Clinical trial results:
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 in Hemophilia A Patients with Residual FVIII Levels <= 1 IU/dL Receiving Prophylactic FVIII Infusions

Summary

EudraCT number	2017-003215-19
Trial protocol	GB DE ES FR BE IT
Global end of trial date	20 November 2024

Results information

Result version number	v1 (current)
This version publication date	20 December 2025
First version publication date	20 December 2025

Trial information

Trial identification

Sponsor protocol code	270-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03370913
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	BioMarin Pharmaceutical Inc
Sponsor organisation address	105 Digital Drive, Novato, CA, United States, 94949
Public contact	Clinical Trials Information, BioMarin Pharmaceutical Inc., medinfo@bmrn.com
Scientific contact	Clinical Trials Information, BioMarin Pharmaceutical Inc., medinfo@bmrn.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 November 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 November 2020
Global end of trial reached?	Yes
Global end of trial date	20 November 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Assess the efficacy of BMN 270 (compared to no treatment) defined as FVIII activity, as measured by chromogenic substrate assay, at Week 260 following intravenous infusion of BMN 270

Protection of trial subjects:

This study was conducted in accordance with the following:

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

The study was conducted under a protocol reviewed and approved by an IRB/IEC and is conducted by scientifically and medically qualified persons. The benefits of the study were in proportion to the risks. The rights and welfare of the participants were respected, and the investigators conducting the study did not find the hazards to outweigh the potential benefits.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 December 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	United Kingdom: 23
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	United States: 30
Country: Number of subjects enrolled	South Africa: 16
Country: Number of subjects enrolled	Korea, Republic of: 1
Country: Number of subjects enrolled	Israel: 5
Country: Number of subjects enrolled	Taiwan: 10
Country: Number of subjects enrolled	Brazil: 19

Country: Number of subjects enrolled	Australia: 14
Worldwide total number of subjects	134
EEA total number of subjects	16

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	133
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 48 sites worldwide (United States, Australia, Belgium, Brazil, France, Germany, Israel, Italy, South Korea, South Africa, Spain, Taiwan, and United Kingdom).

Pre-assignment

Screening details:

Of the 181 participants screened, 37 failed screening. Of the remaining 144 participants in 270-301, 134 were treated with 6E13 vg/kg BMN 270. Ten participants enrolled but were not dosed (5 each from the directly enrolling and from the rollover pools of potential participants).

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Double blind[1]
Roles blinded	Monitor, Data analyst, Assessor

Blinding implementation details:

This was an open-label study. However, the Sponsor implemented role-based access control for certain study data.

Arms

Arm title	BMN 270 (Valoctocogene Roxaparvovec)

Arm description:

Single administration of valoctocogene roxaparvovec at a dose of 6E13 vg/kg

valoctocogene roxaparvovec: Adeno-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII in Hemophilia A subjects

Arm type	Experimental
Investigational medicinal product name	BMN 270
Investigational medicinal product code	
Other name	AAV5-hFVIII-SQ/BMN 270
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

BMN 270 was infused through the catheter or butterfly needle using an appropriate infusion pump at an initial rate of 1 mL/min, which was increased every 30 minutes by 1mL/min up to a maximum of 4 mL/min, provided that the participant’s clinical condition permitted such an increase. Of note, the IP has been shown to be stable at room temperature for 7.5 hours following completion of product thaw. Vital signs (pulse, blood pressure, respiration rate and temperature) were monitored at 15-minute (± 5 minutes) intervals throughout the time period of the infusion.

Notes:

[1] - The roles blinded appear to be inconsistent with a double blind trial.

Justification: This was an open-label study. However, the Sponsor implemented role-based access control for certain study data.

Number of subjects in period 1	BMN 270 (Valoctocogene Roxaparvovec)
Started	134
Completed	128
Not completed	6
Consent withdrawn by subject	1

Death	2
Lost to follow-up	3

Baseline characteristics

Reporting groups	
Reporting group title	overall trial
Reporting group description:	
6E13 vector genomes (vg) per kilogram of body weight, given as a single intravenous dose IV). valoctocogene roxaparvovec: Adeno-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII in Severe Hemophilia A	

Reporting group values	overall trial	Total	
Number of subjects	134	134	
Age categorical			
Age at enrollment, n (%) Intent-to-Treat (ITT) Population (n=134) – all participants dosed in 270-301			
Units: Subjects			
18 to < 30 years	65	65	
30 to < 50 years	56	56	
>=50 years	13	13	
Age continuous			
Age at enrollment, years Intent-to-Treat (ITT) Population (n=134) – all participants dosed in 270-301			
Units: years			
arithmetic mean	31.7		
standard deviation	± 10.3	-	
Gender categorical			
Intent-to-Treat (ITT) Population (n=134) – all participants dosed in 270-301			
Units: Subjects			
Female	0	0	
Male	134	134	
Race			
Intent-to-Treat (ITT) Population (n=134) – all participants dosed in 270-301			
Units: Subjects			
Asian	19	19	
Black or African-American	15	15	
Native Hawaiian or other Pacific Islander	1	1	
White	96	96	
Not provided due to patient privacy	3	3	
Ethnicity			
Intent-to-Treat (ITT) Population (n=134) – all participants dosed in 270-301			
Units: Subjects			
Hispanic or Latino	7	7	
Not Hispanic or Latino	127	127	
Baseline ABR (treated bleeds)			
Intent-to-Treat (ITT) Population (n=134) – all participants dosed in 270-301			
Units: Subjects			
0 bleeds/year	43	43	
> 0 to 4	42	42	

> 4 to 10	29	29	
> 10	20	20	
Baseline ABR (all bleeds)			
Intent-to-Treat (ITT) Population (n=134) – all participants dosed in 270-301			
Units: Subjects			
0 bleeds/year	41	41	
> 0 to 4	40	40	
> 4 to 10	31	31	
> 10	22	22	
History of previous diseases			
Intent-to-Treat (ITT) Population (n=134) – all participants dosed in 270-301			
Units: Subjects			
Hepatitis B	20	20	
Hepatitis C	41	41	
HIV	2	2	
Subjects without History of previous disease	71	71	
Number of target joints			
Intent-to-Treat (ITT) Population (n=134) – all participants dosed in 270-301			
Units: Subjects			
n=0	97	97	
n=1	17	17	
n=2	9	9	
n=3	8	8	
n>3	3	3	
Baseline annualized FVIII usage			
Intent-to-Treat (ITT) Population (n=134) – all participants dosed in 270-301			
Units: IU/kg/year			
arithmetic mean	4113.69		
standard deviation	± 1738.92	-	
Baseline annualized number of FVIII infusions			
Intent-to-Treat (ITT) Population (n=134) – all participants dosed in 270-301			
Units: Infusions/year			
arithmetic mean	137.55		
standard deviation	± 57.04	-	
Baseline ABR (treated bleeds)			
ITT population			
Units: bleeds/year			
arithmetic mean	5.42		
standard deviation	± 9.96	-	
Baseline ABR (all bleeds)			
Intent-to-Treat (ITT) Population (n=134) – all participants dosed in 270-301			
Units: bleeds/year			
arithmetic mean	5.97		
standard deviation	± 11.06	-	

End points

End points reporting groups

Reporting group title	BMN 270 (Valoctocogene Roxaparvovec)

Reporting group description:

Single administration of valoctocogene roxaparvovec at a dose of 6E13 vg/kg

valoctocogene roxaparvovec: Adeno-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII in Hemophilia A subjects

Primary: Mean change from Baseline in FVIII Activity as Measured by Chromogenic Substrate Assay at Week 52 Post-BMN 270 Infusion

End point title	Mean change from Baseline in FVIII Activity as Measured by Chromogenic Substrate Assay at Week 52 Post-BMN 270 Infusion[1]

End point description:

The change from baseline (assuming no treatment for severe hemophilia A) in FVIII activity, as measured by chromogenic substrate assay, Weeks 49-52 post-BMN 270 infusion.

Modified Intent-to-Treat (mITT) Population (n=132): All HIV-negative subjects at study screening who were dosed in 270-301.

End point type	Primary

End point timeframe:

Baseline to Week 52

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was analyzed for this endpoint.

End point values	BMN 270 (Valoctocogene Roxaparvovec)			
Subject group type	Reporting group			
Number of subjects analysed	132			
Units: IU/dL				
arithmetic mean (standard deviation)	41.78 (± 45.55)			

Statistical analyses

No statistical analyses for this end point

Primary: Median change from Baseline in FVIII Activity as Measured by Chromogenic Substrate Assay at Week 52 Post-BMN 270 Infusion

End point title	Median change from Baseline in FVIII Activity as Measured by Chromogenic Substrate Assay at Week 52 Post-BMN 270 Infusion[2]

End point description:

Values for FVIII activity were excluded from analysis if obtained within 72 hours (or 3 calendar days if time is not available) since the last infusion of exogenous FVIII replacement therapy.

FVIII activity levels below the LLOQ (Lower limit of quantification) were imputed with 0 IU/dL.

Modified Intent-to-Treat (mITT) Population (n=132).

End point type	Primary

End point timeframe:

Baseline to Week 52

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was analyzed for this endpoint.

End point values	BMN 270 (Valoctocogene Roxaparvovec)			
Subject group type	Reporting group			
Number of subjects analysed	132			
Units: IU/dL				
median (full range (min-max))	22.93 (-1.0 to 230.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Treatment-related Adverse Events

End point title	Number of Participants with Treatment-related Adverse Events

End point description:

A treatment-emergent Adverse Events (TEAE) is any Adverse Events that newly appeared, increased in frequency or worsened in severity following initiation of study drug administration.

Participants with more than one AE of the same category were counted only once for that category.

Serious adverse event (SAE)

Intent-to-Treat (ITT) Population (n=134) – all participants dosed in 270-301

End point type	Secondary

End point timeframe:

Up to 5 years after dosing

End point values	BMN 270 (Valoctocogene Roxaparvovec)			
Subject group type	Reporting group			
Number of subjects analysed	134			
Units: Participants				
Participants with any AE	134			
Participants with any AE of Grade >= 3	55			
Participants with any SAE	37			
Any AEs assessed by investigator as Related	124			

Any SAEs assessed by investigator as Related	5			
Any AEs Leading to Study Discontinuation	0			
Any AEs Leading to Dose Interruption During Infus	4			
Any AEs assessed as Related to Immunosuppressants	84			
Participants who died	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Annualized FVIII Utilization in EEP

End point title	Mean Change From Baseline in Annualized FVIII Utilization in EEP

End point description:

The change from baseline in the annualized utilization (IU/kg/year) of exogenous FVIII replacement therapy in the Post FVIII Prophylaxis to Last Visit in the EEP.

The annualized utilization (IU/kg/year) of exogenous FVIII replacement therapy is defined as Sum of FVIII use (IU/kg) during calculation period/Total number of days during the calculation period ×365.25

Rollover Population (n=112) – all participants dosed in 270-301 who previously participated in 270-902 (all participants were HIV-negative)

End point type	Secondary

End point timeframe:

Baseline to EEP

Efficacy evaluation period (EEP): Week 5 to Last Visit.

End point values	BMN 270 (Valoctocogene Roxaparvovec)			
Subject group type	Reporting group			
Number of subjects analysed	112			
Units: IU/kg/yr				
arithmetic mean (standard deviation)	-3911.49 (± 1742.85)			

Statistical analyses

No statistical analyses for this end point

Secondary: Median Change From Baseline in the Annualized FVIII Utilization in EEP

End point title	Median Change From Baseline in the Annualized FVIII Utilization in EEP

End point description:

The change from baseline in the annualized utilization (IU/kg/year) of exogenous FVIII replacement therapy in the Post FVIII Prophylaxis to Last Visit in the EEP.

The annualized utilization (IU/kg/year) of exogenous FVIII replacement therapy is defined as Sum of FVIII use (IU/kg) during calculation period/Total number of days during the calculation period ×365.25

Rollover Population (n=112)

End point type	Secondary

End point timeframe:

Baseline to EEP

End point values	BMN 270 (Valoctocogene Roxaparvovec)			
Subject group type	Reporting group			
Number of subjects analysed	112			
Units: IU/kg/yr				
median (full range (min-max))	-3733.48 (-11251.1 to -753.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from baseline in annualized FVIII infusion rate at EEP

End point title	Mean Change from baseline in annualized FVIII infusion rate at EEP

End point description:

Annualized FVIII infusion rate (count/yr) = (sum(Number of FVIII replacement infusions during calculation period)/sum(follow-up days of the period)) x 365.25.

Rollover Population (n=112)

End point type	Secondary

End point timeframe:

Baseline to EEP

End point values	BMN 270 (Valoctocogene Roxaparvovec)			
Subject group type	Reporting group			
Number of subjects analysed	112			
Units: Infusions/ year				
arithmetic mean (standard deviation)	-128.98 (± 51.53)			

Statistical analyses

No statistical analyses for this end point

Secondary: Median Change from baseline in annualized FVIII infusion rate at EEP

End point title	Median Change from baseline in annualized FVIII infusion rate at EEP

End point description:

Annualized FVIII infusion rate (count/yr) = (sum(Number of FVIII replacement infusions during calculation period)/sum(follow-up days of the period)) x 365.25.

Rollover Population (n=112)

End point type	Secondary

End point timeframe:

Baseline to EEP

End point values	BMN 270 (Valoctocogene Roxaparvovec)			
Subject group type	Reporting group			
Number of subjects analysed	112			
Units: infusions / year				
median (full range (min-max))	-118.46 (-361.9 to -28.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in the Annualized Number of Bleeding Episodes Requiring Exogenous FVIII Replacement Therapy (ABR for Treated Bleeds) in the EEP

End point title	Mean Change From Baseline in the Annualized Number of Bleeding Episodes Requiring Exogenous FVIII Replacement Therapy (ABR for Treated Bleeds) in the EEP

End point description:

ABR for treated bleeds=Number of bleeding episodes for treated bleeds during the calculation period/total number of days during the calculation period * 365.25

Rollover Population (n=112)

End point type	Secondary

End point timeframe:

Baseline to EEP

End point values	BMN 270 (Valoctocogene Roxaparvovec)			
Subject group type	Reporting group			
Number of subjects analysed	112			
Units: bleeds/year				
arithmetic mean (standard deviation)	-4.02 (± 6.52)			

Statistical analyses

No statistical analyses for this end point

Secondary: Median Change From Baseline in the Annualized Number of Bleeding Episodes Requiring Exogenous FVIII Replacement Therapy (ABR for Treated Bleeds) in the EEP

End point title	Median Change From Baseline in the Annualized Number of Bleeding Episodes Requiring Exogenous FVIII Replacement Therapy (ABR for Treated Bleeds) in the EEP

End point description:

ABR for treated bleeds=Number of bleeding episodes for treated bleeds during the calculation period/total number of
days during the calculation period * 365.25

Rollover Population (n=112)

End point type	Secondary

End point timeframe:

Baseline to EEP

End point values	BMN 270 (Valoctocogene Roxaparvovec)			
Subject group type	Reporting group			
Number of subjects analysed	112			
Units: bleeds/year				
median (full range (min-max))	-2.02 (-32.7 to 10.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Haemo-QoL-A Quality of Life: Total Score

at Week 260

End point title	Mean Change From Baseline in Haemo-QoL-A Quality of Life: Total Score at Week 260

End point description:

The change from baseline (assuming no treatment for severe hemophilia A) in Haemo-QoL-A Total score, at Week 260 post -BMN 270 infusion.
The Haemo-QoL-A questionnaire is a validated hemophilia-specific Health-related quality of life (HRQoL) questionnaire for adults consisting of 41 questions covering six domains (Physical Functioning, Role Functioning, Worry, Consequences of Bleeding, Emotional Impact and Treatment Concerns), plus a Total Score. Items are answered on a 6-point Likert-type scale, ranging from 0 (None of the time) to 5 (All of the time), with a 1-month recall. Higher scores mean better HRQoL or less impairment (for a subscale).

mITT Population: (n=132)

End point type	Secondary

End point timeframe:

Baseline to Week 260

End point values	BMN 270 (Valoctocogene Roxaparvovec)			
Subject group type	Reporting group			
Number of subjects analysed	132			
Units: score on a scale				
arithmetic mean (standard deviation)	5.70 (± 12.71)			

Statistical analyses

No statistical analyses for this end point

Secondary: Median Change From Baseline in Haemo-QoL-A Quality of Life: Total Score at Week 260

End point title	Median Change From Baseline in Haemo-QoL-A Quality of Life: Total Score at Week 260

End point description:

The change from baseline (assuming no treatment for severe hemophilia A) in Haemo-QoL-A Total score, at Week 260 post -BMN 270 infusion.

The Haemo-QoL-A questionnaire is a validated hemophilia-specific Health-related quality of life (HRQoL) questionnaire for adults consisting of 41 questions covering six domains (Physical Functioning, Role Functioning, Worry, Consequences of Bleeding, Emotional Impact and Treatment Concerns), plus a Total Score. Items are answered on a 6-point Likert-type scale, ranging from 0 (None of the time) to 5 (All of the time), with a 1-month recall. Higher scores mean better HRQoL or less impairment (for a subscale)

mITT Population (n=132)

End point type	Secondary

End point timeframe:

Baseline to Week 260

End point values	BMN 270 (Valoctocogene Roxaparvovec)			
Subject group type	Reporting group			
Number of subjects analysed	132			
Units: score on a scale				
median (full range (min-max))	5.80 (-41.4 to 46.9)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 5 years after dosing.

Adverse event reporting additional description:

AEs with onset or worsening after the investigational product were included.

Intent-to-Treat (ITT) Population: All subjects dosed in 270-301 study

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	BMN 270 (Valoctocogene Roxaparvovec)

Reporting group description:

Single administration of valoctocogene roxaparvovec at a dose of 6E13 vg/kg

valoctocogene roxaparvovec: Adeno-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII in
Hemophilia A subjects

Serious adverse events	BMN 270 (Valoctocogene Roxaparvovec)		
Total subjects affected by serious adverse events			
subjects affected / exposed	37 / 134 (27.61%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell type acute leukaemia			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Melanocytic naevus			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			

subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Hypothermia			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral swelling			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	2 / 134 (1.49%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hypersensitivity			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Apnoea			

subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vocal cord thickening			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Depression			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Major depression			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suicide attempt			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 134 (1.49%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Influenza A virus test positive			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural			

complications			
Acetabulum fracture			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post procedural haemorrhage			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hand fracture			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Head injury			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Lower limb fracture			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Periprosthetic fracture			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin laceration			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Traumatic haematoma			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			

Coronary artery disease			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Presyncope			
subjects affected / exposed	2 / 134 (1.49%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Macular hole			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Retinal detachment			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Rectal haemorrhage			
subjects affected / exposed	3 / 134 (2.24%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	2 / 134 (1.49%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Diverticulum			

subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemoperitoneum				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Melaena				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Dermal cyst				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rash maculo-papular				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Nephrolithiasis				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Arthropathy				
subjects affected / exposed	2 / 134 (1.49%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Haemophilic arthropathy				
subjects affected / exposed	2 / 134 (1.49%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			

Muscle haemorrhage			
subjects affected / exposed	2 / 134 (1.49%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Haemarthrosis			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematoma muscle			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Joint effusion			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Joint swelling			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	2 / 134 (1.49%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			

subjects affected / exposed	2 / 134 (1.49%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cytomegalovirus infection				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia cytomegaloviral				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tooth infection				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cellulitis				

subjects affected / exposed	2 / 134 (1.49%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Steroid diabetes			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	BMN 270 (Valoctocogene Roxaparvovec)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	134 / 134 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	22 / 134 (16.42%)		
occurrences (all)	28		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	42 / 134 (31.34%)		
occurrences (all)	58		
Pyrexia			
subjects affected / exposed	35 / 134 (26.12%)		
occurrences (all)	49		
Influenza like illness			

subjects affected / exposed occurrences (all) Chills subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all) Malaise subjects affected / exposed occurrences (all)	12 / 134 (8.96%) 14 10 / 134 (7.46%) 10 10 / 134 (7.46%) 14 9 / 134 (6.72%) 10		
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	8 / 134 (5.97%) 8		
Social circumstances Pregnancy of partner subjects affected / exposed occurrences (all)	11 / 134 (8.21%) 14		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Nasal congestion subjects affected / exposed occurrences (all) Rhinorrhoea subjects affected / exposed occurrences (all)	28 / 134 (20.90%) 39 28 / 134 (20.90%) 34 9 / 134 (6.72%) 9 9 / 134 (6.72%) 11		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	29 / 134 (21.64%) 49		

Anxiety			
subjects affected / exposed	13 / 134 (9.70%)		
occurrences (all)	14		
Irritability			
subjects affected / exposed	7 / 134 (5.22%)		
occurrences (all)	8		
Mood swings			
subjects affected / exposed	7 / 134 (5.22%)		
occurrences (all)	7		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	125 / 134 (93.28%)		
occurrences (all)	561		
Aspartate aminotransferase increased			
subjects affected / exposed	53 / 134 (39.55%)		
occurrences (all)	122		
Weight increased			
subjects affected / exposed	23 / 134 (17.16%)		
occurrences (all)	39		
Blood creatine phosphokinase increased			
subjects affected / exposed	19 / 134 (14.18%)		
occurrences (all)	29		
Blood lactate dehydrogenase increased			
subjects affected / exposed	11 / 134 (8.21%)		
occurrences (all)	17		
Gamma-glutamyltransferase increased			
subjects affected / exposed	9 / 134 (6.72%)		
occurrences (all)	19		
Injury, poisoning and procedural complications			
Muscle strain			
subjects affected / exposed	18 / 134 (13.43%)		
occurrences (all)	26		
Contusion			

subjects affected / exposed occurrences (all)	13 / 134 (9.70%) 19		
Limb injury subjects affected / exposed occurrences (all)	12 / 134 (8.96%) 13		
Fall subjects affected / exposed occurrences (all)	10 / 134 (7.46%) 15		
Ligament sprain subjects affected / exposed occurrences (all)	10 / 134 (7.46%) 10		
Joint injury subjects affected / exposed occurrences (all)	9 / 134 (6.72%) 9		
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	60 / 134 (44.78%) 223		
Dizziness subjects affected / exposed occurrences (all)	13 / 134 (9.70%) 19		
Migraine subjects affected / exposed occurrences (all)	9 / 134 (6.72%) 12		
Lethargy subjects affected / exposed occurrences (all)	8 / 134 (5.97%) 9		
Tremor subjects affected / exposed occurrences (all)	7 / 134 (5.22%) 7		
Blood and lymphatic system disorders			
Iron deficiency anaemia subjects affected / exposed occurrences (all)	9 / 134 (6.72%) 9		
Gastrointestinal disorders			

Nausea subjects affected / exposed occurrences (all)	53 / 134 (39.55%) 85		
Diarrhoea subjects affected / exposed occurrences (all)	35 / 134 (26.12%) 55		
Vomiting subjects affected / exposed occurrences (all)	28 / 134 (20.90%) 36		
Constipation subjects affected / exposed occurrences (all)	13 / 134 (9.70%) 18		
Abdominal pain upper subjects affected / exposed occurrences (all)	12 / 134 (8.96%) 17		
Dyspepsia subjects affected / exposed occurrences (all)	12 / 134 (8.96%) 15		
Abdominal discomfort subjects affected / exposed occurrences (all)	10 / 134 (7.46%) 10		
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	8 / 134 (5.97%) 9		
Toothache subjects affected / exposed occurrences (all)	8 / 134 (5.97%) 13		
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all)	36 / 134 (26.87%) 45		
Rash subjects affected / exposed occurrences (all)	13 / 134 (9.70%) 14		
Endocrine disorders			

Cushingoid			
subjects affected / exposed	16 / 134 (11.94%)		
occurrences (all)	16		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	61 / 134 (45.52%)		
occurrences (all)	144		
Back pain			
subjects affected / exposed	31 / 134 (23.13%)		
occurrences (all)	45		
Pain in extremity			
subjects affected / exposed	24 / 134 (17.91%)		
occurrences (all)	30		
Myalgia			
subjects affected / exposed	18 / 134 (13.43%)		
occurrences (all)	19		
Arthropathy			
subjects affected / exposed	15 / 134 (11.19%)		
occurrences (all)	19		
Haemophilic arthropathy			
subjects affected / exposed	9 / 134 (6.72%)		
occurrences (all)	11		
Joint swelling			
subjects affected / exposed	8 / 134 (5.97%)		
occurrences (all)	10		
Muscle spasms			
subjects affected / exposed	8 / 134 (5.97%)		
occurrences (all)	8		
Musculoskeletal stiffness			
subjects affected / exposed	7 / 134 (5.22%)		
occurrences (all)	8		
Synovitis			
subjects affected / exposed	7 / 134 (5.22%)		
occurrences (all)	7		
Infections and infestations			

COVID-19 subjects affected / exposed occurrences (all)	47 / 134 (35.07%) 57		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	44 / 134 (32.84%) 70		
Nasopharyngitis subjects affected / exposed occurrences (all)	35 / 134 (26.12%) 74		
Influenza subjects affected / exposed occurrences (all)	15 / 134 (11.19%) 20		
Rhinitis subjects affected / exposed occurrences (all)	15 / 134 (11.19%) 22		
Folliculitis subjects affected / exposed occurrences (all)	11 / 134 (8.21%) 13		
Rash pustular subjects affected / exposed occurrences (all)	11 / 134 (8.21%) 12		
Gastroenteritis subjects affected / exposed occurrences (all)	10 / 134 (7.46%) 13		
Viral infection subjects affected / exposed occurrences (all)	9 / 134 (6.72%) 11		
Gastroenteritis viral subjects affected / exposed occurrences (all)	8 / 134 (5.97%) 9		
Metabolism and nutrition disorders Hypomagnesaemia subjects affected / exposed occurrences (all)	7 / 134 (5.22%) 7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 January 2018	Amendment 1: • Sample size changed to70 • Timing of interim analysis(IA)changed to occur after20 treated participants(prtps)completed Wk26.IA changed to perform hypothesis testing for primary endpoint.Method for adjusting multiplicity changed accordingly • Language(lang)in prot have suggested doses of BMN270>6E13vg/kg may potentially be eval as part of study clarified • Study Saf Eval Crit lang revised to make it clear that enrol will be temp halted if stopping crit listed are met • Lang around Expedited Saf Rept Req amended to clarify which SAEs are subj to expedited rept reqs • Twice weekly eval of LTs added during times when prtp's ALT is>=3xULN • Guidance added for mgmt of prtps who have FVIII activity levels<5IU/dL(after showing initial response toBMN270)foll BMN270 infusion(inf) • Assessment(assmt)of dermatologic & musculoskeletal systems added to brief PE • Testing of expl samples for Direct Thrombin Activity Test&TGA Assay clarified as optional • Specific testing of TNF-α & IL10a single nucleotide polymorphisms removed from biomarker testing • Fasting lipid panel(bld trigly,total chol,HDL chol&LDL chol)added on day of BMN270 inf • Initial von Willebrand Factor antigen(VWF:Ag)assmt moved from SCR to Baseline • Freq of liver function & FVIII testing increased during Yrs2-5 FUP period.Testing performed every4wks(+2wks/as sched to align with other sched study visits)during Yr2,& every6wks(±2wks)during Yrs3-5 • Clarified post-CS testing for HepB/C reactivation should be performed only in prtps who have previous hist of +ve HepB/C tests • PROBE questionnaire added as qual of life assmt • In event of +ve Bethesda assay result during Yrs3-5,addnl sample added to be collected within4wks of visit where+ve result obtained • Emicizumab,fitusiran,&concizumab were added as prohibited meds starting30days before SCR & through EOS • Prtps were advised to abstain blood/sperm donation afterBMN270 inf until there is no evidence of vector shedding

28 June 2018	Amendment 2: • The sample size of the study was changed to 130, and the number of potential sites was increased to 60 • Details of the sample size calculation, missing data handling, and sensitivity analyses were added • Language concerning the occurrence and management of infusion-associated events was added • Language in the inclusion criterion related to a participant's history of FVIII inhibitors was clarified • Language regarding the HIV inclusion criterion was modified. • Language was added to permit use of mobile nursing (MN) services, provided that the site is able to implement them and the participant consents, for non every 3 month visits after Week 52 • Language was added to include ABO blood antigen testing. • Clarified that, on the day of infusion, participants are not required to be admitted to a hospital to receive the infusion (ie, the infusion may be conducted in any facility that has the requisite capabilities to prepare and perform the infusion, as well as monitor participants for at least 8 hours). • Clarified that the requirement for contraception use can end as early as Week 12, in the case that a participant has had 3 consecutive negative semen vector shedding assessments prior to that time point. • Clarified that assessment of concomitant medications and adverse events should be performed at the every 4-week visits during Year 2, and at the every 6 week visits during Years 3-5. • Clarified that vector shedding assessments, if required, could be performed at the every 6 week visits during Years 3-5 • Added language that participants will fast for at least 8 hours prior to collection of pre infusion laboratory samples on the day of infusion.
24 August 2018	Amendment 3: • HIV-positive patients were excluded from the study • Efavirenz and lamivudine were added to the list of prohibited concomitant medications •The exclusion criterion concerning liver test levels at Screening was changed to require all assessed liver tests (ie, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyltransferase, and total bilirubin) to be no higher than the 1.25 times the ULN for eligibility purposes • An additional fasting serum sample was added on Day 1, in case it is needed for future exploratory assessments • The timing of assessment visits during Years 2-5 was modified • An abbreviated visit schedule was made available during Years 2 5 for participants who are considered to have not responded to BMN 270 therapy • Additional details were included concerning information to be collected as part of the medical history assessment at Screening • The statistical analysis population definitions and language surrounding the primary endpoint were updated • Language concerning when to consider restarting FVIII prophylaxis following BMN 270 infusion was modified • An additional criterion to initiate reactive oral CS for elevated ALT levels, following consultation with the medical monitor, of ALT > ULN and > 2x baseline value was added.
09 November 2018	Amendment 4: • Some visits during Year 1 of the study were designated as optional mobile nursing or lab draw-only visits for participants enrolling in 270-301 following participation in 270 902. • Development of anti-FVIII inhibitory antibodies (inhibitors) was added as an Event of Special Interest for safety reporting purposes. • Assessment of the Direct Thrombin Activity test was removed
10 May 2019	Amendment 5: Global Amendment 5 was never submitted to health authorities or sites. The primary change in Amendment 5 was a revision of the interim analysis language to allow for the possibility of a second interim analysis. After the first interim analysis was performed, it was determined that the second interim analysis would not be needed and, as such, the protocol amendment would no longer be needed.

03 April 2020	Amendment 6: • Lang concerning interim analysis was modified • PBMC collection was removed from Wk30 visit • Prohibition on use of non-corticosteroid systemic immunosuppressive agents following BMN 270 dosing was removed • Vector shedding & contraception use language was updated to change determination of a "clear" result from negative to below the limit of detection • Clarifying language was provided for circumstances where a +ve vector shedding sample occurs after 3 consecutive tests below the limit of detection have already been obtained • Requirements around use of MN services to conduct unscheduled visits for assessment of FVIII levels or LTs were clarified • At sites where use of MN services has been approved, at visits not specifically designated for MN eligibility(ie,visits where participant is intended to return to site for assessment)MN services may be used if participant is unable to attend site to complete study visit during acceptable window for that visit, upon prior approval by medical monitor & discussion between medical monitor & investigator • In event that neither an MN visit nor a lab-only visit is possible at a post-infusion visit timepoint, site should telephone participant to collect AE, concomitant medication, & diary(bleeding events & FVIII usage)information • Guidance for monitoring & management of elevated hepatic transaminases was modified • An optional liver biopsy substudy was added to protocol • Occurrence of events of Hy's law was added as an EOSI for purposes of expedited safety reporting, & additional safety monitoring in event of a case potentially meeting Hy's law criteria was added • An optional monthly phone check-in was added during Yrs2-5 for participants who are returning to site only every 12wks due to poor FVIII response following BMN 270 infusion • Option to assess an AE as related/not related to CS or AIS was added • Guidance for tapering CS was updated • Lamivudine was removed as a prohibited medication
15 July 2021	Amendment 7: • Changes were made to enhance screening for potential malignancies (including hepatic cancers) after dosing with BMN 270 • Malignancy (except non-melanoma skin cancer) was added as an Event of Special Interest (EOSI) • Language around the statistical analysis of secondary endpoints and objective was amended • Language was added concerning the use of the SARS-CoV-2 vaccines • The reactive CS regimen for ALT elevation was updated • Thrombin generation assay (TGA) assessment was removed • The definition of treatment failure was changed • Frequency of several laboratory assessments during Years 2-5 was decreased

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported