



## Clinical trial results:

### 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 $\leq 1$ IU/dL and Pre-existing Antibodies Against AAV5

#### Summary

EudraCT number	2017-000662-29
Trial protocol	GB FR
Global end of trial date	07 August 2024

#### Results information

Result version number	v1 (current)
This version publication date	21 August 2025
First version publication date	21 August 2025

#### Trial information

##### Trial identification

Sponsor protocol code	270-203
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03520712
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	31 January 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 August 2024
Global end of trial reached?	Yes
Global end of trial date	07 August 2024
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

Assess the safety of a single intravenous administration of BMN 270 in severe Haemophilia A subjects with pre-existing antibody to AAV5 vector capsid, including development of FVIII neutralizing antibody

Protection of trial subjects:

This study was conducted in accordance with the following:

- Clinical Trial Directive 2001/20/EC and GCP Directive 2005/28/EC
- Other national and local regulations, as applicable
- International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6 (ICH E6) (Committee for Proprietary Medicinal Products (CPMP) guideline CPMP/ICH/135/95)
- The ethical principles established by the Declaration of Helsinki

The study was to be conducted under a protocol reviewed and approved by an IRB/EC and was to be 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	24 April 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	South Africa: 2
Worldwide total number of subjects	3
EEA total number of subjects	0

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)	3
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

This study was conducted by 2 principal investigators at 2 study centers in 2 countries (South Africa and United Kingdom).

Nine investigational sites were activated, 2 subjects in South Africa and 1 subject in the United Kingdom were enrolled in the study.

### Pre-assignment

Screening details:

10 participants were planned to be enrolled. 3 participants met all eligibility criteria & were enrolled in study. There were 26 screen failures.

### Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

Arm title	BMN 270 6E13 vg/kg
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Arm description:

BMN 270 6E13 vg/kg, given as a single intravenous dose (IV)

Valoctocogene Roxaparvovec: Adeno-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII in Hemophilia A

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:

An IV catheter or butterfly needle will be inserted into a suitable peripheral vein (eg, the median cubital vein) and flushed with saline.

BMN 270 was prepared and infused as a pure solution over a dose-dependent time. Prepared drug was kept at room temperature prior to administration. An electric syringe pump was used to infuse through an in-line, low protein binding 0.22-micron filter. BMN 270 was infused through the catheter using an appropriate infusion pump at an initial rate of 1 mL/min. The infusion rate was increased every 30 minutes by 1 mL/min up to a maximum of 4 mL/min, provided that the participants clinical condition permits such an increase.

<b>Number of subjects in period 1</b>	BMN 270 6E13 vg/kg
Started	3
Completed	1
Not completed	2
Early termination of the study by Sponsor	2



## Baseline characteristics

### Reporting groups

Reporting group title	Overall trial (overall period)
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Reporting group description:

BMN 270 6E13 vg/kg, given as a single intravenous dose (IV)

Valoctocogene Roxaparvovec: Adeno-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII in Hemophilia A

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	3	3	
Age categorical			
The intention-to-treat (ITT) population was comprised of all participants who have received the BMN 270 infusion.			
Units: Subjects			
Between 18 and 65 years	3	3	
Gender categorical			
The intention-to-treat (ITT) population was comprised of all participants who have received the BMN 270 infusion.			
Units: Subjects			
Male	3	3	
Race/Ethnicity			
ITT Population			
Units: Subjects			
White Non-Hispanic	2	2	
Black or African American	1	1	

## End points

### End points reporting groups

Reporting group title	BMN 270 6E13 vg/kg
Reporting group description: BMN 270 6E13 vg/kg, given as a single intravenous dose (IV)	
Valoctocogene Roxaparvovec: Adeno-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII in Hemophilia A	

### Primary: Number of participants with Treatment Emergent Adverse Events

End point title	Number of participants with Treatment Emergent Adverse Events <sup>[1]</sup>
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End point description:

A treatment-emergent adverse event (TEAE) is defined as any AE that newly appeared or worsened in severity following initiation of investigational product administration.

The safety analysis was based on the ITT population.

The intention-to-treat (ITT) population was comprised of all participants who have received the BMN 270 infusion.

End point type	Primary
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End point timeframe:

Up to 5 years post-infusion.

