondary Efficacy Variables	Assessment of viral shedding at one week after BMN 270 infusion will also be considered an efficacy variable.	5
9.7.4/Immunogenicity	Immunogenicity assays will be performed on plasma. The assays will include detection of anti-capsid, and anti-FVIII total antibody, and determination of neutralizing antibodies against FVIII. Any increase in total antibody level, especially during the time period of <u>65</u> -12 weeks, will be compared with FVIII activity measurements. Any abnormality of the liver parameters will lead to <u>ana retrospective</u> immunogenicity assessment to determine anti-FVIII and capsid specific CTL. Anti-FVIII and capsid specific CTL assays will be performed on collected PBMCs.	5
9.7.6/Exploratory Biomarker Assessments	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 may be used for exploratory use once the primary use has been completed. No additional genetic or genomic testing will be conducted on any sample (other than testing specified in the protocol).	5
9.7.7/Haemo-QoL-A Quality of Life Assessment	<u>The Haemo-QoL-A is a patient-reported outcome (PRO) questionnaire which will be used to assess subject quality of life (QoL)</u> during the study. Assessments will occur at the time points listed in the Schedules of Assessments.	5
Table 9.7.8.2.1/Clinical Laboratory Tests/Footnotes	ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CO ₂ , carbon dioxide; GGT, gamma-glutamyltransferase; LDH, lactate dehydrogenase; PT, prothrombin time; APTT, activated partial thromboplastin time; RBC, red blood cell; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone; WBC, white blood cell; TT, thrombin time; INR, international normalized ratio.	5

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Section No./Title	Text Revisions	<u>Rationale</u>
9.7.8.3/Liver Function and Hepatitis Testing at Screening	Patients Subjects will be screened for evidence of previous hepatitis B or hepatitis C infection at Screening. If medical records Subjects with documented results showing no evidence an absence of active Hepatitis B or Hepatitis C infection from the previous 30 days are available, then the Screening tests do not need to be done.	1,4
	Evidence of ongoing infection ((as measured by positive surface antigen for hepatitis B or positive RNA testing for hepatitis C) will be an exclusion criteria. If these parameters are negative and therefore no active infection is detected, then the patients may be included if they were vaccinated (for hepatitis B) or cleared the infection (for hepatitis C) and their liver function is acceptable.30 days prior to providing signed informed consent do not need to be screened again.	
	Evidence of ongoing Hepatitis B or Hepatitis C infection is exclusionary. Subjects who have cleared a Hepatitis B infection or are seronegative do not need to receive the Hepatitis B vaccination.	
	A liver ultrasound and liver function testing at Screening will identify any significant hepatic dysfunction, which is defined as:	
	• <u>More than 3x the normal</u> Alkaline phosphatase above the normal cut off level.	
	• INR $over \ge 1.4$.	
	Liver ultrasound results indicative of a liver cirrhosis	
9.7.8.4/Vital Signs, Physical Examinations and Other Observations Related to Safety	Systolic blood pressure, diastolic blood pressure, heart rate, respiration rate, and temperature will be assessed at Screening, Baseline, and at the beginning of each visit during the Post-Infusion Follow-Up and Safety Follow-Up periods. On the day of the BMN 270 Infusion, vital signs will be monitored prior to infusion, during the infusion every 15 minutes (\pm 5 minutes), following the infusion hourly (\pm 5 minutes) for 6 hours and then every 2 hours (\pm 15 minutes) for 6 hours and then at 4 hour intervals-(\pm 15 minutes).	5
	A complete physical examination will include general appearance (head, eyes, ears, nose, and throat), cardiovascular, dermatologic, lymphatic, respiratory, gastrointestinal, genitourinary, musculoskeletal, and neurologic systems (level of consciousness, speech, language, cranial nerves, motor strength, motor tone, abnormal movements, reflexes, upper extremity sensation, lower extremity sensations, gait, Romberg, nystagmus, and coordination).	
9.7.8.5/Viral Shedding	Viral shedding has been extensively studied in all similar clinical trials performed to date. (Nathwani, 2014, N.Eng.J.Med (Supplemental Appendix); Manno, 2006, Nature Med. (Supplemental Appendix); Schenk-Braat, 2007, J Gene Med; Croteau, 2004, Ann Occup Hyg). It has been constantly shown that In the literature referenced above, vector was not no longer detectable	5

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Section No./Title	Text Revisions	Rationale
	anymore at after 40 days, with its persistence in blood, saliva, urine or stool. However, vector persisted in semen for 16 weeks in the seminal fluid but not in motile sperm (Manno, 2006, Nature Med.). In addition, it has always all cases, the amount of vector present in these bodily fluids involved only an extremely small fraction of the injected infused dose.	
	Viral shedding will also be extensively studied in the present clinical trial, every week up to 16 weeks, then every 4 weeks to one year, then every three months-, <u>until at least 3 consecutive negative results are obtained</u> . During the Post-Infusion Follow-Up period, patients subjects will undergo testing of various bodily fluids samples to look for evidence of viral shedding for possible viral transmission. Bodily fluids will be tested by PCR at the time points indicated in Table 9.1.2 and Table 9.1.3.	
10.1.1/Adverse Events	Bleeding events that occur where a normal (ie, non-haemophiliac) patient would bleed, such as bleeding as a result of <u>major</u> trauma, should be recorded as adverse events.	5
10.2/Serious Adverse Events	 A serious adverse event (SAE) is any untoward medical occurrence that at any dose meets 1 or more of the following criteria: Requires or prolongs inpatient hospitalization. Hospitalization for less than 24 hours will not be considered to be an SAE. Hospitalization solely for the purpose of insertion of an in dwelling IV catheter (such as a Port a Cath or other brand) for administration of study drug will not be considered an SAE. 	5
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 liver enzymes triggering (ALT) that triggers a corticosteroid treatment	5
10.3.3/Assessment of Seriousness, Severity, and Causality	The Investigator responsible for the care of the patientsubject 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 should 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).	5
10.4.1.7/Hospitalization, Prolonged Hospitalization, or Surgery	 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: <u>Hospitalization solely for the purpose of insertion of an in-dwelling IV catheter (such as a Port-a-Cath or other brand)</u> for administration of study drug will not be considered an SAE. 	5

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Section No./Title	Text Revisions	<u>Rationale</u>
10.4.1.9/Pregnancy	Pregnancy in partner should be reported within 24 hours of the site becoming aware of the pregnancy by faxing entering the information on the Pregnancy Form in the study reference materials <u>cCRF</u> and submitting to BPV- within 24 hours of the site becoming aware of the event. The Investigator must make every effort to follow the patient subject's partner through resolution of the pregnancy (delivery or termination) and to report the resolution on the Pregnancy Follow-up Form in the study reference materials. In the event of pregnancy in the partner of a study patient subject, the Investigator should make every reasonable attempt to obtain the woman's consent for release of protected health information.	5
10.5.1/Expedited Reporting Requirements	The reporting period for SAEs begins after informed consent is obtained and the first administration of study drug is given. It continues for approximately 5 years or until study discontinuation/termination, whichever is longer.	5
12.2/Screening Visit	The following procedures will be performed during the Screening Period:	4, 5
	• Full medical history, including haemophilia A history, Hepatitis B, Hepatitis C, and HIV. Patients with documented negative results within the last 30 days do not need to be retested.	
	Samples for hFVIII Assays	
	 AAV5 transduction inhibition <u>assays</u> assay 	
	 Screen for Hepatitis B, Hepatitis C, and HIV if required (Patientssubjects with documented negative results within the last-30 days prior to informed consent being obtained do not need to be retested) 	
	 Blood samples for Biomarker testing (<u>including</u> HLA typing genotyping, FVIII mutation genotyping status, TNFα and IL10a single nucleotide polymorphisms) 	
12.2.1/"Smart	Subjects who undergo smart rescreening must complete the rescreening assessments and receive the infusion within 90 days of	3, 5
Rescreening" Visit	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:	
	• <u>Vital signs</u>	

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Section No./Title	Text Revisions	<u>Rationale</u>
	<u>Assessment of Adverse Events and Concomitant Medications</u>	
	Documentation of bleeding episodes and FVIII usage (by either subject or clinical information)	
	<u>hFVIII Assays (only the hFVIII inhibitor level (Bethesda assay with Nijmegen modification)</u>	
	Blood sample for AAV5 Assays	
	• <u>AAV5 antibody titer</u>	
	• <u>AAV5 transduction inhibition assay</u>	
	Blood chemistry, haematology, urine tests, coagulation screen, and CRP (refer to Table 9.7.8.2.1)	
12.3/Baseline Visit	Baseline values will be recorded from 1 to 7 days prior to the treatment visit. The following procedures will be performed during the Baseline Period:	5
	Samples for FVIII Assays	
	↔ FVIII activity chromogenic FXa (plasma)	
	 FVIII coagulation activity exploratory assay 	
	 FVIII inhibitor level (Bethesda assay with Nijmegen modification) 	
	○ 	
	Distribution of subject diaries and training in diary completion	
	<u>Mononuclear cell PBMC</u> collection for CTL baseline	
	• <u>Haemo-QoL-A</u> QoL assessment	
12.4/Treatment Visit/BMN 270 Infusion Visit (Day 1)	There will be one treatment visit for each patient. Patients subject. Subjects will be hospitalized remain in the clinic for 24 hours for the BMN 270 Infusion Visit.	5

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Section No./Title	Text Revisions	<u>Rationale</u>
12.5.1/Every Visit	Every week (Weeks 1 through 16), the following procedures will be performed:	1, 5
	• Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)	
	Samples for FVIII Assays	
	Note: 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.	
	• PCR of vector genomes in blood, saliva, urine, semen, and stools	
	 Collection to occur on Day 1, 3, 7 following BMN 270 infusion, and then weekly until at least 3 consecutive negative results are obtained 	
12.5.3/Week 1 – Day 2	On Day 2 and Day 4 of Week 1, the following procedures will be performed:	5
and Day 4	• <u>PCR of vector genomes in blood, saliva, urine, semen, and stools (Day 2 and Day 4)</u>	
	• <u>Samples for FVIII Assays (Day 4 only)</u>	
	• <u>FVIII activity level (APTT)</u>	
	• FVIII activity level (chromogenic FXa assay)	
	• FVIII coagulation activity exploratory assay	
	• Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level	
	• <u>FVIII antigen (ELISA)</u>	
	Note: 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.	
12.5.4/Every 2 Weeks	Every 42 weeks (Weeks 2, 4, 6, 8, 10, 12, 14 and 16), the following procedure will be performed:	5
	Mononuclear cell-Exploratory biomarker assessments	
12.5.5/Weeks 4, 8, 12,	At Weeks 4, 8, 12, and 16, the following procedure will be performed:	5

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Section No./Title	Text Revisions	Rationale
and 16	<u>PBMC</u> collection	
12.5.7/Weeks 8 and 16	At Weeks 1, 8, and 16, the following procedure will be performed:	5
	• AAV5 antibody titer	
12.5.8/Weeks 1, 2, 3, 4,	At Weeks 1, 2, 3, 4, and 16, the following procedure will be performed:	5
and 16	• <u>Haemo-QoL-A</u> QoL assessment	
12.6/Safety Follow-Up -	After the 16 weekly infusion follow-up visits are complete, subjects will return to the study site at Weeks 20, 28, 36, 44, and 52	5
Year 1	$(\pm 48 \text{ hours} 1 \text{ week})$, when the following procedures will be completed:	
12.6.1/Every Visit	At Weeks 20, 28, 36, 44, and 52, the following procedures will be performed:	5
	 Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use) 	
	• FVIII Assays	
	↔ FVIII activity confirmation (Frozen plasma)	
	Note: 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.	
	Mononuclear cell <u>PBMC</u> collection	
	PCR of vector genomes in blood, saliva, urine, semen, and stools	
	 Sample testing during Safety Follow-Up is not required if <u>at least</u> 3 consecutive samples are clear during the Post-Infusion Follow-Up period. 	
12.6.2/Weeks 28 and 52	At Weeks 28 and 52, the following procedure will be performed:	5
	• <u>Haemo-QoL-A</u> QoL assessment	
12.7/Safety Follow-Up	During Years 2-5 of Safety Follow-up, patients-subjects will be assessed every 3 months (± 72 hours2 weeks). At these times,	5
	the following procedures will be completed:	
12.7.1/Every Visit	Every 3 months (\pm 72 hours 2 weeks), the following procedures will be performed:	5

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Section No./Title	Text Revisions	<u>Rationale</u>
	 Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use) FVIII Assays FVIII activity confirmation (Frozen plasma) <u>Note: 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.</u> <u>Mononuclear cell PBMC</u> collection PCR of vector genomes in blood, saliva, urine, semen, and stools Sample testing during Safety Follow-Up is not required if <u>at least 3</u> consecutive samples are clear during 	
12.7.2/Every Other Visit	the Post-Infusion Follow-Up period. Every six months starting at the Week 78 visit (ie, 26 weeks after the Week 52 visit at the end of Year 1 of the Safety Follow-up	5
(Every 6 months)	period), the following procedure will be performed:	5
	• <u>Haemo-QoL-A</u> QOL assessment	
12.8/Early Termination Visit	 If a patient subject leaves the study prior to the Week 270260 visit, the patient subject will be asked to return to the study site and complete an Early Termination visit. At the Early Termination visit, as many of the following assessments as possible should be done: Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use) Bethesda assay (with Nijmegen modification) for FVIII inhibitor level FVIII activity confirmation (Frozen plasma) FVIII antigen (ELISA) Note: 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. Mononuclear cell PBMC collection PCR of vector genomes in blood, saliva, urine, semen, and stools 	5

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Section No./Title	Text Revisions	<u>Rationale</u>
	 Sample testing at the ETV is not required if <u>at least 3</u> consecutive samples are clear during the Post-Infusion Follow-Up period. 	
	<u>Haemo-QoL-A QOL assessment</u>	
12.9/End of Study	The study will end after the last patientsubject completes the last Safety Follow-Up visit (Week 270260).	5
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, any applicable randomization procedures, source document requirements, CRFs-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 CRFs-eCRFs from source documents, adherence to protocol, randomization (if applicable), SAE reporting and drug accountability records. The designated clinical data management group will enter or transfer CRF data into a study database. Data quality control and analysis will be performed by BioMarin or a designee, based on a predefined analysis plan. 	5
14.2/Primary and Secondary Efficacy Analysis	Data collected in a longitudinal manner may be analyzed using longitudinal methods such as mixed effect model which takes into account the correlation among the observation taken at various time points within a participant. Efficacy is a secondary endpoint, defined as biologically active hFVIII at \geq 5 IU/dL by chromogenic FXa and/or one-stage APTT assay between 1 to at 16 weeks following study treatment.	5
14.3/Immunogenicity	Analysis of neutralizing antibody response and other immunological parameters will be primarily descriptive and involve both inter-participant and intra-participant comparisons across doses.	5
14.6/Determination of Sample Size	No formal sample size calculations based on statistical power were performed. The sample size is determined based upon clinical consideration and could detect a strong clinical efficacy signal. Up to 12 patients <u>subjects</u> may be dosed in the study; the actual number of patients <u>subjects</u> will depend on the criteria for dose escalation. A total of 6 patients may be enrolled at a single dose level.	5
15/Data Review Board	DATA MONITORING COMMITTEEREVIEW BOARD	5
21/References	Den Uijl IEM, Mauser Bunschoten EP, Roosendaal EG, Schutgens REG et al. Clinical severity of haemophilia A: does the	5

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Section No./Title	Text Revisions	<u>Rationale</u>
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	Kaufman RJ, Powell JS. Molecular approaches for improved clotting factors for hemophilia. Blood 2013; 122: 3568–74.	
	Mannucci PM & Tuddenham EGD. The Hemophilias - From Royal Genes to Gene Therapy. NEJM 2001; 344:1773-1779.	
	Nathwani AC, Gray JT, Ng CY, et al. Self-complementary adeno-associated virus vectors containing a novel liver-specific human factor IX expression cassette enable highly efficient transduction of murine and nonhuman primate liver. Blood. 2006; 107(7):2653-2661.	

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1/2, Dose-Escalation Safety, Tolerability and Efficacy Study of BMN 270, an Adenovirus-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII in Patients with Severe Haemophilia A
Protocol Number:	270-201
Active Investigational Product:	AAV5-hFVIII-SQ
IND/European Union Drug Regulating Authorities Clinical Trials (EudraCT) Number:	2014-003880-38
Indication:	Haemophilia A
Sponsor:	BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949
Development Phase:	Phase 1/2
Sponsor's Responsible Medical Monitor:	Pl Pl BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949
Duration of Patient Participation:	Approximately 264 weeks
Dose:	Varied
Study Population:	Males aged 18 or older
Date of Original Protocol:	10 February 2015
Date of Amendment 1:	06 March 2015
Date of Amendment 2:	26 May 2015
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May not be divulged, published, or otherwise disclosed to others without prior written approval from BioMarin.

This study will be conducted according to the principles of Good Clinical Practice as described in the U.S. Code of Federal Regulations and the International Conference on Harmonisation Guidelines, including the archiving of essential documents.

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CLINICAL STUDY PROTOCOL AMENDMENT SUMMARY

Amendment: 2

Date: 26 May 2015

RATIONALE AND SUMMARY OF MAJOR CHANGES

A summary of major changes covered by Amendment 2 to the BMN 270-201 protocol is provided below.

1. Exclusion criterion changed from "Evidence of detectable viral load of HIV" to "Patients that are HIV positive are excluded." In addition, the following exclusion criterion was added: "Any evidence of active infection or any immunosuppressive disorder."

Rationale: The criteria were amended to exclude patients with any disease or condition that may jeopardise patient safety.

2. The Overall Study Design and Plan changed to include details of Sponsor actions should any of the criteria listed in Section 9.3.3.1 occur.

Rationale: Sponsor actions pertaining to the criteria listed in Section 9.3.3.1 reflect a more conservative approach considering this is a first-in-man trial.

3. Expedited Reporting Requirements have been updated to include SUSAR reporting in accordance with European Directive 2001/20/EC.

Rationale: The protocol was amended to include the Sponsor's responsibility to ensure that all relevant information about SUSARs is reported to the competent authorities in all the Member States concerned, and to the Ethics Committee in compliance with current legislation.

4. Removed "Exploratory FVIII activity assay" from Primary Efficacy Variables section.

Rationale: The Exploratory FVIII activity assay is currently used for exploratory purposes only and not to direct patient management.

5. Expanded description of Data Review Board (DRB) in Section 15 to include notification of all DRB meetings and meeting outcomes to participating sites.

Rationale: In view of the multiple sites involved, the DRB meetings and meeting outcomes will be used to disseminate data (safety and efficacy) to participating sites.

6. Removed requirement of FVIII Treatment Washout period.

Rationale: While washout periods are used in some Haemophilia studies, after discussion with Investigators and Experts, it was recommended to remove the washout period. Removing the washout period allows for continued prophylactic treatment up to the day of the infusion and may reduce the risk of a bleeding episode prior to BMN 270 treatment.

Specific changes included in this amendment, including the Synopsis, since Amendment 1 (approved 06 March 2015) are outlined in Section 24.

2 SYNOPSIS

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NAME OF ACTIVE INGREDIENT:	Reference:	
AAV5-hFVIII-SQ		
TITLE OF STUDY:		

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

PROTOCOL NUMBER:

270-201

STUDY SITES:

Approximately 6-10 sites worldwide.

PHASE OF DEVELOPMENT:

Phase 1/2

STUDY RATIONALE:

Haemophilia 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 cascade. This disorder can be either inherited, due to a new mutation 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 is largely governed by the level of residual expression. Severe HA is classified as FVIII activity less than 1% of wild type (< 1 IU/dL), moderate disease comprises 1-5% of wild type activity and the mild form is 5-40% activity. The clinical manifestations of severe HA remain frequent spontaneous bleeding episodes, predominantly in joints and soft tissues, with a substantially increased risk of death from haemorrhage when the brain is involved.

Treatment of severe HA presently consists of intravenous injection of plasma derived or recombinant 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 rhFVIII (under 24 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 treatment (mean of 1 to 7 episodes/year with prophylaxis up to 30 to 50 for on demand treatment). The consequence of multiple bleeding events is the development of an underlying pathology that contributes to debilitating multiple-joint arthropathy and substantially increased risk of death. Chemical modification (e.g. direct conjugation of polyethylene glycol (PEG) polymers) and bioengineering of FVIII (e.g. FVIII-Fc fusion proteins) improve half-life by approximately 50%, and

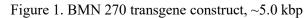
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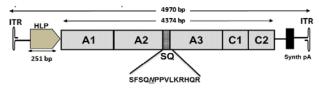
thus, show promise in reduced dosing and maintaining activity levels above 1% trough. However, these longer acting FVIIIs remain dependent on multiple infusions to maintain critical levels of FVIII activity in severe HA patients. There is therefore a strong unmet need for a fully preventive treatment of HA to give patients a FVIII level compatible with a normal and haemorrhage-free life.

Gene therapy offers the potential of disease-modifying therapy by continuous endogenous production of active FVIII following a single intravenous administration of a vector with the appropriate gene sequence. Haemophilia 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 modest increases in the level of FVIII (any increase of the plasma level by 2 ng/ml induces an increase in activity of 1%) can ameliorate the severe form of the disease. Thus, relatively small changes in endogenous FVIII activity results in clinically relevant improvements in disease phenotype. Finally, the 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 for specific tissues such as the liver (for serotypes 2, 5 and 8 among others). Indeed, an on-going gene therapy clinical trial for a related disorder, haemophilia B, has established that stable (>36 months) expression of human factor IX at levels that are sufficient for conversion of their bleeding phenotype from severe to moderate or mild is achievable following a single peripheral vein administration of AAV-8 vector. Several participants in this trial have been able to discontinue factor prophylaxis without suffering spontaneous haemorrhages, 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 rhFVIII under the control of a liver-selective promoter (Figure 1).





BMN 270 will be delivered by single intravenous dose and is designed to achieve stable, potentially life-long expression of active hFVIII in the plasma, synthesized from vector-transduced liver tissue. The clinical study BMN 270-201 is a first-in-human study designed to assess the relationship of vector

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dose to the augmentation of residual FVIII activity, and whether these levels are sufficient to alter the clinical phenotype. The relationship of dose to safety will be correlated to the activity of hFVIII in patients with severe HA.

OBJECTIVES:

The primary objectives of the study are:

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

The secondary objectives of the study are:

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

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AAV5-hFVIII-SQ		

STUDY DESIGN AND PLAN:

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

Patients who provide written informed consent, meet the entry criteria definition of severe HA, and do not have transduction inhibition activity to AAV5 will be eligible to enroll in the study. Participants will be enrolled sequentially into one of up to three cohorts according to dose level:

- 1. 6E12 vector genomes [vg] per kilogram of body weight, given as a single intravenous dose (iv)
- 2. 2E13 vg per kilogram, iv
- 3. 6E13 vg per kilogram, iv

Patients will be enrolled sequentially every 3 weeks or more between cohorts. Dose escalation may occur after a single patient has been safely dosed if the resulting FVIII activity at Week 3 is < 5 IU/dL. Three weeks is expected to be the time the expression will be close to the maximum. This escalation paradigm is intended to minimize the patient numbers exposed to subtherapeutic doses.

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

Approximately three weeks after an injection, the decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and a panel of investigators participating in the study.

If the FVIII activity is ≥ 5 IU/dL, then the other patients of the dose group will be enrolled without waiting for 3 weeks between patients.

Patient 1 will be dosed by intravenous perfusion with 6E12 vector genomes [vg] per kilogram of body weight. If the activity level does not reach \geq 5 IU/dL at 21 days, then a higher dose (2E13 vg per kilogram) will be used for the next patient.

If the activity level does not reach \geq 5 IU/dL after Patient 2, then the highest dose (6E13 vg per kilogram) will be used for the next patient.

For each dose, if the activity level reaches 5 IU/dL and no safety issue is found, then up to four

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patients will receive this dose. If at any time activity levels reach 10 IU/dL or higher, no further dose escalation will take place, but additional patients will then be dosed at this dose level for a total of 6 patients per dose.

Because patients develop neutralizing immunity upon exposure to the capsid, re-challenge of vector is not a treatment option and these patients have effectively a single opportunity for therapy using this AAV capsid. Efficacy will be determined by FVIII activity at 16 weeks post dose. Safety will be evaluated for approximately 5 years after dose. Any safety signal will trigger a review of the data and possible additional analysis including mononuclear collection.

NUMBER OF PATIENTS PLANNED:

Up to 12 patients may enroll into the study; the actual number of patients will depend on the criteria for dose escalation. A total of 6 patients may be enrolled at a single dose level.

DIAGNOSIS AND ALL CRITERIA FOR INCLUSION AND EXCLUSION:

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

- 1. Males that are 18 years or older with established severe haemophilia A as evidenced by their medical history. Patients will be considered as severe if their FVIII baseline level is 1 IU/dL or less
- 2. Treated/exposed to FVIII concentrates or cryoprecipitates for a minimum of 150 exposure days (EDs)
- 3. Greater or equal to 12 bleeding episodes only if receiving on-demand therapy over the previous 12 months. Does not apply to patients on prophylaxis
- 4. Able to sign informed consent and comply with requirements of the trial
- 5. No history of inhibitor, or no inhibitor on 2 consecutive occasions within the past 12 months using a modified Nijmegen Bethesda assay higher than 0.6 Bethesda Unit (BU)
- 6. Sexually active patients must be willing to use an acceptable method of contraception such as double barrier, including hormonal contraception for at least 6 months post-treatment

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

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

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3. Patients that are HIV positive are	excluded.	
4. Significant liver dysfunction as de	fined by abnormal elevation of	ALT (alanine transaminase)

- 4. Significant liver dysfunction as defined by abnormal elevation of ALT (alanine transaminase) to 3 times the upper limit of normal, bilirubin, alkaline phosphatase, or an INR (international normalized ratio) of 1.4. Potential participants who have had a liver biopsy in the past 3 years are excluded if they had significant fibrosis of 3 or 4 as rated on a scale of 0-4
- 5. Evidence of any bleeding disorder not related to Haemophilia A
- 6. Platelet count of $< 100 \times 10^9/L$
- 7. Creatinine $\geq 1.5 \text{ mg/dL}$
- 8. Liver cirrhosis of any etiology as assessed by liver ultrasound
- 9. Hepatitis B if surface antigen is positive
- 10. Hepatitis C if RNA is positive
- 11. Treatment with any IP within 30 days prior to the screening visit
- 12. Any disease or condition at the physician's discretion that would prevent the patient from fully complying with the requirements of the study. The physician may exclude patients unwilling or unable to agree on not using alcohol for the 16-week period following the viral infusion.
- 13. Receipt of any vector or gene transfer agent

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

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

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

The study is open label with comparison of FVIII activity to baseline values. No reference therapy will be evaluated in this study.

DURATION OF TREATMENT:

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

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CRITERIA FOR EVALUATION:		

Safety:

The following safety outcome measurements will be assessed:

- Incidence of adverse events (AEs), including serious AEs (SAEs)
- Change in clinical laboratory tests (serum chemistry and haematology)
- Change in vital signs
- Change in physical examination
- Vector shedding
- Liver function tests (LFT)

No major toxicity is expected based on preclinical studies in mice and monkeys. An asymptomatic transaminitis was observed at week 8-10 after administration with an AAV8-FIX, providing the rationale for the following surveillance plan. Each patient will have comprehensive surveillance plan monitoring LFTs once a week from dose to completion of Week 6, 3 times per week from Weeks 7 to 12, and once a week from Weeks 13 to 16. If a patient's ALT is found to be greater than 1.5x baseline during these periods, then LFTs will be monitored three times per week or until the ALT returns to baseline. LFTs will be monitored every other month for the first year and then every three months for up to 5 years post-dose in the safety extension.

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

Efficacy:

The primary efficacy measure will be to assess plasma FVIII activity. The efficacy goal of the study is to establish the dose relationship to FVIII activity \geq 5 IU/dL at 16 weeks post BMN 270 administration.

Secondary efficacy measures include assessing the impact of BMN 270 on the frequency of FVIII replacement therapy and on the number of bleeding episodes during the study. Patients will be asked to keep a patient diary to record the details in these areas.

Pharmacodynamics:

The FVIII antigen and activity level as measured by an ELISA (antigen level) and by one-stage APTT and/or chromogenic FXa assay (activity level), will be used for plasma profiles; FVIII activity will be

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used to determine PD parameters. Traditional PK analysis is not applicable.

If supported by the FVIII activity data, non-compartmental analysis and observation will be used to estimate individual values of Cb (baseline concentration), Css (steady state concentration), Tss (time to steady state), C(t) and AUC(0-t) where t is 16 weeks.

STATISTICAL METHODS:

The sample size is based upon clinical considerations and could detect a strong clinical efficacy signal. Up to 12 patients may be dosed in the study. The patients will be followed in a longitudinal manner and all the relevant information will be collected. The analysis of the data will be descriptive in nature but data collected in a longitudinal manner may be analyzed using longitudinal methods such as mixed effect model which takes into account the correlation among the observation taken at various time points within a participant. Efficacy is a secondary endpoint, defined as biologically active FVIII at $\geq 5 \text{ IU/dL}$ by chromogenic FXa assay and/or one-stage APTT assay between 1 to 16 weeks following study treatment. FVIII activity will be assessed weekly during the study period. We can only assess the true steady state of FVIII protein produced from BMN 270 after a minimum of 72 hours has elapsed since the last infusion of FVIII protein concentrates.

Analysis of neutralizing antibody response and other immunological parameters as well as viral shedding will be primarily descriptive and involve both inter-participant and intra-participant comparisons across doses.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

AAV	adeno-associated virus
ADL	activities of daily living
ADR	adverse drug reaction
AE	adverse event
ALT	alanine transaminase
APTT	activated partial thromboplastin time
BPV	BioMarin Pharmacovigilance
BU	Bethesda Unit
CFR	Code of Federal Regulations
CRA	clinical research associate
CRF	case report form
eCRF	electronic case report form
DMC	Data Monitoring Committee
DRB	Data Review Board
ED	exposure days
EOSI	events of special interest
ETV	early termination visit
EudraCT	European Union Drug Regulating Authorities Clinical Trials
LuuraCI	
FAS	Full Analysis Set
FAS	Full Analysis Set
FAS FDA	Full Analysis Set Food and Drug Administration
FAS FDA FIH	Full Analysis Set Food and Drug Administration first-in-human
FAS FDA FIH FVIII	Full Analysis Set Food and Drug Administration first-in-human coagulation factor VIII
FAS FDA FIH FVIII FXa	Full Analysis Set Food and Drug Administration first-in-human coagulation factor VIII coagulation factor Xa
FAS FDA FIH FVIII FXa GCP	Full Analysis Set Food and Drug Administration first-in-human coagulation factor VIII coagulation factor Xa Good Clinical Practice
FAS FDA FIH FVIII FXa GCP HA	Full Analysis Set Food and Drug Administration first-in-human coagulation factor VIII coagulation factor Xa Good Clinical Practice Haemophilia A
FAS FDA FIH FVIII FXa GCP HA hFVIII	Full Analysis Set Food and Drug Administration first-in-human coagulation factor VIII coagulation factor Xa Good Clinical Practice Haemophilia A human coagulation factor VIII
FAS FDA FIH FVIII FXa GCP HA hFVIII HIPAA	Full Analysis Set Food and Drug Administration first-in-human coagulation factor VIII coagulation factor Xa Good Clinical Practice Haemophilia A human coagulation factor VIII Health Insurance Portability and Accountability Act
FAS FDA FIH FVIII FXa GCP HA hFVIII HIPAA IB	Full Analysis Set Food and Drug Administration first-in-human coagulation factor VIII coagulation factor Xa Good Clinical Practice Haemophilia A human coagulation factor VIII Health Insurance Portability and Accountability Act investigator brochure informed consent form International Conference on Harmonisation of Technical Requirements for
FAS FDA FIH FVIII FXa GCP HA hFVIII HIPAA IB ICF	Full Analysis Set Food and Drug Administration first-in-human coagulation factor VIII coagulation factor Xa Good Clinical Practice Haemophilia A human coagulation factor VIII Health Insurance Portability and Accountability Act investigator brochure informed consent form

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IEC	independent ethics committee
IND	Investigational New Drug (application)
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IV	intravenous
LFT	liver funtion test
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	no-observed-adverse-effect level
PD	pharmacodynamics
PEG	polyethylene glycol
РК	Pharmacokinetics
PRO	patient-reported outcome
rhFVIII	recombinant human FVIII protein
REB	research ethics board
SAE	serious adverse event
SAP	statistical analysis plan
SDV	source data verification
vg	vector genomes

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]).

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

5 ETHICS

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

5.1 Institutional Review Board or Independent Ethics Committee

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

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

5.2 Ethical Conduct of Study

It is expected that Investigators understand and comply with the protocol. This includes, but is not limited to: establishing and meeting enrollment commitments, including providing eligible patients for study enrollment; adhering to 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)

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

5.3 Patient Information and Informed Consent

A properly written and executed ICF, in compliance with ICH E6 (Section 4.8), United States Code of Federal Regulations (CFR) 21 CFR §50, European Clinical Trial Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC, and other applicable local regulations, will be obtained for each patient prior to entering the patient into the study. The Investigator will prepare the ICF and provide the documents to BioMarin for approval prior to submission to the IRB/IEC/REB approval. BioMarin and the IRB/IEC/REB must approve the documents before they are implemented. A copy of the approved ICF , and if applicable, a copy of the approved patient 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 patient and will maintain the original in the record file of the patient.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

During administration of informed consent, expectations regarding participation in the study should be made clear to patients. 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 US Food and Drug Administration (FDA) Form FDA 1572 and a Financial Disclosure Form. All sub-Investigators must be listed on Form FDA 1572. Financial Disclosure Forms must also be completed for all sub-Investigators listed on the Form FDA 1572 who will be directly involved in the treatment or evaluation of patients 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 patient 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.

Laboratory evaluations will be performed at the local laboratories associated with the study sites. Refer to the Laboratory Manual for more details.

7 INTRODUCTION

Haemophilia A (HA) is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males (Nathwani, 1992, Baillieres Clin.Haematol.). It is caused by mutations in the factor VIII (FVIII) gene that codes for FVIII protein, an essential cofactor in the coagulation cascade. 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 haemorrhage. Treatment in Western (Berntorp, 2012, Haemophilia.) countries consists of intravenous injection of plasma derived or recombinant FVIII protein concentrates at the time of a bleed, 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 haemophilia A patients. These individuals develop debilitating arthropathy and have a substantially increased risk of death from haemorrhage in life (Stonebraker, 2010, Haemophilia.). Chemical modification or bioengineering of FVIII may improve half-life to around 20 hours (Pipe, 2010, Blood). However, these long acting FVIII variants do not eliminate the need for lifelong FVIII protein administration or problems of FVIII inhibitor formation, which occurs in 30% of patients on standard FVIII replacement therapy (Nathwani, 1992, Baillieres Clin.Haematol.).

Gene therapy offers the potential of a cure through continuous endogenous production of human FVIII following a single administration of vector. Haemophilia 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 2ng/ml protein leads to a 1% expression) can ameliorate the severe phenotype (Srivastava, 2012, Haemophilia); thus the therapeutic goal for gene therapy is a modest increase in hFVIII. Finally, the consequences of gene transfer can be assessed using simple quantitative rather than qualitative endpoints that can be easily assayed in most clinical laboratories.

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

7.1 Nonclinical Studies

The nonclinical program supports a single IV administration of BMN 270, the planned clinical route of administration, for the treatment of Haemophilia A in male patients. This nonclinical program took into account the guidelines and reflection papers for gene therapy medicinal products under EMA Advanced Therapies. 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 (normal CD-1 mouse, B and T cell deficient mouse model of haemophilia 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.

The primary PD of BMN 270 was assessed in a series of non-GLP single dose studies in a FVIII KO x Rag2 mouse model of severe Haemophilia A that recapitulates the change in coagulation observed in the human severe disease population without interfering cross species immunogenicity. PD activity and expression of hFVIII was assessed for durations up to 13-weeks in the FVIII KO x Rag2 mouse given dose range of 2E11 through 2E14 vector genomes (vg)/kg. Low levels of plasma hFVIII were observed in mice given 2E12 vg/kg after eight-weeks, post dose. Plasma hFVIII activity using bleeding time as an endpoint was evaluated in the FVIII KO x Rag2 mouse given up to 2E13 and 1E14 vg/kg BMN 270 at 8 weeks, post dose. BMN 270 related correction of bleeding times showed a dose relationship that was similar to that observed in mice given matched IU levels of Refacto®.

All cynomolgus monkeys used in this program were screened for neutralizing anti-AAV5 activity prior to study enrollment. PD activity and plasma hFVIII concentrations were evaluated in the cynomolgus monkey given up to 6E13 vg/kg BMN 270 for eight weeks. Peak expression of hFVIII was observed three to six weeks post administration with a subsequent decrease in expression presumably due to immunogenicity though not necessarily correlated to antibody titer.

The normal mouse was utilized in the GLP toxicology study to assess the safety profile of BMN 270 without the background of disease progression and in sufficient number per parameter. The GLP single dose toxicity study in normal CD-1 mice given 6E12 and 6E13 vg/kg with a 4 and 13-week follow up period monitored clinical pathology, defined potential target organs, immunogenicity, gene expression and activity. No changes in liver function were observed. In a single dose PD study in monkey given BMN 270, formation of anti-AAV5 total antibodies was observed at Week 8 with relatively low formation of anti-hFVIII total antibodies. No changes in liver function was observed.

The overall nonclinical safety profile includes formation of anti-AAV5 total antibodies with relatively lower formation of anti-hFVIII total antibodies. Immunogenicity against the AAV capsid and hFVIII is an anticipated finding for BMN 270 treatment and will be monitored in the nonclinical and clinical programs. Though not observed in the nonclinical species, liver toxicity utilizing clinical pathology parameters will be monitored in the clinical program based on previous literature. Cellular immune response will also be monitored.

Additionally, the BMN 270 transgene product has a final sequence matching that of the protein replacement treatment, Refacto[®] and therefore the safety profile of the BMN 270 transgene product is anticipated to be similar to Refacto[®] and have no unique FVIII-specific target organs of toxicity. The AAV5 capsid has not been modified and therefore no unique capsid-specific safety findings are anticipated. Because the biodistribution pattern of AAV5 after IV administration is consistent across species, BioMarin will confirm the nonclinical distribution pattern of BMN 270 during clinical development. Biodistribution of the AAV5 capsid has been documented to predominately target the liver with relatively lower levels of transduction observed in the lung, kidney, spleen, testes and blood compartment depending on the species and timing of administration. Liver targeted distribution of a similar AAV5 Factor IX gene therapy product was observed in the rhesus macaque monkey with low levels of vector genomes detected in spleen, kidney and testis (Paneda, 2009, Hum.Gene Ther.). Despite distribution to non-liver organs, no expression of Factor IX was detected in these tissues. Additionally, distribution to the testis was observed in another study in monkeys given an AAV5-codon-optimized human porphobilinogen deaminase; however, vector genomes in the semen were only transiently observed within one week but not thereafter (Paneda, 2013, Hum.Gene Ther.).

Both normal and disease model mice and a limited number of monkeys were utilized to establish proof of concept, species scaling and dose response in order to select the first-in-human (FIH) dose of 6E12 vg/kg. This dose represents > 30-fold safety factor from the no observed adverse effect level (NOAEL) in enabling nonclinical studies.

7.2 Previous Clinical Studies

This is the first clinical study for BMN 270.

BioMarin's program for haemophilia A builds on previous clinical trials of AAV-mediated gene transfer for a related condition, haemophilia B, that were conducted with an AAV2 vector (Manno, 2003, Blood) and an AAV8 vector (Nathwani, 2011, N.Eng.J.Med.; Nathwani, 2014, N.Eng.J.Med.). The large size of the FVIII cDNA was shortened and a

preclinical validation of this approach was performed with an AAV8 vector (McIntosh, 2013, Blood).

AAV serotype 5 is also used in clinical trials and has shown good safety in a recent phase 1 study for treatment of Acute Intermittent Porphyria (D'Avola. 2014, J Hepatology).

AAV using other serotypes have been used in 105 clinical studies to date and no safety issue specific to the vector was ever reported.

7.3 Study Rationale

Haemophilia A (HA) is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males (Nathwani, 1992, Baillieres Clin. Haematol). It is caused by deficiency in the activity of coagulation factor VIII (FVIII), an essential cofactor in the intrinsic coagulation cascade. This disorder can be either inherited, due to a new mutation 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 is largely governed by the level of residual expression. Severe HA is classified as FVIII activity less than 1% of wild type (< 1 IU/dL), moderate disease comprises 1-5% of wild type activity and the mild form is 5-40% activity. The clinical manifestations of severe HA remain frequent spontaneous bleeding episodes, predominantly in joints and soft tissues, with a substantially increased risk of death from haemorrhage when the brain is involved.

Treatment of severe HA presently consists of intravenous injection of plasma derived or recombinant 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 rhFVIII (under 24 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 treatment (mean of 1 to 7 episodes/year with prophylaxis up to 30 to 50 for on demand treatment) (Nagel, 2011, Haemophilia). The consequence of multiple bleeding events is the development of an underlying pathology that contributes to debilitating multiple-joint arthropathy and substantially increased risk of death (Nagel, 2011, Haemophilia). Chemical modification (e.g. direct conjugation of polyethylene glycol (PEG) polymers) and bioengineering of FVIII (e.g. FVIII-Fc fusion proteins) improve half-life by approximately 50%, and thus, show promise in reduced dosing and maintaining activity levels above 1% trough (Stonebraker, 2010, Haemophilia), (Mahlangu, 2014, Blood). However, these longer acting FVIIIs remain dependent on multiple infusions to maintain critical levels of FVIII activity in severe HA patients. There is therefore a strong unmet need

for a fully preventive treatment of HA to give patients a FVIII level compatible with a normal and haemorrhage-free life.

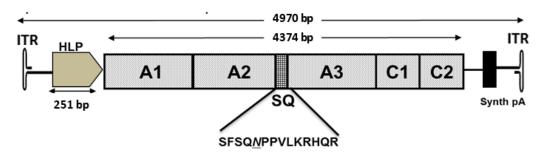
Gene therapy offers the potential of disease-modifying therapy by continuous endogenous production of active FVIII following a single intravenous administration of a vector with the appropriate gene sequence. Haemophilia A is well suited for a gene replacement approach because clinical manifestations 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 modest increases in the level of FVIII (any increase of the plasma level by 2 ng/ml induces an increase in activity of 1%) can ameliorate the severe form of the disease. Thus, relatively small changes in endogenous FVIII activity results in clinically relevant improvements in disease phenotype. Finally, the 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 (Pipe, 2010, Blood). They have an excellent and well defined safety profile, and can direct long term transgene expression with tropism for specific tissues such as the liver (Nathwani, 2005, Curr.Hematol Rep.) for serotypes 2, 5 and 8 among others). Indeed, an on-going gene therapy clinical trial for a related disorder, haemophilia B, has established that stable (>36 months) expression of human factor IX at levels that are sufficient for conversion of their bleeding phenotype from severe to moderate or mild is achievable following a single peripheral vein administration of AAV-8 vector(Nathwani, 2011, NEJM). Several participants in this trial have been able to discontinue factor prophylaxis without suffering spontaneous haemorrhages, 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, 2011, Mol.Ther.). (Bainbridge, 2008, NEJM; Maguire, 2009, Lancet; Simonelli, 2010, Mol.Ther.).

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

BOMARIN

Figure 7.3.1: BMN 270 Transgene Construct, ~5.0 kbp



BMN 270 will be delivered by single intravenous dose and is designed to achieve stable, potentially life-long expression of active hFVIII in the plasma, synthesized from vector-transduced liver tissue. The clinical study BMN 270-201 is a first-in-human study designed to assess the relationship of vector dose to the augmentation of residual FVIII activity, and whether these levels are sufficient to alter the clinical phenotype. The relationship of dose to safety will be correlated to the activity of hFVIII in patients with severe HA.

7.4 Summary of Overall Risks and Benefits

Safety will be assessed by adverse event reporting and clinical laboratory assessment. Based on prior human studies with peripheral injections of AAV vectors, there is no known safety risk of AAV gene therapy. However, a mild asymptomatic transaminitis was observed at week 8-10 after administration with an AAV8-FIX, providing the rationale for the following surveillance plan (Manno, 2006, Nature Med.). Each patient will have comprehensive surveillance plan monitoring LFTs once a week from dose to completion of Week 6, 3 times per week from Weeks 7 to 12, and once a week from Weeks 13 to 16. If a patient's ALT is found to be greater than 1.5x baseline during these periods, then LFTs will be monitored three times per week or until the ALT returns to baseline. LFTs will be monitored every other month for the first year and then every three months for up to 5 years post-dose in the safety extension.

Dose selection: The benefit of this study can only be enhanced by selecting a starting dose that potentially could contribute to a better opportunity of observing a therapeutic effect, and therefore, reducing the possibility of a sub-therapeutic effect. With this consideration in mind, the starting dose 6E12 vg/kg was selected using overall data from the pre-clinical studies conducted in mice (normal and disease model, Rag2 -/- x FVIII -/-) and monkey. A detectable pharmacological response based on activity was observed at 6E12 vg/kg.

A 10-fold safety margin based upon the NOAEL was observed in the GLP 13-week study in normal mouse at the highest dose administered. A 30-fold safety margin in an 8-week dose response study in disease model mice based on histology was observed at the highest dose administered. No BMN 270-related changes in clinical observations or chemistry was observed in the monkey at doses up to 6E13 vg/kg, a 10-fold safety margin after 8-weeks. Overall, no BMN 270-related findings, except expected formation of anti-AAV5 antibodies, were observed at the highest administered doses of 6E13, 2E14 and vg/kg in the normal mouse, disease model mouse and monkey, respectively.

Based on these key pre-clinical findings it can be suggested that the proposed starting dose of 6E12 vg/kg should not pose any risk or safety concerns to patients but may potentially benefit the patient therapeutically.

8 STUDY OBJECTIVES

The primary objectives of the study are:

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

The secondary objectives of the study are:

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

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

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

Patients who provide written informed consent, meet the entry criteria definition of severe HA, and do not have transduction inhibition activity to AAV5 will be eligible to enroll in the study. Participants will be enrolled sequentially into one of up to three cohorts according to dose level:

- 1. 6E12 vector genomes [vg] per kilogram of body weight, given as a single intravenous dose (iv)
- 2. 2E13 vg per kilogram, iv
- 3. 6E13 vg per kilogram, iv

Patients will be enrolled sequentially every 3 weeks or more between cohorts. Dose escalation may occur after a single patient has been safely dosed if the resulting FVIII activity at Week 3 is < 5 IU/dL. Three weeks is expected to be the time the expression will be close to the maximum. This escalation paradigm is intended to minimize the patient numbers exposed to subtherapeutic doses.

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

Approximately three weeks after an injection, the decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and a panel of investigators participating in the study.

If the FVIII activity is ≥ 5 IU/dL, then the other patients of the dose group will be enrolled without waiting for 3 weeks between patients.

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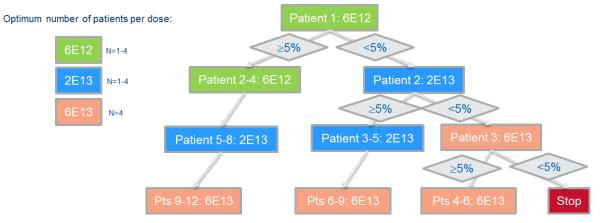


Figure 9.1.1: Flow Chart of Dose Escalation Scheme

Patient 1 will be dosed by intravenous perfusion with 6E12 vector genomes [vg] per kilogram of body weight. If the activity level does not reach \geq 5 IU/dL (expressed as % in Figure 9.1.1) at 21 days, then a higher dose (2E13 vg per kilogram) will be used for the next patient.

If the activity level does not reach \geq 5 IU/dL after Patient 2, then the highest dose (6E13 vg per kilogram) will be used for the next patient.

For each dose, if the activity level reaches 5 IU/dL and if no safety issue is found, then up to four patients will receive this dose. If at any time activity levels reach 10 IU/dL or higher, no further dose escalation will take place, but additional patients will then be dosed at this dose level for a total of 6 patients per dose.

Because patients develop neutralizing immunity upon exposure to the capsid, re-challenge of vector is not a treatment option and these patients have effectively a single opportunity for therapy using this AAV capsid. Efficacy will be determined by FVIII activity at 16 weeks post dose. Safety will be evaluated for approximately 5 years after dose. Any safety signal will trigger a review of the data and possible additional analysis including mononuclear collection. Additionally, if any of the events listed in Section 9.3.3.1 occur, enrollment into the trial will be halted to complete an extensive safety analysis. Notification of the study halt will be sent by the Sponsor to the participating sites via telephone and email immediately after becoming aware of a safety concern. This will ensure no additional subjects are dosed until the signal has been completely evaluated. If, following safety review by the Data Review Board (DRB) and the Sponsor, it is deemed appropriate to restart dosing, a request to restart dosing with pertinent data will be submitted to the health authority.

A summary of events and assessments are provided by visit in Table 9.1.1 for Screening, Baseline and BMN 270 Infusion, in Table 9.1.2 for Post-Infusion Follow-up, and in Table 9.1.3 for Safety Follow-up.

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Table 9.1.1: Schedule of Events – Screening and Infusion

	Prior to BM	IN 270 Infusion			
Assessment	Screening (Day -28 to Day -1)	Baseline (Day -7 to Day -1) ^h	BMN 270 Infusion Visit (Day 1)		
Informed consent	Х				
Medical History	Х				
Physical Exam ^a	Х	X	X		
Vital Signs	Х		X		
Assessment of Adverse Events and Concomitant Medications	Х	X	Х		
Documentation of bleeding episodes and FVIII usage (by either patient or clinical information)	Х	Х			
Electrocardiogram	Х				
Chest X-ray	Х				
Liver Ultrasound	Х				
hFVIII Assays ^b	Х	Х			
AAV5 Assays ^c	Х		Х		
Screen for Hepatitis B, Hepatitis C, HIV ^d	Х				
Blood chemistry, haematology, urine tests, coagulation screen, and CRP ^e	Х	Х			
Mononuclear cell collection for CTL baseline		Х			
PCR of vector genomes in blood, saliva, urine, semen, and stools		Х			
Biomarker testing ^f	X				
Exploratory biomarker assessments ^g		Х			
Quality of Life (QoL) assessment		Х			
BMN 270 Infusion			Х		

^a Complete physical examination should be done at Screening. Brief physical examination may be done at Baseline and at the BMN 270 Infusion Visit. Height and weight will be recorded at Screening only.

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^b Includes baseline hFVIII activity (chromogenic FXa and one-stage APTT assays), hFVIII coagulation activity exploratory assay, hFVIII inhibitor level (Bethesda assay with Nijmegen modification), hFVIII total antibody titer, and hFVIII antigen (ELISA).

^c Screening (done during Screening) and testing (at Infusion Visit) of AAV5 pre-existing immunity may include plasma samples for 3 assays (in vivo transduction inhibition, in vitro transduction inhibition and AAV5 total antibody assays). The assessment on the day of the infusion visit must be performed before the BMN 270 infusion is given.

^d Patients with documented negative results within the last 30 days do not need to be retested.

^e Refer to Table 9.7.8.2.1 for laboratory assessments to be included.

 $^{\rm f}$ Includes HLA typing, FVIII mutation status, TNF α and IL10a single nucleotide polymorphisms.

^g Blood samples will be collected from subjects to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to Haemophilia A disease. The genetic/genomic testing on these exploratory samples is optional.

^h Should the screening visit occur within 7 days of the drug infusion, physical examination, vital signs, blood chemistry, haematology, urine tests, coagulation screen, and CRP do not need to be repeated at Baseline.



	Follow-Up After BMN 270 Administration - Weeks*															
Assessment	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Physical exam ^a	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Assessment of Adverse Events and Concomitant Medications	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Vital Signs	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Blood chemistry, haematology, urine tests, coagulation screen, and CRP ^b	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
hFVIII activity assays ^c	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
hFVIII antibody titer	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
PCR of vector genomes in blood, saliva, urine, semen, and stools ^d	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Exploratory biomarker assessments ^e	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
QoL assessment	Х	Х	Х	Х												Х
AAV5 antibody titer	Х							Х								Х
Testing for reactivation of hepatitis B and hepatitis C	Х		Х			Х										
Mononuclear cell collection				Х				Х				Х				Х

Table 9.1.2: Schedule of Events – Post-Infusion Follow-Up

^{*} Visit windows are ±48 hours

^a Brief physical examination should be done at all weekly visits except Week 16, where a complete physical examination should be performed. Refer to Section 9.7.8.4.

^b Refer to Table 9.7.8.2.1 for laboratory assessments to be included. Each patient will have comprehensive surveillance plan monitoring LFTs once a week from dose to completion of Week 6, 3 times per week (every other day excluding weekends) from Weeks 7 to 12, and once a week from Weeks 13 to 16. If a patient's ALT is found to be greater than 1.5x baseline during these periods, then LFTs will be monitored three times per week or until the ALT returns to baseline.

^c Includes hFVIII activity level (APTT and FXa chromogenic assay), hFVIII activity confirmation (frozen plasma), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, hFVIII coagulation activity exploratory assay, and hFVIII antigen (ELISA).

^d Collection to occur on Day 1, 3, 7 following BMN 270 infusion, and then weekly until 3 consecutive negative results are obtained.

^e Blood samples will be collected from subjects to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to Haemophilia A disease. The genetic/genomic testing on these exploratory samples is optional.

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	Year 1 - Weeks [*]					Years 2-5 [*]	ETV (early termination	
Assessment	20	28	36	44	52	Q3M	visit)	
Physical exam ^a	X	Х	Х	Х	X	X	Х	
Assessment of Adverse Events and Concomitant Medications	X	Х	Х	Х	X	X	Х	
Vital Signs	Х	Х	Х	Х	X	X	Х	
Blood chemistry, haematology, urine tests, coagulation screen, and CRP ^b	X	Х	Х	Х	X	X	Х	
hFVIII activity assays ^c	X	Х	Х	Х	X	X	Х	
AAV5 antibody titer	Х	Х	Х	Х	X	X	Х	
hFVIII antibody titer	Х	Х	Х	Х	X	X	Х	
Mononuclear Cell Collection (for determination of FVIII and Capsid specific CTL activity)	X	Х	Х	Х	X	X	Х	
PCR of vector genomes in blood, saliva, urine, semen, and stools ^d	X	Х	Х	Х	X	X	Х	
QoL assessment		Х			X	X ^e	Х	

* Visit windows are ± 72 hours

^a Complete physical examination should be performed at Weeks 52 and every 52 weeks thereafter; brief physical exam may be performed at other study visits. Refer to Section 9.7.8.4.

^bRefer to Table 9.7.8.2.1 for laboratory assessments to be included.

^c Includes hFVIII activity level (one-stage APTT and chromogenic FXa assay), hFVIII activity confirmation (frozen plasma), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, hFVIII coagulation activity exploratory assay, and hFVIII antigen (ELISA).

^d Sample testing during Safety Follow-Up is not required if 3 consecutive samples are cleared during the Post-Infusion Follow-Up period.

^e QoL assessment during Years 2-5 of Safety Follow-up should be performed at every other visit (every 6 months) starting with the Week 78 visit (ie, 26 weeks after the Week 52 visit at the end of Year 1 of the Safety Follow-up period).

9.2 Discussion of Study Design, Including Choice of Control Group

Study 270-201 is designed to be a first-in-man, phase 1/2 open-label, dose escalation study in patients with severe haemophilia A. Three doses of BMN 270 will be evaluated and the dose escalation decision tree is summarized in Figure 9.1.1.

The decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and a panel of investigators participating in the study.

There will be no control group. Parameters for each patient will be compared to a pre-treatment assessment of safety (liver function) and efficacy (number of bleeds, use of replacement therapy).

As AAV based treatment always leads to anti-capsid immune response, no true control group (for example with an empty AAV) is possible.

9.3 Selection of Study Population

Up to 12 severe haemophilia A patients may enroll into the study; the actual number of patients will depend on the criteria for dose escalation. A total of 6 patients may be enrolled at a single dose level.

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 criteria:

- 1. Males that are 18 years or older with established severe Haemophilia A as evidenced by their medical history. Patients will be considered as severe if their FVIII baseline level is 1 IU/dL or less
- 2. Treated/exposed to FVIII concentrates or cryoprecipitates for a minimum of 150 exposure days (EDs)
- 3. Greater or equal to 12 bleeding episodes only if on on-demand therapy over the previous 12 months. Does not apply to patients on prophylaxis
- 4. Able to sign informed consent and comply with requirements of the trial
- 5. No history of inhibitor, or no inhibitor on 2 consecutive occasions within the past 12 months using a modified Nijmegen Bethesda assay higher than 0.6 Bethesda Unit (BU)

6. Sexually active patients must be willing to use an acceptable method of contraception such as double barrier, including hormonal contraception for at least 6 months post-treatment.

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 immunity to the AAV5 capsid as measured by AAV5 transduction inhibition and AAV5 total antibodies
- 2. Any evidence of active infection or any immunosuppressive disorder.
- 3. Patients that are HIV positive are excluded.
- 4. Significant liver dysfunction as defined by abnormal elevation of ALT (alanine transaminase) to 3 times the upper limit of normal, bilirubin, alkaline phosphatase, or an INR (international normalized ratio) of 1.4. Potential participants who have had a liver biopsy in the past 3 years are excluded if they had significant fibrosis of 3 or 4 as rated on a scale of 0-4
- 5. Evidence of any bleeding disorder not related to Haemophilia A
- 6. Platelet count of $< 100 \text{ x } 10^9/\text{L}$
- 7. Creatinine $\geq 1.5 \text{ mg/dL}$
- 8. Liver cirrhosis of any etiology as assessed by liver ultrasound
- 9. Hepatitis B if surface antigen is positive
- 10. Hepatitis C if RNA is positive
- 11. Treatment with any IP within 30 days prior to the screening visit
- 12. Any disease or condition at the physician's discretion that would prevent the patient from fully complying with the requirements of the study. The physician may exclude patients unwilling or unable to agree on not using alcohol for the 16-week period following the viral infusion.
- 13. Receipt of any vector or gene transfer agent

9.3.3 Removal of Patients from Treatment or Assessment

Patients may withdraw their consent to participate in the study at any time without prejudice. The Investigator must withdraw from the study any patient who requests to be withdrawn. A patient's participation in the study may be discontinued at any time at the discretion 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.

BioMarin must be notified of all patient 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 patient from the study include, but are not limited to, the following:

- Patient requires medication or medical procedure prohibited by the protocol
- Patient does not adhere to study requirements specified in the protocol
- Patient was erroneously admitted into the study or does not meet entry criteria
- Patient is lost to follow-up

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

The Investigator or designee must explain to each patient, before enrollment into the study, that for evaluation of study results, the patient's protected health information obtained during the study may be shared with the study Sponsor, regulatory agencies, and IRB/IEC/REB. It is the Investigator's (or designee's) responsibility to obtain written permission to use protected health information per country-specific regulations, such as the Health Insurance Portability and Accountability Act (HIPAA) in the US, from each patient. 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 patient and the patient will be removed from the study.

9.3.3.1 Study Safety Evaluation Criteria

If any of the following events occur (except the persistence of AAV5) in a patient in the study who has received BMN 270 infusion, enrollment into the trial will be put on halt to complete an extensive safety analysis per Section 9.1.

- A 5-fold increase in ALT after BMN 270 administration
- The occurrence of other drug-related Grade III-IV toxicity, including liver failure and clinical hepatitis
- Drug-related Grade II toxicity that persists for at least 7 days
- The occurrence of neutralizing antibodies to hFVIII following BMN 270 infusion

- The persistent detection of the AAV vector genome in the semen of a participant more than 26 weeks after BMN 270 infusion, as discussed in Section 9.7.8.5
- The occurrence of a malignancy at any point after BMN 270 infusion that is assessed as possibly, probably, or definitely related to the study agent
- Any unexplained serious adverse event ≥ grade 4 assessed as at least possibly related to study drug

9.3.4 Patient Identification and Replacement of Patients

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

Patients who withdraw from the study after Week 16 will not be replaced.

9.3.5 Duration of Patient Participation

The duration of this study will be approximately 264 weeks. This includes 4 weeks of screening, 1 day of BMN 270 infusion, 16 weeks of Post-Infusion Follow-Up, and 244 weeks of Safety Follow-Up. A primary endpoint analysis on safety and efficacy will be performed at 16 weeks.

9.4 Treatments

BioMarin or its designee will provide the study site with study drug sufficient for study completion. BioMarin is responsible for shipping study drug to clinical sites.

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.

9.4.2 Identity of Investigational Product

9.4.2.1 Product Characteristics and Labeling

The study drug label includes the following information: lot number, required storage conditions, a precautionary statement, expiry date, study number, and BioMarin name and address. Labelling will be done according to country specific requirements.

9.4.3 Storage

At the study site, all IP must be stored under the conditions specified in the IB 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

After a physical exam performed by the PI or designee, participants will be admitted on the day of BMN 270 infusion. An IV catheter will be inserted into a suitable peripheral vein (e.g. the median cubital vein) and flushed with saline. FVIII protein concentrate 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. An electric syringe will be used to infuse through an in-line, low protein binding 0.22 micron filter. BMN 270 will be infused through the catheter using an appropriate infusion pump while monitoring the vital signs (pulse, blood pressure, respiration rate and temperature) at 15 minute (\pm 5 minutes) intervals. The anticipated maximum interval from initiation of thawing of BMN 270 to completion of the infusion is 4 hours.

Following completion of the infusion, vital signs will be monitored hourly (\pm 5 minutes) for 6 hours and then every 2 hours (\pm 15 minutes) for 6 hours and then at 4 hour intervals. If the vital signs are stable the catheter will be removed 20-24 hours after the infusion. Hemostasis at the puncture site will be established by applying pressure according to standard protocol for infusing FVIII concentrates. Patients will remain hospitalized for 24 hours to observe for any immediate toxicity of the procedure. After 24 hours of hospitalization, participants will be discharged unless toxicity has been observed in which case hospitalization may be extended or transfer to an outpatient facility may occur based on the evaluation and judgment of the Principal Investigator after consultation with the Medical Monitor.

9.4.5 Method of Assigning Patients to Treatment Groups

Patients 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 Sponsor will be required prior to enrollment of each study patient. Upon their enrollment into the study, patients will be assigned a unique patient number and dose level by the Sponsor.

Patients are enrolled serially and their dose is defined in Section 9.4.6.2 below. Escalation is based on FVIII activity 3 weeks after injection. Patients may receive the next higher dose if the previous patient does not meet the activity criteria, or the same dose if the previous

patient meets the activity criteria. Up to 6 patients can have the same dose, for a total of 12 patients in this study.

9.4.6 Selection of Doses Used in the Study

The starting dose was based on the expression of hFVIII observed in nonclinical studies of mice and monkeys. The starting dose has a significant safety margin (10-fold) from NOAEL in non-human primates. The dose escalation is half-logs based.

9.4.6.1 Selection of Timing of Dose for Each Patient

A minimum of three weeks are required between patients, to allow for evaluation of safety and expression of hFVIII. After three weeks, depending on the activity level, the choice of the dose for the next patient will be made as described below.

9.4.6.2 Selection of Dose for Each Patient

The starting dose was determined by expression of hFVIII observed in mice and monkeys and a scale up factor based on previous experience, an improved purification process over previous trials (thus decreasing the risk of immune response), and a new evaluation of the titer (PCR performed after hairpin removal).

Approximately three weeks after an injection, the decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and a panel of investigators participating in the study.

Patient 1 will be dosed with 6E12 vector genomes [vg] per kilogram of body weight. If the activity level does not reach \geq 5 IU/dL at 21 days, then a higher dose (2E13 vg per kilogram) will be used for the next patient.

If the activity level does not reach \geq 5 IU/dL after Patient 2, then the highest dose (6E13 vg per kilogram) will be used for the next patient.

For each dose, if the activity level reaches 5 IU/dL and if no safety issue is found, then up to four patients will receive this dose. If at any time activity levels reach 10 IU/dL or higher, no further dose escalation will take place, but additional patients will then be dosed at this dose level for a total of 6 patients per dose.

Refer to Figure 9.1.1 for a visual representation of the study design.

9.4.7 Blinding

This is an open-label study.

9.4.8 Prior and Concomitant Medications

All prescription and over-the-counter medications taken by a patient for 30 days before Screening will be recorded on the designated CRF. The Investigator may prescribe additional medications 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 CRF.

The following medications are prohibited starting 30 days before Screening:

- Live vaccines
- Immunosuppressive agents

9.4.8.1 Concomitant Haemophilia Treatments

Patients on "on demand" therapy for FVIII will continue their treatment at will. Patients on prophylactic FVIII therapy will discontinue their treatment starting the day of infusion and switch to an "on demand" schedule. FVIII can always be taken as needed by the patient, who will carefully record his treatment and bleeding episodes in his diary.

9.4.8.2 Glucocorticoid Treatment of Elevated Hepatic Transaminases

During the Post-Infusion Follow-up Period, each patient will have comprehensive surveillance plan monitoring LFTs once a week from dose to completion of Week 6, 3 times per week from Weeks 7 to 12, and once a week from Weeks 13 to 16. If a patient's ALT is found to be greater than 1.5x baseline during these periods, then LFTs will be monitored three times per week or until the ALT returns to baseline.

Reports of abnormal LFTs (defined as 1.5x the patient's baseline level) should be made to BioMarin within 24 hours of the lab value being available. If the LFTs are abnormal, treatment with prednisolone initiated at a dose of 60 mg per day and then gradually tapered (60 mg daily for the first week, then 40 mg the second week, then 30 mg the third week, then 20 mg the fourth week, then stop) will be started immediately.

9.4.9 Treatment Compliance

Study drug will be administered to patients at the study site by a qualified professional. The quantity dispensed, returned, used, lost, etc. must be recorded on the dispensing log provided for the study. Sites will be instructed to return all used and unused study drug containers.

9.5 Investigational Product Accountability

The Investigator or designee is responsible for maintaining accurate records (including dates and quantities) of IP(s) received, patients to whom IP is dispensed (patient-by-patient dose specific accounting), 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.

9.5.1 Return and Disposition of Clinical Supplies

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

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

All study drug and related materials should be stored, inventoried, reconciled, and destroyed or returned according to applicable state and federal regulations and study procedures.

9.6 Dietary or Other Protocol Restrictions

There are no dietary or other protocol restrictions for this study.

9.7 Safety and Efficacy Variables

As this is a first-in-man study, the primary endpoint of safety will be assessed as explained in Section 9.7.8.

The primary efficacy measure will be to assess plasma FVIII activity. The efficacy goal of the study is to establish the dose relationship to FVIII activity \geq 5 IU/dL at 16 weeks post BMN 270 administration.

9.7.1 Safety and Efficacy Measurements Assessed

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

9.7.2 Primary Efficacy Variables

The primary efficacy measure will be the plasma FVIII activity monitored on a regular basis after BMN 270 dose. The efficacy goal of the protocol is to ascertain the dose range of BMN 270 required to convert severe HA patients to stable expression of FVIII at 5 IU/dL, i.e., a mild severity. This is associated in natural history studies with clinically superior long term outcomes (Nathwani, 1992, Baillieres Clin.Haematol.).

To measure the primary efficacy variable, the following assays will be used:

- FVIII activity (chromogenic FXa assay)
- FVIII activity by one-stage APTT (Activated Partial Thromboplastin Time)

The FVIII activity level and the number of patients with FVIII activity ≥ 5 IU/dL will be summarized.

Timing of assessment by these assays is provided in Table 9.1.2 and Table 9.1.3. Details on performing the assays are included in the Laboratory Manual.

9.7.3 Secondary Efficacy Variables

Secondary efficacy measures will be the reduction in the frequency of factor replacement therapy, and reduction in the number of bleeding episodes. Patients 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 patient's diary or other patient records.

Assessment of viral shedding at one week after BMN 270 infusion will also be considered an efficacy variable.

9.7.4 Immunogenicity

Immunogenicity assays will be performed on plasma. The assays will include detection of anti-capsid, and anti-FVIII total antibody, and determination of neutralizing antibodies against FVIII. Any increase in total antibody level, especially during the time period of 6-12 weeks, will be compared with FVIII activity measurements. Any abnormality of the liver parameters will lead to an immunogenicity assessment to determine anti-FVIII and capsid specific CTL. Anti-FVIII and capsid specific CTL assays will be performed on collected PBMCs.

Timing of assessment by these assays is provided in Table 9.1.2 and Table 9.1.3.

9.7.5 Pharmacodynamics

The hFVIII antigen and activity level will be measured by an ELISA (antigen) and by one-stage APTT and/or chromogenic FXa assay (activity). Individual antigen and activity plasma plots will be prepared to assess changes over 16 weeks. FVIII activity measurements will be used to determine PD parameters.

If supported by FVIII activity data, non-compartmental analysis and observation will be used to estimate individual values of C_b (baseline concentration), C_{ss} (steady state concentration), T_{ss} (time to steady state), C(t) and AUC(0-t) where t is 16 weeks. Other parameters that may be used to describe individual FVIII protein and activity plasma profiles are C_{max} (maximum concentration) and C_{avg} (average concentration, AUC(0-t)/t). The PD parameters and dose will be used to assess clinical pharmacology.

Sample collection times are indicated in Table 9.1.2 and Table 9.1.3.

9.7.6 Exploratory Biomarker Assessments

Blood samples will be collected from subjects at the time points indicated in Table 9.1.1 and Table 9.1.2 to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to Haemophilia A disease. The genetic/genomic testing on these exploratory samples is optional.

9.7.7 Quality of Life Assessment

A patient-reported outcome (PRO) questionnaire will be used to assess subject quality of life (QoL) during the study. Assessments will occur at the time points listed in the Schedules of Assessments.

Details regarding the QoL assessment will be included in the Study Reference Manual.

9.7.8 Safety Variables

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

9.7.8.1 Adverse Events

The occurrence of AEs will be assessed continuously from the time the patient signs the ICF. The determination, evaluation and reporting of AEs will be performed as outlined in Section 10. Assessments of AEs will occur at the time points shown in Table 9.1.1.

9.7.8.2 Clinical Laboratory Assessments

Specific visits for obtaining clinical laboratory assessment samples are provided in Table 9.1.1. The scheduled clinical laboratory tests are listed in Table 9.7.8.2.1. Refer to the Study Reference Manual 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 the cause of the abnormality is determined, the value returns to baseline or to within normal limits, or 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 CRF.



Blood Chemistry	Haematology	Urine Tests	Other
Albumin	Haemoglobin	Appearance	CRP
Alkaline phosphatase	Haematocrit	Color	
ALT (SGPT)	WBC count	pН	Coagulation Screen including:
AST (SGOT)	RBC count	Specific gravity	APTT
Direct bilirubin	Platelet count	Ketones	PT/INR
Total bilirubin	Differential cell count	Protein	TT
BUN		Glucose	
Calcium		Bilirubin	
Chloride		Nitrite	
Total cholesterol		Urobilinogen	
CO ₂		Haemoglobin	
Creatinine			
Glucose			
GGT			
LDH			
Phosphorus			
Potassium			
Total protein			
Sodium			
Uric acid			

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CO₂, carbon dioxide; GGT, gamma-glutamyltransferase; LDH, lactate dehydrogenase; PT, prothrombin time; APTT, activated partial thromboplastin time; RBC, red blood cell; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone; WBC, white blood cell; TT, thrombin time; INR, international normalized ratio.

9.7.8.3 Liver function and Hepatitis Testing

Patients will be screened for evidence of previous hepatitis B or hepatitis C infection at Screening. If medical records showing no evidence of Hepatitis B or Hepatitis C infection from the previous 30 days are available, then the Screening tests do not need to be done.

Evidence of ongoing infection (positive surface antigen for hepatitis B or positive RNA testing for hepatitis C) will be an exclusion criteria. If these parameters are negative and therefore no active infection is detected, then the patients may be included if they were vaccinated (for hepatitis B) or cleared the infection (for hepatitis C) and their liver function is acceptable.

A liver ultrasound and liver function testing at Screening will identify any significant hepatic dysfunction, which is defined as:

- More than 3x the normal ALT level
- More than 3x the normal bilirubin level
- Alkaline phosphatase above the normal cut off.
- INR over 1.4.
- Thrombocytopoenia under $100 \ge 10^9/L$

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

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

Systolic blood pressure, diastolic blood pressure, heart rate, respiration rate, and temperature will be assessed at Screening, Baseline, and at the beginning of each visit during the Post-Infusion Follow-Up and Safety Follow-Up periods. On the day of the BMN 270 Infusion, vital signs will be monitored hourly for 6 hours and then every 2 hours for 6 hours and then at 4 hour intervals.

A complete physical examination is necessary during Screening/Baseline; thereafter, brief physical examinations may be performed at the discretion of the investigator based on the patient'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 (level of consciousness, speech, language, cranial nerves, motor strength, motor tone, abnormal movements, reflexes, upper extremity sensation, lower extremity sensations, gait, Romberg, nystagmus, and coordination).

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

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Weight and height will be recorded at Screening only.

9.7.8.5 Viral Shedding

Viral shedding has been extensively studied in all similar clinical trials performed to date. (Nathwani, 2014, N.Eng.J.Med (Supplemental Appendix); Manno, 2006, Nature Med. (Supplemental Appendix); Schenk-Braat, 2007, J Gene Med; Croteau, 2004, Ann Occup Hyg). It has been constantly shown that the vector was not detectable anymore at 40 days, with its persistence in semen for 16 weeks in the seminal fluid but not in motile sperm (Manno, 2006, Nature Med.). In addition, it has always involved only an extremely small fraction of the injected dose.

Viral shedding will also be extensively studied in the present clinical trial, every week up to 16 weeks, then every 4 weeks to one year, then every three months. During the Post-Infusion Follow-Up period, patients will undergo testing of various bodily fluids to look for evidence of viral shedding for possible viral transmission. Bodily fluids will be tested by PCR at the time points indicated in Table 9.1.2 and Table 9.1.3. Fluids tested will include:

- Blood
- Saliva
- Semen
- Urine
- Stool

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 haematology, 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, a reportable adverse event (AE) is any untoward medical occurrence (e.g., sign, symptom, illness, disease or injury) in a patient administered the study-drug or other protocol-imposed intervention, regardless of attribution. This includes the following:

- AEs not previously observed in the patient that emerge during the course of the study.
- Pre-existing medical conditions judged by the Investigator to have worsened in severity or frequency or changed in character during the study.
- Complications that occur as a result of non-drug protocol-imposed interventions (eg, AEs related to screening procedures).

An adverse drug reaction is any AE for which there is a reasonable possibility that the study-drug caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the study-drug and the AE.

Bleeding events that are normal events of haemophilia (ie, bleeding events which occur only because the patient is a haemophiliac) should not be recorded as AEs but will instead be captured in patient diaries. Bleeding events that occur where a normal (ie, non-haemophiliac) patient would bleed, such as bleeding as a result of trauma, should be recorded as adverse events. All bleeding events which meet criteria for being serious should be reported as serious adverse events (SAEs) whether or not they are bleeding events that are normal sequelae of haemophilia.

Whenever possible, it is preferable to record a diagnosis as the AE term rather than a series of terms relating to a diagnosis.

10.2 Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that at any dose meets 1 or more of the following criteria:

- Is fatal
- Is life threatening

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Note: Life-threatening refers to an event that places the patient at immediate risk of death. This definition does not include a reaction that, had it occurred in a more severe form, might have caused death.

- Requires or prolongs inpatient hospitalization. Hospitalization for less than 24 hours will not be considered to be an SAE. Hospitalization solely for the purpose of insertion of an in-dwelling IV catheter (such as a Port-a-Cath or other brand) for administration of study drug will not be considered an SAE.
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect in the child or fetus of a patient exposed to IP prior to conception or during pregnancy
- Is an important medical event or reaction that, based on medical judgment, may jeopardize the patient or require intervention to prevent one of the above consequences (e.g. anaphylaxis)

All adverse events that do not meet any of the criteria for SAEs should be regarded as nonserious AEs.

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 liver enzymes triggering a corticosteroid treatment

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 treatment, only SAEs associated with any protocol-imposed interventions will be reported. After informed consent is obtained and the first administration of study drug, the reporting period for all non-serious AEs and SAEs begins and continues for approximately 5 years or until study discontinuation/termination, whichever is longer. The criteria for determining, and the reporting of SAEs is provided in Section 10.2.

10.3.2 Eliciting Adverse Events

Investigators will seek information on AEs and SAEs and EOSI, at each patient contact by specific questioning and, as appropriate, by examination. Information on all AEs and SAEs and EOSI, should be recorded in the patient's medical record and on the AE Case Report Form (eCRF).

10.3.3 Assessment of Seriousness, Severity, and Causality

The Investigator responsible for the care of the patient or qualified designee will assess AEs for severity, relationship to study drug, and seriousness (refer to Section 10.2 for SAE definitions). These assessments should 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 patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. The severity of each will be assessed using the defined categories in Table 10.3.3.2.1.

The Investigator will determine the severity of each AE and SAE and EOSI using the NCI CTCAE v4. 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 as stated below.

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 instrumental activities of daily living (ADL) ^a	age-appropriate
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 or debilitating: consequences; urgent intervention indicated	Grade 4 and 5 AEs should always be
5	Death related to AE	reported as SAEs

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

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

10.3.3.3 Causality

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

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

Table 10.3.3.3.1: Causality Attribution Guidance

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

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

The investigator's assessment of causality for individual AE reports is part of the study documentation process. Regardless of the Investigator's assessment of causality for individual AE reports, the Sponsor will promptly evaluate all reported SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators and applicable regulatory authorities.

10.4 Procedures for Recording Adverse Events

10.4.1 Recording Adverse Events on a eCRF

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

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

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

10.4.1.1 Diagnosis versus Signs and Symptoms

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 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 haemorrhage 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 is one that extends continuously, without resolution, between patient evaluation time points. Such an event should be recorded only once on the AE eCRF unless its severity increases or decreases (in which case it should be recorded again on the AE eCRF).

A recurrent AE is one that occurs and resolves between patient evaluation time points, but then subsequently recurs. All recurrences of the AE should be recorded on the AE eCRF.

10.4.1.4 Abnormal Laboratory Values

Laboratory test results will be recorded on the laboratory results pages of the AE 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 should be reported as such, in addition to being recorded as an AE in the AE eCRF.

A clinical laboratory abnormality is considered clinically significant and should be documented as AE if **any** of the following conditions is met:

- Accompanied by clinical symptoms
- Leading to a change in study medication (e.g. dose modification, interruption or permanent discontinuation)
- Requiring a change in concomitant therapy (e.g. addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment).
- The laboratory abnormality persists upon repeat confirmatory testing.
- The abnormality suggests a disease and/or organ toxicity

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• 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 hFVIII activity should not be reported as adverse events unless signs of worsening are observed.

10.4.1.5 Pre-existing Conditions

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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 document 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:

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- Perform a protocol-mandated efficacy measurement
- Undergo a diagnostic or elective surgical procedure for a pre-existing medical condition that has not changed
- 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 patient 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 partner should be reported within 24 hours of the site becoming aware of the pregnancy by faxing the Pregnancy Form in the study reference materials to BPV. The Investigator must make every effort to follow the patient through resolution of the pregnancy (delivery or termination) and to report the resolution on the Pregnancy Follow-up Form in the study reference materials. In the event of pregnancy in the partner of a study patient, 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 BioMarin Pharmacovigilance (BPV)

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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.

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

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

The reporting period for SAEs begins after informed consent is obtained and the first administration of study drug is given. It continues for approximately 5 years or until study discontinuation/termination, whichever is longer.

10.5.2 Ethics Committee Reporting Requirements

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

10.6 Follow-up of Patients after Adverse Events

The Investigator should follow all unresolved AEs and SAEs until the events are resolved or have stabilized, the patient is lost to follow-up, or it has been determined that the study treatment or participation is not the cause of the AE/SAE. Resolution of AEs and SAEs (with dates) should be documented on the AE eCRF and submitted to BioMarin Pharmacovigilance and in the patient's medical record to facilitate source data verification.

For some SAEs, 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 report.

10.7 Post-Study Adverse Events

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

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The Investigator should notify the study Sponsor of any death or SAE occurring at any time after a patient has discontinued or terminated study participation, if the Investigator believes that the death or SAE may have been related to prior study treatment. 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 patient 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 patients against any immediate hazards that may affect the safety of patients, and that the appropriate regulatory bodies should be notified according to their respective regulations. According to the European Union (EU) Clinical Trial Directive 2001/20/EC, "…in the light of the circumstances, notably the occurrence of any new event relating to the conduct of the trial or the development of the investigational medicinal product where that new event is likely to affect the safety of the patients, the Sponsor and the Investigator shall take appropriate urgent safety measures to protect the patients against any immediate hazard. The Sponsor shall forthwith inform the competent authorities of those new events and the measures taken and shall ensure that the IRB/IEC/REB is notified at the same time."

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

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

- Immediate need to revise the IP administration (eg, modified dose amount or frequency not defined in protocol)
- 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

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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
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 FXa assay and the APTT assays 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 will be performed within 28 days (\pm 14 days) of BMN 270 infusion while baseline assessments will take place a within 7 days of BMN 270 infusion (Day 1). Should the screening visit occur within 7 days of the drug infusion, physical examination, vital signs, blood chemistry, haematology, urine tests, coagulation screen, and CRP do not need to be repeated at Baseline.

The following procedures will be performed during the Screening Period:

- Full medical history, including haemophilia A history, Hepatitis B, Hepatitis C, and HIV. Patients with documented negative results within the last 30 days do not need to be retested.
- Complete Physical Exam (including 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 patient or clinical information)
- Electrocardiogram
- Chest X-ray
- Liver Ultrasound
- Samples for hFVIII Assays
 - Baseline hFVIII activity chromogenic FXa (plasma)
 - o Baseline hFVIII activity level one-stage APTT assay
 - o hFVIII coagulation activity exploratory assay
 - o hFVIII inhibitor level (Bethesda assay with Nijmegen modification)
 - o hFVIII total antibody assay
 - hFVIII antigen (ELISA)
- Blood sample for AAV5 Assays

- AAV5 antibody titer
- AAV5 transduction inhibition assays
- Screen for Hepatitis B, Hepatitis C, and HIV if required (Patients with documented negative results within the last 30 days do not need to be retested)
- Blood chemistry, haematology, urine tests, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- Blood samples for Biomarker testing (HLA typing, FVIII mutation status, TNFα and IL10a single nucleotide polymorphisms)

12.3 Baseline Visit

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

- Physical exam
- Assessment of Adverse Events and Concomitant Medications
- Documentation of bleeding episodes and FVIII usage (by either patient or clinical information)
- Samples for FVIII Assays
 - FVIII activity chromogenic FXa (plasma)
 - FVIII activity level –APTT One stage assay
 - FVIII coagulation activity exploratory assay
 - o FVIII inhibitor level (Bethesda assay with Nijmegen modification)
 - o FVIII antibody assay
 - FVIII antigen (ELISA)
- Blood chemistry, haematology, urine tests, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- Mononuclear cell collection for CTL baseline
- PCR of vector genomes in blood, saliva, urine, semen, and stools
- Exploratory biomarker assessments
- QoL assessment

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

There will be one treatment visit for each patient. Patients will be hospitalized for 24 hours for the BMN 270 Infusion Visit. The following procedures will be performed during the BMN 270 Infusion Visit:

- Physical exam
- Assessment of Adverse Events and Concomitant Medications
- Blood sample for AAV5 Assays (must be performed before the BMN 270 infusion)
 - AAV5 antibody titer
 - AAV5 transduction inhibition assays
- BMN 270 Infusion
- Vital Signs
 - Vital signs will be recorded prior to BMN 270 infusion and then every 15 minutes (± 5 minutes) during BMN 270 infusion. Following infusion, vital signs will be monitored every 1 hour (± 5 minutes) for the first 6 hours, every 2 hours (± 15 minutes) for the next 6 hours, and then at 4 hour (± 15 minutes) intervals for the remainder of the patient's hospitalization.

12.5 BMN 270 Infusion Follow-Up Visits

After BMN 270 has been infused, patients will return to the study site every week $(\pm 48 \text{ hours})$ for 16 weeks, when the following procedures will be completed:

12.5.1 Every Visit

Every week (Weeks 1 through 16), the following procedures will be performed:

- Physical exam
- Assessment of Adverse Events and Concomitant Medications
- Vital Signs
- Blood chemistry, haematology, urine tests, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
 - Each patient will have comprehensive surveillance plan monitoring LFTs once a week from dose to completion of Week 6, 3 times per week (every other day excluding weekends) from Weeks 7 to 12, and once a week from Weeks 13 to 16. If a patient's ALT is found to be greater than 1.5x baseline during these periods, then LFTs will be monitored three times per week or until the ALT returns to baseline.

- Samples for FVIII Assays
 - FVIII activity level (APTT)
 - FVIII activity level (chromogenic FXa assay)
 - FVIII coagulation activity exploratory assay
 - Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level
 - FVIII activity confirmation (Frozen plasma)
 - FVIII antigen (ELISA)
- FVIII antibody titer
- PCR of vector genomes in blood, saliva, urine, semen, and stools
 - Collection to occur on Day 1, 3, 7 following BMN 270 infusion, and then weekly until 3 consecutive negative results are obtained
- Exploratory biomarker assessments

12.5.2 Every 4 Weeks

Every 4 weeks (Weeks 4, 8, 12, and 16), the following procedure will be performed:

• Mononuclear cell collection

12.5.3 Weeks 1, 3, and 6

At Weeks 1, 3, and 6, the following procedure will be performed:

• Test for Hepatitis B and Hepatitis C reactivation

12.5.4 Weeks 1, 8, and 16

At Weeks 1, 8, and 16, the following procedure will be performed:

• AAV5 antibody titer

12.5.5 Weeks 1, 2, 3, 4, and 16

At Weeks 1, 2, 3, 4, and 16, the following procedure will be performed:

• QoL assessment

12.6 Safety Follow-Up – Year 1

After the 16 weekly infusion follow-up visits are complete, subjects will return to the study site at Weeks 20, 28, 36, 44, and 52 (\pm 48 hours), when the following procedures will be completed:

12.6.1 Every Visit

At Weeks 20, 28, 36, 44, and 52, the following procedures will be performed:

- Physical exam
- Assessment of Adverse Events and Concomitant Medications
- Vital Signs
- Blood chemistry, haematology, urine tests, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- FVIII Assays
 - FVIII activity level (APTT)
 - FVIII activity level (chromogenic FXa assay)
 - FVIII coagulation activity exploratory assay
 - Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - FVIII activity confirmation (Frozen plasma)
 - FVIII antigen (ELISA)
- AAV5 antibody titer
- FVIII antibody titer
- Mononuclear cell collection
- PCR of vector genomes in blood, saliva, urine, semen, and stools
 - Sample testing during Safety Follow-Up is not required if 3 consecutive samples are clear during the Post-Infusion Follow-Up period.

12.6.2 Weeks 28 and 52

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

• QoL assessment

12.7 Safety Follow-Up – Years 2-5

During Years 2-5 of Safety Follow-up, patients will be assessed every 3 months (\pm 72 hours). At these times, the following procedures will be completed:

12.7.1 Every Visit

Every 3 months (\pm 72 hours), the following procedures will be performed:

• Physical exam

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- Complete Physical Exam will be performed every 52 weeks; Brief Physical Exams may be performed at other visits.
- Assessment of Adverse Events and Concomitant Medications
- Blood chemistry, haematology, urine tests, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- FVIII Assays
 - FVIII activity level (APTT)
 - FVIII activity level (FXa chromogenic assay)
 - FVIII coagulation activity exploratory assay
 - Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - FVIII activity confirmation (Frozen plasma)
 - FVIII antigen (ELISA)
- AAV5 antibody titer
- FVIII antibody titer
- Mononuclear cell collection
- PCR of vector genomes in blood, saliva, urine, semen, and stools
 - Sample testing during Safety Follow-Up is not required if 3 consecutive samples are clear during the Post-Infusion Follow-Up period.
- Vital Signs

12.7.2 Every Other Visit (Every 6 Months)

Every six months starting at the Week 78 visit (ie, 26 weeks after the Week 52 visit at the end of Year 1 of the Safety Follow-up period), the following procedure will be performed:

• QOL assessment

12.8 Early Termination Visit

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

If a patient leaves the study prior to the Week 270 visit, the patient will be asked to return to the study site and complete an Early Termination visit. At the Early Termination visit, as many of the following assessments as possible should be done:

- Physical exam
- Assessment of Adverse Events and Concomitant Medications

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- Blood chemistry, haematology, urine tests, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- FVIII Assays
 - FVIII activity level (APTT)
 - FVIII activity level (chromogenic FXa assay)
 - o FVIII coagulation activity exploratory assay
 - Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - FVIII activity confirmation (Frozen plasma)
 - FVIII antigen (ELISA)
- AAV5 antibody titer
- FVIII antibody titer
- Mononuclear cell collection
- PCR of vector genomes in blood, saliva, urine, semen, and stools
 - Sample testing at the ETV is not required if 3 consecutive samples are clear during the Post-Infusion Follow-Up period.
- Vital Signs
- QOL assessment

12.9 End of Study

The study will end after the last patient completes the last Safety Follow-Up visit (Week 270). 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 patients 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, any applicable randomization procedures, source document requirements, CRFs, 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 CRFs from source documents, adherence to protocol, randomization (if applicable), SAE reporting and drug accountability records.

The designated clinical data management group will enter or transfer CRF data into a study database.

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

14 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

14.1 Statistical and Analytical Plans

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

14.1.1 Interim Analyses

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

14.1.2 Procedures for Accounting for Missing, Unused and Spurious Data

Missing data will not be imputed.

14.2 Primary and Secondary Efficacy Analysis

The patients will be followed in a longitudinal manner and all the relevant information will be collected. The analysis of the data will be descriptive in nature. Descriptive statistics include the number of patients, mean, median, standard deviation, minimum, and maximum for continuous variables and count and percent for categorical variables. Efficacy variables will be summarized by dose cohort at each time point. Relationship between dose and efficacy results will be examined.

Data collected in a longitudinal manner may be analyzed using longitudinal methods such as mixed effect model which takes into account the correlation among the observation taken at various time points within a participant. Efficacy is a secondary endpoint, defined as biologically active hFVIII at \geq 5 IU/dL by chromogenic FXa and/or one-stage APTT assay between 1 to 16 weeks following study treatment. hFVIII activity will be assessed weekly during the study period. We can only assess the true steady state of hFVIII protein produced from BMN 270 after a minimum of 72 hours has elapsed since the last infusion of FVIII protein concentrates.

14.3 Immunogenicity

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

14.4 Pharmacodynamic Analyses

The FVIII antigen and activity level as measured by an Elisa (antigen level) and by a one-stage APTT and/or chromogenic FXa assay (activity level), will be used for plasma profiles; FVIII activity will be used to determine PD parameters. Traditional PK analysis is not applicable.

If supported by FVIII activity data, non-compartmental analysis and observation will be used to estimate individual PD parameter values of C_b (baseline), C_{ss} (steady state), T_{ss} (time to steady state), C(t) and AUC(0-t) where t is 16 weeks. Other parameters that may be used to describe individual FVIII protein and activity plasma profiles are C_{max} (maximum concentration) and C_{avg} (average concentration, AUC(0-t)/t). The parameters will be summarized using descriptive statistics.

14.5 Safety Analysis

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

All AEs will be coded using MedDRA. The incidence of AEs will be summarized by system organ class, preferred term, relationship to study drug, and severity. A by-patient listing will be provided for those patients who experience a serious AE (SAE), including death, or experience an AE associated with early withdrawal from the study or study drug. Hepatitis is of interest, and the percentage of patients who report hepatitis will be presented.

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.

14.6 Determination of Sample Size

No formal sample size calculations based on statistical power were performed.

The sample size is determined based upon clinical consideration and could detect a strong clinical efficacy signal. Up to 12 patients may be dosed in the study; the actual number of patients will depend on the criteria for dose escalation. A total of 6 patients may be enrolled at a single dose level.

14.7 Analysis Populations

The Safety analysis population is defined as all enrolled patients who receive any study drug. The analysis of safety data will be performed on Safety Set.

The Full Analysis Set (FAS) is defined as all enrolled patients who receive study drug and have at least one Baseline and post-Baseline assessment. The FAS will be used for efficacy analysis.

14.8 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 patient's safety is compromised without immediate action. In these circumstances, immediate approval of the chairman of the IRB/IEC/REB must be sought, and the Investigator should inform BioMarin and the full IRB/IEC/REB within 2 working days after the emergency occurs.

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

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

Note: If discrepancies exist between the text of the statistical analysis as planned in the protocol, and the final SAP, a protocol amendment will not be issued and the SAP will prevail.

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15 DATA MONITORING COMMITTEE

There will be no formal DMC for this study, however a safety and efficacy evaluation board (the Data Review Board [DRB]) composed of the investigator representatives and the Sponsor will be established.

The DRB will review safety and efficacy on an ongoing basis. The DRB will meet prior to dose escalation or dose expansion to assess available patient safety and efficacy data and make recommendations with regards to the conduct of study. Should a safety signal arise, including one which may warrant a halt of study enrollment, the DRB will promptly convene for further assessment of patient safety. Notification of all DRB meetings and meeting outcomes will be sent to participating sites.

16 COMPENSATION, INSURANCE AND INDEMNITY

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

The Investigator should contact BioMarin immediately upon notification that a study patient has been injured by the IP or by procedures performed as part of the study. Any patient who experiences a study-related injury should be instructed by the Investigator to seek medical treatment at a pre-specified medical institution if possible, or at the closest medical treatment facility if necessary. The patient 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 patient's health insurance company or other third party payer for the cost of this medical treatment. If the patient has followed the Investigator's instructions, BioMarin will pay for reasonable and necessary medical services to treat the injuries caused by the IP or study procedures, if these costs are not covered by health insurance or another third party that usually pays these costs. In some jurisdictions, BioMarin is obligated by law to pay for study-related injuries without prior recourse to third party payer billing. 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 patient. The Investigator must review and electronically sign the completed CRF casebook to verify its accuracy.

CRFs 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 CRF instructions, blank data fields are not acceptable.

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

BioMarin's policy is that study data on the CRFs must be verifiable to the source data, which necessitates access to all original recordings, laboratory reports, and patient 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. Patients must also allow access to their medical records, and patients will be informed of this and will confirm their agreement when giving informed consent. If an Investigator or institution refuses to allow access to patient records because of confidentiality, arrangements must be made to allow an "interview" style of data verification.

A CRA designated by BioMarin will compare the CRFs 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 CRA, 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 CRA 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 patient's CRF 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 CRFs 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

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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 patients, 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, patient 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 patient identifiers for at least 15 years after the completion or discontinuation of the study. Patient 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 patient 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 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).

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22 INVESTIGATOR RESPONSIBILITIES

22.1 Conduct of Study and Protection of Human Patients

In accordance with FDA Form 1572, 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 patients.
- He or she will personally conduct or supervise the study.
- He or she will inform any potential patients, 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 IRB review and approval in 21 CFR Part 56 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.
- 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
- He or she will ensure that adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.
- He or she will ensure that the IRB/IEC/REB complies with the requirements of 21 CFR Part 56, 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 patients or others are reported to the IRB/IEC/REB. Additionally, he or she will not make any changes in the research without IRB/IEC/REB approval, except where necessary to eliminate apparent immediate hazards to human patients.
- 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.

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23 SIGNATURE PAGE

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

Protocol Number: 270-201, 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 E6 ICH, as stated in the protocol, and other information supplied to me.

Investigator Signature		Date
Printed name:		5
Accepted for the Spo	nsor:	
Medic		
Printed name:	MD, PhD,	Clinical Sciences
		PI

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24 PROTOCOL AMENDMENT TEXT REVISIONS

The following table summarizes the revisions made to the protocol and relates the changes to the appropriate rationale (See pages 2-3). Text that has been added or inserted is indicated by <u>underlined</u> font, and deleted text is indicated by <u>strikethrough</u> font.

Section No./Title	Text Revisions	<u>Rationale</u>
2/Synopsis/(Diagnosis and All Criteria for Inclusion and Exclusion)	Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study: 2. <u>Any</u> evidence of detectable viral load of <u>active infection or any immunosuppressive disorder</u> .	1
2/Synopsis/(Diagnosis and All Criteria for Inclusion and Exclusion)	Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study: 3. <u>Patients that are HIV positive are excluded</u> .	1
9.1/Overall Study Design and Plan	Additionally, if any of the events listed in Section 9.3.3.1 occur, enrollment into the trial will be halted to complete an extensive safety analysis. Notification of the study halt will be sent by the Sponsor to the participating sites via telephone and email immediately after becoming aware of a safety concern. This will ensure no additional subjects are dosed until the signal has been completely evaluated. If, following safety review by the DRB and the Sponsor, it is deemed appropriate to restart dosing, a request to restart dosing with pertinent data will be submitted to the health authority.	2
9/Investigational Plan/(Table 9.1.1 – Schedule of Events – Screening and Infusion)	FVIII Treatment Washout ^b	6
9/Investigational Plan/(Table 9.1.1 – Schedule of Events – Screening and Infusion)/Footnotes	^b Patients will have a washout period of 72 hours prior to BMN 270 infusion. If a bleeding occurs, another washout period of 72 hours will be performed. If another bleeding occurs during this second washout period, then the patient may be excluded from the study at the physician's discretion.	6
9/Investigational Plan/(Table 9.1.1 – Schedule of Events – Screening and	^{eb} Includes baseline hFVIII activity (chromogenic FXa and one-stage APTT assays), hFVIII coagulation activity exploratory assay, hFVIII inhibitor level (Bethesda assay with Nijmegen modification), hFVIII total antibody titer, and hFVIII antigen (ELISA). hFVIII assays should be assessed only when the patient has been off FVIII therapy for at least the previous 4 days.	6

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Section No./Title	Text Revisions	<u>Rationale</u>
Infusion)/Footnotes		
9.3.2/Exclusion Criteria	Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study:	1
	2. Any evidence of detectable viral load of active infection or any immunosuppressive disorder.	
9.3.2/Exclusion Criteria	Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study:	1
	3. <u>Patients that are HIV positive are excluded</u> .	
9.3.3.1/Study Safety	If any of the following events occur (except the persistence of AAV5) in a patient in the study who has received BMN 270	2
Evaluation Criteria	infusion, enrollment into the trial will be put on halt to complete an extensive safety analysis will be performed and BioMarin and	
	the Principal Investigator will discuss pursuing the trial or increasing the time before the next patient is enrolled. per Section 9.1.	
9.4.8.1/Concomitant	Concomitant Haemophilia Treatments are discussed in the washout section below (Section).	6
Haemophilia Treatments	9.4.8.2 Factor VIII Washout	
	Patients will have a washout period of 72 hours prior to the BMN 270 infusion. If a bleeding occurs, another washout period of	
	72 hours will be performed. If another bleeding occurs during this second washout period, then the patient may be excluded from	
	the study at the physician's discretion.	
	Patients on "on demand" therapy for FVIII will continue their treatment at will. Patients on prophylactic FVIII therapy will	
	discontinue their treatment starting the day of infusion and switch to an "on demand" schedule. FVIII can always be taken as	
	needed by the patient, who will carefully record his treatment and bleeding episodes in his diary.	
9.7.2/Primary Efficacy	To measure the primary efficacy variable, the following assays will be used:	4
Variables	• FVIII activity (chromogenic FXa assay)	
	• FVIII activity by one-stage APTT (Activated Partial Thromboplastin Time)	
	Exploratory FVIII activity assay	
9.7.8.2/Clinical Laboratory Assessments	All abnormal clinical laboratory result pages results should be initialed and dated by an Investigator, along with a comment regarding whether or not the result is clinically significant.	Admin.

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Section No./Title	Text Revisions	<u>Rationale</u>
10.1.1/Adverse Events	 Complications that occur as a result of non-drug protocol-imposed interventions (eg, AEs related to screening procedures, medication washout, or no treatment run in). 	6
10.5.1/Expedited Reporting Requirements	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.	3
11/Appropriateness of Measurements	The chromogenic FXa assay and the APTT assays are both validated and utilize CE marked reagents. The exploratory FVIII activity assay will be used for exploratory purposes only.	4
12.2/Screening Visit	 Samples for hFVIII Assays Baseline hFVIII activity – chromogenic FXa (plasma) (at least 72 hours off therapy) Baseline hFVIII activity level – one-stage APTT assay (at least 72 hours off therapy) 	6
12.2/Screening Visit	• Screen for Hepatitis B, Hepatitis C, and HIV if required (Patients with documented negative results within the last 30 days do not need to be retested)	Admin.
12.3/Baseline Visit	FVIII Treatment Washout (refer to Section)	6
12.3/Baseline Visit	 Samples for FVIII Assays FVIII activity – chromogenic FXa (plasma) (at least 72 hours off therapy) FVIII activity level –APTT One stage assay (at least 72 hours off therapy) 	6
15/Data Monitoring Committee	There will be no <u>formal DMC</u> for this study, however a safety and efficacy evaluation board <u>(the Data Review Board [DRB])</u> composed of the <u>investigators investigator representatives</u> and <u>the Sponsor will be established</u> . The <u>primary responsibility of the board will be Data Review Board [DRB] will review safety and efficacy on an ongoing basis.</u> <u>The DRB will meet prior to dose escalation or dose expansion</u> to assess <u>patient's available patient</u> safety and efficacy data <u>accumulated for a particular dose level and to and</u> make recommendations regarding dose escalation . <u>with regards to the conduct</u> <u>of study. Should a safety signal arise, including one which may warrant a halt of study enrollment, the DRB will promptly</u> <u>convene for further assessment of patient safety. Notification of all DRB meetings and meeting outcomes will be sent to</u> <u>participating sites.</u>	5

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1/2, Dose-Escalation Safety, Tolerability and Efficacy Study of BMN 270, an Adenovirus-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII in Patients with Severe Haemophilia A		
Protocol Number:	270-201		
Active Investigational Product:	AAV5-hFVIII-SQ		
IND/European Union Drug Regulating Authorities Clinical Trials (EudraCT) Number:	2014-003880-38		
Indication:	Haemophilia A		
Sponsor:	BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949		
Development Phase:	Phase 1/2		
Sponsor's Responsible Medical Monitor:	PI PI BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949		
Duration of Patient Participation:	Approximately 264 weeks		
Dose:	Varied		
Study Population:	Males aged 18 or older		
Date of Original Protocol:	10 February 2015		
Date of Amendment 1:	06 March 2015		
	Property of BioMarin CONFIDENTIAL		

May not be divulged, published, or otherwise disclosed to others without prior written approval from BioMarin.

This study will be conducted according to the principles of Good Clinical Practice as described in the U.S. Code of Federal Regulations and the International Conference on Harmonisation Guidelines, including the archiving of essential documents.

BioMarin is a registered trademark of BioMarin Pharmaceutical Inc.



CLINICAL STUDY PROTOCOL AMENDMENT SUMMARY

Amendment: 1

Date: 06 March 2015

RATIONALE AND SUMMARY OF MAJOR CHANGES

A summary of major changes covered by Amendment 1 to the BMN 270-201 protocol is provided below.

1. Addition of "Receipt of any vector or gene transfer agent" to exclusion criteria.

Rationale: MHRA scientific advice in May 2014 stated that "a rationale has to be provided as to why receipt of any vector or gene transfer agent at any time is not an absolute exclusion criterion, rather than limiting to any vector/gene transfer agent that had been received in the previous 6 months."

2. Drug substance "AAV5-SQ-codop-hFVIII" has been revised to "AAV5-hFVIII-SQ."

Rationale: This change was made to remain consistent with drug substance description in the IMPD and the IB.

3. Appendix 1 has been removed.

Rationale: Appendix 1 contained a detailed schedule of assessments that is not the schedule for this study. Instead, a reference has been made to the Nathwani 2014 supplemental information available online.

4. Appendix 2 has been removed.

Rationale: Appendix 2 contained unpublished data. Instead, a reference has been added to Manno, 2006 supplemental information which includes vector biodistribution data by tissue and vector dose.

5. Inclusion Criterion concerning severe level of FVIII deficiency has been modified to state that "Patients will be considered as severe if their FVIII baseline level is 1 IU/dL or less"

Rationale: Changed description to more accurately describe patients with severe Haemophilia A. Baseline level is never "reached"; it is historical and based on their mutation.

6. Minor edits for clarity and consistency have been incorporated.

Specific changes included in this amendment, including the Synopsis, since the original protocol (approved 10 February 2015) are outlined in Section 24.

2 SYNOPSIS

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

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

PROTOCOL NUMBER:

270-201

STUDY SITES:

Approximately 6-10 sites worldwide.

PHASE OF DEVELOPMENT:

Phase 1/2

STUDY RATIONALE:

Haemophilia 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 cascade. This disorder can be either inherited, due to a new mutation 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 is largely governed by the level of residual expression. Severe HA is classified as FVIII activity less than 1% of wild type (< 1 IU/dL), moderate disease comprises 1-5% of wild type activity and the mild form is 5-40% activity. The clinical manifestations of severe HA remain frequent spontaneous bleeding episodes, predominantly in joints and soft tissues, with a substantially increased risk of death from haemorrhage when the brain is involved.

Treatment of severe HA presently consists of intravenous injection of plasma derived or recombinant 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 rhFVIII (under 24 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 treatment (mean of 1 to 7 episodes/year with prophylaxis up to 30 to 50 for on demand treatment). The consequence of multiple bleeding events is the development of an underlying pathology that contributes to debilitating multiple-joint arthropathy and substantially increased risk of death. Chemical modification (e.g. direct conjugation of polyethylene glycol (PEG) polymers) and bioengineering of FVIII (e.g. FVIII-Fc fusion proteins) improve half-life by approximately 50%, and

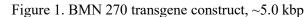
BIOMARIN [®] 270-	201- Amendment 1	Page 4
NAME OF COMPANY	SUMMARY TABLE	FOR NATIONAL
BioMarin Pharmaceutical Inc.	Referring to Part of the	AUTHORITY USE
105 Digital Drive	Dossier:	ONLY:
Novato, CA 94949		
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BMN 270	Page:	
NAME OF ACTIVE INGREDIENT: AAV5-hFVIII-SQ	Reference:	

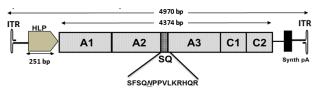
thus, show promise in reduced dosing and maintaining activity levels above 1% trough. However, these longer acting FVIIIs remain dependent on multiple infusions to maintain critical levels of FVIII activity in severe HA patients. There is therefore a strong unmet need for a fully preventive treatment of HA to give patients a FVIII level compatible with a normal and haemorrhage-free life.

Gene therapy offers the potential of disease-modifying therapy by continuous endogenous production of active FVIII following a single intravenous administration of a vector with the appropriate gene sequence. Haemophilia 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 modest increases in the level of FVIII (any increase of the plasma level by 2 ng/ml induces an increase in activity of 1%) can ameliorate the severe form of the disease. Thus, relatively small changes in endogenous FVIII activity results in clinically relevant improvements in disease phenotype. Finally, the 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 for specific tissues such as the liver (for serotypes 2, 5 and 8 among others). Indeed, an on-going gene therapy clinical trial for a related disorder, haemophilia B, has established that stable (>36 months) expression of human factor IX at levels that are sufficient for conversion of their bleeding phenotype from severe to moderate or mild is achievable following a single peripheral vein administration of AAV-8 vector. Several participants in this trial have been able to discontinue factor prophylaxis without suffering spontaneous haemorrhages, 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 rhFVIII under the control of a liver-selective promoter (Figure 1).





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

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NAME OF ACTIVE INGREDIENT:	Reference:	
NAME OF ACTIVE INOREDIENT. $\Delta \Delta V_{5}$ -bFVIII-SO		

The clinical study BMN 270-201 is a first-in-human study designed to assess the relationship of vector dose to the augmentation of residual FVIII activity, and whether these levels are sufficient to alter the clinical phenotype. The relationship of dose to safety will be correlated to the activity of hFVIII in patients with severe HA.

OBJECTIVES:

The primary objectives of the study are:

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

The secondary objectives of the study are:

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

STUDY DESIGN AND PLAN:

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

Patients who provide written informed consent, meet the entry criteria definition of severe HA, and do not have transduction inhibition activity to AAV5 will be eligible to enroll in the study. Participants will be enrolled sequentially into one of up to three cohorts according to dose level:

- 1. 6E12 vector genomes [vg] per kilogram of body weight, given as a single intravenous dose (iv)
- 2. 2E13 vg per kilogram, iv

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NAME OF ACTIVE INGREDIENT: AAV5-hFVIII-SQ	Reference:	
3. 6E13 vg per kilogram, iv		

Patients will be enrolled sequentially every 3 weeks or more between cohorts. Dose escalation may occur after a single patient has been safely dosed if the resulting FVIII activity at Week 3 is < 5 IU/dL. Three weeks is expected to be the time the expression will be close to the maximum. This escalation paradigm is intended to minimize the patient numbers exposed to subtherapeutic doses.

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

Approximately three weeks after an injection, the decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and a panel of investigators participating in the study.

If the FVIII activity is \geq 5 IU/dL, then the other patients of the dose group will be enrolled without waiting for 3 weeks between patients.

Patient 1 will be dosed by intravenous perfusion with 6E12 vector genomes [vg] per kilogram of body weight. If the activity level does not reach \geq 5 IU/dL at 21 days, then a higher dose (2E13 vg per kilogram) will be used for the next patient.

If the activity level does not reach \geq 5 IU/dL after Patient 2, then the highest dose (6E13 vg per kilogram) will be used for the next patient.

For each dose, if the activity level reaches 5 IU/dL and no safety issue is found, then up to four patients will receive this dose. If at any time activity levels reach 10 IU/dL or higher, no further dose escalation will take place, but additional patients will then be dosed at this dose level for a total of 6 patients per dose.

Because patients develop neutralizing immunity upon exposure to the capsid, re-challenge of vector is not a treatment option and these patients have effectively a single opportunity for therapy using this AAV capsid. Efficacy will be determined by FVIII activity at 16 weeks post dose. Safety will be evaluated for approximately 5 years after dose. Any safety signal will trigger a review of the data and possible additional analysis including mononuclear collection.

NUMBER OF PATIENTS PLANNED:

Up to 12 patients may enroll into the study; the actual number of patients will depend on the criteria for dose escalation. A total of 6 patients may be enrolled at a single dose level.

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AAV5-hFVIII-SQ		
	ERIA FOR INCLUSION AND EXCL	LUSION:
Individuals eligible to particip	pate in this study must meet all of the	following criteria:
1. Males that are 18 years of	or older with established severe haemopl	hilia A as evidenced by their
•	*	•
•	s will be considered as severe if their FV	III baseline level is 1 1U/dL
or less		
2. Treated/exposed to FVII	I concentrates or cryoprecipitates for a r	ninimum of 150 exposure

- 3. Greater or equal to 12 bleeding episodes only if receiving on-demand therapy over the previous 12 months. Does not apply to patients on prophylaxis
- 4. Able to sign informed consent and comply with requirements of the trial
- 5. No history of inhibitor, or no inhibitor on 2 consecutive occasions within the past 12 months using a modified Nijmegen Bethesda assay higher than 0.6 Bethesda Unit (BU)
- 6. Sexually active patients must be willing to use an acceptable method of contraception such as double barrier, including hormonal contraception for at least 6 months post-treatment

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

- 1. Detectable pre-existing immunity to the AAV5 capsid as measured by AAV5 transduction inhibition and AAV5 total antibodies
- 2. Evidence of detectable viral load of HIV
- 3. Significant liver dysfunction as defined by abnormal elevation of ALT (alanine transaminase) to 3 times the upper limit of normal, bilirubin, alkaline phosphatase, or an INR (international normalized ratio) of 1.4. Potential participants who have had a liver biopsy in the past 3 years are excluded if they had significant fibrosis of 3 or 4 as rated on a scale of 0-4
- 4. Evidence of any bleeding disorder not related to Haemophilia A
- 5. Platelet count of $< 100 \times 10^9/L$
- 6. Creatinine $\geq 1.5 \text{ mg/dL}$
- 7. Liver cirrhosis of any etiology as assessed by liver ultrasound
- 8. Hepatitis B if surface antigen is positive
- 9. Hepatitis C if RNA is positive

days (EDs)

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10. Treatment with any IP within 30 days	s prior to the screening visit	· · ·
11. Any disease or condition at the physic	cian's discretion that would	prevent the patient from fully

- complying with the requirements of the study. The physician may exclude patients unwilling or unable to agree on not using alcohol for the 16-week period following the viral infusion.
- 12. Receipt of any vector or gene transfer agent

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

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

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

The study is open label with comparison of FVIII activity to baseline values. No reference therapy will be evaluated in this study.

DURATION OF TREATMENT:

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

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AAV5-hFVIII-SQ		
CRITERIA FOR EVALUATION:		

Safety:

The following safety outcome measurements will be assessed:

- Incidence of adverse events (AEs), including serious AEs (SAEs)
- Change in clinical laboratory tests (serum chemistry and haematology)
- Change in vital signs
- Change in physical examination
- Vector shedding
- Liver function tests (LFT)

No major toxicity is expected based on preclinical studies in mice and monkeys. An asymptomatic transaminitis was observed at week 8-10 after administration with an AAV8-FIX, providing the rationale for the following surveillance plan. Each patient will have comprehensive surveillance plan monitoring LFTs once a week from dose to completion of Week 6, 3 times per week from Weeks 7 to 12, and once a week from Weeks 13 to 16. If a patient's ALT is found to be greater than 1.5x baseline during these periods, then LFTs will be monitored three times per week or until the ALT returns to baseline. LFTs will be monitored every other month for the first year and then every three months for up to 5 years post-dose in the safety extension.

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

Efficacy:

The primary efficacy measure will be to assess plasma FVIII activity. The efficacy goal of the study is to establish the dose relationship to FVIII activity \geq 5 IU/dL at 16 weeks post BMN 270 administration.

Secondary efficacy measures include assessing the impact of BMN 270 on the frequency of FVIII replacement therapy and on the number of bleeding episodes during the study. Patients will be asked to keep a patient diary to record the details in these areas.

Pharmacodynamics:

The FVIII antigen and activity level as measured by an ELISA (antigen level) and by one-stage APTT and/or chromogenic FXa assay (activity level), will be used for plasma profiles; FVIII activity will be

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AAV5-hFVIII-SQ		

used to determine PD parameters. Traditional PK analysis is not applicable.

If supported by the FVIII activity data, non-compartmental analysis and observation will be used to estimate individual values of Cb (baseline concentration), Css (steady state concentration), Tss (time to steady state), C(t) and AUC(0-t) where t is 16 weeks.

STATISTICAL METHODS:

The sample size is based upon clinical considerations and could detect a strong clinical efficacy signal. Up to 12 patients may be dosed in the study. The patients will be followed in a longitudinal manner and all the relevant information will be collected. The analysis of the data will be descriptive in nature but data collected in a longitudinal manner may be analyzed using longitudinal methods such as mixed effect model which takes into account the correlation among the observation taken at various time points within a participant. Efficacy is a secondary endpoint, defined as biologically active FVIII at $\geq 5 \text{ IU/dL}$ by chromogenic FXa assay and/or one-stage APTT assay between 1 to 16 weeks following study treatment. FVIII activity will be assessed weekly during the study period. We can only assess the true steady state of FVIII protein produced from BMN 270 after a minimum of 72 hours has elapsed since the last infusion of FVIII protein concentrates.

Analysis of neutralizing antibody response and other immunological parameters as well as viral shedding will be primarily descriptive and involve both inter-participant and intra-participant comparisons across doses.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

AAV	adeno-associated virus
ADL	activities of daily living
ADR	adverse drug reaction
AE	adverse event
ALT	alanine transaminase
APTT	activated partial thromboplastin time
BPV	BioMarin Pharmacovigilance
BU	Bethesda Unit
CFR	Code of Federal Regulations
CRA	clinical research associate
CRF	case report form
eCRF	electronic case report form
DMC	Data Monitoring Committee
ED	exposure days
EOSI	events of special interest
ETV	early termination visit
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIH	first-in-human
FVIII	coagulation factor VIII
FXa	coagulation factor Xa
GCP	Good Clinical Practice
HA	Haemophilia A
hFVIII	human coagulation factor VIII
HIPAA	Health Insurance Portability and Accountability Act
IB	investigator brochure
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for
	Registration of Pharmaceuticals for Human Use
ICH E6	ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6
IEC	independent ethics committee

IND

INR

IP

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Investigational New Drug (application)		
international normalized ratio		
investigational product		
institutional review board		
intravenous		
liver funtion test		
Medical Dictionary for Regulatory Activities		
no-observed-adverse-effect level		

IRB	institutional review board
IV	intravenous
LFT	liver funtion test
MedDRA	Medical Dictionary for Regulatory Activi
NOAEL	no-observed-adverse-effect level
PD	pharmacodynamics
PEG	polyethylene glycol
РК	Pharmacokinetics
PRO	patient-reported outcome
rhFVIII	recombinant human FVIII protein
REB	research ethics board
SAE	serious adverse event
SAP	statistical analysis plan
SDV	source data verification
vg	vector genomes

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]).

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

5 ETHICS

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

5.1 Institutional Review Board or Independent Ethics Committee

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

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

5.2 Ethical Conduct of Study

It is expected that Investigators understand and comply with the protocol. This includes, but is not limited to: establishing and meeting enrollment commitments, including providing eligible patients for study enrollment; adhering to 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)

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

5.3 Patient Information and Informed Consent

A properly written and executed ICF, in compliance with ICH E6 (Section 4.8), United States Code of Federal Regulations (CFR) 21 CFR §50, European Clinical Trial Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC, and other applicable local regulations, will be obtained for each patient prior to entering the patient into the study. The Investigator will prepare the ICF and provide the documents to BioMarin for approval prior to submission to the IRB/IEC/REB approval. BioMarin and the IRB/IEC/REB must approve the documents before they are implemented. A copy of the approved ICF , and if applicable, a copy of the approved patient 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 patient and will maintain the original in the record file of the patient.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

During administration of informed consent, expectations regarding participation in the study should be made clear to patients. 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 US Food and Drug Administration (FDA) Form FDA 1572 and a Financial Disclosure Form. All sub-Investigators must be listed on Form FDA 1572. Financial Disclosure Forms must also be completed for all sub-Investigators listed on the Form FDA 1572 who will be directly involved in the treatment or evaluation of patients 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 patient 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.

Laboratory evaluations will be performed at the local laboratories associated with the study sites. Refer to the Laboratory Manual for more details.

7 INTRODUCTION

Haemophilia A (HA) is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males (Nathwani, 1992, Baillieres Clin.Haematol.). It is caused by mutations in the factor VIII (FVIII) gene that codes for FVIII protein, an essential cofactor in the coagulation cascade. 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 haemorrhage. Treatment in Western (Berntorp, 2012, Haemophilia.) countries consists of intravenous injection of plasma derived or recombinant FVIII protein concentrates at the time of a bleed, 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 haemophilia A patients. These individuals develop debilitating arthropathy and have a substantially increased risk of death from haemorrhage in life (Stonebraker, 2010, Haemophilia.). Chemical modification or bioengineering of FVIII may improve half-life to around 20 hours (Pipe, 2010, Blood). However, these long acting FVIII variants do not eliminate the need for lifelong FVIII protein administration or problems of FVIII inhibitor formation, which occurs in 30% of patients on standard FVIII replacement therapy (Nathwani, 1992, Baillieres Clin.Haematol.).

Gene therapy offers the potential of a cure through continuous endogenous production of human FVIII following a single administration of vector. Haemophilia 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 2ng/ml protein leads to a 1% expression) can ameliorate the severe phenotype (Srivastava, 2012, Haemophilia); thus the therapeutic goal for gene therapy is a modest increase in hFVIII. Finally, the consequences of gene transfer can be assessed using simple quantitative rather than qualitative endpoints that can be easily assayed in most clinical laboratories.

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

7.1 Nonclinical Studies

The nonclinical program supports a single IV administration of BMN 270, the planned clinical route of administration, for the treatment of Haemophilia A in male patients. This nonclinical program took into account the guidelines and reflection papers for gene therapy medicinal products under EMA Advanced Therapies. 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 (normal CD-1 mouse, B and T cell deficient mouse model of haemophilia 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.

The primary PD of BMN 270 was assessed in a series of non-GLP single dose studies in a FVIII KO x Rag2 mouse model of severe Haemophilia A that recapitulates the change in coagulation observed in the human severe disease population without interfering cross species immunogenicity. PD activity and expression of hFVIII was assessed for durations up to 13-weeks in the FVIII KO x Rag2 mouse given dose range of 2E11 through 2E14 vector genomes (vg)/kg. Low levels of plasma hFVIII were observed in mice given 2E12 vg/kg after eight-weeks, post dose. Plasma hFVIII activity using bleeding time as an endpoint was evaluated in the FVIII KO x Rag2 mouse given up to 2E13 and 1E14 vg/kg BMN 270 at 8 weeks, post dose. BMN 270 related correction of bleeding times showed a dose relationship that was similar to that observed in mice given matched IU levels of Refacto®.

All cynomolgus monkeys used in this program were screened for neutralizing anti-AAV5 activity prior to study enrollment. PD activity and plasma hFVIII concentrations were evaluated in the cynomolgus monkey given up to 6E13 vg/kg BMN 270 for eight weeks. Peak expression of hFVIII was observed three to six weeks post administration with a subsequent decrease in expression presumably due to immunogenicity though not necessarily correlated to antibody titer.

The normal mouse was utilized in the GLP toxicology study to assess the safety profile of BMN 270 without the background of disease progression and in sufficient number per parameter. The GLP single dose toxicity study in normal CD-1 mice given 6E12 and 6E13 vg/kg with a 4 and 13-week follow up period monitored clinical pathology, defined potential target organs, immunogenicity, gene expression and activity. No changes in liver function were observed. In a single dose PD study in monkey given BMN 270, formation of anti-AAV5 total antibodies was observed at Week 8 with relatively low formation of anti-hFVIII total antibodies. No changes in liver function was observed.

The overall nonclinical safety profile includes formation of anti-AAV5 total antibodies with relatively lower formation of anti-hFVIII total antibodies. Immunogenicity against the AAV capsid and hFVIII is an anticipated finding for BMN 270 treatment and will be monitored in the nonclinical and clinical programs. Though not observed in the nonclinical species, liver toxicity utilizing clinical pathology parameters will be monitored in the clinical program based on previous literature. Cellular immune response will also be monitored.

Additionally, the BMN 270 transgene product has a final sequence matching that of the protein replacement treatment, Refacto[®] and therefore the safety profile of the BMN 270 transgene product is anticipated to be similar to Refacto® and have no unique FVIII-specific target organs of toxicity. The AAV5 capsid has not been modified and therefore no unique capsid-specific safety findings are anticipated. Because the biodistribution pattern of AAV5 after IV administration is consistent across species, BioMarin will confirm the nonclinical distribution pattern of BMN 270 during clinical development. Biodistribution of the AAV5 capsid has been documented to predominately target the liver with relatively lower levels of transduction observed in the lung, kidney, spleen, testes and blood compartment depending on the species and timing of administration. Liver targeted distribution of a similar AAV5 Factor IX gene therapy product was observed in the rhesus macaque monkey with low levels of vector genomes detected in spleen, kidney and testis (Paneda, 2009, Hum.Gene Ther.). Despite distribution to non-liver organs, no expression of Factor IX was detected in these tissues. Additionally, distribution to the testis was observed in another study in monkeys given an AAV5-codon-optimized human porphobilinogen deaminase; however, vector genomes in the semen were only transiently observed within one week but not thereafter (Paneda, 2013, Hum.Gene Ther.).

Both normal and disease model mice and a limited number of monkeys were utilized to establish proof of concept, species scaling and dose response in order to select the first-in-human (FIH) dose of 6E12 vg/kg. This dose represents > 30-fold safety factor from the no observed adverse effect level (NOAEL) in enabling nonclinical studies.

7.2 Previous Clinical Studies

This is the first clinical study for BMN 270.

BioMarin's program for haemophilia A builds on previous clinical trials of AAV-mediated gene transfer for a related condition, haemophilia B, that were conducted with an AAV2 vector (Manno, 2003, Blood) and an AAV8 vector (Nathwani, 2011, N.Eng.J.Med.; Nathwani, 2014, N.Eng.J.Med.). The large size of the FVIII cDNA was shortened and a

preclinical validation of this approach was performed with an AAV8 vector (McIntosh, 2013, Blood).

AAV serotype 5 is also used in clinical trials and has shown good safety in a recent phase 1 study for treatment of Acute Intermittent Porphyria (D'Avola. 2014, J Hepatology).

AAV using other serotypes have been used in 105 clinical studies to date and no safety issue specific to the vector was ever reported.

7.3 Study Rationale

Haemophilia A (HA) is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males (Nathwani, 1992, Baillieres Clin. Haematol). It is caused by deficiency in the activity of coagulation factor VIII (FVIII), an essential cofactor in the intrinsic coagulation cascade. This disorder can be either inherited, due to a new mutation 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 is largely governed by the level of residual expression. Severe HA is classified as FVIII activity less than 1% of wild type (< 1 IU/dL), moderate disease comprises 1-5% of wild type activity and the mild form is 5-40% activity. The clinical manifestations of severe HA remain frequent spontaneous bleeding episodes, predominantly in joints and soft tissues, with a substantially increased risk of death from haemorrhage when the brain is involved.

Treatment of severe HA presently consists of intravenous injection of plasma derived or recombinant 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 rhFVIII (under 24 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 treatment (mean of 1 to 7 episodes/year with prophylaxis up to 30 to 50 for on demand treatment) (Nagel, 2011, Haemophilia). The consequence of multiple bleeding events is the development of an underlying pathology that contributes to debilitating multiple-joint arthropathy and substantially increased risk of death (Nagel, 2011, Haemophilia). Chemical modification (e.g. direct conjugation of polyethylene glycol (PEG) polymers) and bioengineering of FVIII (e.g. FVIII-Fc fusion proteins) improve half-life by approximately 50%, and thus, show promise in reduced dosing and maintaining activity levels above 1% trough (Stonebraker, 2010, Haemophilia), (Mahlangu, 2014, Blood). However, these longer acting FVIIIs remain dependent on multiple infusions to maintain critical levels of FVIII activity in severe HA patients. There is therefore a strong unmet need

for a fully preventive treatment of HA to give patients a FVIII level compatible with a normal and haemorrhage-free life.

Gene therapy offers the potential of disease-modifying therapy by continuous endogenous production of active FVIII following a single intravenous administration of a vector with the appropriate gene sequence. Haemophilia 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 modest increases in the level of FVIII (any increase of the plasma level by 2 ng/ml induces an increase in activity of 1%) can ameliorate the severe form of the disease. Thus, relatively small changes in endogenous FVIII activity results in clinically relevant improvements in disease phenotype. Finally, the 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 (Pipe, 2010, Blood). They have an excellent and well defined safety profile, and can direct long term transgene expression with tropism for specific tissues such as the liver (Nathwani, 2005, Curr.Hematol Rep.) for serotypes 2, 5 and 8 among others). Indeed, an on-going gene therapy clinical trial for a related disorder, haemophilia B, has established that stable (>36 months) expression of human factor IX at levels that are sufficient for conversion of their bleeding phenotype from severe to moderate or mild is achievable following a single peripheral vein administration of AAV-8 vector(Nathwani, 2011, NEJM). Several participants in this trial have been able to discontinue factor prophylaxis without suffering spontaneous haemorrhages, 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, 2011, Mol.Ther.). (Bainbridge, 2008, NEJM; Maguire, 2009, Lancet; Simonelli, 2010, Mol.Ther.).

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

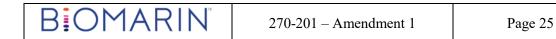
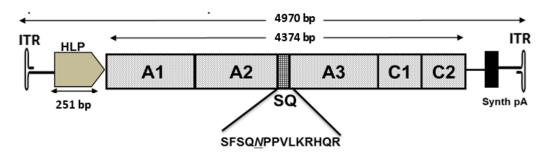


Figure 7.3.1: BMN 270 Transgene Construct, ~5.0 kbp



BMN 270 will be delivered by single intravenous dose and is designed to achieve stable, potentially life-long expression of active hFVIII in the plasma, synthesized from vector-transduced liver tissue. The clinical study BMN 270-201 is a first-in-human study designed to assess the relationship of vector dose to the augmentation of residual FVIII activity, and whether these levels are sufficient to alter the clinical phenotype. The relationship of dose to safety will be correlated to the activity of hFVIII in patients with severe HA.

7.4 Summary of Overall Risks and Benefits

Safety will be assessed by adverse event reporting and clinical laboratory assessment. Based on prior human studies with peripheral injections of AAV vectors, there is no known safety risk of AAV gene therapy. However, a mild asymptomatic transaminitis was observed at week 8-10 after administration with an AAV8-FIX, providing the rationale for the following surveillance plan (Manno, 2006, Nature Med.). Each patient will have comprehensive surveillance plan monitoring LFTs once a week from dose to completion of Week 6, 3 times per week from Weeks 7 to 12, and once a week from Weeks 13 to 16. If a patient's ALT is found to be greater than 1.5x baseline during these periods, then LFTs will be monitored three times per week or until the ALT returns to baseline. LFTs will be monitored every other month for the first year and then every three months for up to 5 years post-dose in the safety extension.

Dose selection: The benefit of this study can only be enhanced by selecting a starting dose that potentially could contribute to a better opportunity of observing a therapeutic effect, and therefore, reducing the possibility of a sub-therapeutic effect. With this consideration in mind, the starting dose 6E12 vg/kg was selected using overall data from the pre-clinical studies conducted in mice (normal and disease model, Rag2 -/- x FVIII -/-) and monkey. A detectable pharmacological response based on activity was observed at 6E12 vg/kg.

A 10-fold safety margin based upon the NOAEL was observed in the GLP 13-week study in normal mouse at the highest dose administered. A 30-fold safety margin in an 8-week dose response study in disease model mice based on histology was observed at the highest dose administered. No BMN 270-related changes in clinical observations or chemistry was observed in the monkey at doses up to 6E13 vg/kg, a 10-fold safety margin after 8-weeks. Overall, no BMN 270-related findings, except expected formation of anti-AAV5 antibodies, were observed at the highest administered doses of 6E13, 2E14 and vg/kg in the normal mouse, disease model mouse and monkey, respectively.

Based on these key pre-clinical findings it can be suggested that the proposed starting dose of 6E12 vg/kg should not pose any risk or safety concerns to patients but may potentially benefit the patient therapeutically.

8 STUDY OBJECTIVES

The primary objectives of the study are:

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

The secondary objectives of the study are:

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

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

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

Patients who provide written informed consent, meet the entry criteria definition of severe HA, and do not have transduction inhibition activity to AAV5 will be eligible to enroll in the study. Participants will be enrolled sequentially into one of up to three cohorts according to dose level:

- 1. 6E12 vector genomes [vg] per kilogram of body weight, given as a single intravenous dose (iv)
- 2. 2E13 vg per kilogram, iv
- 3. 6E13 vg per kilogram, iv

Patients will be enrolled sequentially every 3 weeks or more between cohorts. Dose escalation may occur after a single patient has been safely dosed if the resulting FVIII activity at Week 3 is < 5 IU/dL. Three weeks is expected to be the time the expression will be close to the maximum. This escalation paradigm is intended to minimize the patient numbers exposed to subtherapeutic doses.

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

Approximately three weeks after an injection, the decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and a panel of investigators participating in the study.

If the FVIII activity is ≥ 5 IU/dL, then the other patients of the dose group will be enrolled without waiting for 3 weeks between patients.

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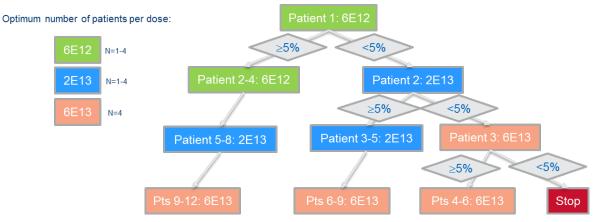


Figure 9.1.1: Flow Chart of Dose Escalation Scheme

Patient 1 will be dosed by intravenous perfusion with 6E12 vector genomes [vg] per kilogram of body weight. If the activity level does not reach \geq 5 IU/dL (expressed as % in Figure 9.1.1) at 21 days, then a higher dose (2E13 vg per kilogram) will be used for the next patient.

If the activity level does not reach \geq 5 IU/dL after Patient 2, then the highest dose (6E13 vg per kilogram) will be used for the next patient.

For each dose, if the activity level reaches 5 IU/dL and if no safety issue is found, then up to four patients will receive this dose. If at any time activity levels reach 10 IU/dL or higher, no further dose escalation will take place, but additional patients will then be dosed at this dose level for a total of 6 patients per dose.

Because patients develop neutralizing immunity upon exposure to the capsid, re-challenge of vector is not a treatment option and these patients have effectively a single opportunity for therapy using this AAV capsid. Efficacy will be determined by FVIII activity at 16 weeks post dose. Safety will be evaluated for approximately 5 years after dose. Any safety signal will trigger a review of the data and possible additional analysis including mononuclear collection.

A summary of events and assessments are provided by visit in Table 9.1.1 for Screening, Baseline and BMN 270 Infusion, in Table 9.1.2 for Post-Infusion Follow-up, and in Table 9.1.3 for Safety Follow-up.

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Table 9.1.1: Schedule of Events – Screening and Infusion

	Prior to BM	IN 270 Infusion	BMN 270	
Assessment	Screening (Day -28 to Day -1)	Baseline (Day -7 to Day -1) ⁱ	Infusion Visit (Day 1)	
Informed consent	X			
Medical History	X			
Physical Exam ^a	X	X	X	
Vital Signs	Х		X	
Assessment of Adverse Events and Concomitant Medications	X	X	X	
Documentation of bleeding episodes and FVIII usage (by either patient or clinical information)	X	Х		
Electrocardiogram	X			
Chest X-ray	X			
Liver Ultrasound	Х			
FVIII Treatment Washout ^b		Х		
hFVIII Assays ^c	Х	Х		
AAV5 Assays ^d	Х		Х	
Screen for Hepatitis B, Hepatitis C, HIV ^e	Х			
Blood chemistry, haematology, urine tests, coagulation screen, and CRP ^f	X	Х		
Mononuclear cell collection for CTL baseline		Х		
PCR of vector genomes in blood, saliva, urine, semen, and stools		Х		
Biomarker testing ^g	X			
Exploratory biomarker assessments ^h		Х		
Quality of Life (QoL) assessment		Х		
BMN 270 Infusion			Х	

^a Complete physical examination should be done at Screening. Brief physical examination may be done at Baseline and at the BMN 270 Infusion Visit. Height and weight will be recorded at Screening only.

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^b Patients will have a washout period of 72 hours prior to BMN 270 infusion. If a bleeding occurs, another washout period of 72 hours will be performed. If another bleeding occurs during this second washout period, then the patient may be excluded from the study at the physician's discretion.

^c Includes baseline hFVIII activity (chromogenic FXa and one-stage APTT assays), hFVIII coagulation activity exploratory assay, hFVIII inhibitor level (Bethesda assay with Nijmegen modification), hFVIII total antibody titer, and hFVIII antigen (ELISA). hFVIII assays should be assessed only when the patient has been off FVIII therapy for at least the previous 4 days.

^d Screening (done during Screening) and testing (at Infusion Visit) of AAV5 pre-existing immunity may include plasma samples for 3 assays (in vivo transduction inhibition, in vitro transduction inhibition and AAV5 total antibody assays). The assessment on the day of the infusion visit must be performed before the BMN 270 infusion is given.

^e Patients with documented negative results within the last 30 days do not need to be retested.

^f Refer to Table 9.7.8.2.1 for laboratory assessments to be included.

^g Includes HLA typing, FVIII mutation status, TNFα and IL10a single nucleotide polymorphisms.

^h Blood samples will be collected from subjects to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to Haemophilia A disease. The genetic/genomic testing on these exploratory samples is optional.

ⁱ Should the screening visit occur within 7 days of the drug infusion, physical examination, vital signs, blood chemistry, haematology, urine tests, coagulation screen, and CRP do not need to be repeated at Baseline.



				Fo	llow-U	Jp Af	ter BN	/IN 27	0 Adı	ninist	ratior	ı - We	eks [*]			
Assessment	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Physical exam ^a	Х	Х	Х	Х	Х	Х	Х	Х	Х	X	X	Х	Х	Х	Х	Х
Assessment of Adverse Events and Concomitant Medications	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Vital Signs	Х	Х	Х	Х	Х	Х	Х	Х	Х	Χ	Χ	Х	Х	Х	Х	Х
Blood chemistry, haematology, urine tests, coagulation screen, and CRP ^b	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
hFVIII activity assays ^c	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
hFVIII antibody titer	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
PCR of vector genomes in blood, saliva, urine, semen, and stools ^d	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Exploratory biomarker assessments ^e	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
QoL assessment	Х	Х	Х	Х												Х
AAV5 antibody titer	Х							Х								Х
Testing for reactivation of hepatitis B and hepatitis C	Х		Х			Х										
Mononuclear cell collection				Х				Х				Х				Х

Table 9.1.2: Schedule of Events – Post-Infusion Follow-Up

^{*} Visit windows are ±48 hours

^a Brief physical examination should be done at all weekly visits except Week 16, where a complete physical examination should be performed. Refer to Section 9.7.8.4.

^b Refer to Table 9.7.8.2.1 for laboratory assessments to be included. Each patient will have comprehensive surveillance plan monitoring LFTs once a week from dose to completion of Week 6, 3 times per week (every other day excluding weekends) from Weeks 7 to 12, and once a week from Weeks 13 to 16. If a patient's ALT is found to be greater than 1.5x baseline during these periods, then LFTs will be monitored three times per week or until the ALT returns to baseline.

^c Includes hFVIII activity level (APTT and FXa chromogenic assay), hFVIII activity confirmation (frozen plasma), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, hFVIII coagulation activity exploratory assay, and hFVIII antigen (ELISA).

^d Collection to occur on Day 1, 3, 7 following BMN 270 infusion, and then weekly until 3 consecutive negative results are obtained

^e Blood samples will be collected from subjects to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to Haemophilia A disease. The genetic/genomic testing on these exploratory samples is optional.

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		Yea	r 1 - We	eks [*]		Years 2-5 [*]	ETV (early termination
Assessment	20	28	36	44	52	Q3M	visit)
Physical exam ^a	Х	Х	Х	Х	X	Х	Х
Assessment of Adverse Events and Concomitant Medications	Х	Х	Х	Х	X	Х	Х
Vital Signs	Х	Х	Х	Х	X	Х	Х
Blood chemistry, haematology, urine tests, coagulation screen, and CRP ^b	Х	Х	Х	Х	X	Х	Х
hFVIII activity assays ^c	Х	Х	Х	Х	X	Х	Х
AAV5 antibody titer	Х	Х	Х	Х	X	Х	Х
hFVIII antibody titer	Х	Х	Х	Х	X	Х	Х
Mononuclear Cell Collection (for determination of FVIII and Capsid specific CTL activity)	Х	Х	Х	Х	X	Х	Х
PCR of vector genomes in blood, saliva, urine, semen, and stools ^d	Х	Х	Х	Х	X	Х	Х
QoL assessment		Х			X	X ^e	Х

* Visit windows are ± 72 hours

^a Complete physical examination should be performed at Weeks 52 and every 52 weeks thereafter; brief physical exam may be performed at other study visits. Refer to Section 9.7.8.4.

^bRefer to Table 9.7.8.2.1 for laboratory assessments to be included.

^c Includes hFVIII activity level (one-stage APTT and chromogenic FXa assay), hFVIII activity confirmation (frozen plasma), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, hFVIII coagulation activity exploratory assay, and hFVIII antigen (ELISA).

^d Sample testing during Safety Follow-Up is not required if 3 consecutive samples are cleared during the Post-Infusion Follow-Up period.

^e QoL assessment during Years 2-5 of Safety Follow-up should be performed at every other visit (every 6 months) starting with the Week 78 visit (ie, 26 weeks after the Week 52 visit at the end of Year 1 of the Safety Follow-up period).

9.2 Discussion of Study Design, Including Choice of Control Group

Study 270-201 is designed to be a first-in-man, phase 1/2 open-label, dose escalation study in patients with severe haemophilia A. Three doses of BMN 270 will be evaluated and the dose escalation decision tree is summarized in Figure 9.1.1.

The decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and a panel of investigators participating in the study.

There will be no control group. Parameters for each patient will be compared to a pre-treatment assessment of safety (liver function) and efficacy (number of bleeds, use of replacement therapy).

As AAV based treatment always leads to anti-capsid immune response, no true control group (for example with an empty AAV) is possible.

9.3 Selection of Study Population

Up to 12 severe haemophilia A patients may enroll into the study; the actual number of patients will depend on the criteria for dose escalation. A total of 6 patients may be enrolled at a single dose level.

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 criteria:

- 1. Males that are 18 years or older with established severe Haemophilia A as evidenced by their medical history. Patients will be considered as severe if their FVIII baseline level is 1 IU/dL or less
- 2. Treated/exposed to FVIII concentrates or cryoprecipitates for a minimum of 150 exposure days (EDs)
- 3. Greater or equal to 12 bleeding episodes only if on on-demand therapy over the previous 12 months. Does not apply to patients on prophylaxis
- 4. Able to sign informed consent and comply with requirements of the trial
- 5. No history of inhibitor, or no inhibitor on 2 consecutive occasions within the past 12 months using a modified Nijmegen Bethesda assay higher than 0.6 Bethesda Unit (BU)

6. Sexually active patients must be willing to use an acceptable method of contraception such as double barrier, including hormonal contraception for at least 6 months post-treatment.

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 immunity to the AAV5 capsid as measured by AAV5 transduction inhibition and AAV5 total antibodies
- 2. Evidence of detectable viral load of HIV
- 3. Significant liver dysfunction as defined by abnormal elevation of ALT (alanine transaminase) to 3 times the upper limit of normal, bilirubin, alkaline phosphatase, or an INR (international normalized ratio) of 1.4. Potential participants who have had a liver biopsy in the past 3 years are excluded if they had significant fibrosis of 3 or 4 as rated on a scale of 0-4
- 4. Evidence of any bleeding disorder not related to Haemophilia A
- 5. Platelet count of $< 100 \text{ x } 10^9/\text{L}$
- 6. Creatinine $\geq 1.5 \text{ mg/dL}$
- 7. Liver cirrhosis of any etiology as assessed by liver ultrasound
- 8. Hepatitis B if surface antigen is positive
- 9. Hepatitis C if RNA is positive
- 10. Treatment with any IP within 30 days prior to the screening visit
- 11. Any disease or condition at the physician's discretion that would prevent the patient from fully complying with the requirements of the study. The physician may exclude patients unwilling or unable to agree on not using alcohol for the 16-week period following the viral infusion.
- 12. Receipt of any vector or gene transfer agent

9.3.3 Removal of Patients from Treatment or Assessment

Patients may withdraw their consent to participate in the study at any time without prejudice. The Investigator must withdraw from the study any patient who requests to be withdrawn. A patient's participation in the study may be discontinued at any time at the discretion 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.

BioMarin must be notified of all patient withdrawals as soon as possible. BioMarin also reserves the right to discontinue the study at any time for either clinical or administrative

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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 patient from the study include, but are not limited to, the following:

- Patient requires medication or medical procedure prohibited by the protocol
- Patient does not adhere to study requirements specified in the protocol
- Patient was erroneously admitted into the study or does not meet entry criteria
- Patient is lost to follow-up

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

The Investigator or designee must explain to each patient, before enrollment into the study, that for evaluation of study results, the patient's protected health information obtained during the study may be shared with the study Sponsor, regulatory agencies, and IRB/IEC/REB. It is the Investigator's (or designee's) responsibility to obtain written permission to use protected health information per country-specific regulations, such as the Health Insurance Portability and Accountability Act (HIPAA) in the US, from each patient. 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 patient and the patient will be removed from the study.

9.3.3.1 Study Safety Evaluation Criteria

If any of the following events occur (except the persistence of AAV5) in a patient in the study who has received BMN 270 infusion, an extensive safety analysis will be performed and BioMarin and the Principal Investigator will discuss pursuing the trial or increasing the time before the next patient is enrolled.

- A 5-fold increase in ALT after BMN 270 administration
- The occurrence of other drug-related Grade III-IV toxicity, including liver failure and clinical hepatitis
- Drug-related Grade II toxicity that persists for at least 7 days
- The occurrence of neutralizing antibodies to hFVIII following BMN 270 infusion

- The persistent detection of the AAV vector genome in the semen of a participant more than 26 weeks after BMN 270 infusion, as discussed in Section 9.7.8.5
- The occurrence of a malignancy at any point after BMN 270 infusion that is assessed as possibly, probably, or definitely related to the study agent
- Any unexplained serious adverse event ≥ grade 4 assessed as at least possibly related to study drug

9.3.4 Patient Identification and Replacement of Patients

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

Patients who withdraw from the study after Week 16 will not be replaced.

9.3.5 Duration of Patient Participation

The duration of this study will be approximately 264 weeks. This includes 4 weeks of screening, 1 day of BMN 270 infusion, 16 weeks of Post-Infusion Follow-Up, and 244 weeks of Safety Follow-Up. A primary endpoint analysis on safety and efficacy will be performed at 16 weeks.

9.4 Treatments

BioMarin or its designee will provide the study site with study drug sufficient for study completion. BioMarin is responsible for shipping study drug to clinical sites.

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.

9.4.2 Identity of Investigational Product

9.4.2.1 Product Characteristics and Labeling

The study drug label includes the following information: lot number, required storage conditions, a precautionary statement, expiry date, study number, and BioMarin name and address. Labelling will be done according to country specific requirements.

9.4.3 Storage

At the study site, all IP must be stored under the conditions specified in the IB 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

After a physical exam performed by the PI or designee, participants will be admitted on the day of BMN 270 infusion. An IV catheter will be inserted into a suitable peripheral vein (e.g. the median cubital vein) and flushed with saline. FVIII protein concentrate 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. An electric syringe will be used to infuse through an in-line, low protein binding 0.22 micron filter. BMN 270 will be infused through the catheter using an appropriate infusion pump while monitoring the vital signs (pulse, blood pressure, respiration rate and temperature) at 15 minute (\pm 5 minutes) intervals. The anticipated maximum interval from initiation of thawing of BMN 270 to completion of the infusion is 4 hours.

Following completion of the infusion, vital signs will be monitored hourly (\pm 5 minutes) for 6 hours and then every 2 hours (\pm 15 minutes) for 6 hours and then at 4 hour intervals. If the vital signs are stable the catheter will be removed 20-24 hours after the infusion. Hemostasis at the puncture site will be established by applying pressure according to standard protocol for infusing FVIII concentrates. Patients will remain hospitalized for 24 hours to observe for any immediate toxicity of the procedure. After 24 hours of hospitalization, participants will be discharged unless toxicity has been observed in which case hospitalization may be extended or transfer to an outpatient facility may occur based on the evaluation and judgment of the Principal Investigator after consultation with the Medical Monitor.

9.4.5 Method of Assigning Patients to Treatment Groups

Patients 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 Sponsor will be required prior to enrollment of each study patient. Upon their enrollment into the study, patients will be assigned a unique patient number and dose level by the Sponsor.

Patients are enrolled serially and their dose is defined in Section 9.4.6.2 below. Escalation is based on FVIII activity 3 weeks after injection. Patients may receive the next higher dose if the previous patient does not meet the activity criteria, or the same dose if the previous

patient meets the activity criteria. Up to 6 patients can have the same dose, for a total of 12 patients in this study.

9.4.6 Selection of Doses Used in the Study

The starting dose was based on the expression of hFVIII observed in nonclinical studies of mice and monkeys. The starting dose has a significant safety margin (10-fold) from NOAEL in non-human primates. The dose escalation is half-logs based.

9.4.6.1 Selection of Timing of Dose for Each Patient

A minimum of three weeks are required between patients, to allow for evaluation of safety and expression of hFVIII. After three weeks, depending on the activity level, the choice of the dose for the next patient will be made as described below.

9.4.6.2 Selection of Dose for Each Patient

The starting dose was determined by expression of hFVIII observed in mice and monkeys and a scale up factor based on previous experience, an improved purification process over previous trials (thus decreasing the risk of immune response), and a new evaluation of the titer (PCR performed after hairpin removal).

Approximately three weeks after an injection, the decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and a panel of investigators participating in the study.

Patient 1 will be dosed with 6E12 vector genomes [vg] per kilogram of body weight. If the activity level does not reach \geq 5 IU/dL at 21 days, then a higher dose (2E13 vg per kilogram) will be used for the next patient.

If the activity level does not reach \geq 5 IU/dL after Patient 2, then the highest dose (6E13 vg per kilogram) will be used for the next patient.

For each dose, if the activity level reaches 5 IU/dL and if no safety issue is found, then up to four patients will receive this dose. If at any time activity levels reach 10 IU/dL or higher, no further dose escalation will take place, but additional patients will then be dosed at this dose level for a total of 6 patients per dose.

Refer to Figure 9.1.1 for a visual representation of the study design.

9.4.7 Blinding

This is an open-label study.

9.4.8 Prior and Concomitant Medications

All prescription and over-the-counter medications taken by a patient for 30 days before Screening will be recorded on the designated CRF. The Investigator may prescribe additional medications 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 CRF.

The following medications are prohibited starting 30 days before Screening:

- Live vaccines
- Immunosuppressive agents

Haemophilia treatments are discussed in the washout section below (Section 9.4.8.1).

9.4.8.1 Factor VIII Washout

Patients will have a washout period of 72 hours prior to the BMN 270 infusion. If a bleeding occurs, another washout period of 72 hours will be performed. If another bleeding occurs during this second washout period, then the patient may be excluded from the study at the physician's discretion.

9.4.8.2 Glucocorticoid Treatment of Elevated Hepatic Transaminases

During the Post-Infusion Follow-up Period, each patient will have comprehensive surveillance plan monitoring LFTs once a week from dose to completion of Week 6, 3 times per week from Weeks 7 to 12, and once a week from Weeks 13 to 16. If a patient's ALT is found to be greater than 1.5x baseline during these periods, then LFTs will be monitored three times per week or until the ALT returns to baseline.

Reports of abnormal LFTs (defined as 1.5x the patient's baseline level) should be made to BioMarin within 24 hours of the lab value being available. If the LFTs are abnormal, treatment with prednisolone initiated at a dose of 60 mg per day and then gradually tapered (60 mg daily for the first week, then 40 mg the second week, then 30 mg the third week, then 20 mg the fourth week, then stop) will be started immediately.

9.4.9 Treatment Compliance

Study drug will be administered to patients at the study site by a qualified professional. The quantity dispensed, returned, used, lost, etc. must be recorded on the dispensing log provided for the study. Sites will be instructed to return all used and unused study drug containers.

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9.5 Investigational Product Accountability

The Investigator or designee is responsible for maintaining accurate records (including dates and quantities) of IP(s) received, patients to whom IP is dispensed (patient-by-patient dose specific accounting), 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.

9.5.1 Return and Disposition of Clinical Supplies

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

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

All study drug and related materials should be stored, inventoried, reconciled, and destroyed or returned according to applicable state and federal regulations and study procedures.

9.6 Dietary or Other Protocol Restrictions

There are no dietary or other protocol restrictions for this study.

9.7 Safety and Efficacy Variables

As this is a first-in-man study, the primary endpoint of safety will be assessed as explained in Section 9.7.8.

The primary efficacy measure will be to assess plasma FVIII activity. The efficacy goal of the study is to establish the dose relationship to FVIII activity \geq 5 IU/dL at 16 weeks post BMN 270 administration.

9.7.1 Safety and Efficacy Measurements Assessed

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

9.7.2 Primary Efficacy Variables

The primary efficacy measure will be the plasma FVIII activity monitored on a regular basis after BMN 270 dose. The efficacy goal of the protocol is to ascertain the dose range of BMN 270 required to convert severe HA patients to stable expression of FVIII at 5 IU/dL, i.e., a mild severity. This is associated in natural history studies with clinically superior long term outcomes (Nathwani, 1992, Baillieres Clin.Haematol.).

To measure the primary efficacy variable, the following assays will be used:

- FVIII activity (chromogenic FXa assay)
- FVIII activity by one-stage APTT (Activated Partial Thromboplastin Time)
- Exploratory FVIII activity assay

The FVIII activity level and the number of patients with FVIII activity ≥ 5 IU/dL will be summarized.

Timing of assessment by these assays is provided in Table 9.1.2 and Table 9.1.3. Details on performing the assays are included in the Laboratory Manual.

9.7.3 Secondary Efficacy Variables

Secondary efficacy measures will be the reduction in the frequency of factor replacement therapy, and reduction in the number of bleeding episodes. Patients 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 patient's diary or other patient records.

Assessment of viral shedding at one week after BMN 270 infusion will also be considered an efficacy variable.

9.7.4 Immunogenicity

Immunogenicity assays will be performed on plasma. The assays will include detection of anti-capsid, and anti-FVIII total antibody, and determination of neutralizing antibodies against FVIII. Any increase in total antibody level, especially during the time period of 6-12 weeks, will be compared with FVIII activity measurements. Any abnormality of the liver parameters will lead to an immunogenicity assessment to determine anti-FVIII and capsid specific CTL. Anti-FVIII and capsid specific CTL assays will be performed on collected PBMCs.

Timing of assessment by these assays is provided in Table 9.1.2 and Table 9.1.3.

9.7.5 Pharmacodynamics

The hFVIII antigen and activity level will be measured by an ELISA (antigen) and by one-stage APTT and/or chromogenic FXa assay (activity). Individual antigen and activity plasma plots will be prepared to assess changes over 16 weeks. FVIII activity measurements will be used to determine PD parameters.

If supported by FVIII activity data, non-compartmental analysis and observation will be used to estimate individual values of C_b (baseline concentration), C_{ss} (steady state concentration), T_{ss} (time to steady state), C(t) and AUC(0-t) where t is 16 weeks. Other parameters that may be used to describe individual FVIII protein and activity plasma profiles are C_{max} (maximum concentration) and C_{avg} (average concentration, AUC(0-t)/t). The PD parameters and dose will be used to assess clinical pharmacology.

Sample collection times are indicated in Table 9.1.2 and Table 9.1.3.

9.7.6 Exploratory Biomarker Assessments

Blood samples will be collected from subjects at the time points indicated in Table 9.1.1 and Table 9.1.2 to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to Haemophilia A disease. The genetic/genomic testing on these exploratory samples is optional.

9.7.7 Quality of Life Assessment

A patient-reported outcome (PRO) questionnaire will be used to assess subject quality of life (QoL) during the study. Assessments will occur at the time points listed in the Schedules of Assessments.

Details regarding the QoL assessment will be included in the Study Reference Manual.

9.7.8 Safety Variables

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

9.7.8.1 Adverse Events

The occurrence of AEs will be assessed continuously from the time the patient signs the ICF. The determination, evaluation and reporting of AEs will be performed as outlined in Section 10. Assessments of AEs will occur at the time points shown in Table 9.1.1.

9.7.8.2 Clinical Laboratory Assessments

Specific visits for obtaining clinical laboratory assessment samples are provided in Table 9.1.1. The scheduled clinical laboratory tests are listed in Table 9.7.8.2.1. Refer to the Study Reference Manual 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 the cause of the abnormality is determined, the value returns to baseline or to within normal limits, or the Investigator determines that the abnormal value is no longer clinically significant.

All abnormal clinical laboratory result pages 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 CRF.



Blood Chemistry	Haematology	Urine Tests	Other
Albumin	Haemoglobin	Appearance	CRP
Alkaline phosphatase	Haematocrit	Color	
ALT (SGPT)	WBC count	pН	Coagulation Screen including:
AST (SGOT)	RBC count	Specific gravity	APTT
Direct bilirubin	Platelet count	Ketones	PT/INR
Total bilirubin	Differential cell count	Protein	TT
BUN		Glucose	
Calcium		Bilirubin	
Chloride		Nitrite	
Total cholesterol		Urobilinogen	
CO ₂		Haemoglobin	
Creatinine			
Glucose			
GGT			
LDH			
Phosphorus			
Potassium			
Total protein			
Sodium			
Uric acid			

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CO₂, carbon dioxide; GGT, gamma-glutamyltransferase; LDH, lactate dehydrogenase; PT, prothrombin time; APTT, activated partial thromboplastin time; RBC, red blood cell; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone; WBC, white blood cell; TT, thrombin time; INR, international normalized ratio.

9.7.8.3 Liver function and Hepatitis Testing

Patients will be screened for evidence of previous hepatitis B or hepatitis C infection at Screening. If medical records showing no evidence of Hepatitis B or Hepatitis C infection from the previous 30 days are available, then the Screening tests do not need to be done.

Evidence of ongoing infection (positive surface antigen for hepatitis B or positive RNA testing for hepatitis C) will be an exclusion criteria. If these parameters are negative and therefore no active infection is detected, then the patients may be included if they were vaccinated (for hepatitis B) or cleared the infection (for hepatitis C) and their liver function is acceptable.

A liver ultrasound and liver function testing at Screening will identify any significant hepatic dysfunction, which is defined as:

- More than 3x the normal ALT level
- More than 3x the normal bilirubin level
- Alkaline phosphatase above the normal cut off.
- INR over 1.4.
- Thrombocytopoenia under $100 \ge 10^9/L$

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

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

Systolic blood pressure, diastolic blood pressure, heart rate, respiration rate, and temperature will be assessed at Screening, Baseline, and at the beginning of each visit during the Post-Infusion Follow-Up and Safety Follow-Up periods. On the day of the BMN 270 Infusion, vital signs will be monitored hourly for 6 hours and then every 2 hours for 6 hours and then at 4 hour intervals.

A complete physical examination is necessary during Screening/Baseline; thereafter, brief physical examinations may be performed at the discretion of the investigator based on the patient'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 (level of consciousness, speech, language, cranial nerves, motor strength, motor tone, abnormal movements, reflexes, upper extremity sensation, lower extremity sensations, gait, Romberg, nystagmus, and coordination).

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

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Weight and height will be recorded at Screening only.

9.7.8.5 Viral Shedding

Viral shedding has been extensively studied in all similar clinical trials performed to date. (Nathwani, 2014, N.Eng.J.Med (Supplemental Appendix); Manno, 2006, Nature Med. (Supplemental Appendix); Schenk-Braat, 2007, J Gene Med; Croteau, 2004, Ann Occup Hyg). It has been constantly shown that the vector was not detectable anymore at 40 days, with its persistence in semen for 16 weeks in the seminal fluid but not in motile sperm (Manno, 2006, Nature Med.). In addition, it has always involved only an extremely small fraction of the injected dose.

Viral shedding will also be extensively studied in the present clinical trial, every week up to 16 weeks, then every 4 weeks to one year, then every three months. During the Post-Infusion Follow-Up period, patients will undergo testing of various bodily fluids to look for evidence of viral shedding for possible viral transmission. Bodily fluids will be tested by PCR at the time points indicated in Table 9.1.2 and Table 9.1.3. Fluids tested will include:

- Blood
- Saliva
- Semen
- Urine
- Stool

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 haematology, 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, a reportable adverse event (AE) is any untoward medical occurrence (e.g., sign, symptom, illness, disease or injury) in a patient administered the study-drug or other protocol-imposed intervention, regardless of attribution. This includes the following:

- AEs not previously observed in the patient that emerge during the course of the study.
- Pre-existing medical conditions judged by the Investigator to have worsened in severity or frequency or changed in character during the study.
- Complications that occur as a result of non-drug protocol-imposed interventions (eg, AEs related to screening procedures, medication washout, or no-treatment run-in).

An adverse drug reaction is any AE for which there is a reasonable possibility that the study-drug caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the study-drug and the AE.

Bleeding events that are normal events of haemophilia (ie, bleeding events which occur only because the patient is a haemophiliac) should not be recorded as AEs but will instead be captured in patient diaries. Bleeding events that occur where a normal (ie, non-haemophiliac) patient would bleed, such as bleeding as a result of trauma, should be recorded as adverse events. All bleeding events which meet criteria for being serious should be reported as serious adverse events (SAEs) whether or not they are bleeding events that are normal sequelae of haemophilia.

Whenever possible, it is preferable to record a diagnosis as the AE term rather than a series of terms relating to a diagnosis.

10.2 Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that at any dose meets 1 or more of the following criteria:

- Is fatal
- Is life threatening

Note: Life-threatening refers to an event that places the patient at immediate risk of death. This definition does not include a reaction that, had it occurred in a more severe form, might have caused death.

- Requires or prolongs inpatient hospitalization. Hospitalization for less than 24 hours will not be considered to be an SAE. Hospitalization solely for the purpose of insertion of an in-dwelling IV catheter (such as a Port-a-Cath or other brand) for administration of study drug will not be considered an SAE.
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect in the child or fetus of a patient exposed to IP prior to conception or during pregnancy
- Is an important medical event or reaction that, based on medical judgment, may jeopardize the patient or require intervention to prevent one of the above consequences (e.g. anaphylaxis)

All adverse events that do not meet any of the criteria for SAEs should be regarded as nonserious AEs.

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 liver enzymes triggering a corticosteroid treatment

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 treatment, only SAEs associated with any protocol-imposed interventions will be reported. After informed consent is obtained and the first administration of study drug, the reporting period for all non-serious AEs and SAEs begins and continues for approximately 5 years or until study discontinuation/termination, whichever is longer. The criteria for determining, and the reporting of SAEs is provided in Section 10.2.

10.3.2 Eliciting Adverse Events

Investigators will seek information on AEs and SAEs and EOSI, at each patient contact by specific questioning and, as appropriate, by examination. Information on all AEs and SAEs and EOSI, should be recorded in the patient's medical record and on the AE Case Report Form (eCRF).

10.3.3 Assessment of Seriousness, Severity, and Causality

The Investigator responsible for the care of the patient or qualified designee will assess AEs for severity, relationship to study drug, and seriousness (refer to Section 10.2 for SAE definitions). These assessments should 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 patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. The severity of each will be assessed using the defined categories in Table 10.3.3.2.1.

The Investigator will determine the severity of each AE and SAE and EOSI using the NCI CTCAE v4. 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 as stated below.

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 or debilitating: consequences; urgent intervention indicated	Grade 4 and 5 AEs should always be				
5	Death related to AE	reported as SAEs				

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

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

10.3.3.3 Causality

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

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

Table 10.3.3.3.1: Causality Attribution Guidance

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

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

The investigator's assessment of causality for individual AE reports is part of the study documentation process. Regardless of the Investigator's assessment of causality for individual AE reports, the Sponsor will promptly evaluate all reported SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators and applicable regulatory authorities.

10.4 Procedures for Recording Adverse Events

10.4.1 Recording Adverse Events on a eCRF

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

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

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

10.4.1.1 Diagnosis versus Signs and Symptoms

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 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 haemorrhage 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 is one that extends continuously, without resolution, between patient evaluation time points. Such an event should be recorded only once on the AE eCRF unless its severity increases or decreases (in which case it should be recorded again on the AE eCRF).

A recurrent AE is one that occurs and resolves between patient evaluation time points, but then subsequently recurs. All recurrences of the AE should be recorded on the AE eCRF.

10.4.1.4 Abnormal Laboratory Values

Laboratory test results will be recorded on the laboratory results pages of the AE 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 should be reported as such, in addition to being recorded as an AE in the AE eCRF.

A clinical laboratory abnormality is considered clinically significant and should be documented as AE if **any** of the following conditions is met:

- Accompanied by clinical symptoms
- Leading to a change in study medication (e.g. dose modification, interruption or permanent discontinuation)
- Requiring a change in concomitant therapy (e.g. addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment).
- The laboratory abnormality persists upon repeat confirmatory testing.
- The abnormality suggests a disease and/or organ toxicity

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• 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 hFVIII activity should not be reported as adverse events unless signs of worsening are observed.

10.4.1.5 Pre-existing Conditions

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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 document 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:

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- Perform a protocol-mandated efficacy measurement
- Undergo a diagnostic or elective surgical procedure for a pre-existing medical condition that has not changed
- 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 patient 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 partner should be reported within 24 hours of the site becoming aware of the pregnancy by faxing the Pregnancy Form in the study reference materials to BPV. The Investigator must make every effort to follow the patient through resolution of the pregnancy (delivery or termination) and to report the resolution on the Pregnancy Follow-up Form in the study reference materials. In the event of pregnancy in the partner of a study patient, 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 BioMarin Pharmacovigilance (BPV)

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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.

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

The reporting period for SAEs begins after informed consent is obtained and the first administration of study drug is given. It continues for approximately 5 years or until study discontinuation/termination, whichever is longer.

10.5.2 Ethics Committee Reporting Requirements

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

10.6 Follow-up of Patients after Adverse Events

The Investigator should follow all unresolved AEs and SAEs until the events are resolved or have stabilized, the patient is lost to follow-up, or it has been determined that the study treatment or participation is not the cause of the AE/SAE. Resolution of AEs and SAEs (with dates) should be documented on the AE eCRF and submitted to BioMarin Pharmacovigilance and in the patient's medical record to facilitate source data verification.

For some SAEs, 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 report.

10.7 Post-Study Adverse Events

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

The Investigator should notify the study Sponsor of any death or SAE occurring at any time after a patient has discontinued or terminated study participation, if the Investigator believes that the death or SAE may have been related to prior study treatment. The Sponsor should

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

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

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

- Immediate need to revise the IP administration (eg, modified dose amount or frequency not defined in protocol)
- 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

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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
Address:	105 Digital Drive
	Novato, CA 94949 USA
Phone:	PI
E-mail:	PI

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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.

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 will be performed within 28 days (\pm 14 days) of BMN 270 infusion while baseline assessments will take place a within 7 days of BMN 270 infusion (Day 1). Should the screening visit occur within 7 days of the drug infusion, physical examination, vital signs, blood chemistry, haematology, urine tests, coagulation screen, and CRP do not need to be repeated at Baseline.

The following procedures will be performed during the Screening Period:

- Full medical history, including haemophilia A history, Hepatitis B, Hepatitis C, and HIV. Patients with documented negative results within the last 30 days do not need to be retested.
- Complete Physical Exam (including 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 patient or clinical information)
- Electrocardiogram
- Chest X-ray
- Liver Ultrasound
- Samples for hFVIII Assays
 - Baseline hFVIII activity chromogenic FXa (plasma) (at least 72 hours off therapy)
 - Baseline hFVIII activity level one-stage APTT assay (at least 72 hours off therapy)
 - hFVIII coagulation activity exploratory assay
 - o hFVIII inhibitor level (Bethesda assay with Nijmegen modification)
 - o hFVIII total antibody assay

- hFVIII antigen (ELISA)
- Blood sample for AAV5 Assays
 - o AAV5 antibody titer
 - AAV5 transduction inhibition assays
- Screen for Hepatitis B, Hepatitis C, and HIV if required
- Blood chemistry, haematology, urine tests, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- Blood samples for Biomarker testing (HLA typing, FVIII mutation status, TNFα and IL10a single nucleotide polymorphisms)

12.3 Baseline Visit

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

- Physical exam
- Assessment of Adverse Events and Concomitant Medications
- Documentation of bleeding episodes and FVIII usage (by either patient or clinical information)
- FVIII Treatment Washout (refer to Section 9.4.8.1)
- Samples for FVIII Assays
 - FVIII activity chromogenic FXa (plasma) (at least 72 hours off therapy)
 - FVIII activity level –APTT One stage assay (at least 72 hours off therapy)
 - FVIII coagulation activity exploratory assay
 - o FVIII inhibitor level (Bethesda assay with Nijmegen modification)
 - o FVIII antibody assay
 - FVIII antigen (ELISA)
- Blood chemistry, haematology, urine tests, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- Mononuclear cell collection for CTL baseline
- PCR of vector genomes in blood, saliva, urine, semen, and stools
- Exploratory biomarker assessments
- QoL assessment

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12.4 Treatment Visit/BMN 270 Infusion Visit (Day 1)

There will be one treatment visit for each patient. Patients will be hospitalized for 24 hours for the BMN 270 Infusion Visit. The following procedures will be performed during the BMN 270 Infusion Visit:

- Physical exam
- Assessment of Adverse Events and Concomitant Medications
- Blood sample for AAV5 Assays (must be performed before the BMN 270 infusion)
 - o AAV5 antibody titer
 - AAV5 transduction inhibition assays
- BMN 270 Infusion
- Vital Signs
 - Vital signs will be recorded prior to BMN 270 infusion and then every 15 minutes (± 5 minutes) during BMN 270 infusion. Following infusion, vital signs will be monitored every 1 hour (± 5 minutes) for the first 6 hours, every 2 hours (± 15 minutes) for the next 6 hours, and then at 4 hour (± 15 minutes) intervals for the remainder of the patient's hospitalization.

12.5 BMN 270 Infusion Follow-Up Visits

After BMN 270 has been infused, patients will return to the study site every week $(\pm 48 \text{ hours})$ for 16 weeks, when the following procedures will be completed:

12.5.1 Every Visit

Every week (Weeks 1 through 16), the following procedures will be performed:

- Physical exam
- Assessment of Adverse Events and Concomitant Medications
- Vital Signs
- Blood chemistry, haematology, urine tests, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
 - Each patient will have comprehensive surveillance plan monitoring LFTs once a week from dose to completion of Week 6, 3 times per week (every other day excluding weekends) from Weeks 7 to 12, and once a week from Weeks 13 to 16. If a patient's ALT is found to be greater than 1.5x baseline during these periods, then LFTs will be monitored three times per week or until the ALT returns to baseline.

- Samples for FVIII Assays
 - FVIII activity level (APTT)
 - FVIII activity level (chromogenic FXa assay)
 - FVIII coagulation activity exploratory assay
 - Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level
 - FVIII activity confirmation (Frozen plasma)
 - FVIII antigen (ELISA)
- FVIII antibody titer
- PCR of vector genomes in blood, saliva, urine, semen, and stools
 - Collection to occur on Day 1, 3, 7 following BMN 270 infusion, and then weekly until 3 consecutive negative results are obtained
- Exploratory biomarker assessments

12.5.2 Every 4 Weeks

Every 4 weeks (Weeks 4, 8, 12, and 16), the following procedure will be performed:

• Mononuclear cell collection

12.5.3 Weeks 1, 3, and 6

At Weeks 1, 3, and 6, the following procedure will be performed:

• Test for Hepatitis B and Hepatitis C reactivation

12.5.4 Weeks 1, 8, and 16

At Weeks 1, 8, and 16, the following procedure will be performed:

• AAV5 antibody titer

12.5.5 Weeks 1, 2, 3, 4, and 16

At Weeks 1, 2, 3, 4, and 16, the following procedure will be performed:

• QoL assessment

12.6 Safety Follow-Up – Year 1

After the 16 weekly infusion follow-up visits are complete, subjects will return to the study site at Weeks 20, 28, 36, 44, and 52 (\pm 48 hours), when the following procedures will be completed:

12.6.1 Every Visit

At Weeks 20, 28, 36, 44, and 52, the following procedures will be performed:

- Physical exam
- Assessment of Adverse Events and Concomitant Medications
- Vital Signs
- Blood chemistry, haematology, urine tests, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- FVIII Assays
 - FVIII activity level (APTT)
 - FVIII activity level (chromogenic FXa assay)
 - FVIII coagulation activity exploratory assay
 - Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - FVIII activity confirmation (Frozen plasma)
 - FVIII antigen (ELISA)
- AAV5 antibody titer
- FVIII antibody titer
- Mononuclear cell collection
- PCR of vector genomes in blood, saliva, urine, semen, and stools
 - Sample testing during Safety Follow-Up is not required if 3 consecutive samples are clear during the Post-Infusion Follow-Up period.

12.6.2 Weeks 28 and 52

At Weeks 28 and 52, the following procedure will be performed:

• QoL assessment

12.7 Safety Follow-Up – Years 2-5

During Years 2-5 of Safety Follow-up, patients will be assessed every 3 months (\pm 72 hours). At these times, the following procedures will be completed:

12.7.1 Every Visit

Every 3 months (\pm 72 hours), the following procedures will be performed:

• Physical exam

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- Complete Physical Exam will be performed every 52 weeks; Brief Physical Exams may be performed at other visits.
- Assessment of Adverse Events and Concomitant Medications
- Blood chemistry, haematology, urine tests, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- FVIII Assays
 - FVIII activity level (APTT)
 - FVIII activity level (FXa chromogenic assay)
 - FVIII coagulation activity exploratory assay
 - Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - FVIII activity confirmation (Frozen plasma)
 - FVIII antigen (ELISA)
- AAV5 antibody titer
- FVIII antibody titer
- Mononuclear cell collection
- PCR of vector genomes in blood, saliva, urine, semen, and stools
 - Sample testing during Safety Follow-Up is not required if 3 consecutive samples are clear during the Post-Infusion Follow-Up period.
- Vital Signs

12.7.2 Every Other Visit (Every 6 Months)

Every six months starting at the Week 78 visit (ie, 26 weeks after the Week 52 visit at the end of Year 1 of the Safety Follow-up period), the following procedure will be performed:

• QOL assessment

12.8 Early Termination Visit

The Early Termination visit will occur on the date the patient withdraws from the study, even if the date does not correspond to a protocol-specific visit.

If a patient leaves the study prior to the Week 270 visit, the patient will be asked to return to the study site and complete an Early Termination visit. At the Early Termination visit, as many of the following assessments as possible should be done:

- Physical exam
- Assessment of Adverse Events and Concomitant Medications

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- Blood chemistry, haematology, urine tests, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- FVIII Assays
 - FVIII activity level (APTT)
 - FVIII activity level (chromogenic FXa assay)
 - o FVIII coagulation activity exploratory assay
 - Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - FVIII activity confirmation (Frozen plasma)
 - FVIII antigen (ELISA)
- AAV5 antibody titer
- FVIII antibody titer
- Mononuclear cell collection
- PCR of vector genomes in blood, saliva, urine, semen, and stools
 - Sample testing at the ETV is not required if 3 consecutive samples are clear during the Post-Infusion Follow-Up period.
- Vital Signs
- QOL assessment

12.9 End of Study

The study will end after the last patient completes the last Safety Follow-Up visit (Week 270). 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 patients 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, any applicable randomization procedures, source document requirements, CRFs, 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 CRFs from source documents, adherence to protocol, randomization (if applicable), SAE reporting and drug accountability records.

The designated clinical data management group will enter or transfer CRF data into a study database.

Data quality control and analysis will be performed by BioMarin or a designee, based on a predefined analysis plan.

14 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

14.1 Statistical and Analytical Plans

The statistical analysis plan (SAP) will provide additional details on the planned statistical analysis. Unless otherwise stated, all analyses will be performed using SAS.

14.1.1 Interim Analyses

No formal interim analysis is planned. An analysis of the primary endpoint will be done following all patients having completed the study assessments through the end of the Post-Infusion Follow-Up Period (Week 16).

14.1.2 Procedures for Accounting for Missing, Unused and Spurious Data

Missing data will not be imputed.

14.2 Primary and Secondary Efficacy Analysis

The patients will be followed in a longitudinal manner and all the relevant information will be collected. The analysis of the data will be descriptive in nature. Descriptive statistics include the number of patients, mean, median, standard deviation, minimum, and maximum for continuous variables and count and percent for categorical variables. Efficacy variables will be summarized by dose cohort at each time point. Relationship between dose and efficacy results will be examined.

Data collected in a longitudinal manner may be analyzed using longitudinal methods such as mixed effect model which takes into account the correlation among the observation taken at various time points within a participant. Efficacy is a secondary endpoint, defined as biologically active hFVIII at \geq 5 IU/dL by chromogenic FXa and/or one-stage APTT assay between 1 to 16 weeks following study treatment. hFVIII activity will be assessed weekly during the study period. We can only assess the true steady state of hFVIII protein produced from BMN 270 after a minimum of 72 hours has elapsed since the last infusion of FVIII protein concentrates.

14.3 Immunogenicity

Analysis of neutralizing antibody response and other immunological parameters will be primarily descriptive and involve both inter-participant and intra-participant comparisons across doses.

14.4 Pharmacodynamic Analyses

The FVIII antigen and activity level as measured by an Elisa (antigen level) and by a one-stage APTT and/or chromogenic FXa assay (activity level), will be used for plasma profiles; FVIII activity will be used to determine PD parameters. Traditional PK analysis is not applicable.

If supported by FVIII activity data, non-compartmental analysis and observation will be used to estimate individual PD parameter values of C_b (baseline), C_{ss} (steady state), T_{ss} (time to steady state), C(t) and AUC(0-t) where t is 16 weeks. Other parameters that may be used to describe individual FVIII protein and activity plasma profiles are C_{max} (maximum concentration) and C_{avg} (average concentration, AUC(0-t)/t). The parameters will be summarized using descriptive statistics.

14.5 Safety Analysis

The Medical Dictionary for Regulatory Activities terminology (MedDRA) will be used by the Sponsor to assign system organ class and preferred term classification to events and diseases, based on the original terms entered on the CRF.

All AEs will be coded using MedDRA. The incidence of AEs will be summarized by system organ class, preferred term, relationship to study drug, and severity. A by-patient listing will be provided for those patients who experience a serious AE (SAE), including death, or experience an AE associated with early withdrawal from the study or study drug. Hepatitis is of interest, and the percentage of patients who report hepatitis will be presented.

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.

14.6 Determination of Sample Size

No formal sample size calculations based on statistical power were performed.

The sample size is determined based upon clinical consideration and could detect a strong clinical efficacy signal. Up to 12 patients may be dosed in the study; the actual number of patients will depend on the criteria for dose escalation. A total of 6 patients may be enrolled at a single dose level.

14.7 Analysis Populations

The Safety analysis population is defined as all enrolled patients who receive any study drug. The analysis of safety data will be performed on Safety Set.

The Full Analysis Set (FAS) is defined as all enrolled patients who receive study drug and have at least one Baseline and post-Baseline assessment. The FAS will be used for efficacy analysis.

14.8 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 patient's safety is compromised without immediate action. In these circumstances, immediate approval of the chairman of the IRB/IEC/REB must be sought, and the Investigator should inform BioMarin and the full IRB/IEC/REB within 2 working days after the emergency occurs.

With the exception of minor administrative or typographical changes, the IRB/IEC/REB must review and approve all protocol amendments. Protocol amendments that have an impact on patient risk or the study objectives, or require revision of the ICF, must receive approval from the IRB/IEC/REB prior to their implementation.

When a protocol amendment substantially alters the study design or the potential risks or burden to patients, the ICF will be amended and approved by BioMarin and the IRB/IEC/REB, and all active patients must again provide informed consent.

Note: If discrepancies exist between the text of the statistical analysis as planned in the protocol, and the final SAP, a protocol amendment will not be issued and the SAP will prevail.

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15 DATA MONITORING COMMITTEE

There will be no DMC for this study, however a safety and efficacy evaluation board composed of the investigators and sponsor will be established. The primary responsibility of the board will be to assess patient's safety and efficacy data accumulated for a particular dose level and to make recommendations regarding dose escalation.

16 COMPENSATION, INSURANCE AND INDEMNITY

There will be no charge to study patients to be in this study. BioMarin will pay all costs of tests, procedures, and treatments that are part of this study. In addition, after IRB/IEC/REB approval, BioMarin may reimburse the cost of travel for study-related visits. BioMarin will not pay for any hospitalizations, tests, or treatments for medical problems of any sort, whether or not related to the study patient's disease, that are not part of this study. Costs associated with hospitalizations, tests, and treatments should be billed and collected in the way that such costs are usually billed and collected.

The Investigator should contact BioMarin immediately upon notification that a study patient has been injured by the IP or by procedures performed as part of the study. Any patient who experiences a study-related injury should be instructed by the Investigator to seek medical treatment at a pre-specified medical institution if possible, or at the closest medical treatment facility if necessary. The patient 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 patient's health insurance company or other third party payer for the cost of this medical treatment. If the patient has followed the Investigator's instructions, BioMarin will pay for reasonable and necessary medical services to treat the injuries caused by the IP or study procedures, if these costs are not covered by health insurance or another third party that usually pays these costs. In some jurisdictions, BioMarin is obligated by law to pay for study-related injuries without prior recourse to third party payer billing. 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 patient. The Investigator must review and electronically sign the completed CRF casebook to verify its accuracy.

CRFs 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 CRF instructions, blank data fields are not acceptable.

In the event of an entry error, or if new information becomes available, the value will be corrected by deselecting the erroneous response and then selecting or entering the factual response. In compliance with ICH GCP Guidelines and 21 CFR Part 11, the system will require the personnel making the correction to enter a reason for changing the value. The documented audit trail will include the reason for the change, the original value, the new value, the time of the correction and the identity of the operator.

BioMarin's policy is that study data on the CRFs must be verifiable to the source data, which necessitates access to all original recordings, laboratory reports, and patient 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. Patients must also allow access to their medical records, and patients will be informed of this and will confirm their agreement when giving informed consent. If an Investigator or institution refuses to allow access to patient records because of confidentiality, arrangements must be made to allow an "interview" style of data verification.

A CRA designated by BioMarin will compare the CRFs 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 CRA, 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 CRA 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 patient's CRF 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 CRFs 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

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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 patients, 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, patient 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 patient identifiers for at least 15 years after the completion or discontinuation of the study. Patient 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 patient 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 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**

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22 INVESTIGATOR RESPONSIBILITIES

22.1 Conduct of Study and Protection of Human Patients

In accordance with FDA Form 1572, 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 patients.
- He or she will personally conduct or supervise the study.
- He or she will inform any potential patients, 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 IRB review and approval in 21 CFR Part 56 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.
- 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
- He or she will ensure that adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.
- He or she will ensure that the IRB/IEC/REB complies with the requirements of 21 CFR Part 56, 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 patients or others are reported to the IRB/IEC/REB. Additionally, he or she will not make any changes in the research without IRB/IEC/REB approval, except where necessary to eliminate apparent immediate hazards to human patients.
- 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.

23 SIGNATURE PAGE

Protocol Title: A Phase 1/2, Dose-Escalation Safety, Tolerability and Efficacy Study of BMN 270, an Adenovirus-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII in Patients with Severe Haemophilia A

Protocol Number: 270-201

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 E6 ICH, as stated in the protocol, and other information supplied to me.

	Investigator Signature	Date
	Printed name:	
	A general for the Sponger	
PI	Accepted for the Sponsor:	
	Printed name: PI, MD, PhD, PI	Clinical Sciences
	Proprietary and Confidential	

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24 PROTOCOL AMENDMENT TEXT REVISIONS

The following table summarizes the revisions made to the protocol and relates the changes to the appropriate rationale (See pages 2-3). Text that has been added or inserted is indicated by <u>underlined</u> font, and deleted text is indicated by <u>strikethrough</u> font.

Section No./Title	Text Revisions	<u>Rationale</u>
2/Synopsis (Objectives)	 The primary objectives of the study are: To assess the safety of a single intravenous administration of a recombinant AAV5 encoding human coagulation FVIII (AAV5-<u>SQ codop hFVIII-SQ</u>) vector. To determine the dose of AAV5-<u>SQ codop hFVIII-SQ</u> required to achieve expression of FVIII at or above 5% of normal activity (≥5 IU/dL) at 16 weeks after infusion. The kinetics, duration and magnitude of AAV-mediated FVIII activity in individuals with haemophilia A will be determined and correlated to an appropriate BMN 270 dose. The secondary objectives of the study are: To describe the immune response to the FVIII transgene and AAV capsid proteins following systemic administration of rAAV5 SQ codopAAV5-hFVIII-SQ 	2
2/Synopsis (Diagnosis and All Criteria for Inclusion and Exclusion)	 Individuals eligible to participate in this study must meet all of the following criteria: 1. Males that are 18 years or older with established severe haemophilia A as evidenced by their medical history. Patients will be considered as severe if their FVIII levels have ever declined to baseline level is 1 IU/dL or less 	5
2/Synopsis (Diagnosis and All Criteria for Inclusion and Exclusion)	Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study: 12. <u>Receipt of any vector or gene transfer agent</u>	1
2/Synopsis (Statistical Methods)	We can only assess the true steady state of FVIII protein produced from BMN 270 after a minimum of <u>9672</u> hours has elapsed since the last infusion of FVIII protein concentrates.	6
8/Study Objectives	 The primary objectives of the study are: To assess the safety of a single intravenous administration of a recombinant AAV5 encoding human coagulation FVIII (AAV5-<u>SQ codop hFVIII-SQ</u>) vector. To determine the dose of AAV5-<u>SQ codop hFVIII-SQ</u> required to achieve expression of hFVIII at or above 5% of 	2

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Section No./Title	Text Revisions	<u>Rationale</u>
	normal activity (≥5 IU/dL) at 16 weeks after infusion. The kinetics, duration and magnitude of AAV-mediated hFVIII activity in individuals with haemophilia A will be determined and correlated to an appropriate BMN 270 dose. The secondary objectives of the study are:	
	 To describe the immune response to the hFVIII transgene product and AAV capsid proteins following systemic administration of rAAV5 SQ codopAAV5-hFVIII-SQ 	
9.3.1/Inclusion Criteria	Individuals eligible to participate in this study must meet all of the following criteria:	5
	1. Males that are 18 years or older with established severe Haemophilia A as evidenced by their medical history. Patients will be considered as severe if their FVIII levels have ever declined to baseline level is 1 IU/dL or less	
9.3.2/Exclusion Criteria	Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study:	1
	12. Receipt of any vector or gene transfer agent	
9.4.8.1/FVIII Washout	Patients will have a washout period of 72 hours prior to the BMN 270 infusion.	6
9.4.8.2/Glucocorticoid Treatment of Elevated Hepatic Transaminases	Reports of abnormal LFTs (defined as 1.5x the patient's baseline level) should be made to BioMarin within 24 hours of the lab value being available. If the LFTs are abnormal, treatment with prednisolone initiated at a dose of <u>60mg60 mg</u> per day and then gradually tapered (<u>60 mg daily for the first week, then 40 mg the second week, then 30 mg the third week, then 20 mg the fourth week, then stop)</u> will be started immediately.	6
9.7.8.5/Viral Shedding	Viral shedding has been extensively studied in all similar clinical trials performed to date. (;;(Nathwani, 2014, N.Eng.J.Med (Supplemental Appendix); Manno, 2006, Nature Med.(Supplemental Appendix); Schenk-Braat, 2007, J Gene Med; Croteau, 2004, Ann Occup Hyg).	3/4/6
10.4.1.4/Abnormal Laboratory Values	A clinical laboratory abnormality is considered clinically significant and should be documented as AE if any of the following conditions is met:	6
	• The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormalitypersists upon repeat confirmatory testing.	

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Section No./Title	Text Revisions	<u>Rationale</u>
10.4.1.9/Pregnancy	Although not an AE per se, pregnancy in the partner of a patient taking trial medication should be reported as an SAE 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.	6
	Pregnancy in partner should be reported within 24 hours of the site becoming aware of the pregnancy by faxing the Pregnancy Form in the study reference materials to BPV. In addition, pregnancy in a patient is also reported on the End of Study eCRF.	
12.2/Screening Visit	 Samples for hFVIII Assays Baseline hFVIII activity – chromogenic FXa (plasma) (at least <u>9672</u> hours off therapy) Baseline hFVIII activity level –one-stage APTT assay (at least <u>9672</u> hours off therapy) FVIII Treatment Washout (refer to Section 9.4.8.1) 	6
12.3/Baseline Visit	 Samples for FVIII Assays FVIII activity – chromogenic FXa (plasma) (at least <u>9672</u> hours off therapy) FVIII activity level –APTT One stage assay (at least <u>9672</u> hours off therapy) <u>FVIII Treatment Washout (refer to Section 9.4.8.1)</u> 	6
12.4/Treatment Visit	Blood sample for AAV5 Assays (must be performed before the BMN 270 infusion) <u>AAV5 antibody titer</u> <u>AAV5 transduction inhibition assays</u>	6
14.2/Primary and Secondary Efficacy Analysis	We can only assess the true steady state of hFVIII protein produced from BMN 270 after a minimum of <u>9672</u> hours has elapsed since the last infusion of FVIII protein concentrates.	6
21/References	Manno CS, Arruda VR, Pierce GF, et al. Successful transduction of liver in hemophilia by AAV-Factor IX and limitations imposed by the host immune response. Nature Med. 2006;12:342-347 and Supplemental Appendix, available at: http://www.nature.com/nm/journal/v12/n3/extref/nm1358-S3.pdf-	3/6

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Section No./Title	Text Revisions	<u>Rationale</u>
21/References	Nathwani AC, Reiss UM, Tuddenham EGD, et al. Long-Term Safety and Efficacy of Factor IX Gene Therapy in Hemophilia B.	4/6
	N.Engl.J.Med. 2014;371:1994-2004 and Supplemental Appendix, available at:	
	http://www.nejm.org/doi/suppl/10.1056/NEJMoa1407309/suppl_file/nejmoa1407309_appendix.pdf	
Appendices	Removal of APPENDIX : NATHWANI APPENDIX 2014	3
Appendices	Removal of APPENDIX : AAV-SPECIFIC ISSUES RELATED TO VECTOR THERAPY (PI	4

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1/2, Dose-Escalation Safety, Tolerability and Efficacy Study of BMN 270, an Adenovirus-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII in Patients with Severe Haemophilia A
Protocol Number:	270-201
Active Investigational Product:	AAV5-hFVIII-SQ
IND/European Union Drug Regulating Authorities Clinical Trials (EudraCT) Number:	2014-003880-38
Indication:	Haemophilia A
Sponsor:	BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949
Development Phase:	Phase 1/2
Sponsor's Responsible Medical Monitor:	PI PI BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949
Duration of Patient Participation:	Approximately 264 weeks
Dose:	Varied
Study Population:	Males aged 18 or older
Date of Original Protocol:	10 February 2015
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May not be divulged, publish	ned, or otherwise disclosed to others without prior written approval from BioMarin.

This study will be conducted according to the principles of Good Clinical Practice as described in the U.S. Code of Federal Regulations and the International Conference on Harmonisation Guidelines, including the archiving of essential documents.

BioMarin is a registered trademark of BioMarin Pharmaceutical Inc.

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2 SYNOPSIS

NAME OF COMPANY	SUMMARY TABLE	FOR NATIONAL
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BMN 270	Page:	
NAME OF ACTIVE INGREDIENT:	Reference:	
AAV5-hFVIII-SQ		

TITLE OF STUDY:

A Phase 1/2, Dose-Escalation Safety, Tolerability and Efficacy Study of BMN 270, an Adenovirus-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII in Patients with Severe Haemophilia A

PROTOCOL NUMBER:

270-201

STUDY SITES:

Approximately 6-10 sites worldwide.

PHASE OF DEVELOPMENT:

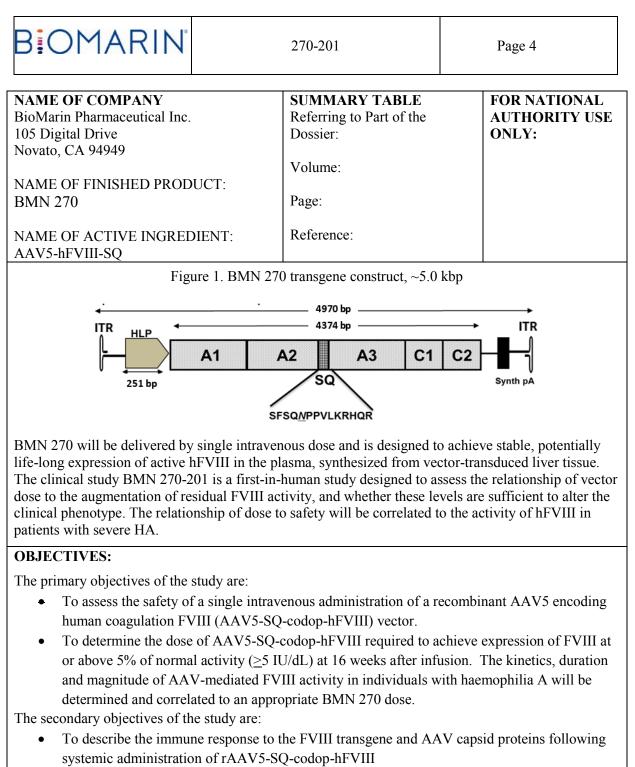
Phase 1/2

STUDY RATIONALE:

Haemophilia 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 cascade. This disorder can be either inherited, due to a new mutation 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 is largely governed by the level of residual expression. Severe HA is classified as FVIII activity less than 1% of wild type (< 1 IU/dL), moderate disease comprises 1-5% of wild type activity and the mild form is 5-40% activity. The clinical manifestations of severe HA remain frequent spontaneous bleeding episodes, predominantly in joints and soft tissues, with a substantially increased risk of death from haemorrhage when the brain is involved.

Treatment of severe HA presently consists of intravenous injection of plasma derived or recombinant 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 rhFVIII (under 24 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 treatment (mean of 1 to 7 episodes/year with prophylaxis up to 30 to 50 for on demand treatment). The consequence of multiple bleeding events is the development of an underlying pathology that contributes to debilitating multiple-joint arthropathy and substantially increased risk of

BIOMARIN	270-201		Page 3
NAME OF COMPANY BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949 NAME OF FINISHED PRODUCT: BMN 270 NAME OF ACTIVE INGREDIENT: AAV5-bFVIII-SO	SUMMARY TABLE Referring to Part of the Dossier: Volume: Page: Reference:		FOR NATIONAL AUTHORITY USE ONLY:
AAV5-hFVIII-SQ death. Chemical modification (e.g. direct conj bioengineering of FVIII (e.g. FVIII-Fc fusion thus, show promise in reduced dosing and ma these longer acting FVIIIs remain dependent of activity in severe HA patients. There is therefo of HA to give patients a FVIII level compatib Gene therapy offers the potential of disease-m of active FVIII following a single intravenous sequence. Haemophilia A is well suited for a p manifestations are attributable to the lack of a amounts (200 ng/ml) in the plasma. Tightly re- modest increases in the level of FVIII (any ind in activity of 1%) can ameliorate the severe for endogenous FVIII activity results in clinically the response to gene transduction can be asses endpoints that are easily assayed using establi Several different gene transfer strategies for F adeno-associated viral (AAV) vectors show th defined safety profile, and can direct long terr such as the liver (for serotypes 2, 5 and 8 amo trial for a related disorder, haemophilia B, has human factor IX at levels that are sufficient for moderate or mild is achievable following a sin Several participants in this trial have been abl- spontaneous haemorrhages, even when they u Thus, gene therapy treatment has resulted in a BMN 270 is an AAV5-based gene therapy vec control of a liver-selective promoter (Figure 1	proteins) improve half-life intaining activity levels abo on multiple infusions to ma- ore a strong unmet need for le with a normal and haemo- nodifying therapy by contin- administration of a vector gene replacement approach single gene product (FVIII egulated control of gene exp crease of the plasma level b orm of the disease. Thus, re- verelevant improvements in sisted using validated quantit shed laboratory techniques. VIII replacement have been ne greatest promise. They has n transgene expression with ong others). Indeed, an on- ge established that stable (>30 or conversion of their bleed ingle peripheral vein admini- te to discontinue factor prop- ndertook activities that pre- a substantial improvement in ctor that expresses the SQ f	by app ove 1% intain c a fully orrhage uous en with th becaus the becaus the becaust the	roximately 50%, and trough. However, ritical levels of FVIII preventive treatment -free life. adogenous production e appropriate gene e clinical irculates in minute n is not essential, and ml induces an increase y small changes in phenotype. Finally, ther than qualitative ated, but excellent and well m for specific tissues ene therapy clinical hs) expression of notype from severe to of AAV-8 vector. without suffering resulted in bleeding. quality of life.



- To assess the impact of BMN 270 on the frequency of FVIII replacement therapy during the study
- To assess the impact of BMN 270 on the number of bleeding episodes requiring treatment during the study

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AAV5-hFVIII-SQ			
STUDY DESIGN AND PLAN:		I	
STODI DESIGNANDI LAN.			
This is a first-in-man, phase 1/2 open-labe	el, dose escalation study in patie	ents with severe haemophilia	

A. Eligible patients will enter the dose escalation part of the study followed by a 16-week Post-Infusion Follow-Up period during which safety and efficacy assessments will be taken. After the primary endpoint analysis at 16 weeks, safety and efficacy will then be assessed for approximately 5 years.

Patients who provide written informed consent, meet the entry criteria definition of severe HA, and do not have transduction inhibition activity to AAV5 will be eligible to enroll in the study. Participants will be enrolled sequentially into one of up to three cohorts according to dose level:

- 1. 6E12 vector genomes [vg] per kilogram of body weight, given as a single intravenous dose (iv)
- 2. 2E13 vg per kilogram, iv
- 3. 6E13 vg per kilogram, iv

Patients will be enrolled sequentially every 3 weeks or more between cohorts. Dose escalation may occur after a single patient has been safely dosed if the resulting FVIII activity at Week 3 is < 5 IU/dL. Three weeks is expected to be the time the expression will be close to the maximum. This escalation paradigm is intended to minimize the patient numbers exposed to subtherapeutic doses.

The starting dose was based on the expression and safety of FVIII observed in nonclinical studies of mice and monkeys. The starting dose has a significant safety margin (10-fold) from no observed adverse effect level (NOAEL) in non-human primates.

Approximately three weeks after an injection, the decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and a panel of investigators participating in the study.

If the FVIII activity is \geq 5 IU/dL, then the other patients of the dose group will be enrolled without waiting for 3 weeks between patients.

Patient 1 will be dosed by intravenous perfusion with 6E12 vector genomes [vg] per kilogram of body weight. If the activity level does not reach \geq 5 IU/dL at 21 days, then a higher dose (2E13 vg per kilogram) will be used for the next patient.

If the activity level does not reach \geq 5 IU/dL after Patient 2, then the highest dose (6E13 vg per kilogram) will be used for the next patient.

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NAME OF COMPANY	SUMMARY TABLE	FOR NATIONAL			
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NAME OF ACTIVE INGREDIENT:	Reference:				
AAV5-hFVIII-SQ					
For each dose, if the activity level reaches 5					
patients will receive this dose. If at any tim					
escalation will take place, but additional par	tients will then be dosed at th	is dose level for a total of			
6 patients per dose.					
Because patients develop neutralizing immunity upon exposure to the capsid, re-challenge of vector is					
not a treatment option and these patients have effectively a single opportunity for therapy using this AAV capsid. Efficacy will be determined by FVIII activity at 16 weeks post dose. Safety will be					
evaluated for approximately 5 years after dose. Any safety signal will trigger a review of the data and					
possible additional analysis including mono		lgger a review of the data and			
	inderedi concetion.				
NUMBER OF PATIENTS PLANNED:					
Up to 12 patients may enroll into the study; the actual number of patients will depend on the criteria					
for dose escalation. A total of 6 patients may be enrolled at a single dose level.					
Individuals eligible to participate in this study must meet all of the following criteria:					
1. Males that are 18 years or older with established severe haemophilia A as evidenced by their					
	ites or cryoprecipitates for a r	ninimum of 150 exposure			
*					
	sodes only if receiving on-de	nand therapy over the			
DIAGNOSIS AND ALL CRITERIA FOR INCLUSION AND EXCLUSION:					

- 5. No history of inhibitor, or no inhibitor on 2 consecutive occasions within the past 12 months using a modified Nijmegen Bethesda assay higher than 0.6 Bethesda Unit (BU)
- 6. Sexually active patients must be willing to use an acceptable method of contraception such as double barrier, including hormonal contraception for at least 6 months post-treatment

Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study:

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NAME OF COMPANY BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949 NAME OF FINISHED PROD		FOR NATIONAL AUTHORITY USE ONLY:		
BMN 270 NAME OF ACTIVE INGREE AAV5-hFVIII-SQ				
 Detectable pre-existing immunity to the AAV5 capsid as measured by AAV5 transduction inhibition and AAV5 total antibodies Evidence of detectable viral load of HIV Significant liver dysfunction as defined by abnormal elevation of ALT (alanine transaminase) to 3 times the upper limit of normal, bilirubin, alkaline phosphatase, or an INR (international normalized ratio) of 1.4. Potential participants who have had a liver biopsy in the past 3 years are excluded if they had significant fibrosis of 3 or 4 as rated on a scale of 0-4 Evidence of any bleeding disorder not related to Haemophilia A Platelet count of < 100 x 10⁹/L Creatinine ≥ 1.5 mg/dL 				
 Liver cirrhosis of any etiology as assessed by liver ultrasound Hepatitis B if surface antigen is positive Hepatitis C if RNA is positive Treatment with any IP within 30 days prior to the screening visit Any disease or condition at the physician's discretion that would prevent the patient from fully complying with the requirements of the study. The physician may exclude patients unwilling or unable to agree on not using alcohol for the 16-week period following the viral infusion. 				
INVESTIGATIONAL PRODUCT(S), DOSE, ROUTE AND REGIMEN: Each patient will receive a single injection of BMN 270 as an intravenous infusion. The volume of infusion will depend on the dose level.				
REFERENCE THERAPY(IES), DOSE, ROUTE AND REGIMEN : The study is open label with comparison of FVIII activity to baseline values. No reference therapy will be evaluated in this study.				
DURATION OF TREATMENT : BMN 270 is given as a single dose by intravenous perfusion.				
CRITERIA FOR EVALUATION: Safety: The following safety outcome measurements will be assessed:				

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NAME OF COMPANY BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949	SUMMARY TABLE Referring to Part of the Dossier:	FOR NATIONAL AUTHORITY USE ONLY:		
NAME OF FINISHED PRODUCT: BMN 270 NAME OF ACTIVE INGREDIENT:	Volume: Page: Reference:			
 AAV5-hFVIII-SQ Incidence of adverse events (AEs), including serious AEs (SAEs) Change in clinical laboratory tests (serum chemistry and haematology) Change in vital signs Change in physical examination Vector shedding Liver function tests (LFT) 				
No major toxicity is expected based on preclinical studies in mice and monkeys. An asymptomatic transaminitis was observed at week 8-10 after administration with an AAV8-FIX, providing the rationals for the following surveillance plan.				

rationale for the following surveillance plan. Each patient will have comprehensive surveillance plan monitoring LFTs once a week from dose to completion of Week 6, 3 times per week from Weeks 7 to 12, and once a week from Weeks 13 to 16. If a patient's ALT is found to be greater than 1.5x baseline during these periods, then LFTs will be monitored three times per week or until the ALT returns to baseline. LFTs will be monitored every other month for the first year and then every three months for up to 5 years post-dose in the safety extension.

There will be a detailed monitoring plan for assessment of cellular and humoral responses to AAV5 capsid and FVIII protein.

Efficacy:

The primary efficacy measure will be to assess plasma FVIII activity. The efficacy goal of the study is to establish the dose relationship to FVIII activity \geq 5 IU/dL at 16 weeks post BMN 270 administration.

Secondary efficacy measures include assessing the impact of BMN 270 on the frequency of FVIII replacement therapy and on the number of bleeding episodes during the study. Patients will be asked to keep a patient diary to record the details in these areas.

Pharmacodynamics:

The FVIII antigen and activity level as measured by an ELISA (antigen level) and by one-stage APTT and/or chromogenic FXa assay (activity level), will be used for plasma profiles; FVIII activity will be used to determine PD parameters. Traditional PK analysis is not applicable.

If supported by the FVIII activity data, non-compartmental analysis and observation will be used to estimate individual values of Cb (baseline concentration), Css (steady state concentration), Tss (time to steady state), C(t) and AUC(0-t) where t is 16 weeks.

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The sample size is based upon clinical considerations and could detect a strong clinical efficacy signal. Up to 12 patients may be dosed in the study. The patients will be followed in a longitudinal manner and all the relevant information will be collected. The analysis of the data will be descriptive in nature but data collected in a longitudinal manner may be analyzed using longitudinal methods such as mixed effect model which takes into account the correlation among the observation taken at various time points within a participant. Efficacy is a secondary endpoint, defined as biologically active FVIII at $\geq 5 \text{ IU/dL}$ by chromogenic FXa assay and/or one-stage APTT assay between 1 to 16 weeks following study treatment. FVIII activity will be assessed weekly during the study period. We can only assess the true steady state of FVIII protein produced from BMN 270 after a minimum of 96 hours has elapsed since the last infusion of FVIII protein concentrates.

Analysis of neutralizing antibody response and other immunological parameters as well as viral shedding will be primarily descriptive and involve both inter-participant and intra-participant comparisons across doses.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

AAV	adeno-associated virus
ADL	activities of daily living
ADR	adverse drug reaction
AE	adverse event
ALT	alanine transaminase
APTT	activated partial thromboplastin time
BPV	BioMarin Pharmacovigilance
BU	Bethesda Unit
CFR	Code of Federal Regulations
CRA	clinical research associate
CRF	case report form
eCRF	electronic case report form
DMC	Data Monitoring Committee
ED	exposure days
EOSI	events of special interest
ETV	early termination visit
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIH	first-in-human
FVIII	coagulation factor VIII
FXa	coagulation factor Xa
FXa GCP	•
	coagulation factor Xa
GCP	coagulation factor Xa Good Clinical Practice
GCP HA	coagulation factor Xa Good Clinical Practice Haemophilia A
GCP HA hFVIII	coagulation factor Xa Good Clinical Practice Haemophilia A human coagulation factor VIII
GCP HA hFVIII HIPAA	coagulation factor Xa Good Clinical Practice Haemophilia A human coagulation factor VIII Health Insurance Portability and Accountability Act
GCP HA hFVIII HIPAA IB	 coagulation factor Xa Good Clinical Practice Haemophilia A human coagulation factor VIII Health Insurance Portability and Accountability Act investigator brochure informed consent form International Conference on Harmonisation of Technical Requirements for
GCP HA hFVIII HIPAA IB ICF ICH	 coagulation factor Xa Good Clinical Practice Haemophilia A human coagulation factor VIII Health Insurance Portability and Accountability Act investigator brochure informed consent form International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
GCP HA hFVIII HIPAA IB ICF ICH	 coagulation factor Xa Good Clinical Practice Haemophilia A human coagulation factor VIII Health Insurance Portability and Accountability Act investigator brochure informed consent form International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6
GCP HA hFVIII HIPAA IB ICF ICH	 coagulation factor Xa Good Clinical Practice Haemophilia A human coagulation factor VIII Health Insurance Portability and Accountability Act investigator brochure informed consent form International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

Investigational New Drug (application)
international normalized ratio
investigational product
institutional review board
intravenous
liver funtion test
Medical Dictionary for Regulatory Activities
no-observed-adverse-effect level
pharmacodynamics
polyethylene glycol
Pharmacokinetics
patient-reported outcome
recombinant human FVIII protein
research ethics board
serious adverse event
statistical analysis plan
source data verification
vector genomes

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]).

The terms "IP" and "study drug" may be used interchangeably in the protocol.

5 ETHICS

BioMarin Pharmaceutical Inc. (hereafter referred to as BioMarin or the Sponsor) conducts its studies according to the highest ethical and scientific standards. The following sections articulate standards to which Investigators will be held accountable, as well as matters of compliance to document adherence to such standards.

5.1 Institutional Review Board or Independent Ethics Committee

Investigators are expected to interact with Ethics Committees (ECs) promptly, as required, during the course of the study. This includes, but is not limited to, providing appropriate documentation to support study initiation and maintaining appropriate flow of safety and other information during the course of the study and for study close-out activities. BioMarin (or designee) will assist Investigators with access to timely and accurate information and with assurance of prompt resolution of any queries.

Prior to initiating the study, the Investigator will obtain written confirmation that the institutional review board (IRB) or independent ethics committee (IEC) [for Canadian protocols, Research Ethics Board (REB)] is properly constituted and compliant with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and Good Clinical Practice (GCP) requirements, applicable laws and local regulations. A copy of the confirmation from the IRB/IEC/REB will be provided to BioMarin Pharmaceutical Inc. (BioMarin) or its designee. The Investigator will provide the IRB/IEC/REB with all appropriate material, including the protocol, Investigator's Brochure (IB), the Informed Consent Form (ICF) including compensation procedures, and any other written information provided to the patients, including all ICFs translated to a language other than the native language of the clinical site. The study will not be initiated and Investigational Product (IP) supplies will not be shipped to the site until appropriate documents from the IRB/IEC/REB confirming unconditional approval of the protocol, the ICF and all patient recruitment materials are obtained in writing by the Investigator and copies are received at BioMarin or its designee. The approval document should refer to the study by protocol title and BioMarin protocol number (if possible), identify the documents reviewed, and include the date of the review and approval. BioMarin will ensure that the appropriate reports on the progress of the study are made to the IRB/IEC/REB and BioMarin by the Investigator in accordance with applicable guidance documents and governmental regulations.

5.2 Ethical Conduct of Study

It is expected that Investigators understand and comply with the protocol. This includes, but is not limited to: establishing and meeting enrollment commitments, including providing eligible patients for study enrollment; adhering to 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)

Specifically, this study is based on adequately performed laboratory and animal experimentation. The study will be conducted under a protocol reviewed and approved by an IRB/IEC/REB and will be conducted by scientifically and medically qualified persons. The benefits of the study are in proportion to the risks. The rights and welfare of the patients will be respected and the investigators conducting the study do not find the hazards to outweigh the potential benefits. Each patient will provide written, informed consent before any study-related tests or evaluations are performed.

5.3 Patient Information and Informed Consent

A properly written and executed ICF, in compliance with ICH E6 (Section 4.8), United States Code of Federal Regulations (CFR) 21 CFR §50, European Clinical Trial Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC, and other applicable local regulations, will be obtained for each patient prior to entering the patient into the study. The Investigator will prepare the ICF and provide the documents to BioMarin for approval prior to submission to the IRB/IEC/REB approval. BioMarin and the IRB/IEC/REB must approve the documents before they are implemented. A copy of the approved ICF , and if applicable, a copy of the approved patient 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 patient and will maintain the original in the record file of the patient.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

During administration of informed consent, expectations regarding participation in the study should be made clear to patients. 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 US Food and Drug Administration (FDA) Form FDA 1572 and a Financial Disclosure Form. All sub-Investigators must be listed on Form FDA 1572. Financial Disclosure Forms must also be completed for all sub-Investigators listed on the Form FDA 1572 who will be directly involved in the treatment or evaluation of patients 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 patient 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.

Laboratory evaluations will be performed at the local laboratories associated with the study sites. Refer to the Laboratory Manual for more details.

7 INTRODUCTION

Haemophilia A (HA) is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males (Nathwani, 1992, Baillieres Clin.Haematol.). It is caused by mutations in the factor VIII (FVIII) gene that codes for FVIII protein, an essential cofactor in the coagulation cascade. 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 haemorrhage. Treatment in Western (Berntorp, 2012, Haemophilia.) countries consists of intravenous injection of plasma derived or recombinant FVIII protein concentrates at the time of a bleed, 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 haemophilia A patients. These individuals develop debilitating arthropathy and have a substantially increased risk of death from haemorrhage in life (Stonebraker, 2010, Haemophilia.). Chemical modification or bioengineering of FVIII may improve half-life to around 20 hours (Pipe, 2010, Blood). However, these long acting FVIII variants do not eliminate the need for lifelong FVIII protein administration or problems of FVIII inhibitor formation, which occurs in 30% of patients on standard FVIII replacement therapy (Nathwani, 1992, Baillieres Clin.Haematol.).

Gene therapy offers the potential of a cure through continuous endogenous production of human FVIII following a single administration of vector. Haemophilia 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 2ng/ml protein leads to a 1% expression) can ameliorate the severe phenotype (Srivastava, 2012, Haemophilia); thus the therapeutic goal for gene therapy is a modest increase in hFVIII. Finally, the consequences of gene transfer can be assessed using simple quantitative rather than qualitative endpoints that can be easily assayed in most clinical laboratories.

BMN 270 contains the cDNA for the B-domain deleted SQ FVIII with a liver-specific HLP transcription promoter. The expression cassette is inserted between AAV2 ITRs and this genome is packaged in the AAV5 capsid. A comprehensive review of BMN 270 is contained in the IB supplied by BioMarin. Investigators are to review this document prior to initiating this study.

7.1 Nonclinical Studies

The nonclinical program supports a single IV administration of BMN 270, the planned clinical route of administration, for the treatment of Haemophilia A in male patients. This nonclinical program took into account the guidelines and reflection papers for gene therapy medicinal products under EMA Advanced Therapies. 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 (normal CD-1 mouse, B and T cell deficient mouse model of haemophilia 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.

The primary PD of BMN 270 was assessed in a series of non-GLP single dose studies in a FVIII KO x Rag2 mouse model of severe Haemophilia A that recapitulates the change in coagulation observed in the human severe disease population without interfering cross species immunogenicity. PD activity and expression of hFVIII was assessed for durations up to 13-weeks in the FVIII KO x Rag2 mouse given dose range of 2E11 through 2E14 vector genomes (vg)/kg. Low levels of plasma hFVIII were observed in mice given 2E12 vg/kg after eight-weeks, post dose. Plasma hFVIII activity using bleeding time as an endpoint was evaluated in the FVIII KO x Rag2 mouse given up to 2E13 and 1E14 vg/kg BMN 270 at 8 weeks, post dose. BMN 270 related correction of bleeding times showed a dose relationship that was similar to that observed in mice given matched IU levels of Refacto®.

All cynomolgus monkeys used in this program were screened for neutralizing anti-AAV5 activity prior to study enrollment. PD activity and plasma hFVIII concentrations were evaluated in the cynomolgus monkey given up to 6E13 vg/kg BMN 270 for eight weeks. Peak expression of hFVIII was observed three to six weeks post administration with a subsequent decrease in expression presumably due to immunogenicity though not necessarily correlated to antibody titer.

The normal mouse was utilized in the GLP toxicology study to assess the safety profile of BMN 270 without the background of disease progression and in sufficient number per parameter. The GLP single dose toxicity study in normal CD-1 mice given 6E12 and 6E13 vg/kg with a 4 and 13-week follow up period monitored clinical pathology, defined potential target organs, immunogenicity, gene expression and activity. No changes in liver function were observed. In a single dose PD study in monkey given BMN 270, formation of anti-AAV5 total antibodies was observed at Week 8 with relatively low formation of anti-hFVIII total antibodies. No changes in liver function was observed.

The overall nonclinical safety profile includes formation of anti-AAV5 total antibodies with relatively lower formation of anti-hFVIII total antibodies. Immunogenicity against the AAV capsid and hFVIII is an anticipated finding for BMN 270 treatment and will be monitored in the nonclinical and clinical programs. Though not observed in the nonclinical species, liver toxicity utilizing clinical pathology parameters will be monitored in the clinical program based on previous literature. Cellular immune response will also be monitored.

Additionally, the BMN 270 transgene product has a final sequence matching that of the protein replacement treatment, Refacto[®] and therefore the safety profile of the BMN 270 transgene product is anticipated to be similar to Refacto[®] and have no unique FVIII-specific target organs of toxicity. The AAV5 capsid has not been modified and therefore no unique capsid-specific safety findings are anticipated. Because the biodistribution pattern of AAV5 after IV administration is consistent across species, BioMarin will confirm the nonclinical distribution pattern of BMN 270 during clinical development. Biodistribution of the AAV5 capsid has been documented to predominately target the liver with relatively lower levels of transduction observed in the lung, kidney, spleen, testes and blood compartment depending on the species and timing of administration. Liver targeted distribution of a similar AAV5 Factor IX gene therapy product was observed in the rhesus macaque monkey with low levels of vector genomes detected in spleen, kidney and testis (Paneda, 2009, Hum.Gene Ther.). Despite distribution to non-liver organs, no expression of Factor IX was detected in these tissues. Additionally, distribution to the testis was observed in another study in monkeys given an AAV5-codon-optimized human porphobilinogen deaminase; however, vector genomes in the semen were only transiently observed within one week but not thereafter (Paneda, 2013, Hum.Gene Ther.).

Both normal and disease model mice and a limited number of monkeys were utilized to establish proof of concept, species scaling and dose response in order to select the first-in-human (FIH) dose of 6E12 vg/kg. This dose represents > 30-fold safety factor from the no observed adverse effect level (NOAEL) in enabling nonclinical studies.

7.2 Previous Clinical Studies

This is the first clinical study for BMN 270.

BioMarin's program for haemophilia A builds on previous clinical trials of AAV-mediated gene transfer for a related condition, haemophilia B, that were conducted with an AAV2 vector (Manno, 2003, Blood) and an AAV8 vector (Nathwani, 2011, N.Eng.J.Med.; Nathwani, 2014, N.Eng.J.Med.). The large size of the FVIII cDNA was shortened and a preclinical validation of this approach was performed with an AAV8 vector (McIntosh, 2013, Blood).

AAV serotype 5 is also used in clinical trials and has shown good safety in a recent phase 1 study for treatment of Acute Intermittent Porphyria (D'Avola. 2014, J Hepatology).

AAV using other serotypes have been used in 105 clinical studies to date and no safety issue specific to the vector was ever reported.

7.3 Study Rationale

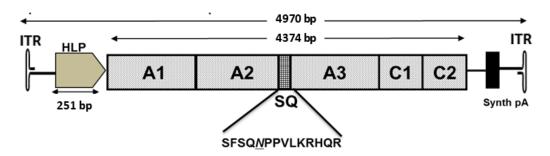
Haemophilia A (HA) is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males (Nathwani, 1992, Baillieres Clin. Haematol). It is caused by deficiency in the activity of coagulation factor VIII (FVIII), an essential cofactor in the intrinsic coagulation cascade. This disorder can be either inherited, due to a new mutation 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 is largely governed by the level of residual expression. Severe HA is classified as FVIII activity less than 1% of wild type (< 1 IU/dL), moderate disease comprises 1-5% of wild type activity and the mild form is 5-40% activity. The clinical manifestations of severe HA remain frequent spontaneous bleeding episodes, predominantly in joints and soft tissues, with a substantially increased risk of death from haemorrhage when the brain is involved.

Treatment of severe HA presently consists of intravenous injection of plasma derived or recombinant 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 rhFVIII (under 24 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 treatment (mean of 1 to 7 episodes/year with prophylaxis up to 30 to 50 for on demand treatment) (Nagel, 2011, Haemophilia). The consequence of multiple bleeding events is the development of an underlying pathology that contributes to debilitating multiple-joint arthropathy and substantially increased risk of death (Nagel, 2011, Haemophilia). Chemical modification (e.g. direct conjugation of polyethylene glycol (PEG) polymers) and bioengineering of FVIII (e.g. FVIII-Fc fusion proteins) improve half-life by approximately 50%, and thus, show promise in reduced dosing and maintaining activity levels above 1% trough (Stonebraker, 2010, Haemophilia), (Mahlangu, 2014, Blood). However, these longer acting FVIIIs remain dependent on multiple infusions to maintain critical levels of FVIII activity in severe HA patients. There is therefore a strong unmet need for a fully preventive treatment of HA to give patients a FVIII level compatible with a normal and haemorrhage-free life.

Gene therapy offers the potential of disease-modifying therapy by continuous endogenous production of active FVIII following a single intravenous administration of a vector with the appropriate gene sequence. Haemophilia 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 modest increases in the level of FVIII (any increase of the plasma level by 2 ng/ml induces an increase in activity of 1%) can ameliorate the severe form of the disease. Thus, relatively small changes in endogenous FVIII activity results in clinically relevant improvements in disease phenotype. Finally, the 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 (Pipe, 2010, Blood). They have an excellent and well defined safety profile, and can direct long term transgene expression with tropism for specific tissues such as the liver (Nathwani, 2005, Curr.Hematol Rep.) for serotypes 2, 5 and 8 among others). Indeed, an on-going gene therapy clinical trial for a related disorder, haemophilia B, has established that stable (>36 months) expression of human factor IX at levels that are sufficient for conversion of their bleeding phenotype from severe to moderate or mild is achievable following a single peripheral vein administration of AAV-8 vector(Nathwani, 2011, NEJM). Several participants in this trial have been able to discontinue factor prophylaxis without suffering spontaneous haemorrhages, 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, 2011, Mol.Ther.). (Bainbridge, 2008, NEJM; Maguire, 2009, Lancet; Simonelli, 2010, Mol.Ther.).

BMN 270 is an AAV5-based gene therapy vector that expresses the SQ form of rhFVIII under the control of a liver-selective promoter (Figure 7.3.1).





BMN 270 will be delivered by single intravenous dose and is designed to achieve stable, potentially life-long expression of active hFVIII in the plasma, synthesized from vector-transduced liver tissue. The clinical study BMN 270-201 is a first-in-human study designed to assess the relationship of vector dose to the augmentation of residual FVIII activity, and whether these levels are sufficient to alter the clinical phenotype. The relationship of dose to safety will be correlated to the activity of hFVIII in patients with severe HA.

7.4 Summary of Overall Risks and Benefits

Safety will be assessed by adverse event reporting and clinical laboratory assessment. Based on prior human studies with peripheral injections of AAV vectors, there is no known safety risk of AAV gene therapy. However, a mild asymptomatic transaminitis was observed at week 8-10 after administration with an AAV8-FIX, providing the rationale for the following surveillance plan (Manno, 2006, Nature Med.). Each patient will have comprehensive surveillance plan monitoring LFTs once a week from dose to completion of Week 6, 3 times per week from Weeks 7 to 12, and once a week from Weeks 13 to 16. If a patient's ALT is found to be greater than 1.5x baseline during these periods, then LFTs will be monitored three times per week or until the ALT returns to baseline. LFTs will be monitored every other month for the first year and then every three months for up to 5 years post-dose in the safety extension.

Dose selection: The benefit of this study can only be enhanced by selecting a starting dose that potentially could contribute to a better opportunity of observing a therapeutic effect, and therefore, reducing the possibility of a sub-therapeutic effect. With this consideration in mind, the starting dose 6E12 vg/kg was selected using overall data from the pre-clinical studies conducted in mice (normal and disease model, Rag2 -/- x FVIII -/-) and monkey. A detectable pharmacological response based on activity was observed at 6E12 vg/kg. A 10-fold safety margin based upon the NOAEL was observed in the GLP 13-week study in normal mouse at the highest dose administered. A 30-fold safety margin in an 8-week dose response study in disease model mice based on histology was observed at the highest dose administered. No BMN 270-related changes in clinical observations or chemistry was observed in the monkey at doses up to 6E13 vg/kg, a 10-fold safety margin after 8-weeks. Overall, no BMN 270-related findings, except expected formation of anti-AAV5 antibodies, were observed at the highest administered doses of 6E13, 2E14 and vg/kg in the normal mouse, disease model mouse and monkey, respectively.

Based on these key pre-clinical findings it can be suggested that the proposed starting dose of 6E12 vg/kg should not pose any risk or safety concerns to patients but may potentially benefit the patient therapeutically.

8 STUDY OBJECTIVES

The primary objectives of the study are:

- To assess the safety of a single intravenous administration of a recombinant AAV5 encoding human coagulation FVIII (AAV5-SQ-codop-hFVIII) vector.
- To determine the dose of AAV5-SQ-codop-hFVIII required to achieve expression of hFVIII at or above 5% of normal activity (≥5 IU/dL) at 16 weeks after infusion. The kinetics, duration and magnitude of AAV-mediated hFVIII activity in individuals with haemophilia A will be determined and correlated to an appropriate BMN 270 dose.

The secondary objectives of the study are:

- To describe the immune response to the hFVIII transgene product and AAV capsid proteins following systemic administration of rAAV5-SQ-codop-hFVIII
- To assess the impact of BMN 270 on the frequency of FVIII replacement therapy during the study
- To assess the impact of BMN 270 on the number of bleeding episodes requiring treatment during the study

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a first-in-man, phase 1/2 open-label, dose escalation study in patients with severe haemophilia A. Eligible patients will enter the dose escalation part of the study followed by a 16-week Post-Infusion Follow-Up period during which safety and efficacy assessments will be taken. After the primary endpoint analysis at 16 weeks, safety and efficacy will then be assessed for approximately 5 years.

Patients who provide written informed consent, meet the entry criteria definition of severe HA, and do not have transduction inhibition activity to AAV5 will be eligible to enroll in the study. Participants will be enrolled sequentially into one of up to three cohorts according to dose level:

- 1. 6E12 vector genomes [vg] per kilogram of body weight, given as a single intravenous dose (iv)
- 2. 2E13 vg per kilogram, iv
- 3. 6E13 vg per kilogram, iv

Patients will be enrolled sequentially every 3 weeks or more between cohorts. Dose escalation may occur after a single patient has been safely dosed if the resulting FVIII activity at Week 3 is < 5 IU/dL. Three weeks is expected to be the time the expression will be close to the maximum. This escalation paradigm is intended to minimize the patient numbers exposed to subtherapeutic doses.

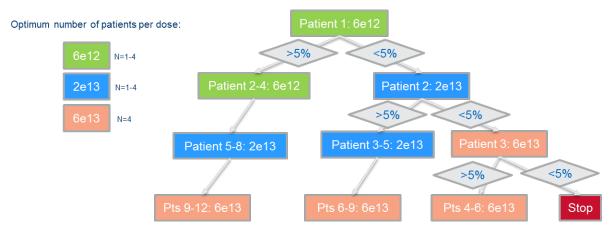
The starting dose was based on the expression and safety of FVIII observed in nonclinical studies of mice and monkeys. The starting dose has a significant safety margin (10-fold) from no observed adverse effect level (NOAEL) in non-human primates.

Approximately three weeks after an injection, the decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and a panel of investigators participating in the study.

If the FVIII activity is ≥ 5 IU/dL, then the other patients of the dose group will be enrolled without waiting for 3 weeks between patients.

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Figure 9.1.1: Flow Chart of Dose Escalation Scheme



Patient 1 will be dosed by intravenous perfusion with 6E12 vector genomes [vg] per kilogram of body weight. If the activity level does not reach \geq 5 IU/dL (expressed as % in Figure 9.1.1) at 21 days, then a higher dose (2E13 vg per kilogram) will be used for the next patient.

If the activity level does not reach \geq 5 IU/dL after Patient 2, then the highest dose (6E13 vg per kilogram) will be used for the next patient.

For each dose, if the activity level reaches 5 IU/dL and if no safety issue is found, then up to four patients will receive this dose. If at any time activity levels reach 10 IU/dL or higher, no further dose escalation will take place, but additional patients will then be dosed at this dose level for a total of 6 patients per dose.

Because patients develop neutralizing immunity upon exposure to the capsid, re-challenge of vector is not a treatment option and these patients have effectively a single opportunity for therapy using this AAV capsid. Efficacy will be determined by FVIII activity at 16 weeks post dose. Safety will be evaluated for approximately 5 years after dose. Any safety signal will trigger a review of the data and possible additional analysis including mononuclear collection.

A summary of events and assessments are provided by visit in Table 9.1.1 for Screening, Baseline and BMN 270 Infusion, in Table 9.1.2 for Post-Infusion Follow-up, and in Table 9.1.3 for Safety Follow-up.

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Table 9.1.1: Schedule of Events – Screening and Infusion

	Prior to BMN 270 Infusion		BMN 270
Assessment	Screening (Day -28 to Day -1)	Baseline (Day -7 to Day -1) ⁱ	Infusion Visit (Day 1)
Informed consent	X		
Medical History	X		
Physical Exam ^a	X	X	X
Vital Signs	X		Х
Assessment of Adverse Events and Concomitant Medications	X	X	X
Documentation of bleeding episodes and FVIII usage (by either patient or clinical information)	X	X	
Electrocardiogram	X		
Chest X-ray	X		
Liver Ultrasound	X		
FVIII Treatment Washout ^b	X		
hFVIII Assays ^c	X	Х	
AAV5 Assays ^d	X		
Screen for Hepatitis B, Hepatitis C, HIV ^e	X		
Blood chemistry, haematology, urine tests, coagulation screen, and CRP ^f	X	X	
Mononuclear cell collection for CTL baseline		Х	
PCR of vector genomes in blood, saliva, urine, semen, and stools		Х	
Biomarker testing ^g	X		
Exploratory biomarker assessments ^h		X	
Quality of Life (QoL) assessment		Х	
BMN 270 Infusion			Х

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^a Complete physical examination should be done at Screening. Brief physical examination may be done at Baseline and at the BMN 270 Infusion Visit. Height and weight will be recorded at Screening only.

^b Patients will have a washout period of 72 hours. If a bleeding occurs, another washout period of 72 hours will be performed. If another bleeding occurs during this second washout period, then the patient may be excluded from the study at the physician's discretion.

^c Includes baseline hFVIII activity (chromogenic FXa and one-stage APTT assays), hFVIII coagulation activity exploratory assay, hFVIII inhibitor level (Bethesda assay with Nijmegen modification), hFVIII total antibody titer, and hFVIII antigen (ELISA). hFVIII assays should be assessed only when the patient has been off FVIII therapy for at least the previous 4 days.

^d Screening (done during screening) and confirmation (at baseline) of AAV5 pre-existing immunity may include plasma samples for 3 assays (in vivo transduction inhibition, in vitro transduction inhibition and AAV5 total antibody assays).

^e Patients with documented negative results within the last 30 days do not need to be retested.

^f Refer to Table 9.7.8.2.1 for laboratory assessments to be included.

^g Includes HLA typing, FVIII mutation status, $TNF\alpha$ and IL10a single nucleotide polymorphisms.

^h Blood samples will be collected from subjects to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to Haemophilia A disease. The genetic/genomic testing on these exploratory samples is optional.

ⁱ Should the screening visit occur within 7 days of the drug infusion, physical examination, vital signs, blood chemistry, haematology, urine tests, coagulation screen, and CRP do not need to be repeated at Baseline.

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	Follow-Up After BMN 270 Administration - Weeks*															
Assessment	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Physical exam ^a	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Assessment of Adverse Events and Concomitant Medications	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Vital Signs	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Blood chemistry, haematology, urine tests, coagulation screen, and CRP ^b	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
hFVIII activity assays ^c	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
hFVIII antibody titer	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
PCR of vector genomes in blood, saliva, urine, semen, and stools ^d	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Exploratory biomarker assessments ^e	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
QoL assessment	Х	Х	Х	Х												Х
AAV5 antibody titer	Х							Х								Х
Testing for reactivation of hepatitis B and hepatitis C	Х		Х			Х										
Mononuclear cell collection				Х				Х				Х				Х

Table 9.1.2: Schedule of Events – Post-Infusion Follow-Up

* Visit windows are ± 48 hours

^a Brief physical examination should be done at all weekly visits except Week 16, where a complete physical examination should be performed. Refer to Section 9.7.8.4.

^b Refer to Table 9.7.8.2.1 for laboratory assessments to be included. Each patient will have comprehensive surveillance plan monitoring LFTs once a week from dose to completion of Week 6, 3 times per week (every other day excluding weekends) from Weeks 7 to 12, and once a week from Weeks 13 to 16. If a patient's ALT is found to be greater than 1.5x baseline during these periods, then LFTs will be monitored three times per week or until the ALT returns to baseline.

^c Includes hFVIII activity level (APTT and FXa chromogenic assay), hFVIII activity confirmation (frozen plasma), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, hFVIII coagulation activity exploratory assay, and hFVIII antigen (ELISA).

^d Collection to occur on Day 1, 3, 7 following BMN 270 infusion, and then weekly until 3 consecutive negative results are obtained

^e Blood samples will be collected from subjects to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to Haemophilia A disease. The genetic/genomic testing on these exploratory samples is optional.

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		Year	r 1 - We	Years 2-5 [*]	ETV (early termination		
Assessment	20	28	36	44	52	Q3M	visit)
Physical exam ^a	Х	Х	Х	Х	X	Х	Х
Assessment of Adverse Events and Concomitant Medications	Х	Х	Х	Х	X	Х	Х
Vital Signs	Х	Х	Х	Х	X	Х	Х
Blood chemistry, haematology, urine tests, coagulation screen, and CRP ^b	Х	Х	Х	Х	Х	Х	Х
hFVIII activity assays ^c	Х	Х	Х	Х	X	Х	Х
AAV5 antibody titer	Х	Х	Х	Х	X	Х	Х
hFVIII antibody titer	Х	Х	Х	Х	Х	Х	Х
Mononuclear Cell Collection (for determination of FVIII and Capsid specific CTL activity)	Х	Х	Х	Х	X	Х	Х
PCR of vector genomes in blood, saliva, urine, semen, and stools ^d	Х	Х	Х	Х	X	Х	Х
QoL assessment		Х			Х	X ^e	Х

Table 9.1.3: Schedule of Events – Safety Follow-Up

* Visit windows are ± 72 hours

^a Complete physical examination should be performed at Weeks 52 and every 52 weeks thereafter; brief physical exam may be performed at other study visits. Refer to Section 9.7.8.4.

^b Refer to Table 9.7.8.2.1 for laboratory assessments to be included.

^c Includes hFVIII activity level (one-stage APTT and chromogenic FXa assay), hFVIII activity confirmation (frozen plasma), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, hFVIII coagulation activity exploratory assay, and hFVIII antigen (ELISA).

^d Sample testing during Safety Follow-Up is not required if 3 consecutive samples are cleared during the Post-Infusion Follow-Up period.

^e QoL assessment during Years 2-5 of Safety Follow-up should be performed at every other visit (every 6 months) starting with the Week 78 visit (ie, 26 weeks after the Week 52 visit at the end of Year 1 of the Safety Follow-up period).

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9.2 Discussion of Study Design, Including Choice of Control Group

Study 270-201 is designed to be a first-in-man, phase 1/2 open-label, dose escalation study in patients with severe haemophilia A. Three doses of BMN 270 will be evaluated and the dose escalation decision tree is summarized in Figure 9.1.1.

The decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and a panel of investigators participating in the study.

There will be no control group. Parameters for each patient will be compared to a pre-treatment assessment of safety (liver function) and efficacy (number of bleeds, use of replacement therapy).

As AAV based treatment always leads to anti-capsid immune response, no true control group (for example with an empty AAV) is possible.

9.3 Selection of Study Population

Up to 12 severe haemophilia A patients may enroll into the study; the actual number of patients will depend on the criteria for dose escalation. A total of 6 patients may be enrolled at a single dose level.

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 criteria:

- 1. Males that are 18 years or older with established severe Haemophilia A as evidenced by their medical history. Patients will be considered as severe if their FVIII levels have ever declined to 1 IU/dL or less
- 2. Treated/exposed to FVIII concentrates or cryoprecipitates for a minimum of 150 exposure days (EDs)
- 3. Greater or equal to 12 bleeding episodes only if on on-demand therapy over the previous 12 months. Does not apply to patients on prophylaxis
- 4. Able to sign informed consent and comply with requirements of the trial
- 5. No history of inhibitor, or no inhibitor on 2 consecutive occasions within the past 12 months using a modified Nijmegen Bethesda assay higher than 0.6 Bethesda Unit (BU)

6. Sexually active patients must be willing to use an acceptable method of contraception such as double barrier, including hormonal contraception for at least 6 months post-treatment.

9.3.2 Exclusion Criteria

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Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study:

- 1. Detectable pre-existing immunity to the AAV5 capsid as measured by AAV5 transduction inhibition and AAV5 total antibodies
- 2. Evidence of detectable viral load of HIV
- 3. Significant liver dysfunction as defined by abnormal elevation of ALT (alanine transaminase) to 3 times the upper limit of normal, bilirubin, alkaline phosphatase, or an INR (international normalized ratio) of 1.4. Potential participants who have had a liver biopsy in the past 3 years are excluded if they had significant fibrosis of 3 or 4 as rated on a scale of 0-4
- 4. Evidence of any bleeding disorder not related to Haemophilia A
- 5. Platelet count of $< 100 \times 10^9/L$
- 6. Creatinine $\geq 1.5 \text{ mg/dL}$
- 7. Liver cirrhosis of any etiology as assessed by liver ultrasound
- 8. Hepatitis B if surface antigen is positive
- 9. Hepatitis C if RNA is positive
- 10. Treatment with any IP within 30 days prior to the screening visit
- 11. Any disease or condition at the physician's discretion that would prevent the patient from fully complying with the requirements of the study. The physician may exclude patients unwilling or unable to agree on not using alcohol for the 16-week period following the viral infusion.

9.3.3 Removal of Patients from Treatment or Assessment

Patients may withdraw their consent to participate in the study at any time without prejudice. The Investigator must withdraw from the study any patient who requests to be withdrawn. A patient's participation in the study may be discontinued at any time at the discretion 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.

BioMarin must be notified of all patient withdrawals as soon as possible. BioMarin also reserves the right to discontinue the study at any time for either clinical or administrative

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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 patient from the study include, but are not limited to, the following:

- Patient requires medication or medical procedure prohibited by the protocol
- Patient does not adhere to study requirements specified in the protocol
- Patient was erroneously admitted into the study or does not meet entry criteria
- Patient is lost to follow-up

If a patient fails to return for scheduled visits, a documented effort must be made to determine the reason. If the patient cannot be reached by telephone, a certified letter should be sent to the patient requesting contact with the Investigator. This information should be recorded in the study records.

The Investigator or designee must explain to each patient, before enrollment into the study, that for evaluation of study results, the patient's protected health information obtained during the study may be shared with the study Sponsor, regulatory agencies, and IRB/IEC/REB. It is the Investigator's (or designee's) responsibility to obtain written permission to use protected health information per country-specific regulations, such as the Health Insurance Portability and Accountability Act (HIPAA) in the US, from each patient. 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 patient and the patient will be removed from the study.

9.3.3.1 Study Safety Evaluation Criteria

If any of the following events occur (except the persistence of AAV5) in a patient in the study who has received BMN 270 infusion, an extensive safety analysis will be performed and BioMarin and the Principal Investigator will discuss pursuing the trial or increasing the time before the next patient is enrolled.

- A 5-fold increase in ALT after BMN 270 administration
- The occurrence of other drug-related Grade III-IV toxicity, including liver failure and clinical hepatitis
- Drug-related Grade II toxicity that persists for at least 7 days
- The occurrence of neutralizing antibodies to hFVIII following BMN 270 infusion

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- The persistent detection of the AAV vector genome in the semen of a participant more than 26 weeks after BMN 270 infusion, as discussed in Section 9.7.8.5
- The occurrence of a malignancy at any point after BMN 270 infusion that is assessed as possibly, probably, or definitely related to the study agent
- Any unexplained serious adverse event ≥ grade 4 assessed as at least possibly related to study drug

9.3.4 Patient Identification and Replacement of Patients

Each patient will be assigned a unique patient identifier. This unique identifier will be on all CRF pages. In legal jurisdictions where use of initials is not permitted, a substitute identifier will be used.

Patients who withdraw from the study after Week 16 will not be replaced.

9.3.5 Duration of Patient Participation

The duration of this study will be approximately 264 weeks. This includes 4 weeks of screening, 1 day of BMN 270 infusion, 16 weeks of Post-Infusion Follow-Up, and 244 weeks of Safety Follow-Up. A primary endpoint analysis on safety and efficacy will be performed at 16 weeks.

9.4 Treatments

BioMarin or its designee will provide the study site with study drug sufficient for study completion. BioMarin is responsible for shipping study drug to clinical sites.

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.

9.4.2 Identity of Investigational Product

9.4.2.1 Product Characteristics and Labeling

The study drug label includes the following information: lot number, required storage conditions, a precautionary statement, expiry date, study number, and BioMarin name and address. Labelling will be done according to country specific requirements.

9.4.3 Storage

At the study site, all IP must be stored under the conditions specified in the IB in a secure area accessible only to the designated pharmacists and clinical site personnel. All IP must be

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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

After a physical exam performed by the PI or designee, participants will be admitted on the day of BMN 270 infusion. An IV catheter will be inserted into a suitable peripheral vein (e.g. the median cubital vein) and flushed with saline. FVIII protein concentrate 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. An electric syringe will be used to infuse through an in-line, low protein binding 0.22 micron filter. BMN 270 will be infused through the catheter using an appropriate infusion pump while monitoring the vital signs (pulse, blood pressure, respiration rate and temperature) at 15 minute (\pm 5 minutes) intervals. The anticipated maximum interval from initiation of thawing of BMN 270 to completion of the infusion is 4 hours.

Following completion of the infusion, vital signs will be monitored hourly (± 5 minutes) for 6 hours and then every 2 hours (± 15 minutes) for 6 hours and then at 4 hour intervals. If the vital signs are stable the catheter will be removed 20-24 hours after the infusion. Hemostasis at the puncture site will be established by applying pressure according to standard protocol for infusing FVIII concentrates. Patients will remain hospitalized for 24 hours to observe for any immediate toxicity of the procedure. After 24 hours of hospitalization, participants will be discharged unless toxicity has been observed in which case hospitalization may be extended or transfer to an outpatient facility may occur based on the evaluation and judgment of the Principal Investigator after consultation with the Medical Monitor.

9.4.5 Method of Assigning Patients to Treatment Groups

Patients 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 Sponsor will be required prior to enrollment of each study patient. Upon their enrollment into the study, patients will be assigned a unique patient number and dose level by the Sponsor.

Patients are enrolled serially and their dose is defined in Section 9.4.6.2 below. Escalation is based on FVIII activity 3 weeks after injection. Patients may receive the next higher dose if the previous patient does not meet the activity criteria, or the same dose if the previous

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patient meets the activity criteria. Up to 6 patients can have the same dose, for a total of 12 patients in this study.

9.4.6 Selection of Doses Used in the Study

The starting dose was based on the expression of hFVIII observed in nonclinical studies of mice and monkeys. The starting dose has a significant safety margin (10-fold) from NOAEL in non-human primates. The dose escalation is half-logs based.

9.4.6.1 Selection of Timing of Dose for Each Patient

A minimum of three weeks are required between patients, to allow for evaluation of safety and expression of hFVIII. After three weeks, depending on the activity level, the choice of the dose for the next patient will be made as described below.

9.4.6.2 Selection of Dose for Each Patient

The starting dose was determined by expression of hFVIII observed in mice and monkeys and a scale up factor based on previous experience, an improved purification process over previous trials (thus decreasing the risk of immune response), and a new evaluation of the titer (PCR performed after hairpin removal).

Approximately three weeks after an injection, the decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and a panel of investigators participating in the study.

Patient 1 will be dosed with 6E12 vector genomes [vg] per kilogram of body weight. If the activity level does not reach \geq 5 IU/dL at 21 days, then a higher dose (2E13 vg per kilogram) will be used for the next patient.

If the activity level does not reach \geq 5 IU/dL after Patient 2, then the highest dose (6E13 vg per kilogram) will be used for the next patient.

For each dose, if the activity level reaches 5 IU/dL and if no safety issue is found, then up to four patients will receive this dose. If at any time activity levels reach 10 IU/dL or higher, no further dose escalation will take place, but additional patients will then be dosed at this dose level for a total of 6 patients per dose.

Refer to Figure 9.1.1 for a visual representation of the study design.

9.4.7 Blinding

This is an open-label study.

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9.4.8 Prior and Concomitant Medications

All prescription and over-the-counter medications taken by a patient for 30 days before Screening will be recorded on the designated CRF. The Investigator may prescribe additional medications 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 CRF.

The following medications are prohibited starting 30 days before Screening:

- Live vaccines
- Immunosuppressive agents

Haemophilia treatments are discussed in the washout section below (Section 9.4.8.1).

9.4.8.1 Factor VIII Washout

Patients will have a washout period of 72 hours. If a bleeding occurs, another washout period of 72 hours will be performed. If another bleeding occurs during this second washout period, then the patient may be excluded from the study at the physician's discretion.

9.4.8.2 Glucocorticoid Treatment of Elevated Hepatic Transaminases

During the Post-Infusion Follow-up Period, each patient will have comprehensive surveillance plan monitoring LFTs once a week from dose to completion of Week 6, 3 times per week from Weeks 7 to 12, and once a week from Weeks 13 to 16. If a patient's ALT is found to be greater than 1.5x baseline during these periods, then LFTs will be monitored three times per week or until the ALT returns to baseline.

Reports of abnormal LFTs (defined as 1.5x the patient's baseline level) should be made to BioMarin within 24 hours of the lab value being available. If the LFTs are abnormal, treatment with prednisolone initiated at a dose of 60mg per day and then gradually tapered will be started immediately.

9.4.9 Treatment Compliance

Study drug will be administered to patients at the study site by a qualified professional. The quantity dispensed, returned, used, lost, etc. must be recorded on the dispensing log provided for the study. Sites will be instructed to return all used and unused study drug containers.

9.5 Investigational Product Accountability

The Investigator or designee is responsible for maintaining accurate records (including dates and quantities) of IP(s) received, patients to whom IP is dispensed (patient-by-patient dose specific accounting), 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.

9.5.1 Return and Disposition of Clinical Supplies

Unused study drug must be kept in a secure location for accountability and reconciliation by the study monitor. The Investigator or designee must provide an explanation for any destroyed or missing study drug or study materials.

Unused study drug may be destroyed on site, per the site's standard operating procedures, but only after BioMarin has granted approval for drug destruction. The monitor must account for all study drug in a formal reconciliation process prior to study drug destruction. All study drug destroyed on site must be documented. Documentation must be provided to BioMarin and retained in the Investigator study files. If a site is unable to destroy study drug appropriately, the site can return unused study drug to BioMarin upon request. The return of study drug or study drug materials must be accounted for on a Study Drug Return Form provided by BioMarin.

All study drug and related materials should be stored, inventoried, reconciled, and destroyed or returned according to applicable state and federal regulations and study procedures.

9.6 Dietary or Other Protocol Restrictions

There are no dietary or other protocol restrictions for this study.

9.7 Safety and Efficacy Variables

As this is a first-in-man study, the primary endpoint of safety will be assessed as explained in Section 9.7.8.

The primary efficacy measure will be to assess plasma FVIII activity. The efficacy goal of the study is to establish the dose relationship to FVIII activity \geq 5 IU/dL at 16 weeks post BMN 270 administration.

9.7.1 Safety and Efficacy Measurements Assessed

The Schedule of Events (Table 9.1.1) describes the timing of required evaluations.

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9.7.2 Primary Efficacy Variables

The primary efficacy measure will be the plasma FVIII activity monitored on a regular basis after BMN 270 dose. The efficacy goal of the protocol is to ascertain the dose range of BMN 270 required to convert severe HA patients to stable expression of FVIII at 5 IU/dL, i.e., a mild severity. This is associated in natural history studies with clinically superior long term outcomes (Nathwani, 1992, Baillieres Clin.Haematol.).

To measure the primary efficacy variable, the following assays will be used:

- FVIII activity (chromogenic FXa assay)
- FVIII activity by one-stage APTT (Activated Partial Thromboplastin Time)
- Exploratory FVIII activity assay

The FVIII activity level and the number of patients with FVIII activity ≥ 5 IU/dL will be summarized.

Timing of assessment by these assays is provided in Table 9.1.2 and Table 9.1.3. Details on performing the assays are included in the Laboratory Manual.

9.7.3 Secondary Efficacy Variables

Secondary efficacy measures will be the reduction in the frequency of factor replacement therapy, and reduction in the number of bleeding episodes. Patients 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 patient's diary or other patient records.

Assessment of viral shedding at one week after BMN 270 infusion will also be considered an efficacy variable.

9.7.4 Immunogenicity

Immunogenicity assays will be performed on plasma. The assays will include detection of anti-capsid, and anti-FVIII total antibody, and determination of neutralizing antibodies against FVIII. Any increase in total antibody level, especially during the time period of 6-12 weeks, will be compared with FVIII activity measurements. Any abnormality of the liver parameters will lead to an immunogenicity assessment to determine anti-FVIII and capsid specific CTL. Anti-FVIII and capsid specific CTL assays will be performed on collected PBMCs.

Timing of assessment by these assays is provided in Table 9.1.2 and Table 9.1.3.

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9.7.5 **Pharmacodynamics**

The hFVIII antigen and activity level will be measured by an ELISA (antigen) and by onestage APTT and/or chromogenic FXa assay (activity). Individual antigen and activity plasma plots will be prepared to assess changes over 16 weeks. FVIII activity measurements will be used to determine PD parameters.

If supported by FVIII activity data, non-compartmental analysis and observation will be used to estimate individual values of C_b (baseline concentration). C_{ss} (steady state concentration). T_{ss} (time to steady state), C(t) and AUC(0-t) where t is 16 weeks. Other parameters that may be used to describe individual FVIII protein and activity plasma profiles are C_{max} (maximum concentration) and Cavg (average concentration, AUC(0-t)/t). The PD parameters and dose will be used to assess clinical pharmacology.

Sample collection times are indicated in Table 9.1.2 and Table 9.1.3.

9.7.6 **Exploratory Biomarker Assessments**

Blood samples will be collected from subjects at the time points indicated in Table 9.1.1 and Table 9.1.2 to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to Haemophilia A disease. The genetic/genomic testing on these exploratory samples is optional.

9.7.7 Quality of Life Assessment

A patient-reported outcome (PRO) questionnaire will be used to assess subject quality of life (QoL) during the study. Assessments will occur at the time points listed in the Schedules of Assessments.

Details regarding the QoL assessment will be included in the Study Reference Manual.

Safety Variables 9.7.8

Safety in this study will be determined from evaluation of AEs, clinical laboratory assessments with a particular attention to the liver function, vital signs assessments, physical examinations, and immunogenicity.

9.7.8.1 **Adverse Events**

The occurrence of AEs will be assessed continuously from the time the patient signs the ICF. The determination, evaluation and reporting of AEs will be performed as outlined in Section 10. Assessments of AEs will occur at the time points shown in Table 9.1.1.

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9.7.8.2 Clinical Laboratory Assessments

Specific visits for obtaining clinical laboratory assessment samples are provided in Table 9.1.1. The scheduled clinical laboratory tests are listed in Table 9.7.8.2.1. Refer to the Study Reference Manual 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 the cause of the abnormality is determined, the value returns to baseline or to within normal limits, or the Investigator determines that the abnormal value is no longer clinically significant.

All abnormal clinical laboratory result pages 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 CRF.



Table 9.7.8.2.1: Clinical Laboratory Tests

Blood Chemistry	Haematology	Urine Tests	Other
Albumin	Haemoglobin	Appearance	CRP
Alkaline phosphatase	Haematocrit	Color	
ALT (SGPT)	WBC count	рН	Coagulation Screen including:
AST (SGOT)	RBC count	Specific gravity	APTT
Direct bilirubin	Platelet count	Ketones	PT/INR
Total bilirubin	Differential cell count	Protein	TT
BUN		Glucose	
Calcium		Bilirubin	
Chloride		Nitrite	
Total cholesterol		Urobilinogen	
CO ₂		Haemoglobin	
Creatinine			
Glucose			
GGT			
LDH			
Phosphorus			
Potassium			
Total protein			
Sodium			
Uric acid			

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CO₂, carbon dioxide; GGT, gamma-glutamyltransferase; LDH, lactate dehydrogenase; PT, prothrombin time; APTT, activated partial thromboplastin time; RBC, red blood cell; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone; WBC, white blood cell; TT, thrombin time; INR, international normalized ratio.

9.7.8.3 Liver function and Hepatitis Testing

Patients will be screened for evidence of previous hepatitis B or hepatitis C infection at Screening. If medical records showing no evidence of Hepatitis B or Hepatitis C infection from the previous 30 days are available, then the Screening tests do not need to be done.

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Evidence of ongoing infection (positive surface antigen for hepatitis B or positive RNA testing for hepatitis C) will be an exclusion criteria. If these parameters are negative and therefore no active infection is detected, then the patients may be included if they were vaccinated (for hepatitis B) or cleared the infection (for hepatitis C) and their liver function is acceptable.

A liver ultrasound and liver function testing at Screening will identify any significant hepatic dysfunction, which is defined as:

- More than 3x the normal ALT level
- More than 3x the normal bilirubin level
- Alkaline phosphatase above the normal cut off.
- INR over 1.4.
- Thrombocytopoenia under $100 \times 10^9/L$

9.7.8.4 Vital Signs, Physical Examinations and Other Observations Related to Safety

Vital signs will include seated systolic and diastolic blood pressure, heart rate, respiration rate, and temperature. Any clinically significant change in vital signs will be recorded as an AE.

Systolic blood pressure, diastolic blood pressure, heart rate, respiration rate, and temperature will be assessed at Screening, Baseline, and at the beginning of each visit during the Post-Infusion Follow-Up and Safety Follow-Up periods. On the day of the BMN 270 Infusion, vital signs will be monitored hourly for 6 hours and then every 2 hours for 6 hours and then at 4 hour intervals.

A complete physical examination is necessary during Screening/Baseline; thereafter, brief physical examinations may be performed at the discretion of the investigator based on the patient'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 (level of consciousness, speech, language, cranial nerves, motor strength, motor tone, abnormal movements, reflexes, upper extremity sensation, lower extremity sensations, gait, Romberg, nystagmus, and coordination).

A brief physical examination will include general appearance, cardiovascular, respiratory, neurologic, and gastrointestinal assessments.

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Weight and height will be recorded at Screening only.

9.7.8.5 Viral Shedding

Viral shedding has been extensively studied in all similar clinical trials performed to date. (Appendix 1; Appendix 2; Schenk-Braat, 2007, J Gene Med; Croteau, 2004, Ann Occup Hyg). It has been constantly shown that the vector was not detectable anymore at 40 days, with its persistence in semen for 16 weeks in the seminal fluid but not in motile sperm (Manno, 2006, Nature Med.). In addition, it has always involved only an extremely small fraction of the injected dose.

Viral shedding will also be extensively studied in the present clinical trial, every week up to 16 weeks, then every 4 weeks to one year, then every three months. During the Post-Infusion Follow-Up period, patients will undergo testing of various bodily fluids to look for evidence of viral shedding for possible viral transmission. Bodily fluids will be tested by PCR at the time points indicated in Table 9.1.2 and Table 9.1.3. Fluids tested will include:

- Blood
- Saliva
- Semen
- Urine
- Stool

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 haematology, 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, a reportable adverse event (AE) is any untoward medical occurrence (e.g., sign, symptom, illness, disease or injury) in a patient administered the study-drug or other protocol-imposed intervention, regardless of attribution. This includes the following:

- AEs not previously observed in the patient that emerge during the course of the study.
- Pre-existing medical conditions judged by the Investigator to have worsened in severity or frequency or changed in character during the study.
- Complications that occur as a result of non-drug protocol-imposed interventions (eg, AEs related to screening procedures, medication washout, or no-treatment run-in).

An adverse drug reaction is any AE for which there is a reasonable possibility that the study-drug caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the study-drug and the AE.

Bleeding events that are normal events of haemophilia (ie, bleeding events which occur only because the patient is a haemophiliac) should not be recorded as AEs but will instead be captured in patient diaries. Bleeding events that occur where a normal (ie, non-haemophiliac) patient would bleed, such as bleeding as a result of trauma, should be recorded as adverse events. All bleeding events which meet criteria for being serious should be reported as serious adverse events (SAEs) whether or not they are bleeding events that are normal sequelae of haemophilia.

Whenever possible, it is preferable to record a diagnosis as the AE term rather than a series of terms relating to a diagnosis.

10.2 Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that at any dose meets 1 or more of the following criteria:

- Is fatal
- Is life threatening

Note: Life-threatening refers to an event that places the patient at immediate risk of death. This definition does not include a reaction that, had it occurred in a more severe form, might have caused death.

- Requires or prolongs inpatient hospitalization. Hospitalization for less than 24 hours will not be considered to be an SAE. Hospitalization solely for the purpose of insertion of an in-dwelling IV catheter (such as a Port-a-Cath or other brand) for administration of study drug will not be considered an SAE.
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect in the child or fetus of a patient exposed to IP prior to conception or during pregnancy
- Is an important medical event or reaction that, based on medical judgment, may jeopardize the patient or require intervention to prevent one of the above consequences (e.g. anaphylaxis)

All adverse events that do not meet any of the criteria for SAEs should be regarded as nonserious AEs.

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 liver enzymes triggering a corticosteroid treatment

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 treatment, only SAEs associated with any protocol-imposed interventions will be reported. After informed consent is obtained and the first administration of study drug, the reporting period for all non-serious AEs and SAEs begins and continues for approximately 5 years or until study discontinuation/termination, whichever is longer. The criteria for determining, and the reporting of SAEs is provided in Section 10.2.

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10.3.2 Eliciting Adverse Events

Investigators will seek information on AEs and SAEs and EOSI, at each patient contact by specific questioning and, as appropriate, by examination. Information on all AEs and SAEs and EOSI, should be recorded in the patient's medical record and on the AE Case Report Form (eCRF).

10.3.3 Assessment of Seriousness, Severity, and Causality

The Investigator responsible for the care of the patient or qualified designee will assess AEs for severity, relationship to study drug, and seriousness (refer to Section 10.2 for SAE definitions). These assessments should 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 patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. The severity of each will be assessed using the defined categories in Table 10.3.3.2.1.

The Investigator will determine the severity of each AE and SAE and EOSI using the NCI CTCAE v4. 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 as stated below.

Table 10.3.3.2.1: Adverse Event Grading (Severity) Scale

Grade	Description		
1	Mild: asymptomatic or mild symptoms; clinical or diagnostic observation indicated	s only; intervention not	
2	Moderate: minimal, local or noninvasive intervention indicated; limiting instrumental activities of daily living (ADL) ^a	age-appropriate	
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 or debilitating: consequences; urgent intervention indicated	Grade 4 and 5 AEs should always be	
5	Death related to AE reported as SAEs		

^a Instrumental ADL refer to the following examples: preparing meals, shopping for groceries or clothes, using the telephone, managing money.

^b Self-care ADL refer to the following examples: bathing, dressing and undressing, feeding oneself, using the toilet, taking medications, not bedridden.

10.3.3.3 Causality

The Investigator will determine the relationship of an AE to the study drug and will record it on the source documents and AE CRF. To ensure consistency of causality assessments, Investigators should apply the guidance in Table 10.3.3.3.1.

Relationship	Description
Not Related	• Exposure to the IP has not occurred
	OR
	• The administration of the IP and the occurrence of the AE are not reasonably related in time
	OR
	• The AE is considered likely to be related to an etiology other than the use of the IP; that is, there are no facts, evidence, or arguments to suggest a causal relationship to the IP.
Related	• The administration of the IP and the occurrence of the AE are reasonably related in time
	AND
	• The AE could possibly be explained by factors or causes other than exposure to the IP
	OR
	• The administration of IP and the occurrence of the AE are reasonably related in time
	AND
	• The AE is more likely explained by exposure to the IP than by other factors or causes.

Factors suggestive of a causal relationship could include (but are not limited to):

- Plausible temporal relationship
- Absence of alternative explanations
- Rarity of event in a given patient or disease state
- Absence of event prior to study drug exposure
- Consistency with study product pharmacology
- Known relationship to underlying mechanism of study drug action
- Similarity to adverse reactions seen with related drug products
- Abatement of AE with discontinuation of study drug, and/or recurrence of AE with reintroduction of study drug

The investigator's assessment of causality for individual AE reports is part of the study documentation process. Regardless of the Investigator's assessment of causality for individual AE reports, the Sponsor will promptly evaluate all reported SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators and applicable regulatory authorities.

10.4 Procedures for Recording Adverse Events

10.4.1 Recording Adverse Events on a eCRF

Investigators should use precise medical terminology when recording AEs or SAEs on the AE eCRF. Avoid colloquialisms and abbreviations.

Record only one diagnosis, sign, or symptom per event field on the AE eCRF (eg, nausea and vomiting should not be recorded in the same entry, but as 2 separate entries).

In order to classify AEs and diseases, preferred terms will be assigned by the Sponsor to the original terms entered on the AE eCRF, using MedDRA (Medical Dictionary for Regulatory Activities) terminology.

10.4.1.1 Diagnosis versus Signs and Symptoms

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 eCRF, replacing the original entries where appropriate.

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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 haemorrhage 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 is one that extends continuously, without resolution, between patient evaluation time points. Such an event should be recorded only once on the AE eCRF unless its severity increases or decreases (in which case it should be recorded again on the AE eCRF).

A recurrent AE is one that occurs and resolves between patient evaluation time points, but then subsequently recurs. All recurrences of the AE should be recorded on the AE eCRF.

10.4.1.4 Abnormal Laboratory Values

Laboratory test results will be recorded on the laboratory results pages of the AE 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 should be reported as such, in addition to being recorded as an AE in the AE eCRF.

A clinical laboratory abnormality should be documented as AE if **any** of the following conditions is met:

- Accompanied by clinical symptoms
- Leading to a change in study medication (e.g. dose modification, interruption or permanent discontinuation)
- Requiring a change in concomitant therapy (e.g. addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment).
- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity

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• 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 hFVIII activity should not be reported as adverse events unless signs of worsening are observed.

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 document 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:

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- Perform a protocol-mandated efficacy measurement
- Undergo a diagnostic or elective surgical procedure for a pre-existing medical condition that has not changed
- 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 patient taking trial medication should be reported as an SAE 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 partner should be reported within 24 hours of the site becoming aware of the pregnancy by faxing the Pregnancy Form in the study reference materials to BPV. In addition, pregnancy in a patient is also reported on the End of Study eCRF. The Investigator must make every effort to follow the patient through resolution of the pregnancy (delivery or termination) and to report the resolution on the Pregnancy Follow-up Form in the study reference materials. In the event of pregnancy in the partner of a study patient, 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 BioMarin Pharmacovigilance (BPV) Proprietary and Confidential 10 February 2015

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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.

If the EDC is unavailable, all SAEs should be reported to BPV by completing the SAE Report Form and faxing or emailing the completed form to BPV within 24 hours of the site becoming aware of the event. Once the EDC is available, the information should be entered in the AE eCRF.

The reporting period for SAEs begins after informed consent is obtained and the first administration of study drug is given. It continues for approximately 5 years or until study discontinuation/termination, whichever is longer.

10.5.2 Ethics Committee Reporting Requirements

Reporting of SAEs to the Independent Ethics Committee (IEC) will be done in compliance with the standard operating procedures and policies of the IEC and with applicable regulatory requirements. Adequate documentation must be obtained by BioMarin showing that the IEC was properly and promptly notified as required.

10.6 Follow-up of Patients after Adverse Events

The Investigator should follow all unresolved AEs and SAEs until the events are resolved or have stabilized, the patient is lost to follow-up, or it has been determined that the study treatment or participation is not the cause of the AE/SAE. Resolution of AEs and SAEs (with dates) should be documented on the AE eCRF and submitted to BioMarin Pharmacovigilance and in the patient's medical record to facilitate source data verification.

For some SAEs, 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 report.

10.7 Post-Study Adverse Events

At the last scheduled visit, the Investigator should instruct each patient to report, to the Investigator and/or to BPV directly, any subsequent SAEs that the patient's personal physician(s) believes might be related to prior study treatment.

The Investigator should notify the study Sponsor of any death or SAE occurring at any time after a patient has discontinued or terminated study participation, if the Investigator believes

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that the death or SAE may have been related to prior study treatment. 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 patient 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 patients against any immediate hazards that may affect the safety of patients, and that the appropriate regulatory bodies should be notified according to their respective regulations. According to the European Union (EU) Clinical Trial Directive 2001/20/EC, "…in the light of the circumstances, notably the occurrence of any new event relating to the conduct of the trial or the development of the investigational medicinal product where that new event is likely to affect the safety of the patients, the Sponsor and the Investigator shall take appropriate urgent safety measures to protect the patients against any immediate hazard. The Sponsor shall forthwith inform the competent authorities of those new events and the measures taken and shall ensure that the IRB/IEC/REB is notified at the same time."

The reporting period for these events which may require the implementation of urgent safety measures is the period from the time of signing of the ICF through the completion of the last study visit or at the Early Termination Visit (ETV). Investigators are required to report any events which may require the implementation of urgent safety measures to BioMarin within 24 hours.

Examples of situations that may require urgent safety measures include discovery of the following:

- Immediate need to revise the IP administration (eg, modified dose amount or frequency not defined in protocol)
- 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

10.8 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		
Address:	105 Digital	Drive	
	Novato, CA	94949	USA
Phone:	PI		
E-mail:	PI		

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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.

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 will be performed within 28 days (\pm 14 days) of BMN 270 infusion while baseline assessments will take place a within 7 days of BMN 270 infusion (Day 1). Should the screening visit occur within 7 days of the drug infusion, physical examination, vital signs, blood chemistry, haematology, urine tests, coagulation screen, and CRP do not need to be repeated at Baseline.

The following procedures will be performed during the Screening Period:

- Full medical history, including haemophilia A history, Hepatitis B, Hepatitis C, and HIV. Patients with documented negative results within the last 30 days do not need to be retested.
- Complete Physical Exam (including 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 patient or clinical information)
- Electrocardiogram
- Chest X-ray
- Liver Ultrasound
- FVIII Treatment Washout (refer to Section 9.4.8.1)
- Samples for hFVIII Assays
 - Baseline hFVIII activity chromogenic FXa (plasma) (at least 96 hours off therapy)
 - Baseline hFVIII activity level –one-stage APTT assay (at least 96 hours off therapy)
 - hFVIII coagulation activity exploratory assay
 - hFVIII inhibitor level (Bethesda assay with Nijmegen modification)

- hFVIII total antibody assay
- hFVIII antigen (ELISA)
- Blood sample for AAV5 Assays

- AAV5 antibody titer
- o AAV5 transduction inhibition assays
- Screen for Hepatitis B, Hepatitis C, and HIV if required
- Blood chemistry, haematology, urine tests, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- Blood samples for Biomarker testing (HLA typing, FVIII mutation status, TNFα and IL10a single nucleotide polymorphisms)

12.3 Baseline Visit

Baseline values will be recorded from 1 to 7 days prior to the treatment visit. The following procedures will be performed during the Baseline Period:

- Physical exam
- Assessment of Adverse Events and Concomitant Medications
- Documentation of bleeding episodes and FVIII usage (by either patient or clinical information)
- Samples for FVIII Assays
 - FVIII activity chromogenic FXa (plasma) (at least 96 hours off therapy)
 - FVIII activity level –APTT One stage assay (at least 96 hours off therapy)
 - FVIII coagulation activity exploratory assay
 - FVIII inhibitor level (Bethesda assay with Nijmegen modification)
 - FVIII antibody assay
 - FVIII antigen (ELISA)
- Blood chemistry, haematology, urine tests, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- Mononuclear cell collection for CTL baseline
- PCR of vector genomes in blood, saliva, urine, semen, and stools
- Exploratory biomarker assessments
- QoL assessment

12.4 Treatment Visit/BMN 270 Infusion Visit (Day 1)

There will be one treatment visit for each patient. Patients will be hospitalized for 24 hours for the BMN 270 Infusion Visit. The following procedures will be performed during the BMN 270 Infusion Visit:

- Physical exam
- Assessment of Adverse Events and Concomitant Medications
- BMN 270 Infusion
- Vital Signs
 - Vital signs will be recorded prior to BMN 270 infusion and then every 15 minutes (± 5 minutes) during BMN 270 infusion. Following infusion, vital signs will be monitored every 1 hour (± 5 minutes) for the first 6 hours, every 2 hours (± 15 minutes) for the next 6 hours, and then at 4 hour (± 15 minutes) intervals for the remainder of the patient's hospitalization.

12.5 BMN 270 Infusion Follow-Up Visits

After BMN 270 has been infused, patients will return to the study site every week $(\pm 48 \text{ hours})$ for 16 weeks, when the following procedures will be completed:

12.5.1 Every Visit

Every week (Weeks 1 through 16), the following procedures will be performed:

- Physical exam
- Assessment of Adverse Events and Concomitant Medications
- Vital Signs
- Blood chemistry, haematology, urine tests, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
 - Each patient will have comprehensive surveillance plan monitoring LFTs once a week from dose to completion of Week 6, 3 times per week (every other day excluding weekends) from Weeks 7 to 12, and once a week from Weeks 13 to 16. If a patient's ALT is found to be greater than 1.5x baseline during these periods, then LFTs will be monitored three times per week or until the ALT returns to baseline.
- Samples for FVIII Assays
 - FVIII activity level (APTT)

- FVIII activity level (chromogenic FXa assay)
- FVIII coagulation activity exploratory assay
- Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level
- FVIII activity confirmation (Frozen plasma)
- FVIII antigen (ELISA)
- FVIII antibody titer

- PCR of vector genomes in blood, saliva, urine, semen, and stools
 - Collection to occur on Day 1, 3, 7 following BMN 270 infusion, and then weekly until 3 consecutive negative results are obtained
- Exploratory biomarker assessments

12.5.2 Every 4 Weeks

Every 4 weeks (Weeks 4, 8, 12, and 16), the following procedure will be performed:

• Mononuclear cell collection

12.5.3 Weeks 1, 3, and 6

At Weeks 1, 3, and 6, the following procedure will be performed:

• Test for Hepatitis B and Hepatitis C reactivation

12.5.4 Weeks 1, 8, and 16

At Weeks 1, 8, and 16, the following procedure will be performed:

• AAV5 antibody titer

12.5.5 Weeks 1, 2, 3, 4, and 16

At Weeks 1, 2, 3, 4, and 16, the following procedure will be performed:

• QoL assessment

12.6 Safety Follow-Up – Year 1

After the 16 weekly infusion follow-up visits are complete, subjects will return to the study site at Weeks 20, 28, 36, 44, and 52 (\pm 48 hours), when the following procedures will be completed:

12.6.1 Every Visit

At Weeks 20, 28, 36, 44, and 52, the following procedures will be performed:

- Physical exam
- Assessment of Adverse Events and Concomitant Medications
- Vital Signs
- Blood chemistry, haematology, urine tests, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- FVIII Assays
 - FVIII activity level (APTT)
 - FVIII activity level (chromogenic FXa assay)
 - FVIII coagulation activity exploratory assay
 - Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - FVIII activity confirmation (Frozen plasma)
 - FVIII antigen (ELISA)
- AAV5 antibody titer
- FVIII antibody titer
- Mononuclear cell collection
- PCR of vector genomes in blood, saliva, urine, semen, and stools
 - Sample testing during Safety Follow-Up is not required if 3 consecutive samples are clear during the Post-Infusion Follow-Up period.

12.6.2 Weeks 28 and 52

At Weeks 28 and 52, the following procedure will be performed:

• QoL assessment

12.7 Safety Follow-Up – Years 2-5

During Years 2-5 of Safety Follow-up, patients will be assessed every 3 months (\pm 72 hours). At these times, the following procedures will be completed:

12.7.1 Every Visit

Every 3 months (\pm 72 hours), the following procedures will be performed:

• Physical exam

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- Complete Physical Exam will be performed every 52 weeks; Brief Physical Exams may be performed at other visits.
- Assessment of Adverse Events and Concomitant Medications
- Blood chemistry, haematology, urine tests, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- FVIII Assays

- FVIII activity level (APTT)
- FVIII activity level (FXa chromogenic assay)
- FVIII coagulation activity exploratory assay
- Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
- FVIII activity confirmation (Frozen plasma)
- FVIII antigen (ELISA)
- AAV5 antibody titer
- FVIII antibody titer
- Mononuclear cell collection
- PCR of vector genomes in blood, saliva, urine, semen, and stools
 - Sample testing during Safety Follow-Up is not required if 3 consecutive samples are clear during the Post-Infusion Follow-Up period.
- Vital Signs

12.7.2 Every Other Visit (Every 6 Months)

Every six months starting at the Week 78 visit (ie, 26 weeks after the Week 52 visit at the end of Year 1 of the Safety Follow-up period), the following procedure will be performed:

• QOL assessment

12.8 Early Termination Visit

The Early Termination visit will occur on the date the patient withdraws from the study, even if the date does not correspond to a protocol-specific visit.

If a patient leaves the study prior to the Week 270 visit, the patient will be asked to return to the study site and complete an Early Termination visit. At the Early Termination visit, as many of the following assessments as possible should be done:

• Physical exam

- Assessment of Adverse Events and Concomitant Medications
- Blood chemistry, haematology, urine tests, coagulation screen, and CRP (refer to Table 9.7.8.2.1)
- FVIII Assays
 - FVIII activity level (APTT)
 - FVIII activity level (chromogenic FXa assay)
 - FVIII coagulation activity exploratory assay
 - Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
 - FVIII activity confirmation (Frozen plasma)
 - FVIII antigen (ELISA)
- AAV5 antibody titer
- FVIII antibody titer
- Mononuclear cell collection
- PCR of vector genomes in blood, saliva, urine, semen, and stools
 - Sample testing at the ETV is not required if 3 consecutive samples are clear during the Post-Infusion Follow-Up period.
- Vital Signs
- QOL assessment

12.9 End of Study

The study will end after the last patient completes the last Safety Follow-Up visit (Week 270). 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 patients may be compromised.

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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, any applicable randomization procedures, source document requirements, CRFs, 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 CRFs from source documents, adherence to protocol, randomization (if applicable), SAE reporting and drug accountability records.

The designated clinical data management group will enter or transfer CRF data into a study database.

Data quality control and analysis will be performed by BioMarin or a designee, based on a predefined analysis plan.

14 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

14.1 Statistical and Analytical Plans

The statistical analysis plan (SAP) will provide additional details on the planned statistical analysis. Unless otherwise stated, all analyses will be performed using SAS.

14.1.1 Interim Analyses

No formal interim analysis is planned. An analysis of the primary endpoint will be done following all patients having completed the study assessments through the end of the Post-Infusion Follow-Up Period (Week 16).

14.1.2 Procedures for Accounting for Missing, Unused and Spurious Data

Missing data will not be imputed.

14.2 Primary and Secondary Efficacy Analysis

The patients will be followed in a longitudinal manner and all the relevant information will be collected. The analysis of the data will be descriptive in nature. Descriptive statistics include the number of patients, mean, median, standard deviation, minimum, and maximum for continuous variables and count and percent for categorical variables. Efficacy variables will be summarized by dose cohort at each time point. Relationship between dose and efficacy results will be examined.

Data collected in a longitudinal manner may be analyzed using longitudinal methods such as mixed effect model which takes into account the correlation among the observation taken at various time points within a participant. Efficacy is a secondary endpoint, defined as biologically active hFVIII at \geq 5 IU/dL by chromogenic FXa and/or one-stage APTT assay between 1 to 16 weeks following study treatment. hFVIII activity will be assessed weekly during the study period. We can only assess the true steady state of hFVIII protein produced from BMN 270 after a minimum of 96 hours has elapsed since the last infusion of FVIII protein concentrates.

14.3 Immunogenicity

Analysis of neutralizing antibody response and other immunological parameters will be primarily descriptive and involve both inter-participant and intra-participant comparisons across doses.

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14.4 Pharmacodynamic Analyses

The FVIII antigen and activity level as measured by an Elisa (antigen level) and by a one-stage APTT and/or chromogenic FXa assay (activity level), will be used for plasma profiles; FVIII activity will be used to determine PD parameters. Traditional PK analysis is not applicable.

If supported by FVIII activity data, non-compartmental analysis and observation will be used to estimate individual PD parameter values of C_b (baseline), C_{ss} (steady state), T_{ss} (time to steady state), C(t) and AUC(0-t) where t is 16 weeks. Other parameters that may be used to describe individual FVIII protein and activity plasma profiles are C_{max} (maximum concentration) and C_{avg} (average concentration, AUC(0-t)/t). The parameters will be summarized using descriptive statistics.

14.5 Safety Analysis

The Medical Dictionary for Regulatory Activities terminology (MedDRA) will be used by the Sponsor to assign system organ class and preferred term classification to events and diseases, based on the original terms entered on the CRF.

All AEs will be coded using MedDRA. The incidence of AEs will be summarized by system organ class, preferred term, relationship to study drug, and severity. A by-patient listing will be provided for those patients who experience a serious AE (SAE), including death, or experience an AE associated with early withdrawal from the study or study drug. Hepatitis is of interest, and the percentage of patients who report hepatitis will be presented.

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.

14.6 Determination of Sample Size

No formal sample size calculations based on statistical power were performed.

The sample size is determined based upon clinical consideration and could detect a strong clinical efficacy signal. Up to 12 patients may be dosed in the study; the actual number of patients will depend on the criteria for dose escalation. A total of 6 patients may be enrolled at a single dose level.

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14.7 Analysis Populations

The Safety analysis population is defined as all enrolled patients who receive any study drug. The analysis of safety data will be performed on Safety Set.

The Full Analysis Set (FAS) is defined as all enrolled patients who receive study drug and have at least one Baseline and post-Baseline assessment. The FAS will be used for efficacy analysis.

14.8 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 patient's safety is compromised without immediate action. In these circumstances, immediate approval of the chairman of the IRB/IEC/REB must be sought, and the Investigator should inform BioMarin and the full IRB/IEC/REB within 2 working days after the emergency occurs.

With the exception of minor administrative or typographical changes, the IRB/IEC/REB must review and approve all protocol amendments. Protocol amendments that have an impact on patient risk or the study objectives, or require revision of the ICF, must receive approval from the IRB/IEC/REB prior to their implementation.

When a protocol amendment substantially alters the study design or the potential risks or burden to patients, the ICF will be amended and approved by BioMarin and the IRB/IEC/REB, and all active patients must again provide informed consent.

Note: If discrepancies exist between the text of the statistical analysis as planned in the protocol, and the final SAP, a protocol amendment will not be issued and the SAP will prevail.

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15 DATA MONITORING COMMITTEE

There will be no DMC for this study, however a safety and efficacy evaluation board composed of the investigators and sponsor will be established. The primary responsibility of the board will be to assess patient's safety and efficacy data accumulated for a particular dose level and to make recommendations regarding dose escalation.

16 COMPENSATION, INSURANCE AND INDEMNITY

There will be no charge to study patients to be in this study. BioMarin will pay all costs of tests, procedures, and treatments that are part of this study. In addition, after IRB/IEC/REB approval, BioMarin may reimburse the cost of travel for study-related visits. BioMarin will not pay for any hospitalizations, tests, or treatments for medical problems of any sort, whether or not related to the study patient's disease, that are not part of this study. Costs associated with hospitalizations, tests, and treatments should be billed and collected in the way that such costs are usually billed and collected.

The Investigator should contact BioMarin immediately upon notification that a study patient has been injured by the IP or by procedures performed as part of the study. Any patient who experiences a study-related injury should be instructed by the Investigator to seek medical treatment at a pre-specified medical institution if possible, or at the closest medical treatment facility if necessary. The patient 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 patient's health insurance company or other third party payer for the cost of this medical treatment. If the patient has followed the Investigator's instructions, BioMarin will pay for reasonable and necessary medical services to treat the injuries caused by the IP or study procedures, if these costs are not covered by health insurance or another third party that usually pays these costs. In some jurisdictions, BioMarin is obligated by law to pay for study-related injuries without prior recourse to third party payer billing. 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 patient. The Investigator must review and electronically sign the completed CRF casebook to verify its accuracy.

CRFs 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 CRF instructions, blank data fields are not acceptable.

In the event of an entry error, or if new information becomes available, the value will be corrected by deselecting the erroneous response and then selecting or entering the factual response. In compliance with ICH GCP Guidelines and 21 CFR Part 11, the system will require the personnel making the correction to enter a reason for changing the value. The documented audit trail will include the reason for the change, the original value, the new value, the time of the correction and the identity of the operator.

BioMarin's policy is that study data on the CRFs must be verifiable to the source data, which necessitates access to all original recordings, laboratory reports, and patient 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. Patients must also allow access to their medical records, and patients will be informed of this and will confirm their agreement when giving informed consent. If an Investigator or institution refuses to allow access to patient records because of confidentiality, arrangements must be made to allow an "interview" style of data verification.

A CRA designated by BioMarin will compare the CRFs 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 CRA, 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 CRA 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 patient's CRF 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 CRFs is accurate and complete. The Data Manager, or designee,

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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.

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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 patients, 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.

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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, patient 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 patient identifiers for at least 15 years after the completion or discontinuation of the study. Patient 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 patient 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.

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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 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).

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22 INVESTIGATOR RESPONSIBILITIES

22.1 Conduct of Study and Protection of Human Patients

In accordance with FDA Form 1572, 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 patients.
- He or she will personally conduct or supervise the study.
- He or she will inform any potential patients, 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 IRB review and approval in 21 CFR Part 56 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.
- 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
- He or she will ensure that adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.
- He or she will ensure that the IRB/IEC/REB complies with the requirements of 21 CFR Part 56, 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 patients or others are reported to the IRB/IEC/REB. Additionally, he or she will not make any changes in the research without IRB/IEC/REB approval, except where necessary to eliminate apparent immediate hazards to human patients.
- 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.

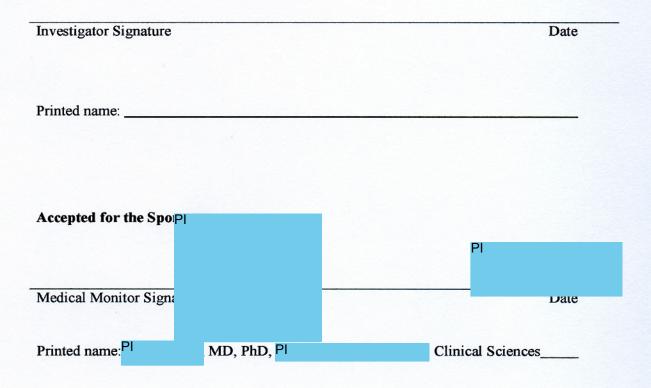
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23 SIGNATURE PAGE

Protocol Title: A Phase 1/2, Dose-Escalation Safety, Tolerability and Efficacy Study of BMN 270, an Adenovirus-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII in Patients with Severe Haemophilia A

Protocol Number: 270-201

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 E6 ICH, as stated in the protocol, and other information supplied to me.



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10 February 2015