



## Clinical trial results:

### A Multicenter, Multinational, Extension Study to Evaluate the Long-Term Efficacy and Safety of BMN 190 in Patients with CLN2 Disease

#### Summary

EudraCT number	2014-003480-37
Trial protocol	GB DE IT
Global end of trial date	10 December 2020

#### Results information

Result version number	v1 (current)
This version publication date	03 November 2021
First version publication date	03 November 2021

#### Trial information

##### Trial identification

Sponsor protocol code	190-202
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02485899
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., clinicaltrials@bmrn.com
Scientific contact	Clinical Trials Information, BioMarin Pharmaceutical Inc., clinicaltrials@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?	Yes

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 December 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	10 December 2020
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objectives of this study include the following:

- to evaluate the long-term safety of BMN 190 administration at 300 mg qow in patients with CLN2
- to assess change in motor and language subscales of the CLN2 disease rating scale in patients with CLN2 receiving BMN 190 at 300 mg qow

Protection of trial subjects:

This clinical study was designed, conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP) guidelines. These guidelines are stated in U.S. federal regulations as well as Guidance for Good Clinical Practice, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 February 2015
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 States: 3
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	United Kingdom: 3
Worldwide total number of subjects	24
EEA total number of subjects	18

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)	24
Adolescents (12-17 years)	0

Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 5 clinic sites in Germany, Italy, United Kingdom and United States for 190-201 study. The only subject from one of the sites from United Kingdom withdrew after 1 dose of BMN 190 in 190-201 and therefore this site was not activated in 190-202.

### Pre-assignment

Screening details:

Total 24 subjects were enrolled in 190-201 study, of these 23 subjects completed 190-201 & enrolled in 190-202 study. 1 subject terminated from 190 201 after a single infusion of study drug & is not included in ITT population for 190 202. The subject terminated at the parents' request due to subject's unwillingness to continue with study procedures

### Period 1

Period 1 title	Overall period (BMN190-201/202) (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

Arm title	BMN 190-201/202 (300 mg)
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Arm description:

All study subjects administered BMN 190 300 mg by continuous Intracerebroventricular (ICV) infusion at a rate of 2.5 mL/hour for approximately 4 hours) every 14 days preferably in the morning after a fast of at least 2hrs.

Arm type	Experimental
Investigational medicinal product name	BMN 190
Investigational medicinal product code	
Other name	recombinant human tripeptidyl peptidase 1, cerliponase alfa
Pharmaceutical forms	Solution for infusion
Routes of administration	Intracerebroventricular use

Dosage and administration details:

All study subjects administered BMN 190 300 mg by continuous Intracerebroventricular (ICV) infusion at 2.5 mL/hr for approximately 4hrs every 14 days in the morning after a fast of at least 2hrs.

Number of subjects in period 1	BMN 190-201/202 (300 mg)
Started	24
Completed	17
Not completed	7
Consent withdrawn by subject	1
Withdrawal by Parent/ Guardian	4
Protocol-Specified Withdrawal Criterion Met	2

## Baseline characteristics

### Reporting groups

Reporting group title	Overall period (BMN190-201/202)
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Reporting group description:

Subjects received a BMN 190 300 mg every 14 days for up to Week 239.

Reporting group values	Overall period (BMN190-201/202)	Total	
Number of subjects	24	24	
Age categorical			
The demographic characteristics of the 24 subjects (enrolled population) are summarized for 190-201/202 study.			
Age at Enrollment (yrs) in Study 201			
Units: Subjects			
Children (2-11 years)	24	24	
Age continuous			
The demographic characteristics of the 24 subjects (enrolled population) are summarized for 190-201/202 study.			
Age at Enrollment (yrs) in Study 201.			
Units: years			
arithmetic mean	4.9		
standard deviation	± 1.28	-	
Gender categorical			
The demographic characteristics of the 24 subjects (enrolled population) are summarized for 190-201/202 study.			
Units: Subjects			
Female	15	15	
Male	9	9	
Race			
The demographic characteristics of the 24 subjects (enrolled population) are summarized for 190-201/202 study.			
Units: Subjects			
Asian	1	1	
White	23	23	
Ethnicity			
The demographic characteristics of the 24 subjects (enrolled population) are summarized for 190-201/202 study.			
Units: Subjects			
Hispanic Or Latino	1	1	
Not Hispanic Or Latino	23	23	

## End points

### End points reporting groups

Reporting group title	BMN 190-201/202 (300 mg)
Reporting group description: All study subjects administered BMN 190 300 mg by continuous Intracerebroventricular (ICV) infusion at a rate of 2.5 mL/hour for approximately 4 hours) every 14 days preferably in the morning after a fast of at least 2hrs.	
Subject analysis set title	BMN 190-201/202 (300 mg)
Subject analysis set type	Intention-to-treat
Subject analysis set description: The intent-to-treat (ITT) population: Study 190-202 final efficacy results include pooled data from the complete dataset from Study 190-201 and Study 190-202 for all subjects who received >1 dose (N=23).	