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 6E13 vg/kg			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: count of participants				
Participants with any AE	3			
Participants with any SAE	1			
Participants with any treatment-related AE	3			
Treatment-related SAEs	1			
Participants with any AE of Grade $\geq 3$	1			
AEs leading to dose adjustment during infusion	0			
AEs leading to dose interruption during infusion	0			
AEs leading to study drug discontinuation	0			
Participants who died	0			

## Statistical analyses

No statistical analyses for this end point

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**Secondary: Number of Participant With FVIII Activity  $\geq$  5 IU/dL at Week 26. Using Chromogenic Substrate Assay (CSA).**

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End point title	Number of Participant With FVIII Activity $\geq$ 5 IU/dL at Week 26. Using Chromogenic Substrate Assay (CSA).
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End point description:

Prior to BMN270 infusion, screening FVIII activity levels where participants had not received exogenous FVIII within 72 hours of assessment were below the lower limit of quantitation (LLOQ) as measured by CSA (LLOQ = 0.015 IU/mL).

The intention-to-treat (ITT) population was comprised of all participants who have received the BMN 270 infusion.

End point type	Secondary
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End point timeframe:

26 weeks

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<b>End point values</b>	BMN 270 6E13 vg/kg			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: count of participants				
Participant with FVIII activity $\geq$ 5 IU/dL	1			
Participant with FVIII activity < 5 IU/dL	2			

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Mean Annualized Factor VIII Utilization During Week 5 and Beyond**

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End point title	Mean Annualized Factor VIII Utilization During Week 5 and Beyond
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End point description:

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  $\times$  365.25

The intention-to-treat (ITT) population was comprised of all participants who have received the BMN 270 infusion.

End point type	Secondary
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End point timeframe:

Week 5 and Beyond (Follow-Up, up to 1782 Days)

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<b>End point values</b>	BMN 270 6E13 vg/kg			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: IU/kg/yr				
geometric mean (standard deviation)	661.1 (± 912.92)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Mean Annualized Factor VIII Infusion Rate During Week 5 and Beyond

End point title	Mean Annualized Factor VIII Infusion Rate During Week 5 and Beyond
End point description:	
Annualized FVIII replacement infusion rate=(number of FV FIII replacement infusions during calculation period/sum(follow-up days) of the period)*365.25	
The intention-to-treat (ITT) population was comprised of all participants who have received the BMN 270 infusion.	
End point type	Secondary
End point timeframe:	
Week 5 and Beyond (Follow-Up, up to 1782 Days)	

<b>End point values</b>	BMN 270 6E13 vg/kg			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: ml/min				
geometric mean (standard deviation)	21.9 (± 30.61)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants Showed Reduction in the ABR Post-BMN 270 Infusion.

End point title	Number of Participants Showed Reduction in the ABR Post-BMN 270 Infusion.
End point description:	
Annualized bleeding rate (ABR) (counts/yr.)=Number of bleeding episodes during calculation period/Total number of days during the calculation period ×365.25	
The intention-to-treat (ITT) population was comprised of all participants who have received the BMN 270 infusion.	
End point type	Secondary

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End point timeframe:

Week 5 and Beyond (Follow-Up, up to 1782 Days)

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<b>End point values</b>	BMN 270 6E13 vg/kg			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Participants	3			

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

up to 5 years post-infusion.

Adverse event reporting additional description:

The safety analysis was based on the ITT population.

A treatment-emergent adverse event (TEAE) is defined as any AE that newly appeared or worsened in severity following initiation of investigational product administration.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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### Reporting groups

Reporting group title	BMN 270 6E13 vg/kg
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Reporting group description:

6E13 vector genomes/kilogram, given as a single intravenous dose (IV)

Serious adverse events	BMN 270 6E13 vg/kg		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	BMN 270 6E13 vg/kg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 3 (66.67%)		
occurrences (all)	3		
Injury, poisoning and procedural			

complications			
Animal scratch			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Face injury			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Limb injury			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Skin abrasion			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Muscle injury			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Thermal burns			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
General disorders and administration site conditions			
Hernia			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	3		
Tendon disorder			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Infections and infestations			

Onychomycosis			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Covid-19			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Conjunctivitis viral			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Gastrointestinal infection			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 October 2018	<ul style="list-style-type: none"><li>•Lang concerning occurrence&amp;mgmt of Inf-associated events added</li><li>•HIV+ve patients excluded from study</li><li>•Efavirenz, lamivudine,&amp;exptl hemophilia trts(emicizumab, fitusiran&amp;concizumab)were added to prohibited CM</li><li>•EXC criterion concerning liver test levels at SCR was changed to require all assessed liver tests(ie,ALT, AST, ALP, GGT&amp;total bilirubin)be no&gt;1.25XULN for elig purposes</li><li>•Visit after Wk26 expanded</li><li>•Visit schedule made available after Wk26/Wk52 for pts who are considered to have not responded to BMN270 therapy</li><li>•Fasting serum sample added on D1</li><li>•lang in INC criterion related to H/O FVIII inhibitors clarified</li><li>•lang concerning when to consider restarting FVIII prophylaxis following BMN270 Inf modified</li><li>•Addnl criterion initiate therapeutic oral corticosteroids for elevated ALT levels of ALT&gt;ULN&amp;&gt;2×BL value added</li><li>•lang added to include ABO testing at BL</li><li>•Clarified requirement for contraception use can end as early Wk12, if stopping criteria met</li><li>•Added lang to clarify local lab testing in additional to central lab samples permitted at Investigator's discretion when required to make clinical mgmt decisions.</li><li>•Added lang pts will fast for at least 8hrs prior to collection of preinfusion lab samples on day of Inf.</li><li>•Assmts of dermatologic&amp;musculoskeletal systems added to brief physical examination</li><li>•Specific testing of TNF-α&amp;IL10a single nucleotide polymorphisms removed from biomarker testing</li><li>•Clarified post-steroid testing for hep B/C reactivation should be performed only in pts who have previous h/o +ve hep B/C tests</li><li>•Added lang advising pts to abstain from blood or sperm donation after BMN 270 Inf until there is no further evidence of vector shedding</li><li>•In event of +ve Bethesda assay result during Yrs3-5, addnl sample was added to collected within 4 wks of visit where +ve result obtained</li><li>•Testing of AAV5 antibody titers added to D8 visit</li><li>•Clarified hepB testing at SCR should include HBsAg, HBsAb&amp;HBcAb) testing</li><li>•Vector genome schematic figure updated</li></ul>

04 October 2019	<ul style="list-style-type: none"> <li>•Prophylactic corticosteroids starting on D1(day of BMN270 infusion)were added for all participants (ptps)</li> <li>•Threshold for considering Additional(Addnl) use of therapeutic oral corticosteroids been lowered</li> <li>•Participants considered to be treatment (trt) failures(ie, those who either fail to achieve FVIII activity &gt; 5IU/dL by chromogenic substrate assay or are unable to maintain independence from prophylactic FVIII replacement therapy due to joint bleeding episodes)may now start following abbreviated visit schedule only after Wk52, not after Wk26</li> <li>•Vector shedding&amp;contraception use Language(lang) updated to change determination of 'clear' result from negative to below limit of detection</li> <li>•Direct Thrombin Assay removed</li> <li>•Option to assess adverse event as related/not related to corticosteroids added</li> <li>•Two-step SCR process introduced</li> <li>•Language added to permit use of mobile nursing (MN) services, provided site able to implement them&amp;participant consents, for certain designated study visits</li> <li>•Period of recommended abstinence from alcohol after BMN270 infusion(Inf)increased from 26wks to 52wks, to support participant liver health &amp; participant safety</li> <li>•Period in exclusion criteria during which participants should not have planned major surgeries following BMN270 infusion increased from 26-52wks, purposes of aligning with other BMN270 studies and for protection of patient safety</li> <li>•Product characteristics &amp; labeling were updated to reflect current manufacturing process</li> <li>•Identity of MM updated</li> <li>•Data Review Board (DRB) changed to independent Data Monitoring Committee (DMC)</li> <li>•Vector genome schematic updated</li> <li>•Risk-benefit language updated to reflect more current clinical results.</li> <li>•Inconsistency in SOA concerning collection of AAV5 TI &amp; TAb assay clarified</li> <li>•Proposed number of study sites increased</li> <li>•To reduce participant burden &amp; align with other studies in BMN270 clinical development program, every 4wk visits during Year 2 post-infusion were changed every 6wk visits</li> </ul>
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24 August 2020	<ul style="list-style-type: none"> <li>•Testing for COVID-19 added</li> <li>•Complement panel details updated</li> <li>•Addnl complement panel assmts added during 1st 12wks post BMN270 Inf</li> <li>•Occurrence of events of Hy's law added as EOSI &amp; addnl safety monitoring in event of case potentially meeting Hy's law criteria added</li> <li>•Lang added concerning use of liver biopsy sample info for biopsies performed for safety-related reasons</li> <li>•FibroScan added as alternative liver ultrasound at SCR&amp;fasting FibroTest added to D1(inf day)assmts</li> <li>•Clarifying lang provided for circumstances where +ve vector shedding sample occurs after 3 consecutive tests below limit of detection have already been obtained</li> <li>•Prohibition use non-corticosteroid systemic immunosuppressive agents following BMN270 dosing removed</li> <li>•Guidance for monitoring&amp;mgmt of elevated hepatic transaminases modified</li> <li>•Optional monthly phone check-in added during Yrs2-5 for pts who are returning site only every 12wks due to poor FVIII response following BMN270 inf</li> <li>•Option to assess AE as related/not related to corticosteroids/other systemic immunosuppressive agents added</li> <li>•Lamivudine removed as prohibited medication</li> <li>•Requirements around use mobile nursing(MN)services to conduct UNS visits for assmt FVIII levels/liver tests(LTs)were clarified</li> <li>•Corrections to timing of weight assmt footnotes in SOA;Clarification of visit window for AAV5 TAB testing during SCR;Update Sec9.7.6.6 to clarify vector shedding should be performed every 6wks during Yrs2-5;Update to Sec12 include FVIII antibody titer at Wk24;Update to Sec12.5.2.7 to state that cytokine bead array assay should be performed at Wk24(rather than Wk22);Update to ETV in Sec12 to add cytokine bead array assay(as is reflected in SOA);Update to Wks28,30,&amp;34 in SOA&amp;in Sec12 to add AAV5 TAB&amp;TI assays</li> <li>•Guidance concerning how to determine whether pt has been lost to followup added</li> <li>•Summary of risks&amp;benefits updated</li> <li>•Required timepoints for vector shedding sample collection during Yrs2-5 clarified</li> </ul>
04 August 2021	<ul style="list-style-type: none"> <li>•Changes have been made to enhance screening for potential malignancies (including hepatic cancers) and establishing baseline liver health during Screening Period.</li> <li>•Changes have been made to enhance screening for potential malignancies (including hepatic cancers) after dosing with BMN 270</li> <li>•Malignancy (except non-melanoma skin cancer) has been added as an Event of Special Interest (EOSI)</li> <li>•HIV-positive patients (serological evidence of HIV-1 or HIV-2 infection) may now enroll in the study, provided their HIV infection is stable and well-controlled with an adequate CD4 count (<math>&gt;200/\text{mm}^3</math>)and an undetectable viral load, respectively, at Screening and they are on an antiretroviral therapy (ART) regimen that does not contain efavirenz or another potentially hepatotoxic ART.</li> <li>•Language has been added concerning the use of the SARS-CoV-2 vaccines.</li> <li>•The reactive corticosteroid regimen for ALT elevation has been updated.</li> <li>•Thrombin generation assay (TGA) assessment has been removed.</li> <li>•The definition of treatment failure has changed.</li> <li>•Frequency of several laboratory assmts during Years 2-5 has been decreased. These changes include: Reducing FVIII Antigen BDD Assay to Q12W for Years 2-5; Reducing AAV5 TAB to End of Year Visits only for Years 3-5; Reducing FVIII TAB to End of Year Visits only for Years 3-5; Reducing AAV5 TI assay to End of Year visits only for Years 2-5; Reducing PBMC collection to every other Q12W visit during Years 3-5</li> <li>•The identity of the Medical Monitor (MM) has been updated.</li> <li>•The option for a legally authorized representative to provide informed consent where needed has been added.</li> <li>•Addnl minor changes have been made for consistency and clarity.</li> </ul>

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No



## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

BioMarin, in accordance with the study enrollment stopping criteria in 270-203 study protocol & DMC recommendation, decided to terminate 270-203, since 2 of 3 participants in had FVIII activity < 5IU/dL after a minimum of 6 wks post-BMN 270 infusion

Notes: