BIOMARIN®

INTERIM STATISTICAL ANALYSIS PLAN

Protocol Number: 270-302

Study Title: A Phase 3 Open-Label, Single-Arm Study To Evaluate The Efficacy and Safety of BMN 270, an Adeno-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII at a dose of 4E13 vg/kg in Hemophilia A Patients with Residual FVIII Levels ≤ 1 IU/dL Receiving Prophylactic FVIII Infusions

Sponsor: BioMarin Pharmaceutical Inc.
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Version: 2

Date: 17 February 2021

Approvals

Interim Statistical Analysis Plan

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Protocol: 270-302, Amendment 4 (Global), 9 November 2018

Date: 17 February 2021

Approvals

[redacted]

1 INTERIM SAP SYNOPSIS

TITLE OF STUDY: A Phase 3 Open-Label, Single-Arm Study To Evaluate The Efficacy and Safety of BMN 270, an Adeno-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII at a dose of 4E13 vg/kg in Hemophilia A Patients with Residual FVIII Levels ≤ 1 IU/dL Receiving Prophylactic FVIII Infusions

PROTOCOL NUMBER: 270-302

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

The objectives of the study are to assess the efficacy of BMN 270 on FVIII activity, usage of exogenous FVIII replacement therapy, and number of bleeding episodes; patient-reported outcomes (PROs); and to evaluate the long-term safety of BMN 270 following intravenous infusion.

This is a Phase 3, single-arm, open-label study in hemophilia A (HA) patients with residual FVIII levels ≤ 1 IU/dL treated continuously with prophylactic exogenous FVIII for a minimum of one year prior to enrollment. It was planned that subjects would be enrolled at approximately 40 sites worldwide. Approximately 40 adult subjects with severe HA were planned to receive a 4E13 vg/kg dose of BMN 270 as a single intravenous infusion:

- Directly enrolled subjects: The first approximately 5 subjects will enroll in the study with at least 12 months of well-documented high-quality historical data concerning previous bleeding episodes and exogenous FVIII usage.
- Study 270-902 rollover subjects: The rest, approximately 35 subjects, will enroll in the study after having completed approximately 6 months' participation in the BioMarin-sponsored non-interventional study 270-902, in which bleeding and FVIII use data prior to gene therapy will be prospectively collected.

In order to minimize bias and to preserve the scientific and business integrity of the single-arm and open-label study, a data access plan (DAP) was implemented. This document provided guidelines for accessing post-treatment study data and applies to study team members, including personnel from within BioMarin, from external vendors and service providers, from the Data Monitoring Committee (DMC), and from study sites. Role-based access control to study data, both individual patient-level data values as well as aggregated summaries of longitudinal data in an individual patient or across multiple patients, was implemented to minimize potential bias and achieve appropriately controlled decision-making, while preserving operational efficiency. It was enforced by the DAP that individuals who had knowledge of the key efficacy variables (FVIII activity, FVIII usage, and bleeding counts) did not make or influence decisions that would alter the study design or conduct, or the collection or analysis of the key efficacy variables so as to bias the studies' key efficacy results. The data access control has been lifted from Study 270-302 since September 2019 because only one subject was enrolled in the study and enrollment has been terminated.

In addition, an independent DMC, consisting of experts in clinical trials, statistics, and hemophilia, has been convened in order to assure safe and ethical conduct of the clinical trial. The DMC, supported by an independent statistical service provider, have access to all available data, including both safety and efficacy (e.g., FVIII activity), during the study on an ongoing basis.

An interim analysis was planned after the first approximately 20 HIV-negative subjects have completed the Week 26 visit (or have discontinued study participation prior to Week 26). The concept of the interim analysis was to facilitate initiation of regulatory review of the ongoing study in the event that robust improvements (essentially normalization) in Factor VIII activity in a sufficient proportion

of the population are observed. The interim analysis will not be implemented since enrollment of the study has been terminated since only one subject was enrolled

In order to support a filing of application for marketing approval of BMN 270 based on Study 270-301 interim data, an additional interim analysis of Study 270-302, which was covered in interim analysis plan version 1 (dated 24 April 2019), was implemented around the same time of the Study 270-301 interim analysis to provide supportive baseline and safety data.

In order to provide ancillary baseline, 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 is planned; this analysis plan is for this second interim analysis. Additional interim analyses of Study 270-302 may also be performed depending on the amount of additional data accumulated when necessary

INTERIM ANALYSIS POPULATIONS

As mentioned above, in order to support a filing of application for marketing approval of BMN 270 based on Study 270-301 Year 1 data, an interim analysis of Study 270-302 is planned to provide supportive baseline, efficacy and safety data. The following are populations for this interim analysis.

All *Screened Subjects:* all screened subjects in the study.

All *Enrolled Subjects:* all enrolled subjects in the study.

Intention-***to-treat (ITT) Population:*** all enrolled, treated subjects in the study.

Screening status and screen failure reasons will be listed for all screened subjects. [redacted]

ENDPOINTS AND ANALYSES:

Primary and secondary efficacy endpoints and analyses:

Since only one subject was enrolled in the study, no summary tables will be generated and only [redacted]

Safety endpoints and analyses:

[redacted]

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
AST	Aspartate transaminase
BU	Bethesda Unit
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T lymphocytes
DAP	Data access plan
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
FVIII	Coagulation factor VIII
HA	Hemophilia A
hFVIII	Human coagulation factor VIII
HLT	High Level Term
ICH	International Conference on Harmonisation
IV	Intravenous
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
NAb	Neutralizing antibody
PBMC	Peripheral blood mononuclear cells
PRO	Patient reported outcome
QoL	Quality of life
rhFVIII	Recombinant human FVIII protein
SAE	Serious adverse event
SAP	Statistical analysis plan

SFU	Spot-forming units
TAb	Total antibody
TEAE	Treatment-emergent adverse event
TI	Transduction Inhibition
ULN	Upper limit of normal
Vg/kg	Vector genomes per kilogram
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 270-302, "A Phase 3 Open-Label, Single-Arm Study To Evaluate The Efficacy and Safety of BMN 270, an Adeno-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII at a dose of 4E13 vg/kg in Hemophilia A Patients with Residual FVIII Levels ≤ 1 IU/dL Receiving Prophylactic FVIII Infusions" (Global Amendment 4, 09 November 2018). The Interim SAP contains definitions of analysis populations, derived variables, and statistical methods for the analyses of baseline, efficacy and safety data in order to support a filing of application for marketing approval of BMN 270 based on Study 270-301 Year 1 data.

The objectives of the study are to assess the efficacy of BMN 270 on FVIII activity, usage of exogenous FVIII replacement therapy, and number of bleeding episodes; patient-reported outcomes (PROs); and to evaluate the long-term safety of BMN 270 following intravenous infusion.

This is a Phase 3, single-arm, open-label study in hemophilia A (HA) patients with residual FVIII levels ≤ 1 IU/dL treated continuously with prophylactic exogenous FVIII for a minimum of one year prior to enrollment. It was planned that subjects would be enrolled at approximately 40 sites worldwide. Approximately 40 adult subjects with severe HA were planned to receive a 4E13 vg/kg dose of BMN 270 as a single intravenous infusion:

- Directly enrolled subjects: The first approximately 5 subjects will enroll in the study with at least 12 months of well-documented high-quality historical data concerning previous bleeding episodes and exogenous FVIII usage.
- Study 270-902 rollover subjects: The rest, approximately 35 subjects, will enroll in the study after having completed approximately 6 months' participation in the BioMarin-sponsored non-interventional study 270-902, in which bleeding and FVIII use data prior to gene therapy will be prospectively collected.

In order to minimize bias and to preserve the scientific and business integrity of the single-arm and open-label study, a data access plan (DAP) was implemented. This document provided guidelines for accessing post-treatment study data and applies to study team members, including personnel from within BioMarin, from external vendors and service providers, from the Data Monitoring Committee (DMC), and from study sites. Role-based access control to study data, both individual patient-level data values as well as aggregated summaries of longitudinal data in an individual patient or across multiple patients, was implemented to minimize potential bias and achieve appropriately controlled decision-making, while preserving operational efficiency. It was enforced by the DAP that individuals

who had knowledge of the key efficacy variables (FVIII activity, FVIII usage, and bleeding counts) did not make or influence decisions that would alter the study design or conduct, or the collection or analysis of the key efficacy variables so as to bias the study's key efficacy results. The data access control has been lifted from Study 270-302 since September 2019 because only one subject was enrolled in the study and enrollment has been terminated.

In addition, an independent DMC, consisting of experts in clinical trials, statistics, and hemophilia, has been convened in order to assure safe and ethical conduct of the clinical trial. The DMC, supported by an independent statistical service provider, have access to all available data, including both safety and efficacy (e.g., FVIII activity), during the study on an ongoing basis.

An interim analysis was planned after the first approximately 20 HIV-negative subjects have completed the Week 26 visit (or have discontinued study participation prior to Week 26). The concept of the interim analysis was to facilitate initiation of regulatory review of the ongoing study in the event that robust improvements (essentially normalization) in Factor VIII activity in a sufficient proportion of the population are observed. This interim analysis will not be implemented since enrollment of the study has been terminated since only one subject was enrolled.

In order to support a filing of application for marketing approval of BMN 270 based on Study 270-301 interim data, an additional interim analysis of Study 270-302 was implemented around the same time of the Study 270-301 interim analysis to provide supportive baseline and safety data.

In order to provide ancillary baseline, 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 is planned; this analysis plan is for this additional interim analysis. Additional interim analyses of Study 270-302 may also be performed depending on the amount of additional data accumulated when necessary.

5 GENERAL ANALYSIS CONSIDERATIONS

Since only one subject was enrolled in the study, [redacted]

5.1 Interim Analysis Populations

As mentioned above, in order to support a filing of application for marketing approval of BMN 270 based on Study 270-301 interim Year 1 data, an interim analysis of Study 270-302 is planned to provide supportive baseline, efficacy and safety data. The following are populations for this interim analysis.

All Screened Subjects: all screened subjects in the study.

All Enrolled Subjects: all enrolled subjects in the study.

Intention-to-treat (ITT) Population: all enrolled, treated subjects.

Screening status and screen failure reasons will be listed for all screened subjects. Disposition data will be listed for all enrolled subjects. [redacted]

5.2 Treatment Group Presentation

Only listings will be provided since only one subject was enrolled.

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 Visit Windows for Analysis

All data will be summarized by week, wherever applicable. An assessment for a subject will be classified according to the study day of the assessment where it falls within a given window (see Appendix Section 19.1).

For safety endpoints, such as liver tests and vital signs, windows are designated for each scheduled week of visit and centered on a target day; for example, the target day for a Week 4 visit is Study Day 29. If there are two or more assessments within a designated window, the assessment that is closest to the target day will be used for analyses. If the two

closest assessments to the target day are equidistant from the target day, then the mean of the two assessments will be used for analyses unless otherwise specified.

Appendix (Section 19.1) lists the weeks assigned for the analyses of the clinical endpoint assessments and the corresponding range of treatment days (window) during which a visit may have occurred by analysis parameter.

5.5 Baseline Value

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

- annualized utilization of exogenous FVIII replacement therapy
- annualized number of treated bleeding episodes
- baseline ABR for treated bleeds
- baseline ABR for all bleeds

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

[redacted]

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

Screening status and screen failure reasons will be listed for all screened subjects.

7 DISCONTINUATION AND COMPLETION

A listing will be presented to show whether the enrolled subject completed Week 26, and Week 52 and discontinuation reason if the subject permanently discontinue study participation by data cutoff.

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 for ITT population. COVID-19 pandemic related deviations will be flagged in the listing.

9 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

A listing will be provided for the following demographic and baseline characteristics for ITT population:

i. age at enrollment (year)
- age group (>=18-<65, >=65)
- age group (>=18-<30, >=30-<=50, >50)

ii. sex (Female/Male)
iii. ethnicity
iv. race
v. height (cm)
vi. weight (kg)
vii. BMI (kg/m^2)
viii. baseline disease characteristics including
    1. time since diagnosis of hemophilia A (year)
    2. type of FVIII treatment for hemophilia A (prophylaxis/on-demand)
    3. any history of FVIII inhibitor (Yes/No)
    4. FVIII genotyping results
    5. number of target joints
    6. body location of target joints
    7. ambulatory assist device requirement (Yes/No)
ix. history of liver disease (Yes/No)
x. history of hepatitis B (Yes/No)
xi. history of hepatitis C (Yes/No)
xii. history of HIV (Yes/No)
xiii. baseline FVIII activity (IU/dL)
xiv. duration of baseline data collection periods, months
xv. baseline annualized utilization (IU/kg/year) of exogenous FVIII replacement therapy

xvi. baseline annualized number of FVIII infusions (infusions/year)

xvii. baseline ABR (treated bleeds/year)

xviii. baseline ABR (all bleeds/year)

10 MEDICAL HISTORY

Medical history will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) at the time of coding. A listing will be provided for medical history data in ITT population.

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 medication use will be listed for ITT population.

12 EXTENT OF EXPOSURE TO INVESTIGATIONAL PRODUCT

A data listing of drug exposure will be provided for ITT population.

13 EFFICACY EVALUATIONS

[redacted]

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.

14.1 Adverse Events

[redacted] 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).

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 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 treatment, only SAEs associated with any protocol-imposed interventions will be reported. After informed consent is obtained and following the administration of investigational product, the reporting period for all non-serious AEs and SAEs begins and continues for approximately 5 years or until study discontinuation/termination.

[redacted]

If the onset date or end date of an AE is partial, the same imputation rules described in Section 5.0 will be applied.

14.1.1 All Adverse Events

A listing of all AEs will be provided.

14.1.2 Drug-Related Adverse Events

All TEAEs assessed by investigator as investigational product related (i.e., ADRs) will be included in a listing.

14.1.3 Deaths and Serious Adverse Events

A list of subjects who died and all SAEs and SAEs assessed by investigator as investigational product related (i.e., serious ADRs) will be provided.

14.1.4 Adverse Events Causing Early Discontinuation

A list of subjects with the AEs resulting in discontinuation of study will be provided.

14.1.5 Events of Special Interest (EOSIs)

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

- Transaminitis
  - ALT elevations (AE Preferred term: "Alanine aminotransferase increased").
  - AEs of liver dysfunction, defined using the MedDRA search strategy high level term (HLT = "Liver function analyses").
  - Potential Hy's law cases
    - ALT or AST ≥ 3x ULN and serum TBL > 2x ULN
    - Assessments of ALT/AST and TBL must be on the same day

  A listing will be provided.
- Infusion related reaction, Hypersensitivity, Anaphylactic or Anaphylactoid reactions
  - Infusion related reactions, defined as AEs occurring during BMN 270 infusion or up to 48 hours post-infusion[a], will be summarized as follows:

        - Subjects who receive infusion with initial rate of approximately 4 mL/min
        - The rest of the subjects, i.e. subjects who receive infusion with initial rate of 1 mL/min
        - All treated subjects
    - Systemic hypersensitivity (Hypersensitivity [SMQ] - narrow scope), occurring during BMN 270 infusion or up to 48 hours post-infusion[a].
    - Anaphylactic, or anaphylactoid reactions (Anaphylactic reaction [SMQ] – algorithmic), occurring during BMN 270 infusion or up to 48 hours post-infusion[a] – listing only.
- Thromboembolic events:
    - Embolic and thrombotic events (SMQ).
    - AEs suggestive of thromboembolic events: for subjects who have FVIII elevation > 150% any time during study, a listing of clinical terms suggestive of thromboembolic events observed from the time point prior to when FVIII was elevated until FVIII falls below 150%. (The AE preferred terms are listed in Appendix 19.2.)
- Development of anti-FVIII neutralizing antibodies as measured by the Nijmegen modified Bethesda assay (Preferred term: "Anti factor VIII antibody positive", reported as EOSI)

[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. A supportive listing of abnormal test values with CTCAE v4.03 grade 3 or greater will be produced.

Liver tests by central labs will be assessed on a regular basis, as detailed in the protocol. Summaries of ALT elevations including baseline ALT, time from infusion to ALT > ULN, ALT ≥ 3x ULN, ALT ≥ 5x ULN, ALT ≥ 1.5x ULN or (> ULN & > 2x baseline value), peak ALT level, duration of ALT elevation, corticosteroid treatments for ALT elevations including type, dose, time to initiation of treatment, and duration of treatment will be

provided. Correlation of ALT elevation to FVIII levels, as well correlation of steroid treatment to ALT elevation and FVIII levels will be presented in a listing. Local ALT assessments will be analyzed similarly as the central ALT assessments, if needed. Similar analyses will be applied to other liver tests including aspartate transaminase (AST), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), bilirubin, alkaline phosphatase (ALP), if needed.

In addition, incidences of potential drug-induced liver injury (DILI) that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law, will be 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, Chest X-Ray and Liver Ultrasound

Electrocardiogram (ECG), chest X-ray and liver ultrasound are performed at the Screening visit with additional evaluations to be performed if clinically indicated during the study. [redacted]

14.5 Viral Shedding

Viral shedding will be extensively studied at Baseline, Day 4, Day 8, Week 2, Week 3, Week 4, Week 6, Week 8, Week 12, Week 16, Week 20, Week 24, Week 26, every 4 weeks between Weeks 32-52 until at least 3 consecutive negative results are obtained. Body fluids including blood, saliva, semen, urine and stool will be tested by polymerase chain reaction (PCR) at 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 52 should continue to have PCR testing in semen every 4 weeks (during Year 2) or every 6 weeks (during Years 3-5) until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor).

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. [redacted]

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. [redacted]

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 positive or negative by peptide pool stimulation based on the number of 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. In addition, immunogenicity and alanine transaminase data will be plotted over time and overlaid in the figure.

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

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	24Apr2019		Initial version
2.0	17Feb2021		Clarified that DAP and the interim analysis planned for Week 26 were removed from the study. [redacted] the interim analysis since only one subject was enrolled.

19 APPENDICES

19.1 Visit Windows

Assessment	Derived Visit	Scheduled Visit Day[a]	Window[b]
Liver tests, Vital signs, and other central lab tests	Baseline[c]	Day -1	≤ Day 1
	Week 1	Day 8	Days [2, 11]
	Week 2	Day 15	Days [12, 18]
	Week 3	Day 22	Days [19, 25]
	Week 4	Day 29	Days [26, 32]
	Week 5	Day 36	Days [33, 39]
	Week 6	Day 43	Days [40, 46]
	Week 7	Day 50	Days [47, 53]
	Week 8	Day 57	Days [54, 60]
	Week 9	Day 64	Days [61, 67]
	Week 10	Day 71	Days [68, 74]
	Week 11	Day 78	Days [75, 81]
	Week 12	Day 85	Days [82, 88]
	Week 13	Day 92	Days [89, 95]
	Week 14	Day 99	Days [96, 102]
	Week 15	Day 106	Days [103, 109]
	Week 16	Day 113	Days [110, 116]
	Week 17	Day 120	Days [117, 123]
	Week 18	Day 127	Days [124, 130]
	Week 19	Day 134	Days [131, 137]
	Week 20	Day 141	Days [138, 144]
	Week 21	Day 148	Days [145, 151]
	Week 22	Day 155	Days [152, 158]
	Week 23	Day 162	Days [159, 165]
	Week 24	Day 169	Days [166, 172]
	Week 25	Day 176	Days [173, 179]
	Week 26	Day 183	Days [180, 186]
	Week 27	Day 190	Days [187, 193]
	Week 28	Day 197	Days [194, 200]
	Week 29	Day 204	Days [201, 207]
	Week 30	Day 211	Days [208, 214]
	Week 31	Day 218	Days [215, 221]
	Week 32	Day 225	Days [222, 228]
	Week 33	Day 232	Days [229, 235]
	Week 34	Day 239	Days [236, 242]
	Week 35	Day 246	Days [243, 249]
	Week 36	Day 253	Days [250, 259]
	Week 38	Day 267	Days [260, 273]
	Week 40	Day 281	Days [274, 287]

Assessment	Derived Visit	Scheduled Visit Day[a]	Window[b]
	Week 42	Day 295	Days [288, 301]
	Week 44	Day 309	Days [302, 315]
	Week 46	Day 323	Days [316, 329]
	Week 48	Day 337	Days [330, 343]
	Week 50	Day 351	Days [344, 357]
	Week 52	Day 365	Days [358, 371]
	Week 56	Day 393	Days [372, 406]
	Week 60	Day 421	Days [407, 434]
	Week 64	Day 449	Days [435, 462]
	Week 68	Day 477	Days [463, 490]
	Week 72	Day 505	Days [491, 518]
	Week 76	Day 533	Days [519, 546]
	Week 80	Day 561	Days [547, 574]
	Week 84	Day 589	Days [575, 602]
	Week 88	Day 617	Days [603, 630]
	Week 92	Day 645	Days [631, 658]
	Week 96	Day 673	Days [659, 686]
	Week 100	Day 701	Days [687, 714]
	Week 104	Day 729	Days [715, 742]

[a] Relative to the BMN 270 infusion day (Day 1)

[b] Visit day is calculated as (visit date – date of infusion date + 1) if post infusion and (visit date – date of infusion date) if before infusion

[c] Baseline visit value is defined as the last available measurement prior to BMN 270 dosing.

19.2 Preferred Terms Suggestive of Thromboembolic Events

confusional state (10010305)
muscular weakness (10028372)
swelling (10042674)
peripheral swelling (10048959)
odema Peripheral (10030124)
jaundice (10023126)
urine output decreased (10059895)
pain in extremity (10033425)
erythema (10015150)
dyspnea (10013968)
chest pain (10008479)
chest discomfort (10008469)
tachycardia (10043071)
haemoptysis (10018964)
presyncope (10036653)
headache (10019211)
hypoaesthesia (10020937)
eye pain (10015958)
eye swelling (10015967)
visual impairment (10047571)
visual acuity reduced (10047531)