### Primary: Time to unreversed motor-language (ML) 2-point decline or score of 0.

End point title	Time to unreversed motor-language (ML) 2-point decline or score of 0. <sup>[1]</sup>
End point description: ITT population  Time to unreversed ML 2-point decline or score of 0 was analyzed using the Kaplan-Meier method and the Cox proportional hazards model.  The Cox model compared treated (ITT) and 42 natural history (NH) patients adjusting for baseline ML score, age, genotype (common alleles), and sex. This analysis demonstrated a significant reduction on loss of function: hazard ratio=0.14 (p<0.0001).  Motor and Language are each 0-3 point subscales in which 3 represents best function and 0 represents loss of function. Thus, the 0-6 point ML score was used as the primary mode of evaluation of loss of function.	
End point type	Primary
End point timeframe: Up to Week 289.	
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: Statistical analysis was conducted against a population from a natural history study 190-901 Evaluable Population. Due to system limitations, the comparator population cannot be displayed in this format.

End point values	BMN 190-201/202 (300 mg)			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Probability of decline				
number (confidence interval 95%)				
Probability of decline: Week 49 (No. at risk=20)	0.13 (0.04 to 0.35)			
Probability of decline: Week 97 (No. at risk=18)	0.22 (0.10 to 0.45)			
Probability of decline: Week 145 (No. at risk=18)	0.22 (0.10 to 0.45)			
Probability of decline: Week 193 (No. at risk=16)	0.26 (0.13 to 0.50)			
Probability of decline: Week 241 (No. at risk=13)	0.40 (0.23 to 0.63)			

Probability of decline: Week 289 (No. at risk=09)	0.54 (0.35 to 0.75)			
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## Statistical analyses

No statistical analyses for this end point

### Primary: Time to First Unreversed motor-language (ML) Score of Zero.

End point title	Time to First Unreversed motor-language (ML) Score of Zero. <sup>[2]</sup>
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End point description:

ITT population

Time to unreversed ML score of 0 was analyzed using the Kaplan-Meier method and the Cox proportional hazards model.

The Cox model compared treated (ITT) and 42 natural history (NH) patients adjusting for baseline ML score, age, genotype (common alleles), and sex. This analysis demonstrated a significant reduction on loss of function: hazard ratio=0.01 (p<0.0001).

Motor and Language are each 0-3 point subscales in which 3 represents best function and 0 represents loss of function. Thus, the 0-6 point ML score was used as the primary mode of evaluation of loss of function.

End point type	Primary
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End point timeframe:

Up to Week 289

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: Statistical analysis was conducted against a population from a natural history study 190-901 Evaluable Population. Due to system limitations, the comparator population cannot be displayed in this format.

End point values	BMN 190-201/202 (300 mg)			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: Probability of decline				
number (confidence interval 95%)				
Probability of decline: Week 49 (No. at risk=23)	0.00 (0.00 to 0.00)			
Probability of decline: Week 97 (No. at risk=23)	0.00 (0.00 to 0.00)			
Probability of decline: Week 145 (No. at risk=23)	0.00 (0.00 to 0.00)			
Probability of decline: Week 193 (No. at risk=21)	0.05 (0.01 to 0.28)			
Probability of decline: Week 241 (No. at risk=21)	0.05 (0.01 to 0.28)			
Probability of decline: Week 289 (No. at risk=16)	0.15 (0.05 to 0.39)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage change from Baseline to Last Observation: Whole Brain volume

End point title	Percentage change from Baseline to Last Observation: Whole Brain volume
End point description:	
Intent-to-treat (ITT) population	
End point type	Secondary
End point timeframe:	
Baseline to Last observation	

<b>End point values</b>	BMN 190-201/202 (300 mg)			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: Percentage				
arithmetic mean (standard deviation)	-4.7 ( $\pm$ 10.54)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage Change from Baseline to last observation: Volume of cerebrospinal fluid

End point title	Percentage Change from Baseline to last observation: Volume of cerebrospinal fluid
End point description:	
Intent-to-treat (ITT) population	
End point type	Secondary
End point timeframe:	
Baseline to Last observation	

<b>End point values</b>	BMN 190-201/202 (300 mg)			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: Percentage				
arithmetic mean (standard deviation)	8.5 ( $\pm$ 21.94)			



## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage Change from Baseline to last observation: Volume of total cortical gray matter

End point title	Percentage Change from Baseline to last observation: Volume of total cortical gray matter
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End point description:

Intent-to-treat (ITT) population

End point type	Secondary
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End point timeframe:

Baseline to Last observation

<b>End point values</b>	BMN 190-201/202 (300 mg)			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: Percentage				
arithmetic mean (standard deviation)	-14.7 (± 10.25)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage Change from Baseline to last observation: Total white matter volume

End point title	Percentage Change from Baseline to last observation: Total white matter volume
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End point description:

Intent-to-treat (ITT) population

End point type	Secondary
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End point timeframe:

Baseline to Last observation

<b>End point values</b>	BMN 190-201/202 (300 mg)			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: Percentage				
arithmetic mean (standard deviation)	-2.4 ( $\pm$ 12.07)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline to last observation Whole brain apparent diffusion coefficient

End point title	Change from Baseline to last observation Whole brain apparent diffusion coefficient
End point description:	
Intent-to-treat (ITT) population	
End point type	Secondary
End point timeframe:	
Baseline to Last observation	

<b>End point values</b>	BMN 190-201/202 (300 mg)			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: mm <sup>2</sup> /s				
arithmetic mean (standard deviation)	0.00 ( $\pm$ 0.030)			

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up-to Safety Follow-Up (6 months after last dose).

Adverse event reporting additional description:

Subjects who experience more than 1 AE within a given MedDRA system organ class or preferred term were counted once within that system organ class or preferred term.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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### Reporting groups

Reporting group title	BMN 190-201/202
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Reporting group description:

Safety population : Twenty-four (24) subjects were enrolled in Study 190-201 and comprise the safety population for 190-201/202.

Serious adverse events	BMN 190-201/202		
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 24 (87.50%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	7 / 24 (29.17%)		
occurrences causally related to treatment / all	9 / 9		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Vaginal discharge			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal			

disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Adenoidal hypertrophy			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Choking			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sleep apnoea syndrome			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tonsillar hypertrophy			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device end of service			
subjects affected / exposed	13 / 24 (54.17%)		
occurrences causally related to treatment / all	0 / 13		
deaths causally related to treatment / all	0 / 0		
Device leakage			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Device malfunction subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 24 (4.17%) 0 / 1 0 / 0		
Investigations CSF culture positive subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 24 (4.17%) 0 / 2 0 / 0		
Injury, poisoning and procedural complications Device deployment issue subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 24 (8.33%) 0 / 2 0 / 0		
Infusion related reaction subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 24 (4.17%) 2 / 2 0 / 0		
Lower limb fracture subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 24 (4.17%) 0 / 1 0 / 0		
Post procedural haemorrhage subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 24 (4.17%) 0 / 1 0 / 0		
Subdural haematoma subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 24 (4.17%) 0 / 1 0 / 0		
Nervous system disorders Pleocytosis			

subjects affected / exposed	3 / 24 (12.50%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	2 / 24 (8.33%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Generalised tonic-clonic seizure				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhage intracranial				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hemiparesis				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lethargy				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Motor dysfunction				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Status epilepticus				

subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Blindness			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Dental caries			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteonecrosis			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	5 / 24 (20.83%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Pharyngitis bacterial			

subjects affected / exposed	2 / 24 (8.33%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Adenoviral upper respiratory infection				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	2 / 24 (8.33%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile colitis				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Corona virus infection				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mycoplasma infection				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Otitis media				



subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pharyngitis				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pharyngotonsillitis				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Propionibacterium infection				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection viral				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rhinovirus infection				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin infection				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				

subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral pharyngitis			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	7 / 24 (29.17%)		
occurrences causally related to treatment / all	0 / 11		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	1 / 24 (4.17%)		
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 %

<b>Non-serious adverse events</b>	BMN 190-201/202		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 24 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Vascular disorders			
Hypotension			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		
Haematoma			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Surgical and medical procedures			

Tooth extraction subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 3		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)  Gait disturbance subjects affected / exposed occurrences (all)  Abasia subjects affected / exposed occurrences (all)  Complication associated with device subjects affected / exposed occurrences (all)  Developmental delay subjects affected / exposed occurrences (all)  Pain subjects affected / exposed occurrences (all)  Feeling jittery subjects affected / exposed occurrences (all)	20 / 24 (83.33%) 219  12 / 24 (50.00%) 15  3 / 24 (12.50%) 3  3 / 24 (12.50%) 3  3 / 24 (12.50%) 4  2 / 24 (8.33%) 5		
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)  Seasonal allergy subjects affected / exposed occurrences (all)	10 / 24 (41.67%) 16  3 / 24 (12.50%) 4		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	11 / 24 (45.83%) 23		

Epistaxis			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	5		
Rhinorrhoea			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	4		
Tonsillar hypertrophy			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Choking			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	9 / 24 (37.50%)		
occurrences (all)	14		
Insomnia			
subjects affected / exposed	5 / 24 (20.83%)		
occurrences (all)	5		
Irritability			
subjects affected / exposed	5 / 24 (20.83%)		
occurrences (all)	6		
Agitation			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	5		
Abnormal behaviour			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	4		
Product issues			
Device end of service			
subjects affected / exposed	13 / 24 (54.17%)		
occurrences (all)	13		
Device leakage			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	10		
Needle issue			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Device malfunction</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Device issue</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>9 / 24 (37.50%)</p> <p>11</p> <p>4 / 24 (16.67%)</p> <p>9</p> <p>2 / 24 (8.33%)</p> <p>2</p>		
<p>Investigations</p> <p>Body temperature increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>CSF red blood cell count positive</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Oxygen saturation decreased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>CSF test abnormal</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>4 / 24 (16.67%)</p> <p>5</p> <p>3 / 24 (12.50%)</p> <p>3</p> <p>3 / 24 (12.50%)</p> <p>11</p> <p>2 / 24 (8.33%)</p> <p>2</p>		
<p>Injury, poisoning and procedural complications</p> <p>Fall</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Contusion</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Head injury</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Procedural pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Device deployment issue</p>	<p>8 / 24 (33.33%)</p> <p>36</p> <p>8 / 24 (33.33%)</p> <p>11</p> <p>3 / 24 (12.50%)</p> <p>8</p> <p>3 / 24 (12.50%)</p> <p>3</p>		

subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Device difficult to use			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	7		
Laceration			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	6		
Limb injury			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	3		
Lower limb fracture			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Procedural vomiting			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Stoma site reaction			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	3		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	4		
Nervous system disorders			
Generalised tonic-clonic seizure			
subjects affected / exposed	16 / 24 (66.67%)		
occurrences (all)	250		
Seizure			
subjects affected / exposed	14 / 24 (58.33%)		
occurrences (all)	201		
Epilepsy			
subjects affected / exposed	13 / 24 (54.17%)		
occurrences (all)	180		
Tremor			

subjects affected / exposed	11 / 24 (45.83%)		
occurrences (all)	13		
Extensor plantar response			
subjects affected / exposed	9 / 24 (37.50%)		
occurrences (all)	13		
Myoclonus			
subjects affected / exposed	10 / 24 (41.67%)		
occurrences (all)	24		
Petit mal epilepsy			
subjects affected / exposed	8 / 24 (33.33%)		
occurrences (all)	22		
Partial seizures			
subjects affected / exposed	7 / 24 (29.17%)		
occurrences (all)	15		
Pleocytosis			
subjects affected / exposed	6 / 24 (25.00%)		
occurrences (all)	6		
Speech disorder			
subjects affected / exposed	6 / 24 (25.00%)		
occurrences (all)	6		
Language disorder			
subjects affected / exposed	5 / 24 (20.83%)		
occurrences (all)	5		
Dyskinesia			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	11		
Athetosis			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	6		
Headache			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	13		
Ataxia			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		
Atonic seizures			

subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	6		
Myoclonic epilepsy			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	6		
Muscle spasticity			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		
Movement disorder			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		
Seizure cluster			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	7		
Clonus			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Chorea			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Balance disorder			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Drop attacks			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Hypotonia			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Status epilepticus			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Somnolence			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	4		
Dystonia			



subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 3		
Blood and lymphatic system disorders Thrombocytopenia subjects affected / exposed occurrences (all)	5 / 24 (20.83%) 7		
Anaemia subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 3		
Eye disorders Visual impairment subjects affected / exposed occurrences (all)	11 / 24 (45.83%) 16		
Blindness subjects affected / exposed occurrences (all)	4 / 24 (16.67%) 4		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	13 / 24 (54.17%) 22		
Vomiting subjects affected / exposed occurrences (all)	19 / 24 (79.17%) 78		
Dysphagia subjects affected / exposed occurrences (all)	13 / 24 (54.17%) 26		
Dental caries subjects affected / exposed occurrences (all)	5 / 24 (20.83%) 6		
Abdominal pain subjects affected / exposed occurrences (all)	6 / 24 (25.00%) 10		
Diarrhoea subjects affected / exposed occurrences (all)	9 / 24 (37.50%) 19		
Salivary hypersecretion			

subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	4		
Gastrointestinal disorder			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Toothache			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	4		
Teething			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		
Oesophagitis			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	5 / 24 (20.83%)		
occurrences (all)	6		
Rash			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	9		
Urticaria			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Dermatitis diaper			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	10		
Musculoskeletal and connective tissue disorders			

Pain in extremity subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2		
Muscle spasms subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 3		
Infections and infestations			
Upper respiratory tract infection subjects affected / exposed occurrences (all)	21 / 24 (87.50%) 73		
Gastroenteritis subjects affected / exposed occurrences (all)	9 / 24 (37.50%) 15		
Device related infection subjects affected / exposed occurrences (all)	9 / 24 (37.50%) 14		
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	19 / 24 (79.17%) 46		
Rhinitis subjects affected / exposed occurrences (all)	13 / 24 (54.17%) 22		
Conjunctivitis subjects affected / exposed occurrences (all)	6 / 24 (25.00%) 7		
Viral infection subjects affected / exposed occurrences (all)	9 / 24 (37.50%) 16		
Pharyngitis subjects affected / exposed occurrences (all)	7 / 24 (29.17%) 14		
Respiratory tract infection subjects affected / exposed occurrences (all)	6 / 24 (25.00%) 9		
Influenza			

subjects affected / exposed	5 / 24 (20.83%)		
occurrences (all)	5		
Otitis media			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	5		
Rhinovirus infection			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	8		
Bronchitis			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	4		
Lower respiratory tract infection			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	5		
Urinary tract infection			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	8		
Corona virus infection			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Cystitis			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Oral herpes			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	7		
Gastroenteritis viral			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Epstein-Barr virus infection			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	4		
Pharyngitis bacterial			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	3		
Pneumonia			

subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	5		
Tonsillitis bacterial			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Respiratory tract infection viral			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Varicella			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Pyelonephritis			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Tonsillitis			
subjects affected / exposed	5 / 24 (20.83%)		
occurrences (all)	12		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	5		
Decreased appetite			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	4		
Vitamin D deficiency			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	4		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 February 2016	<ul style="list-style-type: none"> <li>• Device definition was added and device malfunction reporting requirements were more clearly defined.</li> <li>• The Ratings Assessment Guidelines were replaced with the document specific to the BMN 190 program.</li> <li>• Added that the 6-month Safety Follow-Up Visit is to be waived for subjects who receive study drug in another BioMarin-sponsored study or registry within the 6-month period to reduce subject burden. AE and SAE reporting instructions were updated for subjects who receive study drug in another BioMarin-sponsored study or registry.</li> <li>• Clarity was added around the timing of device removal for the sake of patient safety, in order to ensure that the device is removed in a timely manner following the end of study drug administration.</li> <li>• The visit window for the MRI was increased to <math>\pm 4</math> weeks to aid with the feasibility of the assessment.</li> <li>• CSF anti-drug immunogenicity testing was removed from the Safety Follow-Up visit because the ICV device and associated infusion system are to be removed from the patient by the time of the visit.</li> <li>• Per Regulatory Agency feedback, modified the inclusion criterion for contraception use to specify that if sexually active and not practicing true abstinence, defined as no sexual activity, males and females of reproductive age were to use a highly effective method of contraception while participating in the study.</li> <li>• The Device Safety Follow-Up Visit was added.</li> </ul>
17 March 2017	<p>Clarified: Vital signs (SBP, DBP, Heart rate (HR), Respiration rate &amp; temperature) measured within 30 (+/-5) min before infusion start/restart, every 30 (+/-5) min during infusion, 0.5 hrs (+/-5 min), 1 hr (+/-5 min) &amp; 4 hrs (+/-15 min) after infusion end, every 4 hrs (+/-15 min) for next 16 hrs</p> <p>To collect accurate BP measurements, BP measured in upper arm using appropriate sized BP cuff. If BP abnormal, manual BP was obtained by trained healthcare professional</p> <p>Subjects with present/past bradycardia, conduction disorders/structural heart disease, ECG (12 lead (HR, Rhythm, Intervals, Axis, Conduction defects &amp; anatomic abnormalities) performed within 30 min before start of infusion (+/-5 min), at 2 hrs (+/-15 min) during infusion, within 15 (+/-5) min after infusion end, &amp; 12 hrs (+/-3 hrs) after infusion end for each study drug infusion</p> <p>Clarified standard ECG performed at first infusion &amp; every 24 wks within 15 (+/-5) min after infusion end</p> <p>Added cardiovascular &amp; ECG AEs as AEs of special interest required reporting to BioMarin Pharmacovigilance, irrespective of severity, seriousness/causality within 24 hrs of study site awareness</p> <p>Revised wording requiring fasting for minimum of 2 hrs before each BMN190 infusion to state fasting could be considered until subject's reaction to study drug was determined. There were no efficacy/safety considerations required fasting</p> <p>Clarified: If needle dislodged during infusion, it could not be reinserted, as sterility would have been compromised</p> <p>Clarified: Medical device was defined as infusion pump &amp; all contact parts (reservoir &amp; catheter, needles, infusion line with filter, extension sets, &amp; syringes) intended to be used for BMN190</p> <p>Clarified: language for pregnancy reporting &amp; monitoring</p> <p>Clarified requirement for IV access line during study drug infusion to allow omitting placement in event there had not been significant infusion-related AEs during prior 3 infusions</p> <p>Clarified: In event ICV device was replaced, next infusion to occur at least 14 days, no more than 28 days</p>

05 May 2017	<ul style="list-style-type: none"> <li>• For at least one infusion of BMN 190 (and preferably the next infusion), continuous ECG monitoring (3- or 5-lead) was performed for all subjects. The ECG was to begin 15 (<math>\pm</math> 5) minutes prior to infusion start, continue through infusion of BMN 190, and end after infusion of flushing solution. If a 12-lead ECG was required during this time, continuous monitoring was to be interrupted in order to obtain the 12-lead ECG.</li> <li>• Revised 12-lead ECG assessment was to occur 30 (<math>\pm</math> 5) minutes after infusion end for all subjects to provide adequate time for the infusion of flushing solution and completion of telemetry prior to the 12-lead ECG assessment.</li> <li>• Added requirement that all removed or replaced implantable ICV devices must be returned to BioMarin in order to evaluate the material integrity of the reservoir, and any other devices (as defined in the protocol) were also to be returned.</li> </ul>
17 December 2018	<ul style="list-style-type: none"> <li>• Updates were made to the immunogenicity assessment section to include serum NAb sample collection. This change was made in response to a Regulatory Agency request to evaluate the presence of neutralizing antibodies to BMN 190 in serum. No changes were made to the frequency or schedule of assessments.</li> <li>• Added clarification that for subjects who do not participate in an extension study or registry after the last dose of study drug, the 4-week device safety follow-up visit and 6-month safety follow-up visit was to capture information regarding ongoing events at the time of the last dose or new events related to study drug.</li> <li>• Re-classified EEG from the list of safety assessment to efficacy assessments as this test provides information regarding changes in electrical activity in the brain while on study drug, but does not provide safety information used to determine whether dose modification or interruption is warranted.</li> <li>• Added that central laboratories (or a central reviewer) were used to evaluate EEG scans in order to standardize review and data presentation, and limit site-associated variability.</li> <li>• Added CLN2 disease rating scale assessment to the 4-week device safety follow-up visit and 6-month safety follow-up visit in order to ascertain whether there were any functional changes associated with any reported AEs.</li> <li>• Added ophthalmology/VA assessment every 12 weeks and OCT every 24 weeks in order to provide additional data to supplement the vision domain of the CLN2 rating scale.</li> <li>• Removed EQ-5D-5L Questionnaire in order to decrease study burden and the determination that the other Quality of Life questionnaires administered may be more relevant to this patient population.</li> </ul>

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported