Official Title: A Phase 1/2 Safety, Tolerability, and Efficacy Study of BMN 270, an Adeno-Associated Virus Vector‑Mediated Gene Transfer of Human Factor VIII in Hemophilia A Patients with Residual FVIII levels ≤1 IU/dL and Pre-existing Antibodies Against AAV5

NCT Number: NCT03520712

Applicant/MAH: BioMarin Pharmaceutical Inc.

Version Date: 26 March 2024

16.1.9 Documentation of Statistical Methods

16.1.9.1 Statistical Analysis Plan

270-203 Interim SAP v1.0 (dated 11 March 2019)

270-203 Interim SAP v2.0 (dated 25 January 2021)

270-203 Final SAP v1.0 (dated 26 March 2024)

16.1.9.2 Data Monitoring Committee Details

Data Monitoring Committee (DMC) Charter v5.0 (dated 13 June 2024)

The Data Monitoring Committee (DMC) met on the following dates, with meeting minutes linked and DMC recommendations (if given) noted:

Date of DMC Meeting	
28 February 2019	07 May 2021
25 March 2019	29 July 2021
25 April 2019	03 December 2021
24 May 2019	28 February 2022
19 July 2019	23 May 2022
29 August 2019	26 August 2022
31 October 2019	16 December 2022
16 December 2019	10 March 2023
10 February 2020	02 June 2023
16 April 2020	06 July 2023
17 August 2020	12 October 2023
23 October 2020	26 January 2024
17 December 2020	11 April 2024
18 February 2021	02 October 2024

BIOMARIN	SART Document Approval Form

Study name: 270-203

Overview

Purpose (Check only 1):

- ☐ Final draft SAP
- ☐ Revision(s) to the final draft SAP
- ☑ Final SAP
- ☐ Amendment(s) to the final SAP
- ☐ The TOC of TLGs defined by the SAP
- ☐ TLG mockups and specifications defined by a SAP
- ☐ Revision(s) to the TLG mockups and specifications document after its approval, determined by the Biostatistican to require SART approval
- ☐ Request(s) for major changes to mockups and specifications after review of TLG outputs produced for the Dry Run
- ☐ Other:

Comments

Approval

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Statistical Pr... PI yyyy
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Clinical Scien... PI dd MON yyyy
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INTERIM ANALYSIS PLAN

Protocol Number: 270-203

Study Title: A Phase 1/2 Safety, Tolerability, and Efficacy Study of BMN 270, an Adeno-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII in Hemophilia A Patients with Residual FVIII Levels ≤ 1 IU/dL and Pre-existing Antibodies Against AAV5

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

Version: 1.0

Date: 11 March 2019

1.0 INTERIM SAP SYNOPSIS

TITLE OF STUDY: A Phase 1/2 Safety, Tolerability, and Efficacy Study of BMN 270, an Adeno-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII in Hemophilia A Patients with Residual FVIII Levels ≤ 1 IU/dL and Pre-existing Antibodies Against AAV5

PROTOCOL NUMBER: 270-203

STUDY OBJECTIVES, DESIGN, DATA ACCESS PLAN, AND INTERIM ANALYSIS

The primary objective of the study is to assess the safety of a single intravenous administration of BMN 270 in severe HA subjects with pre-existing antibody to AAV5 vector capsid, including development of FVIII neutralizing antibody. Secondary objectives of the study are:

- to assess the efficacy of BMN 270 defined as FVIII activity at or above 5 IU/dL at Week 26
- to assess the impact of BMN 270 on usage of exogenous FVIII replacement therapy,
- to assess the impact of BMN 270 on number of bleeding episodes requiring exogenous FVIII therapy,
- to evaluate the pharmacodynamics of FVIII expression following IV infusion of BMN 270
- to assess the impact of BMN 270 on patient-reported outcomes (PROs).

This is a Phase 1/2, single-arm, open-label study in severe HA patients (FVIII ≤ 1 IU/dL), with a history of at least 150 exposure days to FVIII concentrates/cryoprecipitates, with pre-existing antibodies to the AAV5 vector capsid as measured by total antibody [TAb] assay. Approximately 10 subjects may be enrolled at 2-3 sites in 2 cohorts (5 subjects in each cohort) and will receive a single dose of 6E13 vg/kg BMN 270 as an IV infusion. Subjects in Cohort 1 will have a Screening AAV5 TAb titer ≤ 500, while subjects in Cohort 2 will have a Screening AAV5 TAb titer > 500. Choosing a titer cutoff of 500 reflects the observed distribution of existing titer data with the BioMarin titer assay seen to date.

The Data Review Board (DRB) will consist of the Principal Investigators and Sponsor's Medical Monitor, as well as hemophilia expert advisors experienced in the conduct and evaluation of safety and efficacy parameters from 270-201. The DRB will review available safety and efficacy data throughout the study and provide recommendations based on their review (Protocol Figure 2 represents one dosing schedule scenario).

Subjects will be dosed sequentially in Cohort 1 or Cohort 2, based on the results of their Screening AAV5 TAb titers. Subjects in Cohort 2 can be dosed after a minimum of 3 and a maximum of 5 subjects have been dosed in Cohort 1 and had their safety and efficacy data (from a minimum of 6 weeks post-infusion) reviewed. FVIII activity ≥ 5% after six weeks post-infusion is expected to be the earliest differentiating time point for the majority of subjects dosed with 6E13 vg/kg who later achieved normal FVIII activity levels, compared with the one subject who had a slightly lower response, based on data from 270-201. Up to 6 weeks post-infusion will provide an appropriate timeframe to evaluate the

guidance on proceeding from Cohort 1 to Cohort 2 and completion of each cohort will be based on DRB evaluation of safety and efficacy in treated subjects, with the following triggers that may potentially pause further enrollment:

- any related SAE;
- any related AE with a severity > CTCAE Grade 3; or
- FVIII activity < 5% in at least 2/3 subjects after a minimum of 6 weeks post-BMN 270 infusion.

Following a temporary halt of enrolment, the DRB may approve resumption of enrolment in either cohort at a later date at its discretion based on further analysis of accumulating data.

Dosing will be administered at a qualified infusion site, and subjects will be monitored for at least 24 hours post-infusion for any immediate hypersensitivity or adverse drug reaction. In case of suspected hypersensitivity or adverse drug reaction, safety assessments, in addition to physical examination and vital signs, will be performed; details may be found in the protocol.

Data from 270-201 suggest that achievement of therapeutic FVIII levels ≥ 5 I U/dL occurs approximately 4 weeks after BMN 270 infusion, although the FVIIII PD in AAV+ subjects is unknown and requires close monitoring. As such, in order to provide adequate FVIII protection while subjects are projected to reach clinically relevant FVIII levels ≥ 5 IU/dL, prior FVIII prophylaxis for each subject will be continued at the discretion of the DRB based on individual subject status and data review or when FVIII activity has reached at least 5 IU/dL. In subjects who experience recurring bleeding episodes, the Investigator and Medical Monitor will discuss whether to resume prior FVIII prophylaxis.

The study analysis will be performed after all subjects have been followed for 26 weeks post-BMN 270 infusion, with presentation of safety, efficacy, and FVIII PD assessments. After the safety, efficacy, and FVIII PD analyses at 26 weeks post-BMN 270 infusion, long-term safety and efficacy will be assessed in all subjects for up to a total of 5 years post-infusion. During the trial, additional subjects may be recruited into each cohort at any time, if deemed necessary by the DRB.

An interim analysis is planned in order to support a filing of application for marketing approval of BMN 270. Due to the expected small number of enrolled subjects, the data will be listed, not summarized.

INTERIM ANALYSIS POPULATIONS

As mentioned above, an interim analysis is planned in order to support a filing of application for marketing approval of BMN 270. The data available for analysis will include baseline data and safety data.

Intention-to-treat (ITT) Population: all subjects who have received BMN 270 infusion at the time of the interim analysis (regardless of follow-up duration)

Data listings will be provided for ITT population.

ENDPOINTS AND ANALYSES:

Primary and secondary efficacy endpoints and analyses:

Efficacy analyses will not be performed for this interim analysis.

Safety endpoints and analyses:

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 hematology)
- Change in vital signs
- Change in physical examination
- Vector shedding (blood, urine, semen, feces, saliva)
- Liver tests (LTs, including ALT, AST, GGT, total bilirubin, and alkaline phosphatase)
- Immune response to FVIII transgene product and AAV5 vector capsid

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

For this interim analysis, all safety endpoints will be provided in data listings; no tabular summaries will be generated.

2.0 TABLE OF CONTENTS

3.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AAV	Adeno-associated virus
ABR	Annualized bleeding rate
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
APTT	Activated partial thromboplastin time
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical
BPV	BioMarin Pharmacovigilance
BU	Bethesda Unit
CI	Confidence interval
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T lymphocytes
DILI	Drug-Induced Liver Injury
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EOSI	Events of special interest
ETV	Early termination visit
FDA	Food and Drug Administration
FVIII	Coagulation factor VIII
FXa	Coagulation factor Xa
GCP	Good Clinical Practice
HA	Hemophilia A

HAART	Highly active antiretroviral therapy
hFVIII	Human coagulation factor VIII
HLT	High Level Term
ICH	International Conference on Harmonisation
IV	Intravenous
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantitation
LOCF	Last observation carried forward
LS	Least Squares
MedDRA	Medical Dictionary for Regulatory Activities
NAb	Neutralizing antibody
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PP	Per-protocol
PRO	Patient reported outcome
PT	Preferred term
QoL	Quality of life
rhFVIII	Recombinant human FVIII protein
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDTM	Study Data Tabulation Model
SE	Standard error
SFU	Spot-forming units
SOC	System organ class
TAb	Total antibody
TEAE	Treatment-emergent adverse event
TI	Transduction Inhibition
TLGs	Tables, listings, and graphs

VAS	Visual analog scale
vg	Vector genomes
WHO	World Health Organization

4.0 INTRODUCTION

This document describes the statistical methods to be implemented in the interim analysis of data collected under clinical study protocol 270-203, "A Phase 1/2 Safety, Tolerability, and Efficacy Study of BMN 270, an Adeno-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII in Hemophilia A Patients with Residual FVIII Levels ≤ 1 IU/dL and Pre-existing Antibodies Against AAV5" (Amendment 1, 05 October 2018). The Interim SAP contains definitions of analysis populations, derived variables, and statistical methods for the analyses of safety for the interim analysis, which is planned in order to support a filing of application for marketing approval of BMN 270.

The primary objective of the study is to assess the safety of a single intravenous administration of BMN 270 in severe HA subjects with pre-existing antibody to AAV5 vector capsid, including development of FVIII neutralizing antibody. Secondary objectives of the study are:

- to assess the efficacy of BMN 270 defined as FVIII activity at or above 5 IU/dL at Week 26
- to assess the impact of BMN 270 on usage of exogenous FVIII replacement therapy, number of bleeding episodes requiring exogenous FVIII therapy, and patient-reported outcomes (PROs), and
- to evaluate the pharmacodynamics of FVIII expression following IV infusion of BMN 270.

This is a Phase 1/2, single-arm, open-label study in severe HA patients (FVIII ≤ 1 IU/dL), with a history of at least 150 exposure days to FVIII concentrates/cryoprecipitates, with pre-existing antibodies to the AAV5 vector capsid as measured by total antibody [TAb] assay. Approximately 10 subjects may be enrolled at 2-3 sites in 2 cohorts (5 subjects in each cohort) and will receive a single dose of 6E13 vg/kg BMN 270 as an IV infusion. Subjects in Cohort 1 will have a Screening AAV5 TAb titer ≤ 500, while subjects in Cohort 2 will have a Screening AAV5 TAb titer > 500. Choosing a titer cutoff of 500 reflects the observed distribution of existing titer data with the BioMarin titer assay seen to date.

The Data Review Board (DRB) will consist of the Principal Investigators and Sponsor's Medical Monitor, as well as hemophilia expert advisors experienced in the conduct and evaluation of safety and efficacy parameters from 270-201. The DRB will review available safety and efficacy data throughout the study and provide recommendations based on their review (one dosing schedule scenario is represented in Protocol Figure 2).

Subjects will be dosed sequentially in Cohort 1 or Cohort 2, based on the results of their Screening AAV5 TAb titers. Subjects in Cohort 2 can be dosed after a minimum of 3 and a maximum of 5 subjects have been dosed in Cohort 1 and had their safety and efficacy data (from a minimum of 6 weeks post-infusion) reviewed. FVIII activity ≥ 5% after six weeks post-infusion is expected to be the earliest differentiating time point for the majority of subjects dosed with 6E13 vg/kg who later achieved normal FVIII activity levels, compared with the one subject who had a slightly lower response, based on data from 270-201. Up to 6 weeks post-infusion will provide an appropriate timeframe to evaluate the development of any potential delayed hypersensitivity reaction (e.g., serum sickness).

Guidance on proceeding from Cohort 1 to Cohort 2 and completion of each cohort will be based on DRB evaluation of safety and efficacy in treated subjects, with the following triggers that may potentially pause further enrollment:

- any related SAE;
- any related AE with a severity > CTCAE Grade 3; or
- FVIII activity < 5% in at least 2/3 subjects after a minimum of 6 weeks post-BMN 270 infusion.

Following a temporary halt of enrolment, the DRB may approve resumption of enrolment in either cohort at a later date at its discretion based on further analysis of accumulating data.

Dosing will be administered at a qualified infusion site, and subjects will be monitored for at least 24 hours

post-infusion for any immediate hypersensitivity or adverse drug reaction. In case of suspected hypersensitivity or adverse drug reaction, safety assessments, in addition to physical examination and vital signs, will be performed; details may be found in the protocol.

Data from 270-201 suggest that achievement of therapeutic FVIII levels ≥ 5 IU/dL occurs approximately 4 weeks after BMN 270 infusion, although the FVIIII PD in AAV+ subjects is unknown and requires close monitoring. As such, in order to provide adequate FVIII protection while subjects are projected to reach clinically relevant FVIII levels ≥ 5 IU/dL, prior FVIII prophylaxis for each subject will be continued at the discretion of the DRB based on individual subject status and data review or when FVIII activity has reached at least 5 IU/dL. In subjects who experience recurring bleeding episodes, the Investigator and Medical Monitor will discuss whether to resume prior FVIII prophylaxis.

The study analysis will be performed after all subjects have been followed for 26 weeks post-BMN 270 infusion, with presentation of safety, efficacy, and FVIII PD assessments. After the safety, efficacy, and FVIII PD analyses at 26 weeks post-BMN 270 infusion, long-term safety and efficacy will be assessed in all subjects for up to a total of 5 years post-infusion. During the trial, additional subjects may be recruited into each cohort at any time, if deemed necessary by the DRB.

An interim analysis is planned in order to support a filing of application for marketing approval of BMN 270.

5.0 GENERAL ANALYSIS CONSIDERATIONS

Safety variables will be provided in data listings; no tabular summaries will be generated.

5.1 Interim Analysis Populations

As mentioned above, an interim analysis is planned in order to support a filing of application for marketing approval of BMN 270. Due to the expected small number of enrolled subjects, the data will be listed, not summarized.

Intention-to-treat (ITT) Population: all subjects who have received BMN 270 infusion at the time of the interim analysis (regardless of follow-up duration)

Data listings will be provided for ITT population.

5.2 Treatment Group Presentation

Not applicable for this interim analysis, which is comprised of data listings only.

5.3 Study Day Derivation

Study day is assigned as follows:

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

5.5 Baseline Value

The baseline values are calculated using data during the one year prior to enrollment for the following endpoints:

- annualized utilization of exogenous FVIII replacement therapy,

- the annualized number of treated bleeding episodes,

The baseline values of other assessments are defined as the last available measurement prior to the administration of investigational product.

5.6 Handling of Dropouts and Missing Data

If a subject withdraws from the study prematurely, the subject will be asked to complete an Early Termination Visit (ETV), the data from which will be included in data listings for this interim analysis.

Missing dates or partially missing dates will be imputed conservatively for concomitant medications and adverse events (AEs) to ensure that an AE is considered treatment emergent when possible and the duration is the longest possible duration.

Other missing data will not be imputed unless otherwise stated.

6.0 SUBJECT DISPOSITION

A data listing will present for each subject whether the Week 26 visit was completed and whether the Week 52 visit was completed.

7.0 DISCONTINUATION AND COMPLETION

For subjects who prematurely discontinue study participation, a data listing will present for each subject the date of exit from the study and the reason for exit from the study.

8.0 PROTOCOL DEVIATIONS

The trial's Study Specific Guideline for Managing Protocol Deviations defines protocol deviations, including whether they are minor or major. A data listing of protocol deviations will be provided.

9.0 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Subject demographic and baseline characteristics to be provided in data listings include

- age (year)
- sex (Female/Male)
- ethnicity
- race
- height (cm)
- weight (kg)
- BMI (kg/m^2)
- baseline disease characteristics including
    - date of diagnosis of hemophilia A
    - time since diagnosis of hemophilia A (year)
    - type of FVIII treatment for hemophilia A (prophylaxis/on-demand)
    - any history of FVIII inhibitor (Yes/No/Unknown)
    - date of assessment and results for FVIII genotyping
    - any target joints/bleeding sites (Yes/No)

  - motion limitation for target joint/bleeding site (Yes/No)
  - surgery/synovectomy on target joint/bleeding site (Yes/No)
  - ambulatory assist device requirement (Yes/No)
- baseline FVIII activity (IU/dL)
- baseline annualized utilization (IU/kg) of exogenous FVIII replacement therapy
- baseline ABR (bleeds/year)

10.0 MEDICAL HISTORY

Medical history will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) at the time of coding. Medical history will be provided in a data listing. The following targeted medical history will be provided in a separate data listing:

- history of exposure to hepatitis B (Yes/No) and current infection status (Yes/No)
- history of exposure to hepatitis C (Yes/No) and current infection status (Yes/No)
- history of liver disease (Yes/No)
  - if Yes: liver biopsy (Yes/No) and findings; liver imaging (Yes/No), type, and findings
- history of HIV (Yes/No)
  - if Yes: current CD4 count, current viral load, and whether patient is on HAART

11.0 PRIOR AND CONCOMITANT MEDICATIONS/PROCEDURES

Prior and concomitant medications are defined as follows:

- prior medication—any medication taken within 30 days prior to screening;
- concomitant medication—any medication taken after initiation of the investigational product.

All medications will be coded using the current version of the World Health Organization Drug (WHO Drug) Dictionary. Prior and concomitant medications will be provided in a data listing.

Corticosteroid usage including type (i.e., whether for therapeutic or prophylactic purpose), duration, dosage time to initiation of treatment, and duration of treatment will be provided in a data listing.

12.0 EXTENT OF EXPOSURE TO INVESTIGATIONAL PRODUCT

Each subject will receive a single intravenous infusion of BMN 270, and the volume of infusion will depend on subject's weight. A data listing of drug exposure will be provided.

13.0 EFFICACY EVALUATIONS

Efficacy analyses will not be performed for this interim analysis.

14.0 SAFETY EVALUATIONS

Safety will be assessed by adverse event reporting; clinical laboratory assessments, with particular attention to liver function; vital signs assessments; physical examinations; and immunogenicity. No formal statistical testing will be performed or tabular summaries generated, only data listings will be provided. The interim safety analysis will be based on ITT populations, with available data up to the interim data cutoff.

14.1 Adverse Events

A TEAE is defined as any AE that newly appeared or worsened in severity following initiation of

investigational product administration. Adverse events will be coded in accordance with Medical Dictionary for Regulatory Activities (MedDRA). TEAE will be flagged in listings.

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

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

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

- All bleeding events and suspected bleeding events which meet one or more of the criteria for being serious (refer to the Protocol Section 10.2) should be reported as serious adverse events (whether or not they are bleeding events that are normal sequelae of hemophilia, and whether or not they required exogenous FVIII as treatment).

The study AE reporting period is as follows: After informed consent but prior to initiation of study drug, only SAEs associated with any protocol-imposed interventions will be reported. After informed consent is obtained and following infusion of study drug, the reporting period for all non-serious AEs and SAEs begins and continues for approximately 5 years or until study discontinuation/termination, whichever is longer.

If the onset date or end date of an AE is partial, the same imputation rules described in Section 5.06 will be applied.

14.1.1 All Adverse Events

All AEs will be provided in a data listing, including system organ class (SOC) and preferred term (PT).

14.1.2 Drug-Related Adverse Events

The AE listing will include assessment by the investigator(s) as to whether the AE was related to investigational product (i.e., an ADR).

14.1.3 Deaths and Serious Adverse Events

Serious adverse events will be provided in a data listing, including assessment by the investigator(s) as to whether the SAE was related to investigational product (i.e., a serious ADR). Deaths (i.e., SAEs resulting in death) will be provided in a separate data listing.

14.1.4 Adverse Events Causing Early Discontinuation

AEs resulting in discontinuation of study will be presented in a data listing.

14.1.5 Events of Interest

The following events of interest, which include EOSI defined in the protocol, will be provided in a data listing for each type of EOSI.

Table 1: Sponsor-defined Events of Special Interest

Name of EOSI	Definition
ALT elevations reported as EOSIs	• Reported as EOSIs with AE preferred term = "Alanine aminotransferase increased"
AEs of liver dysfunction	• MedDRA search strategy ○ High level term (HLT) = "Liver function analyses"
Potential Hy's law cases	• ALT or AST ≥ 3x ULN and serum TBL > 2x ULN • Assessments of ALT/AST and TBL must be on the same day
Infusion related reactions	Any AE occurring during BMN 270 infusion or up to 48 hours post-infusion[a]
Systemic hypersensitivity	• MedDRA search strategy ○ Hypersensitivity (SMQ) – narrow scope • Occurring during BMN 270 infusion or up to 48 hours post-infusion[a]
Anaphylactic or anaphylactoid reactions	• MedDRA search strategy ○ Anaphylactic reaction (SMQ) – algorithmic • Occurring during BMN 270 infusion or up to 48 hours post-infusion[a]
Thromboembolic events	• MedDRA search strategy ○ Embolic and thrombotic events (SMQ)
AEs suggestive of thromboembolic events	• See **Appendix** for list of AE preferred terms • In the time periods FVIII activity levels > 150%
Development of anti-FVIII neutralizing antibodies	Reported as EOSIs with AE preferred term = "Anti factor VIII antibody positive"

[a] If the number of hours post-infusion cannot be determined, AEs that start two days after the infusion day are excluded.

14.2 Clinical Laboratory Tests

Clinical laboratory tests include blood chemistry, hematology, urine tests, and coagulation will be presented in data listings, including the CTCAE v4.03 grade.

Liver tests by central labs will be assessed on a regular basis, as detailed in the protocol. ALT elevations including baseline ALT, time from infusion to ALT above ULN, time from infusion to ALT above 1.5xULN (and 3xULN, if applicable), peak ALT level, and duration of ALT elevation, will be provided in a data listing.

In addition, incidences of potential drug-induced liver injury (DILI) that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law, will be provided in a data listing.

14.3 Vital Signs and Physical Examination

Vital signs variables include systolic blood pressure, diastolic blood pressure, heart rate, respiration rate, and temperature. Vital signs will be provided in a data listing. Physical examinations will include assessments of general appearance; head, eyes, ears, nose, and throat; the cardiovascular, dermatologic, lymphatic, respiratory, gastrointestinal, genitourinary, musculoskeletal, and neurologic systems. Physical examination results (normal or abnormal) will be provided in a data listing.

14.4 Electrocardiogram and Liver Ultrasound

Electrocardiogram (ECG) and liver ultrasound are performed at the Screening visit with additional evaluations to be performed if clinically indicated during the study. Test results (normal, abnormal, unknown) will be provided in data listings.

14.5 Viral Shedding

Viral shedding will be extensively studied at Baseline, Day 2, Day 4, Day 8, Week 2, Week 3, Week 4, Week 6, Week 8, Week 12, Week 16, Week 20, Week 24, Week 26, every 4 weeks between Weeks 32-52, every 4 weeks (during Year 2), and every 6 weeks (during Years 3-5), until at least 3 consecutive negative results are obtained. Body fluids including blood, saliva, semen, urine and stool will be tested by polymerase chain reaction (PCR) at the time points. Testing of semen will continue at least through Week 12, even if 3 consecutive negative results have been recorded in that compartment prior to that time point. Subjects who have not had 3 consecutive negative semen samples by Week 26 should continue to have PCR testing in semen every 4 weeks until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor).

Viral shedding will be provided in a data listing.

15.0 IMMUNOGENICITY ASSESSMENT

Assays to detect pre-existing immunogenicity specific for AAV5, including plasma derived inhibitors of transduction (transduction inhibition or TI) and total antibody (TAb) assays, will be tested at the Screening visit before BMN 270 infusion is given and at post-baseline visits according to the protocol's schedule of events. Test results (negative and positive with titer) will be provided in data listings.

Two assays are in place to determine immunogenicity to the human FVIII transgene product. The first is a total antibody (TAb) assay to detect binding antibodies in patient plasma directed against human FVIII and is reported as negative or positive with titer. The second is to evaluate neutralizing antibodies (NAb) capable of interfering with FVIII activity (FVIII Inhibitors) and is determined using the Bethesda assay with Nijmegen modification. This assay is reported out in Bethesda Units (BU), with a value of <0.6 considered negative. Both assays will be performed on patient plasma samples obtained at the screening visit, and at post-baseline visits according to the protocol's schedule of events. Test results will be provided in data listings.

Cellular immunity in the form of cytotoxic T lymphocytes (CTL) will be evaluated by Interferon-gamma (IFN-γ) ELISpot assay of peripheral blood mononuclear cells (PBMC). PBMC will be stimulated with overlapping peptide pools derived from the AAV5 capsid protein or human FVIII protein sequences to evaluate IFN-g secretion by CTL targeting both the AAV5 capsid and the FVIII transgene product. Cellular immunity will be evaluated at baseline and at post-infusion visits according to the protocol's schedule of events and is reported as spot forming units (SFU) per 10^6 PBMC. A data listing will be generated reporting the number of SFU 10^6 PBMC for each peptide pool and control (positive and negative) stimulation for each patient at each study visit tested.

16.0 CLINICAL PHARMACOLOGY

If applicable for this interim analysis, clinical pharmacology analyses will be specified in a separate clinical pharmacology interim analysis plan.

17.0 REFERENCES

Den Uijl, IE, Mauser Bunschoten, EP, Roosendaal, G, Schutgens, RE et al. Clinical severity of haemophilia A: does the classification of the 1950s still stand? Haemophilia 17[6], 849-853. 2011.

ICH, E9. Statistical principles for clinical trials. 1998.

18.0 SUMMARY OF CHANGES TO STUDY SAP

Version		Affected Section(s)	Summary of Revisions
Number	Date		
1.0	11MAR2019		Initial version

19.0 APPENDICES

19.1 Preferred terms suggestive of thromboembolic events

confusional state (10010305)
muscular weakness (10028372)
swelling (100426740)
peripheral swelling-10030124)
odema Peripheral (10048959)
jaundice (10023126)
urine output decreased (10059895)
pain in extremity (10033425)
erythema (10015150)
dyspnea (10013968)
chest pain (10008479)
chest discomfort (10008469)
tachycardia (10043071)
haemoptysis (10018964)
presyncope (10026653)
headache (10019211)
hypoaesthesia (10020937)
eye pain (10015958)
eye swelling (10015967)
visual impairment (10047571)
visual acuity reduced (10047531)

BIOMARIN

SART Document Approval Form

Study name: 270-203

Overview

Purpose (Check only 1):

- ☐ Final draft SAP
- ☐ Revision(s) to the final draft SAP
- ☑ Final SAP
- ☐ Amendment(s) to the final SAP
- ☐ The TOC of TLGs defined by the SAP
- ☐ TLG mockups and specifications defined by a SAP
- ☐ Revision(s) to the TLG mockups and specifications document after its approval, determined by the Biostatistican to require SART approval
- ☐ Request(s) for major changes to mockups and specifications after review of TLG outputs produced for the Dry Run
- ☐ Other:

Comments

Approval

DocuSigned by:

Biostat PI __/__/____ dd MON yyyy

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Statist PI __/__/____ his document dd MON yyyy

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Clinical PI __/__/____ s document dd MON yyyy

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BIOMARIN®

INTERIM ANALYSIS PLAN

Protocol Number:	270-203
Study Title:	A Phase 1/2 Safety, Tolerability, and Efficacy Study of BMN 270, an Adeno-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII in Hemophilia A Patients with Residual FVIII Levels ≤ 1 IU/dL and Pre-existing Antibodies Against AAV5
Sponsor:	BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949
Version:	2.0
Date:	25 January 2021

BIOMARIN	Study 270-203 Interim Analysis Plan

1 INTERIM SAP SYNOPSIS

TITLE OF STUDY: A Phase 1/2 Safety, Tolerability, and Efficacy Study of BMN 270, an Adeno-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII in Hemophilia A Patients with Residual FVIII Levels ≤ 1 IU/dL and Pre-existing Antibodies Against AAV5
PROTOCOL NUMBER: 270-203
STUDY OBJECTIVES, DESIGN, DATA ACCESS PLAN, AND INTERIM ANALYSIS The primary objective of the study is to assess the safety of a single intravenous administration of BMN 270 in severe HA subjects with pre-existing antibody to AAV5 vector capsid, including development of FVIII neutralizing antibody. Secondary objectives of the study are: to assess the efficacy of BMN 270 defined as FVIII activity at or above 5 IU/dL at Week 26 to assess the impact of BMN 270 on usage of exogenous FVIII replacement therapy, to assess the impact of BMN 270 on number of bleeding episodes requiring exogenous FVIII therapy, to evaluate the pharmacodynamics of FVIII expression following IV infusion of BMN 270 to assess the impact of BMN 270 on patient-reported outcomes (PROs). This is a Phase 1/2, single-arm, open-label study in severe HA patients (FVIII ≤ 1 IU/dL), with a history of at least 150 exposure days to FVIII concentrates/cryoprecipitates, with pre-existing antibodies to the AAV5 vector capsid as measured by total antibody [TAb] assay. Approximately 10 subjects may be enrolled at 5-6 sites in 2 cohorts (5 subjects in each cohort) and will receive a single dose of 6E13 vg/kg BMN 270 as an IV infusion. Subjects in Cohort 1 will have a Screening AAV5 TAb titer ≤ 500, while subjects in Cohort 2 will have a Screening AAV5 TAb titer > 500. Choosing a titer cutoff of 500 reflects the observed distribution of existing titer data with the BioMarin titer assay seen to date.

An independent Data Monitoring Committee (DMC) will consist of experts in clinical trials, statistics, and hemophilia. The DMC will review available safety and efficacy data throughout the study and provide recommendations based on their review (Protocol Figure 2 represents one dosing schedule scenario). Subjects will be dosed sequentially in Cohort 1 or Cohort 2, based on the results of their Screening AAV5 TAb titers. Subjects in Cohort 2 can be dosed after a minimum of 3 and a maximum of 5 subjects have been dosed in Cohort 1 and had their safety and efficacy data (from a minimum of 6 weeks post-infusion) reviewed. FVIII activity ≥ 5% after six weeks post-infusion is expected to be the earliest differentiating time point for the majority of subjects dosed with 6E13 vg/kg who later achieved normal FVIII activity levels, compared with the one subject who had a slightly lower response, based on data from 270-201. Up to 6 weeks post-infusion will provide an appropriate timeframe to evaluate the development of any potential delayed hypersensitivity reaction (e.g., serum sickness).guidance on proceeding from Cohort 1 to Cohort 2 and completion of each cohort will be based on DMC evaluation of safety and efficacy in treated subjects, with the following triggers that may potentially pause further enrollment:

- any related SAE;
- any related AE with a severity > CTCAE Grade 3; or
- FVIII activity < 5% in at least 2/3 subjects after a minimum of 6 weeks post-BMN 270 infusion.

Following a temporary halt of enrolment, the DMC may approve resumption of enrolment in either cohort at a later date at its discretion based on further analysis of accumulating data.

Dosing will be administered at a qualified infusion site, and subjects will be monitored for at least 24 hours post-infusion for any immediate hypersensitivity or adverse drug reaction. In case of suspected hypersensitivity or adverse drug reaction, safety assessments, in addition to physical examination and vital signs, will be performed; details may be found in the protocol.

Data from 270-201 suggest that achievement of therapeutic FVIII levels ≥ 5 I U/dL occurs approximately 4 weeks after BMN 270 infusion, although the FVIIII PD in AAV+ subjects is unknown and requires close monitoring. As such, in order to provide adequate FVIII protection while subjects are projected to reach clinically relevant FVIII levels ≥ 5 IU/dL, prior FVIII prophylaxis for each subject will be continued at the discretion of the DMC based on individual subject status and data review or when FVIII activity has reached at least 5 IU/dL. In subjects who experience recurring bleeding episodes, the Investigator and Medical Monitor will discuss whether to resume prior FVIII prophylaxis.

BIOMARIN	**Study 270-203 Interim Analysis Plan**

The study analysis will be performed after all subjects have been followed for 26 weeks post-BMN 270 infusion, with presentation of safety, efficacy, and FVIII PD assessments. After the safety, efficacy, and FVIII PD analyses at 26 weeks post-BMN 270 infusion, long-term safety and efficacy will be assessed in all subjects for up to a total of 5 years post-infusion. During the trial, additional subjects may be recruited into each cohort at any time, if deemed necessary by the DMC.

This interim analysis plan is to support a filing of application for marketing approval of BMN 270. Due to the expected small number of enrolled subjects, the data will be listed, not summarized.

INTERIM ANALYSIS POPULATIONS

As mentioned above, this interim analysis is planned in order to support a filing of application for marketing approval of BMN 270. The data available for analysis will include baseline data, efficacy and safety data.

Intention-to-treat (ITT) Population: all subjects who have received BMN 270 infusion at the time of the interim analysis (regardless of follow-up duration)

Data listings will be provided for ITT population.

ENDPOINTS AND ANALYSES:

Primary and secondary efficacy endpoints and analyses:

For this interim analysis, chromogenic FVIII activity levels and bleeding episodes will be provided in data listings; no tabular summaries will be generated.

Safety endpoints and analyses:

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 hematology)
- Change in vital signs
- Change in physical examination
- Vector shedding (blood, urine, semen, feces, saliva)
- Liver tests (LTs, including ALT, AST, GGT, total bilirubin, and alkaline phosphatase)
- Immune response to FVIII transgene product and AAV5 vector capsid

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

For this interim analysis, all safety endpoints will be provided in data listings; no tabular summaries will be generated.

2 TABLE OF CONTENTS

3 LIST OF ABBREVIATIONS

Abbreviation	Definition
AAV	Adeno-associated virus
ABR	Annualized bleeding rate
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
APTT	Activated partial thromboplastin time
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical
BPV	BioMarin Pharmacovigilance
BU	Bethesda Unit
CI	Confidence interval
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T lymphocytes
DILI	Drug-Induced Liver Injury
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EOSI	Events of special interest
ETV	Early termination visit
FDA	Food and Drug Administration
FVIII	Coagulation factor VIII
FXa	Coagulation factor Xa
GCP	Good Clinical Practice
HA	Hemophilia A
HAART	Highly active antiretroviral therapy
hFVIII	Human coagulation factor VIII
HLT	High Level Term
ICH	International Conference on Harmonisation
IV	Intravenous
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantitation

LOCF	Last observation carried forward
LS	Least Squares
MedDRA	Medical Dictionary for Regulatory Activities
NAb	Neutralizing antibody
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PP	Per-protocol
PRO	Patient reported outcome
PT	Preferred term
QoL	Quality of life
rhFVIII	Recombinant human FVIII protein
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDTM	Study Data Tabulation Model
SE	Standard error
SFU	Spot-forming units
SOC	System organ class
TAb	Total antibody
TEAE	Treatment-emergent adverse event
TI	Transduction Inhibition
TLGs	Tables, listings, and graphs
VAS	Visual analog scale
vg	Vector genomes
WHO	World Health Organization

4 INTRODUCTION

This document describes the statistical methods to be implemented in the interim analysis of data collected under clinical study protocol 270-203, "A Phase 1/2 Safety, Tolerability, and Efficacy Study of BMN 270, an Adeno-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII in Hemophilia A Patients with Residual FVIII Levels ≤ 1 IU/dL and Pre-existing Antibodies Against AAV5" (Amendment 3, 24 August 2020). The Interim SAP contains definitions of analysis populations, derived variables, and statistical methods for the analyses of efficacy and safety for the interim analysis, which is planned in order to support a filing of application for marketing approval of BMN 270.

The primary objective of the study is to assess the safety of a single intravenous administration of BMN 270 in severe HA subjects with pre-existing antibody to AAV5 vector capsid, including development of FVIII neutralizing antibody. Secondary objectives of the study are:

- to assess the efficacy of BMN 270 defined as FVIII activity at or above 5 IU/dL at Week 26
- to assess the impact of BMN 270 on usage of exogenous FVIII replacement therapy, number of bleeding episodes requiring exogenous FVIII therapy, and patient-reported outcomes (PROs), and
- to evaluate the pharmacodynamics of FVIII expression following IV infusion of BMN 270.

This is a Phase 1/2, single-arm, open-label study in severe HA patients (FVIII ≤ 1 IU/dL), with a history of at least 150 exposure days to FVIII concentrates/cryoprecipitates, with pre-existing antibodies to the AAV5 vector capsid as measured by total antibody [TAb] assay. Approximately 10 subjects may be enrolled at 5-6 sites in 2 cohorts (5 subjects in each cohort) and will receive a single dose of 6E13 vg/kg BMN 270 as an IV infusion. Subjects in Cohort 1 will have a Screening AAV5 TAb titer ≤ 500, while subjects in Cohort 2 will have a Screening AAV5 TAb titer > 500. Choosing a titer cutoff of 500 reflects the observed distribution of existing titer data with the BioMarin titer assay seen to date.

An independent Data Monitoring Committee (DMC) will consist of experts in clinical trials, statistics, and hemophilia. The DMC will review available safety and efficacy data throughout the study and provide recommendations based on their review (one dosing schedule scenario is represented in Protocol Figure 2).

Subjects will be dosed sequentially in Cohort 1 or Cohort 2, based on the results of their Screening AAV5 TAb titers. Subjects in Cohort 2 can be dosed after a minimum of 3 and a

maximum of 5 subjects have been dosed in Cohort 1 and had their safety and efficacy data (from a minimum of 6 weeks post-infusion) reviewed. FVIII activity ≥ 5% after six weeks post-infusion is expected to be the earliest differentiating time point for the majority of subjects dosed with 6E13 vg/kg who later achieved normal FVIII activity levels, compared with the one subject who had a slightly lower response, based on data from 270-201. Up to 6 weeks post-infusion will provide an appropriate timeframe to evaluate the development of any potential delayed hypersensitivity reaction (e.g., serum sickness).

Guidance on proceeding from Cohort 1 to Cohort 2 and completion of each cohort will be based on DMC evaluation of safety and efficacy in treated subjects, with the following triggers that may potentially pause further enrollment:

- • any related SAE;
- • any related AE with a severity > CTCAE Grade 3; or
- • FVIII activity < 5% in at least 2/3 subjects after a minimum of 6 weeks post-BMN 270 infusion.

Following a temporary halt of enrolment, the DMC may approve resumption of enrolment in either cohort at a later date at its discretion based on further analysis of accumulating data.

Dosing will be administered at a qualified infusion site, and subjects will be monitored for at least 24 hours post-infusion for any immediate hypersensitivity or adverse drug reaction. In case of suspected hypersensitivity or adverse drug reaction, safety assessments, in addition to physical examination and vital signs, will be performed; details may be found in the protocol.

Data from 270-201 suggest that achievement of therapeutic FVIII levels ≥ 5 IU/dL occurs approximately 4 weeks after BMN 270 infusion, although the FVIIII PD in AAV+ subjects is unknown and requires close monitoring. As such, in order to provide adequate FVIII protection while subjects are projected to reach clinically relevant FVIII levels ≥ 5 IU/dL, prior FVIII prophylaxis for each subject will be continued at the discretion of the DMC based on individual subject status and data review or when FVIII activity has reached at least 5 IU/dL. In subjects who experience recurring bleeding episodes, the Investigator and Medical Monitor will discuss whether to resume prior FVIII prophylaxis.

The study analysis will be performed after all subjects have been followed for 26 weeks post-BMN 270 infusion, with presentation of safety, efficacy, and FVIII PD assessments. After the safety, efficacy, and FVIII PD analyses at 26 weeks post-BMN 270 infusion, long-term safety and efficacy will be assessed in all subjects for up to a total of 5 years post-infusion. During the trial, additional subjects may be recruited into each cohort at any time, if deemed necessary by the DMC.

5 GENERAL ANALYSIS CONSIDERATIONS

Efficacy and Safety variables will be provided in data listings; no tabular summaries will be generated.

5.1 Interim Analysis Populations

This interim analysis is planned in order to support a filing of application for marketing approval of BMN 270. Due to the expected small number of enrolled subjects, the data will be listed, not summarized.

Intention-to-treat (ITT) Population: all subjects who have received BMN 270 infusion at the time of the interim analysis (regardless of follow-up duration)

Data listings will be provided for ITT population.

5.2 Treatment Group Presentation

Not applicable for this interim analysis, which is comprised of data listings only.

5.3 Study Day Derivation

Study day is assigned as follows:

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

5.4 Baseline Value

The baseline values are calculated using data during the one year prior to enrollment for the following endpoints:

- annualized utilization of exogenous FVIII replacement therapy,
- the annualized number of treated bleeding episodes,

The baseline values of other assessments are defined as the last available measurement prior to the administration of investigational product.

5.5 Handling of Dropouts and Missing Data

If a subject withdraws from the study prematurely, the subject will be asked to complete an Early Termination Visit (ETV), the data from which will be included in data listings for this interim analysis.

Missing dates or partially missing dates will be imputed conservatively for concomitant medications and adverse events (AEs) to ensure that an AE is considered treatment emergent when possible and the duration is the longest possible duration.

Other missing data will not be imputed unless otherwise stated.

6 SUBJECT DISPOSITION

A data listing will present for each subject whether the Week 26 visit was completed and whether the Week 52 visit was completed.

7 DISCONTINUATION AND COMPLETION

For subjects who prematurely discontinue study participation, a data listing will present for each subject the date of exit from the study and the reason for exit from the study.

8 PROTOCOL DEVIATIONS

The trial's Study Specific Guideline for Managing Protocol Deviations defines protocol deviations, including whether they are minor or major. A data listing of protocol deviations will be provided.

9 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Subject demographic and baseline characteristics to be provided in data listings include

- age (year)
- sex (Female/Male)
- ethnicity
- race
- height (cm)
- weight (kg)
- BMI (kg/m^2)
- baseline disease characteristics including
    - date of diagnosis of hemophilia A
    - time since diagnosis of hemophilia A (year)
    - type of FVIII treatment for hemophilia A (prophylaxis/on-demand)
    - any history of FVIII inhibitor (Yes/No/Unknown)
    - date of assessment and results for FVIII genotyping
    - any target joints/bleeding sites (Yes/No)
    - motion limitation for target joint/bleeding site (Yes/No)
    - surgery/synovectomy on target joint/bleeding site (Yes/No)
    - ambulatory assist device requirement (Yes/No)
- baseline FVIII activity (IU/dL)
- baseline annualized utilization (IU/kg) of exogenous FVIII replacement therapy
- baseline ABR (bleeds/year)

10 MEDICAL HISTORY

Medical history will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) at the time of coding. Medical history will be provided in a data listing. The following targeted medical history will be provided in a separate data listing:

- history of exposure to hepatitis B (Yes/No) and current infection status (Yes/No)
- history of exposure to hepatitis C (Yes/No) and current infection status (Yes/No)
- history of liver disease (Yes/No)
    - if Yes: liver biopsy (Yes/No) and findings; liver imaging (Yes/No), type, and findings
- history of HIV (Yes/No)
    - if Yes: current CD4 count, current viral load, and whether patient is on HAART

11 PRIOR AND CONCOMITANT MEDICATIONS/PROCEDURES

Prior and concomitant medications are defined as follows:

- prior medication—any medication taken within 30 days prior to screening;
- concomitant medication—any medication taken after initiation of the investigational product.

All medications will be coded using the current version of the World Health Organization Drug (WHO Drug) Dictionary. Prior and concomitant medications will be provided in a data listing.

Corticosteroid usage including type (i.e., whether for therapeutic or prophylactic purpose), duration, dosage time to initiation of treatment, and duration of treatment will be provided in a data listing.

12 EXTENT OF EXPOSURE TO INVESTIGATIONAL PRODUCT

Each subject will receive a single intravenous infusion of BMN 270, and the volume of infusion will depend on subject's weight. A data listing of drug exposure will be provided.

13 EFFICACY EVALUATIONS

For this interim analysis, FVIII activity levels and bleeding episodes will be provided in data listings based on ITT population; no tabular summaries will be generated.

14 SAFETY EVALUATIONS

Safety will be assessed by adverse event reporting; clinical laboratory assessments, with particular attention to liver function; vital signs assessments; physical examinations; and immunogenicity. No formal statistical testing will be performed or tabular summaries generated, only data listings will be provided. The interim safety analysis will be based on ITT populations, with available data up to the interim data cutoff.

14.1 Adverse Events

A TEAE is defined as any AE that newly appeared or worsened in severity following initiation of investigational product administration. Adverse events will be coded in accordance with Medical Dictionary for Regulatory Activities (MedDRA). TEAE will be flagged in listings.

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

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

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

- All bleeding events and suspected bleeding events which meet one or more of the criteria for being serious (refer to the Protocol Section 10.2) should be reported as serious adverse events (whether or not they are bleeding events that are normal sequelae of hemophilia, and whether or not they required exogenous FVIII as treatment).

The study AE reporting period is as follows: After informed consent but prior to initiation of study drug, only SAEs associated with any protocol-imposed interventions will be reported. After informed consent is obtained and following infusion of study drug, the reporting period for all non-serious AEs and SAEs begins and continues for approximately 5 years or until study discontinuation/termination, whichever is longer.

If the onset date or end date of an AE is partial, the same imputation rules described in Section 5.5 will be applied.

14.1.1 All Adverse Events

All AEs will be provided in a data listing, including system organ class (SOC) and preferred term (PT).

14.1.2 Drug-Related Adverse Events

The AE listing will include assessment by the investigator(s) as to whether the AE was related to investigational product (i.e., an ADR).

14.1.3 Deaths and Serious Adverse Events

Serious adverse events will be provided in a data listing, including assessment by the investigator(s) as to whether the SAE was related to investigational product (i.e., a serious ADR). Deaths (i.e., SAEs resulting in death) will be provided in a separate data listing.

14.1.4 Adverse Events Causing Early Discontinuation

AEs resulting in discontinuation of study will be presented in a data listing.

14.1.5 Events of Interest

The following events of interest, which include EOSI defined in the protocol, will be provided in a data listing for each type of EOSI.

Table 1: Sponsor-defined Events of Special Interest

Name of EOSI	Definition
ALT elevations reported as EOSIs	• Reported as EOSIs with AE preferred term = "Alanine aminotransferase increased"
AEs of liver dysfunction	• MedDRA search strategy ○ High level term (HLT) = "Liver function analyses"
Potential Hy's law cases	• ALT or AST ≥ 3x ULN and serum TBL > 2x ULN • Assessments of ALT/AST and TBL must be on the same day
Infusion related reactions	Any AE occurring during BMN 270 infusion or up to 48 hours post-infusion[a]
Systemic hypersensitivity	• MedDRA search strategy ○ Hypersensitivity (SMQ) – narrow scope • Occurring during BMN 270 infusion or up to 48 hours post-infusion[a]
Anaphylactic or anaphylactoid reactions	• MedDRA search strategy ○ Anaphylactic reaction (SMQ) – algorithmic • Occurring during BMN 270 infusion or up to 48 hours post-infusion[a]

Thromboembolic events	• MedDRA search strategy ○ Embolic and thrombotic events (SMQ)
AEs suggestive of thromboembolic events	• See **Appendix** for list of AE preferred terms • In the time periods FVIII activity levels > 150%
Development of anti-FVIII neutralizing antibodies	Reported as EOSIs with AE preferred term = "Anti factor VIII antibody positive"

[a] If the number of hours post-infusion cannot be determined, AEs that start two days after the infusion day are excluded.

14.2 Clinical Laboratory Tests

Clinical laboratory tests include blood chemistry, hematology, urine tests, and coagulation will be presented in data listings, including the CTCAE v4.03 grade.

Liver tests by central labs will be assessed on a regular basis, as detailed in the protocol. ALT elevations including baseline ALT, time from infusion to ALT above ULN, time from infusion to ALT above 1.5xULN (and 3xULN, if applicable), peak ALT level, and duration of ALT elevation, will be provided in a data listing.

In addition, incidences of potential drug-induced liver injury (DILI) that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law, will be provided in a data listing.

14.3 Vital Signs and Physical Examination

Vital signs variables include systolic blood pressure, diastolic blood pressure, heart rate, respiration rate, and temperature. Vital signs will be provided in a data listing. Physical examinations will include assessments of general appearance; head, eyes, ears, nose, and throat; the cardiovascular, dermatologic, lymphatic, respiratory, gastrointestinal, genitourinary, musculoskeletal, and neurologic systems. Physical examination results (normal or abnormal) will be provided in a data listing.

14.4 Electrocardiogram and Liver Ultrasound

Electrocardiogram (ECG) and liver ultrasound are performed at the Screening visit with additional evaluations to be performed if clinically indicated during the study. Test results (normal, abnormal, unknown) will be provided in data listings.

14.5 Viral Shedding

Viral shedding will be extensively studied at Baseline, Day 2, Day 4, Day 8, Week 2, Week 3, Week 4, Week 6, Week 8, Week 12, Week 16, Week 20, Week 24, Week 26, every 4 weeks between Weeks 32-52, every 4 weeks (during Year 2), and every 6 weeks (during

Years 3-5), until at least 3 consecutive negative results are obtained. Body fluids including blood, saliva, semen, urine and stool will be tested by polymerase chain reaction (PCR) at the time points. Testing of semen will continue at least through Week 12, even if 3 consecutive negative results have been recorded in that compartment prior to that time point. Subjects who have not had 3 consecutive negative semen samples by Week 26 should continue to have PCR testing in semen every 4 weeks until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor).

Viral shedding will be provided in a data listing.

15 IMMUNOGENICITY ASSESSMENT

Assays to detect pre-existing immunogenicity specific for AAV5, including plasma derived inhibitors of transduction (transduction inhibition or TI) and total antibody (TAb) assays, will be tested at the Screening visit before BMN 270 infusion is given and at post-baseline visits according to the protocol's schedule of events. Test results (negative and positive with titer) will be provided in data listings.

Two assays are in place to determine immunogenicity to the human FVIII transgene product. The first is a total antibody (TAb) assay to detect binding antibodies in patient plasma directed against human FVIII and is reported as negative or positive with titer. The second is to evaluate neutralizing antibodies (NAb) capable of interfering with FVIII activity (FVIII Inhibitors) and is determined using the Bethesda assay with Nijmegen modification. This assay is reported out in Bethesda Units (BU), with a value of <0.6 considered negative. Both assays will be performed on patient plasma samples obtained at the screening visit, and at post-baseline visits according to the protocol's schedule of events. Test results will be provided in data listings.

Cellular immunity in the form of cytotoxic T lymphocytes (CTL) will be evaluated by Interferon-gamma (IFN-γ) ELISpot assay of peripheral blood mononuclear cells (PBMC). PBMC will be stimulated with overlapping peptide pools derived from the AAV5 capsid protein or human FVIII protein sequences to evaluate IFN-g secretion by CTL targeting both the AAV5 capsid and the FVIII transgene product. Cellular immunity will be evaluated at baseline and at post-infusion visits according to the protocol's schedule of events and is reported as spot forming units (SFU) per 10^6 PBMC. A data listing will be generated reporting the number of SFU 10^6 PBMC for each peptide pool and control (positive and negative) stimulation for each patient at each study visit tested.

16 CLINICAL PHARMACOLOGY

If applicable for this interim analysis, clinical pharmacology analyses will be specified in a separate clinical pharmacology interim analysis plan.

17 REFERENCES

Den Uijl, IE, Mauser Bunschoten, EP, Roosendaal, G, Schutgens, RE et al. Clinical severity of haemophilia A: does the classification of the 1950s still stand? Haemophilia 17[6], 849-853. 2011.

ICH, E9. Statistical principles for clinical trials. 1998.

18 SUMMARY OF CHANGES TO STUDY SAP

Version		Affected Section(s)	Summary of Revisions
Number	Date		
1.0	11MAR2019		Initial version
2.0	25JAN2021		Updated based on protocol amendment 3. Included efficacy data in scope of analysis.

19 APPENDICES

19.1 Preferred terms Suggestive of Thromboembolic Events

Confusional State (10010305)
Muscular Weakness (10028372)
Swelling (100426740)
Peripheral Swelling-10030124)
Odema Peripheral (10048959)
Jaundice (10023126)
Urine Output Decreased (10059895)
Pain In Extremity (10033425)
Erythema (10015150)
Dyspnea (10013968)
Chest Pain (10008479)
Chest Discomfort (10008469)
Tachycardia (10043071)
Haemoptysis (10018964)
Presyncope (10026653)
Headache (10019211)
Hypoaesthesia (10020937)
Eye Pain (10015958)
Eye Swelling (10015967)
Visual Impairment (10047571)
Visual Acuity Reduced (10047531)

STATISTICAL ANALYSIS PLAN

Protocol Number: 270-203

Study Title: A Phase 1/2 Safety, Tolerability, and Efficacy Study of BMN 270, an Adeno-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII in Hemophilia A Patients with Residual FVIII Levels ≤ 1 IU/dL and Pre-existing Antibodies Against AAV5

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

Version: 1.0

Date: 26 March 2024

BIOMARIN	Study 270-203 Final Statistical Analysis Plan

Approvals

Statistical Analysis Plan

Title: A Phase 1/2 Safety, Tolerability, and Efficacy Study of BMN 270, an Adeno-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII in Hemophilia A Patients with Residual FVIII Levels ≤ 1 IU/dL and Pre-existing Antibodies Against AAV5

Protocol: 270-203, Amendment 4, 04 August 2021

Date: 26 March 2024

Approvals

_____	___/___/___	_____	___/___/___
PI [redacted] PI [redacted] Statistical Science	DD MM YY	PI [redacted], MB BS, PhD PI [redacted] Late-Stage Clinical Development	DD MM YY
_____	___/___/___	_____	___/___/___
PI [redacted] PI [redacted] Data Analytics Science	DD MM YY	PI [redacted] PhD PI [redacted] Late-Stage Clinical Development	DD MM YY
_____	___/___/___	_____	___/___/___
PI [redacted], PhD PI [redacted], Statistical Science	DD MM YY	PI [redacted], MD PI [redacted], Pharmacovigilance	DD MM YY

{See Appended Electronic Signature Pages}

1 FINAL SAP SYNOPSIS

TITLE OF STUDY: A Phase 1/2 Safety, Tolerability, and Efficacy Study of BMN 270, an Adeno-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII in Hemophilia A Patients with Residual FVIII Levels ≤ 1 IU/dL and Pre-existing Antibodies Against AAV5

PROTOCOL NUMBER: 270-203

STUDY OBJECTIVES, DESIGN, DATA ACCESS PLAN, AND INTERIM ANALYSIS

The primary objective of the study is to assess the safety of a single intravenous administration of BMN 270 in severe HA subjects with pre-existing antibody to AAV5 vector capsid, including development of FVIII neutralizing antibody. Secondary objectives of the study are:

- to assess the efficacy of BMN 270 defined as FVIII activity at or above 5 IU/dL at Week 26
- to assess the impact of BMN 270 on usage of exogenous FVIII replacement therapy,
- to assess the impact of BMN 270 on number of bleeding episodes requiring exogenous FVIII therapy,
- to evaluate the pharmacodynamics of FVIII expression following IV infusion of BMN 270
- to assess the impact of BMN 270 on patient-reported outcomes (PROs).

This is a Phase 1/2, single-arm, open-label study in severe HA patients (FVIII ≤ 1 IU/dL), with a history of at least 150 exposure days to FVIII concentrates/cryoprecipitates, with pre-existing antibodies to the AAV5 vector capsid as measured by total antibody [TAb] assay. Approximately 10 subjects may be enrolled at 5-14 sites in 2 cohorts (5 subjects in each cohort) and will receive a single dose of 6E13 vg/kg BMN 270 as an IV infusion. Subjects in Cohort 1 will have a Screening AAV5 TAb titer ≤ 500, while subjects in Cohort 2 will have a Screening AAV5 TAb titer > 500. Choosing a titer cutoff of 500 reflects the observed distribution of existing titer data with the BioMarin titer assay seen to date.

An independent Data Monitoring Committee (DMC) will consist of experts in clinical trials, statistics, and hemophilia. The DMC will review available safety and efficacy data throughout the study and provide recommendations based on their review (Protocol Figure 2 represents one dosing schedule scenario).

Subjects will be dosed sequentially in Cohort 1 or Cohort 2, based on the results of their Screening AAV5 TAb titers. Subjects in Cohort 2 can be dosed after a minimum of 3 and a maximum of 5 subjects have been dosed in Cohort 1 and had their safety and efficacy data (from 1-6 weeks post-infusion) reviewed. FVIII activity ≥ 5% after six weeks post-infusion is expected to be the earliest differentiating time point for the majority of subjects dosed with 6E13 vg/kg who later achieved normal FVIII activity levels, compared with the one subject who had a slightly lower response, based on data from 270-201. Between 1 and 6 weeks post-infusion will provide an appropriate timeframe to evaluate the development of any potential delayed hypersensitivity reaction (e.g., serum sickness).

Guidance on proceeding from Cohort 1 to Cohort 2 and completion of each cohort will be based on DMC evaluation of safety and efficacy in treated subjects, with the following triggers that may potentially pause further enrollment:

- any related SAE;
- any related AE with a severity > CTCAE Grade 3; or
- FVIII activity < 5% in at least 2/3 subjects after a minimum of 6 weeks post-BMN 270 infusion.

Following a temporary halt of enrolment, the DMC may approve resumption of enrolment in either cohort at a later date at its discretion based on further analysis of accumulating data.

Dosing will be administered at a qualified infusion site, and subjects will be monitored for at least 24 hours post-infusion for any immediate hypersensitivity or adverse drug reaction. In case of suspected hypersensitivity or adverse drug reaction, safety assessments, in addition to physical examination and vital signs, will be performed; details may be found in the protocol.

Data from 270-201 suggest that achievement of therapeutic FVIII levels ≥ 5 I U/dL occurs approximately 4 weeks after BMN 270 infusion, although the FVIIII PD in AAV+ subjects is unknown and requires close monitoring. As such, in order to provide adequate FVIII protection while subjects are projected to reach clinically relevant FVIII levels ≥ 5 IU/dL, prior FVIII prophylaxis for each subject will be continued at the discretion of the DMC based on individual subject status and data review or when FVIII activity has reached at least 5 IU/dL. In subjects who experience recurring bleeding episodes, the Investigator and Medical Monitor will discuss whether to resume prior FVIII prophylaxis.

The enrollment of the study was terminated after only three subjects had been enrolled. The decision to terminate the enrollment of Study 270-203 was informed on the FVIII results from the first 3 subjects and followed a DMC review based on the guidance from the protocol. The FVIII activity from all three dosed subjects were < 5% after a minimum of 6 weeks post-BMN 270 infusion.

In order to support a filing of application for marketing approval of BMN 270 based on Study 270 301 interim data, an interim analysis of Study 270-203, which was covered in interim analysis plan version 1 (dated 11 March 2019), was implemented around the same time of the Study 270-301 interim analysis to provide supportive safety data. And to provide ancillary efficacy and safety data to support filing of application for marketing approval of BMN 270 based on Study 270-301 Year 1 data, a second interim analysis covered in interim analysis plan version 2 (dated 25 January 2021) was implemented.

ANALYSIS POPULATIONS

This analysis plan will cover all data collected during Study 270-203 and should be considered final. The data available for analysis will include baseline, subject disposition, BMN 270 administration, concomitant medication, efficacy, and safety data. Due to the small number of enrolled subjects, the data will be listed, not summarized.

Intention-to-treat (ITT) Population: all subjects who have received BMN 270 infusion.

Data listings will be provided for ITT population.

ENDPOINTS AND ANALYSES:

Primary and secondary efficacy endpoints and analyses:

Chromogenic FVIII activity levels over time and bleeding episodes will be provided in data listings; no tabular summaries will be generated. Listings for annualized bleeding rate (ABR), annualized FVIII use and annualized FVIII infusion rate will also be provided.

Tertiary Efficacy Endpoints:

Data listings for following patient-reported outcomes (PROs) will be provided to assess subject quality of life (QoL) during the study:

- Haemo-QoL-A
- EQ-5D-5L
- Haemophilia Activities List (HAL)
- Work Productivity and Activity Impairment plus Classroom Impairment Questions: Hemophilia Specific (WPAI+CIQ:HS)

Safety Endpoints And Analyses:

The following safety outcome measurements will be assessed:

Incidence of adverse events (AEs), including serious AEs (SAEs) and events of special interest (EOSIs)

Change in clinical laboratory tests (serum chemistry and hematology)

Change in vital signs

Change in physical examination findings

Vector shedding (blood, urine, semen, feces, saliva)

Immune response to FVIII transgene product and AAV5 vector capsid

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

All safety endpoints will be provided in data listings; no tabular summaries will be generated.

2 TABLEOF CONTENTS

LIST OF TABLES

3 LIST OF ABBREVIATIONS

Abbreviation	Definition
AAV	Adeno-associated virus
ABR	Annualized bleeding rate
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
APTT	Activated partial thromboplastin time
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical
BPV	BioMarin Pharmacovigilance
BU	Bethesda Unit
CI	Confidence interval
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T lymphocytes
DILI	Drug-Induced Liver Injury
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EOSI	Events of special interest
ETV	Early termination visit
FDA	Food and Drug Administration
FVIII	Coagulation factor VIII
FXa	Coagulation factor Xa
GCP	Good Clinical Practice
HA	Hemophilia A
HAART	Highly active antiretroviral therapy
hFVIII	Human coagulation factor VIII
HLT	High Level Term
HLGT	High Level Group Term
ICH	International Conference on Harmonisation
IV	Intravenous
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantitation
LOCF	Last observation carried forward
LS	Least Squares
MedDRA	Medical Dictionary for Regulatory Activities
NAb	Neutralizing antibody
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction

Abbreviation	Definition
PP	Per-protocol
PRO	Patient reported outcome
PT	Preferred term
QoL	Quality of life
rhFVIII	Recombinant human FVIII protein
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDTM	Study Data Tabulation Model
SE	Standard error
SFU	Spot-forming units
SOC	System organ class
TAb	Total antibody
TEAE	Treatment-emergent adverse event
TI	Transduction Inhibition
TLGs	Tables, listings, and graphs
VAS	Visual analog scale
vg	Vector genomes
WHO	World Health Organization

4 INTRODUCTION

This document describes the statistical methods to be implemented in the final analysis of data collected under clinical study protocol 270-203, "A Phase 1/2 Safety, Tolerability, and Efficacy Study of BMN 270, an Adeno-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII in Hemophilia A Patients with Residual FVIII Levels ≤ 1 IU/dL and Pre-existing Antibodies Against AAV5" (Amendment 4, 04 August 2021). The SAP contains definitions of analysis populations, derived variables, and statistical methods for the analyses of safety for the analyses of baseline, subject disposition, BMN 270 administration, concomitant medication, efficacy and safety data.

The primary objective of the study is to assess the safety of a single intravenous administration of BMN 270 in severe HA subjects with pre-existing antibody to AAV5 vector capsid, including development of FVIII neutralizing antibody. Secondary objectives of the study are:

- to assess the efficacy of BMN 270 defined as FVIII activity at or above 5 IU/dL at Week 26
- to assess the impact of BMN 270 on usage of exogenous FVIII replacement therapy, number of bleeding episodes requiring exogenous FVIII therapy, and patient-reported outcomes (PROs), and
- to evaluate the pharmacodynamics of FVIII expression following IV infusion of BMN 270.

This is a Phase 1/2, single-arm, open-label study in severe HA patients (FVIII ≤ 1 IU/dL), with a history of at least 150 exposure days to FVIII concentrates/cryoprecipitates, with pre-existing antibodies to the AAV5 vector capsid as measured by total antibody [TAb] assay. Approximately 10 subjects may be enrolled at 5-14 sites in 2 cohorts (5 subjects in each cohort) and will receive a single dose of 6E13 vg/kg BMN 270 as an IV infusion. Subjects in Cohort 1 will have a Screening AAV5 TAb titer ≤ 500, while subjects in Cohort 2 will have a Screening AAV5 TAb titer > 500. Choosing a titer cutoff of 500 reflects the observed distribution of existing titer data with the BioMarin titer assay seen to date.

An independent Data Monitoring Committee (DMC) will consist of experts in clinical trials, statistics, and hemophilia. The DMC will review available safety and efficacy data throughout the study and provide recommendations based on their review (one dosing schedule scenario is represented in Protocol Figure 2).

Subjects will be dosed sequentially in Cohort 1 or Cohort 2, based on the results of their Screening AAV5 TAb titers. Subjects in Cohort 2 can be dosed after a minimum of 3 and a maximum of 5 subjects have been dosed in Cohort 1 and had their safety and efficacy data

(from a minimum of 6 weeks post-infusion) reviewed. FVIII activity ≥ 5% after six weeks post-infusion is expected to be the earliest differentiating time point for the majority of subjects dosed with 6E13 vg/kg who later achieved normal FVIII activity levels, compared with the one subject who had a slightly lower response, based on data from 270-201. Up to 6 weeks post-infusion will provide an appropriate timeframe to evaluate the development of any potential delayed hypersensitivity reaction (e.g., serum sickness).

Guidance on proceeding from Cohort 1 to Cohort 2 and completion of each cohort will be based on DMC evaluation of safety and efficacy in treated subjects, with the following triggers that may potentially pause further enrollment:

- any related SAE;
- any related AE with a severity > CTCAE Grade 3; or
- FVIII activity < 5% in at least 2/3 subjects at 6 weeks post-BMN 270 infusion.

Following a temporary halt of enrolment, the DMC may approve resumption of enrolment in either cohort at a later date at its discretion based on further analysis of accumulating data.

Dosing will be administered at a qualified infusion site, and subjects will be monitored for at least 24 hours post-infusion for any immediate hypersensitivity or adverse drug reaction. In case of suspected hypersensitivity or adverse drug reaction, safety assessments, in addition to physical examination and vital signs, will be performed; details may be found in the protocol.

Data from 270-201 suggest that achievement of therapeutic FVIII levels ≥ 5 IU/dL occurs approximately 4 weeks after BMN 270 infusion, although the FVIIII PD in AAV+ subjects is unknown and requires close monitoring. As such, in order to provide adequate FVIII protection while subjects are projected to reach clinically relevant FVIII levels ≥ 5 IU/dL, prior FVIII prophylaxis for each subject will be continued at the discretion of the DMC based on individual subject status and data review or when FVIII activity has reached at least 5 IU/dL. In subjects who experience recurring bleeding episodes, the Investigator and Medical Monitor will discuss whether to resume prior FVIII prophylaxis.

The enrollment of the study was terminated after only three subjects had been enrolled in Cohort 1. The decision to terminate the enrollment of Study 270-203 was informed on the FVIII results from the first 3 subjects and followed a DMC review based on the guidance from the protocol. The FVIII activity from all three dosed subjects were < 5% after a minimum of 6 weeks post-BMN 270 infusion.

Two unplanned interim analyses were previously performed. In order to support a filing of application for marketing approval of BMN 270 based on Study 270-301 interim data, an interim analysis of Study 270-203, which was covered in interim analysis plan version 1 (dated 11 March 2019), was implemented around the same time of the Study 270-301 interim

analysis to provide supportive safety data. And to provide ancillary efficacy and safety data to support filing of application for marketing approval of BMN 270 based on Study 270-301 Year 1 data, a second interim analysis covered in interim analysis plan version 2 (dated 25 January 2021) was implemented.

5 GENERAL ANALYSIS CONSIDERATIONS

Due to the small number of enrolled subjects, efficacy and safety variables will be provided in data listings; no tabular summaries will be generated.

5.1 Analysis Populations

The following population is used:

Intention-to-treat (ITT) Population: all subjects who have received BMN 270 infusion.

Data listings will be provided for ITT population.

5.2 Treatment Group Presentation

Only listings will be provided due to the small number of enrolled subjects.

5.3 Study Day Derivation

Study day is assigned as follows:

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

5.4 Baseline Value

The baseline values are calculated using data during the one year prior to enrollment for the following endpoints:

- annualized utilization of exogenous FVIII replacement therapy,
- the annualized number of treated bleeding episodes,

The baseline values of other assessments are defined as the last available measurement prior to the administration of investigational product.

5.5 Handling of Dropouts and Missing Data

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

Missing dates or partially missing dates will be imputed conservatively for concomitant medications and adverse events (AEs) to ensure that an AE is considered treatment emergent when possible and the duration is the longest possible duration.

Other missing data will not be imputed unless otherwise stated.

6 SUBJECT DISPOSITION

A data listing will present for each subject the date of informed consent, date of enrollment, date of infusion, end of study date, and whether the Week 26 visit was completed and whether the Week 52 visit was completed. The screening information including the screen failure reasons will also be provided in a listing.

7 DISCONTINUATION AND COMPLETION

For subjects who prematurely discontinue study participation, a data listing will present for each subject the date of exit from the study and the reason for exit from the study.

8 PROTOCOL DEVIATIONS

The trial's Study Specific Guideline for Managing Protocol Deviations defines protocol deviations, including whether they are minor or major. A data listing of protocol deviations will be provided.

9 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Subject demographic and baseline characteristics to be provided in data listings include:

- age at enrollment (year)
- sex (Female/Male)
- ethnicity
- race
- height (cm)
- weight (kg)
- BMI (kg/m^2)
- baseline disease characteristics including
    - date of diagnosis of hemophilia A
    - time since diagnosis of hemophilia A (year)
    - type of FVIII treatment for hemophilia A (prophylaxis/on-demand)
    - any history of FVIII inhibitor (Yes/No/Unknown)
    - date of assessment and results for FVIII genotyping
    - any target joints/bleeding sites (Yes/No)
    - motion limitation for target joint/bleeding site (Yes/No)
    - surgery/synovectomy on target joint/bleeding site (Yes/No)
    - ambulatory assist device requirement (Yes/No)
- baseline FVIII activity (IU/dL)
- baseline annualized utilization (IU/kg) of exogenous FVIII replacement therapy
- baseline ABR (bleeds/year) for treated bleeds

10 MEDICAL HISTORY

Medical history will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) at the time of coding. Medical history will be provided in a data listing. The following targeted medical history will be provided in a separate data listing:

- history of exposure to hepatitis B (Yes/No) and current infection status (Yes/No)
- history of exposure to hepatitis C (Yes/No) and current infection status (Yes/No)
- history of liver disease (Yes/No)
    - if Yes: liver biopsy (Yes/No) and findings; liver imaging (Yes/No), type, and findings
- history of HIV (Yes/No)
    - if Yes: current CD4 count, current viral load, and whether patient is on HAART

11 PRIOR AND CONCOMITANT MEDICATIONS/PROCEDURES

Prior and concomitant medications are defined as follows:

- prior medication - any medication taken prior to the initiation of the investigational product and within 30 days prior to screening.;
- concomitant medication - any medication taken after initiation of the investigational product.

All medications will be coded using the current version of the World Health Organization Drug (WHO Drug) Dictionary. Prior and concomitant medications will be provided in a data listing.

Corticosteroid usage including type (i.e., whether for therapeutic or prophylactic purpose), dosage, time to initiation of treatment, and total duration of treatment will be provided in a data listing.

12 EXTENT OF EXPOSURE TO INVESTIGATIONAL PRODUCT

Each subject will receive a single intravenous infusion of BMN 270, and the volume of infusion will depend on subject's weight. A data listing of drug exposure including actual dose (vg/kg), change of dose, rate of dose will be provided.

13 EFFICACY EVALUATIONS

FVIII activity levels over time and bleeding episodes will be provided in data listings based on ITT population; no tabular summaries will be generated.

Listings for annualized bleeding rate (ABR) for treated bleeds, annualized FVIII use and annualized FVIII infusion rate will also be provided.

Annualized bleeding rate (ABR) (counts/yr.)

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

Annualized FVIII use (IU/kg/yr.)

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

Annualized FVIII infusion rate (count/yr.)

$$= \frac{\text{Number of FVIII replacement infusions during calculation period}}{\text{Total number of days during the calculation period}} \times 365.25$$

The calculation period in the above formulas for post-baseline values will be Weeks 1-4, Weeks 5-26, Weeks 5-52, and Weeks 5 and beyond.

Data listings for following patient-reported outcomes (PROs) will be provided to assess subject quality of life (QoL) during the study:

- Haemo-QoL-A
- EQ-5D-5L
- Haemophilia Activities List (HAL)
- Work Productivity and Activity Impairment plus Classroom Impairment Questions: Hemophilia Specific (WPAI+CIQ:HS)

14 SAFETY EVALUATIONS

Safety will be assessed by adverse event reporting; clinical laboratory assessments, with particular attention to liver function; vital signs assessments; physical examinations; and immunogenicity. No formal statistical testing will be performed or tabular summaries generated, only data listings will be provided. The safety analysis will be based on the ITT population.

14.1 Adverse Events

A TEAE is defined as any AE that newly appeared or worsened in severity following initiation of investigational product administration. Adverse events will be coded in accordance with Medical Dictionary for Regulatory Activities (MedDRA). TEAE will be flagged in listings.

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

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

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

- All bleeding events and suspected bleeding events which meet one or more of the criteria for being serious (refer to the Protocol Section 10.2) should be reported as serious adverse events (whether or not they are bleeding events that are normal sequelae of hemophilia, and whether or not they required exogenous FVIII as treatment).

The study AE reporting period is as follows: After informed consent but prior to initiation of study drug, only SAEs associated with any protocol-imposed interventions will be reported. After informed consent is obtained and following infusion of study drug, the reporting period for all non-serious AEs and SAEs begins and continues for approximately 5 years or until study discontinuation/termination, whichever is longer.

If the onset date or end date of an AE is partial, the same imputation rules described in Section 56 will be applied.

14.1.1 All Adverse Events

All AEs will be provided in a data listing, including system organ class (SOC) and preferred term (PT).

14.1.2 Drug-Related Adverse Events

The AE listing will include assessment by the investigator(s) as to whether the AE was related to investigational product (i.e., an ADR).

14.1.3 Deaths and Serious Adverse Events

Serious adverse events will be provided in a data listing, including assessment by the investigator(s) as to whether the SAE was related to investigational product (i.e., a serious ADR). Deaths (i.e., SAEs resulting in death) will be provided in a separate data listing.

14.1.4 Adverse Events Causing Early Discontinuation

AEs resulting in discontinuation of study will be presented in a data listing.

14.1.5 Events of Interest

The following events of interest, which include EOSI defined in the protocol, will be provided in a data listing for each type of EOSI.

Table 1: Sponsor-defined Events of Special Interest

Name of EOSI	Definition
ALT elevations reported as EOSIs	• Reported as EOSIs with AE preferred term = "Alanine aminotransferase increased"
AEs of liver dysfunction	• MedDRA search strategy ○ High level term (HLT) = "Liver function analyses"
Potential Hy's law cases	• ALT or AST ≥ 3x ULN and serum TBL > 2x ULN • Assessments of ALT/AST and TBL must be on the same day
Infusion related reactions	Any AE occurring during BMN 270 infusion or up to 48 hours post-infusion[a]
Systemic hypersensitivity	• MedDRA search strategy ○ Hypersensitivity (SMQ) – narrow scope • Occurring during BMN 270 infusion or up to 48 hours post-infusion[a]
Anaphylactic or anaphylactoid reactions	• MedDRA search strategy ○ Anaphylactic reaction (SMQ) – algorithmic • Occurring during BMN 270 infusion or up to 48 hours post-infusion[a]
Thromboembolic events	• MedDRA search strategy ○ Embolic and thrombotic events (SMQ)

Name of EOSI	Definition
AEs suggestive of thromboembolic events	• See **Appendix** for list of AE preferred terms • In the time periods FVIII activity levels > 150%
Development of anti-FVIII neutralizing antibodies	Reported as EOSIs with AE preferred term = "Anti factor VIII antibody positive"
AEs suggestive of new diagnosis of malignancy (except non-melanoma skin cancer)	• See **Appendix** for list of AE High Level Group Terms (HLGT) • SOC = Neoplasm benign malignant and unspecified (including cysts and polyps)

[a] If the number of hours post-infusion cannot be determined, AEs that start two days after the infusion day are excluded.

14.2 Clinical Laboratory Tests

Clinical laboratory tests include blood chemistry, hematology, urine tests, and coagulation will be presented in data listings, including the CTCAE v4.03 grade.

Liver tests by central labs will be assessed on a regular basis, as detailed in the protocol. ALT elevations including baseline ALT, time from infusion to ALT above ULN, time from infusion to ALT above 1.5xULN (and 3xULN, if applicable), peak ALT level, and total duration of ALT elevation, will be provided in a data listing.

In addition, incidences of potential drug-induced liver injury (DILI) that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law, will be provided in a data listing.

14.3 Vital Signs and Physical Examination

Vital signs variables include systolic blood pressure, diastolic blood pressure, heart rate, respiration rate, and temperature. Vital signs will be provided in a data listing. Physical examinations will include assessments of general appearance; head, eyes, ears, nose, and throat; the cardiovascular, dermatologic, lymphatic, respiratory, gastrointestinal, genitourinary, musculoskeletal, and neurologic systems. Physical examination results (normal or abnormal) will be provided in a data listing.

14.4 Electrocardiogram and Liver Ultrasound

Electrocardiogram (ECG) and liver ultrasound are performed at the Screening visit with additional evaluations to be performed if clinically indicated during the study. Test results (normal, abnormal, unknown) will be provided in data listings.

14.5 Viral Shedding

Viral shedding will be extensively studied at Baseline, Day 2, Day 4, Day 8, Week 2, Week 3, Week 4, Week 6, Week 8, Week 12, Week 16, Week 20, Week 24, Week 26, every

4 weeks between Weeks 32-52, every 4 weeks (during Year 2), and every 6 weeks (during Years 3-5), until at least 3 consecutive negative results are obtained. Body fluids including blood, saliva, semen, urine and stool will be tested by polymerase chain reaction (PCR) at the time points. Testing of semen will continue at least through Week 12, even if 3 consecutive negative results have been recorded in that compartment prior to that time point. Subjects who have not had 3 consecutive negative semen samples by Week 26 should continue to have PCR testing in semen every 4 weeks until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor).

Viral shedding will be provided in a data listing.

15 IMMUNOGENICITY ASSESSMENT

Assays to detect pre-existing immunogenicity specific for AAV5, including plasma derived inhibitors of transduction (transduction inhibition or TI) and total antibody (TAb) assays, will be tested at the Screening visit before BMN 270 infusion is given and at post-baseline visits according to the protocol's schedule of events. Test results (negative and positive with titer) will be provided in data listings.

Two assays are in place to determine immunogenicity to the human FVIII transgene product. The first is a total antibody (TAb) assay to detect binding antibodies in patient plasma directed against human FVIII and is reported as negative or positive with titer. The second is to evaluate neutralizing antibodies (NAb) capable of interfering with FVIII activity (FVIII Inhibitors) and is determined using the Bethesda assay with Nijmegen modification. This assay is reported out in Bethesda Units (BU), with a value of <0.6 considered negative. Both assays will be performed on patient plasma samples obtained at the screening visit, and at post-baseline visits according to the protocol's schedule of events. Test results will be provided in data listings.

Cellular immunity in the form of cytotoxic T lymphocytes (CTL) will be evaluated by Interferon-gamma (IFN-γ) ELISpot assay of peripheral blood mononuclear cells (PBMC). PBMC will be stimulated with overlapping peptide pools derived from the AAV5 capsid protein or human FVIII protein sequences to evaluate IFN- γ secretion by CTL targeting both the AAV5 capsid and the FVIII transgene product. Cellular immunity will be evaluated at baseline and at post-infusion visits according to the protocol's schedule of events and is reported as spot forming units (SFU) per 10^6 PBMC. A data listing will be generated reporting the number of SFU 10^6 PBMC for each peptide pool and control (positive and negative) stimulation for each patient at each study visit tested.

16 CLINICAL PHARMACOLOGY

Clinical pharmacology analyses will not be performed.

17 REFERENCES

Den Uijl, IE, Mauser Bunschoten, EP, Roosendaal, G, Schutgens, RE et al. Clinical severity of haemophilia A: does the classification of the 1950s still stand? Haemophilia 17[6], 849-853. 2011.

ICH, E9. Statistical principles for clinical trials. 1998.

18 SUMMARY OF CHANGES TO STUDY SAP

Version		Affected Section(s)	Summary of Revisions
Number	Date		
1.0	26MAR2024		Initial version

19 APPENDICES

19.1 Preferred terms suggestive of thromboembolic events

confusional state (10010305)	chest discomfort (10008469)
muscular weakness (10028372)	tachycardia (10043071)
swelling (100426740)	haemoptysis (10018964)
peripheral swelling-10030124)	presyncope (10026653)
odema Peripheral (10048959)	headache (10019211)
jaundice (10023126)	hypoaesthesia (10020937)
urine output decreased (10059895)	eye pain (10015958)
pain in extremity (10033425)	eye swelling (10015967)
erythema (10015150)	visual impairment (10047571)
dyspnea (10013968)	visual acuity reduced (10047531)

19.2 High Level Group Terms (HLGT) suggestive of malignant

Breast neoplasms malignant and unspecified (incl nipple)	Miscellaneous and site unspecified neoplasms malignant and unspecified
Endocrine neoplasms malignant and unspecified	Neoplasm related morbidities
Gastrointestinal neoplasms malignant and unspecified	Nervous system neoplasms malignant and unspecified NEC
Haematopoietic neoplasms (excl leukaemias and lymphomas)	Ocular neoplasms
Hepatobiliary neoplasms malignant and unspecified	Plasma cell neoplasms
Leukaemias	Renal and urinary tract neoplasms malignant and unspecified
Lymphomas Hodgkin's disease	Reproductive and genitourinary neoplasms gender unspecified NEC
Lymphomas NEC	Reproductive neoplasms male malignant and unspecified
Lymphomas non-Hodgkin's B-cell	Respiratory and mediastinal neoplasms malignant and unspecified
Lymphomas non-Hodgkin's T-cell	Skeletal neoplasms malignant and unspecified
Lymphomas non-Hodgkin's unspecified histology	Soft tissue neoplasms malignant and unspecified
Mesothelioma	Skin melanomas (excl ocular)
Metastases	

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Every: Approval Task	PI Author Associate Director, Statistical Science PI
Every: Approval Task	PI Functional Representative Senior Manager, Data Analytics Science PI
Every: Approval Task	PI Management Executive Director, Statistical Science PI
Every: Approval Task	PI Management Group Vice President, Late - Stage Clinical Development PI
Every: Approval Task	PI Medical Monitor Director, Clinical Science PI
Every: Approval Task	PI Functional Representative Medical Director PI

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