Clinical trial results:
A Phase 2, Open-Label, Multicenter Study to Evaluate Safety, Tolerability, and Efficacy of Intracerebroventricular BMN 190 in Pediatric Patients < 18 years of age with CLN2 Disease

Summary

EudraCT number	2015-000891-85
Trial protocol	GB IT
Global end of trial date	20 April 2022

Results information

Result version number	v1 (current)
This version publication date	14 March 2023
First version publication date	14 March 2023

Trial information

Trial identification

Sponsor protocol code	190-203

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02678689
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)	Yes
EMA paediatric investigation plan number(s)	EMEA-001362-PIP01-12
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	20 April 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 April 2022
Global end of trial reached?	Yes
Global end of trial date	20 April 2022
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:
• evaluate safety and tolerability of BMN 190 administered via intracerebroventricular (ICV) device
• evaluate treatment effectiveness as a delay in progression of motor-language (ML) score on the Hamburg CLN2 clinical rating scale
• assess immunogenicity of BMN 190 in CSF and serum

Protection of trial subjects:

This clinical study was designed, conducted, recorded, and reported in compliance 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
• US Code of Federal Regulations (CFR) sections that address clinical research studies, and/or other national and local regulations, as applicable.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 January 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	United States: 3
Worldwide total number of subjects	14
EEA total number of subjects	10

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)	5
Children (2-11 years)	9
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:

This was a multi-center study conducted by four principal investigators at four study centers in four countries (Germany, Italy, United Kingdom and United States).

Pre-assignment

Screening details:

A total of 14 participants were enrolled and treated in Study.

Period 1

Period 1 title	BMN190-203 (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	BMN 190-203

Arm description:

All subjects were administered BMN 190 by continuous Intracerebroventricular (ICV) infusion at the rate of 2.5 mL/hour for approximately 1.3 to 4 hours every 14 (+/-3) days.

Arm type	Experimental
Investigational medicinal product name	BMN 190
Investigational medicinal product code	
Other name	recombinant human tripeptidyl peptidase-1 (rhTPP1), cerliponase alfa
Pharmaceutical forms	Solution for infusion
Routes of administration	Intracerebroventricular use

Dosage and administration details:

BMN 190 was administered by continuous Intracerebroventricular (ICV) infusion at the rate of 2.5 mL/hour for approximately 4 hours every 14 (+-3) days, according to the participant's age: Birth to < 6 months: 100 mg, 6 months to < 1 year: 150 mg, 1 year to < 2 years: 200 mg (first four doses), 300 mg (subsequent doses) >=2 years: 300 mg.

Number of subjects in period 1	BMN 190-203
Started	14
Completed	13
Not completed	1
Parent/Guardian choice	1

Baseline characteristics

Reporting groups	
Reporting group title	BMN190-203
Reporting group description:	
Subjects received BMN 190 every 14 days for up to Week 144.	

Reporting group values	BMN190-203	Total	
Number of subjects	14	14	
Age categorical			
The demographic characteristics of the 14 subjects (enrolled population) are summarized for 190- 203 study.			
Units: Subjects			
< 2	5	5	
>= 2	9	9	
Gender categorical			
The demographic characteristics of the 14 subjects (enrolled population) are summarized for 190-203 study.			
Units: Subjects			
Female	8	8	
Male	6	6	
Race			
The demographic characteristics of the 14 subjects (enrolled population) are summarized for 190-203 study.			
Units: Subjects			
White	14	14	
Ethnicity			
The demographic characteristics of the 14 subjects (enrolled population) are summarized for 190-203 study			
Units: Subjects			
Hispanic or Latino	2	2	
Not Hispanic or Latino	12	12	
Age Category			
The demographic characteristics of the 14 subjects (enrolled population) are summarized for 190- 203 study.			
Units: Subjects			
< 3	8	8	
>=3	6	6	
Age at Enrollment, years			
The demographic characteristics of the 14 subjects (enrolled population) are summarized for 190 203 study.			
Units: Years			
arithmetic mean	3.0		
standard deviation	± 1.46	-	
Age at Baseline, years			
Units: Years			
arithmetic mean	3.1		
standard deviation	± 1.45	-	
CLN2 motor-language (ML) score at Baseline			

The demographic characteristics of the 14 subjects (enrolled population) are summarized for 190-203 study.			
Units: score on scale			
arithmetic mean	4.6		
standard deviation	± 1.69	-	
CLN2 motor scale score at Baseline			
The demographic characteristics of the 14 subjects (enrolled population) are summarized for 190-203 study.			
Units: Score on a scale			
arithmetic mean	2.3		
standard deviation	± 0.83	-	
CLN2 language scale score at Baseline			
The demographic characteristics of the 14 subjects (enrolled population) are summarized for 190-203 study.			
Units: Score on a scale			
arithmetic mean	2.4		
standard deviation	± 0.93	-	

End points

End points reporting groups

Reporting group title	BMN 190-203

Reporting group description:

All subjects were administered BMN 190 by continuous Intracerebroventricular (ICV) infusion at the rate of 2.5 mL/hour for approximately 1.3 to 4 hours every 14 (+/-3) days.

Subject analysis set title	Matched ITT BMN 190-203
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Two participants in the 190-203 ITT population (N = 14) were excluded from the 190-203 ITT analysis with matching (N = 12) who did not match with any 190-901 participants on the matching criteria.
The matching criteria at baseline were:
• Equal ML score
• Age within 3 months
• Genome: equal number of common alleles (c.622CT, c.509.1GC)

Primary: Motor Language (ML) Scale: Rate of Decline in the 0 to 6-point ML score.

End point title	Motor Language (ML) Scale: Rate of Decline in the 0 to 6-point ML score.[1]

End point description:

The rate of decline in the 0 to 6-point ML score, and the primary analysis was based on up to 3-1 matching of Study 190-901 evaluable participants with Study 190-203 ITT participants.
Rate of decline = (-1) x (48 x 7) x (Ending score - Starting score)/(Ending date - Starting date)

ML score decline is measured by motor and language domains on the CLN2 rating scale (which ranges from 0 to 6, with 0 representing no function and 3 representing normal function in each of the two domains).

There was a statistically significant attenuation of the rate of decline on the ML scale for the matched 190-203 ITT participants when compared with the rate of decline in untreated 190- 901 evaluable participants, as demonstrated by a mean difference between groups (901-203) of 1.15 points (SE 0.174); 95% CI, 0.80, 1.50 points; $p < 0.0001$. These results show a significant treatment benefit for participants treated with BMN 190 compared with matched natural history participants.

End point type	Primary

End point timeframe:

Baseline to Week 48.

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	Matched ITT BMN 190-203			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: Points per 48 weeks				
arithmetic mean (standard deviation)	0.15 (± 0.243)			

Statistical analyses

No statistical analyses for this end point

Primary: Time to Unreversed 2-Point Decline or Score of 0 in ML Score

End point title	Time to Unreversed 2-Point Decline or Score of 0 in ML Score[2]

End point description:

An unreversed 2-point decline is any decline of 2 points or more that had not reversed to a 1-point decline (or better) at the last recorded observation. An unreversed score of 0 is a decline to 0 that had not increased to a score > 0 at last recorded observation.

ML score decline is measured by motor and language domains on the CLN2 rating scale (which ranges from 0 to 6, with 0 representing no function and 3 representing normal function in each of the two domains).

Time to unreversed 2-point decline or score of 0 in ML score by last assessment relative to baseline, was analyzed using Kaplan-Meier methods and the Cox proportional hazards model. A Cox proportional hazards model of time to unreversed 2-point decline or score of 0 in ML score demonstrated a statistically significant difference in matched 190-203 ITT participants as compared to matched 190-901 evaluable participants (hazard ratio, 0.091; 95% CI, 0.021 to 0.393; p < 0.0001).

End point type	Primary

End point timeframe:

Baseline to Week 49, Week 97, and Week 145.

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	Matched ITT BMN 190-203			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: Probability of decline				
number (confidence interval 95%)				
Probability of decline: Week 49 (No. at risk=12)	0.0 (0.00 to 0.00)			
Probability of decline: Week 97 (No. at risk=11)	0.083 (0.01 to 0.46)			
Probability of decline: Week 145 (No. at risk=10)	0.167 (0.04 to 0.52)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change from Baseline to Last Assessment: Volume of cerebrospinal fluid

End point title	Percentage Change from Baseline to Last Assessment: Volume of cerebrospinal fluid

End point description:

Intent-to-treat (ITT) population.

End point type	Secondary

End point timeframe:

Baseline to Last Assessment

End point values	BMN 190-203			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Percentage				
arithmetic mean (standard deviation)	0.7 (± 13.18)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change from Baseline to Last Assessment: Volume of Total Cortical Gray Matter

End point title	Percentage Change from Baseline to Last Assessment: Volume of Total Cortical Gray Matter

End point description:

Intent-to-treat (ITT) population.

End point type	Secondary

End point timeframe:

Baseline to Last Assessment

End point values	BMN 190-203			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Percentage				
arithmetic mean (standard deviation)	-10.3 (± 13.86)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change from Baseline to Last Assessment: Volume of Total White Matter

End point title	Percentage Change from Baseline to Last Assessment: Volume of Total White Matter

End point description:

End point type	Secondary

End point timeframe:

Baseline to Last Assessment

End point values	BMN 190-203			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Percentage				
arithmetic mean (standard deviation)	5.4 (± 20.86)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Last Assessment: Whole Brain Apparent Diffusion Coefficient Value

End point title	Change from Baseline to Last Assessment: Whole Brain Apparent Diffusion Coefficient Value

End point description:

End point type	Secondary

End point timeframe:

Baseline to Last Assessment

End point values	BMN 190-203			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: mm^2/s				
arithmetic mean (standard deviation)	-2.5 (± 4.60)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Disease Manifestation

End point title	Time to Disease Manifestation

End point description:

Time of disease manifestation is defined as time of the first of the two measurements demonstrating the deficit. Time to disease manifestation was assessed for pre-symptomatic participants, defined as having MLVS=12. MLVS is the combined score of motor, language, vision, seizure subscales on the CLN2 disease rating scale. Within each domain, a score from 0 to 3 is assigned and overall scores are calculated by summing the four domain scores for a final rating of 0 (severely impaired) to 12 (normal).

Subsequent disease manifestation is defined as post-baseline consecutive measurements of M, L, V, or S scores <3, measured at least 22 days apart.

Median (95% CI) time to disease manifestation was 67(34, 94) wks in history participants vs median not reached in 190-203 participants.

End point type	Secondary

End point timeframe:

Baseline to Week 49, Week 97, and Week 145.

End point values	Matched ITT BMN 190-203			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: Probability of decline				
number (confidence interval 95%)				
Probability of decline: Week 49 (No. at risk=6)	0.143 (0.02 to 0.67)			
Probability of decline: Week 97 (No. at risk=5)	0.286 (0.08 to 0.74)			
Probability of decline: Week 145 (No. at risk=4)	0.429 (0.16 to 0.83)			

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).Respiratory syncytial virus infection.

Adverse event reporting additional description:

Atrioventricular block 2nd degree assessed as non-serious by inv. later upgraded to SAE by BioMarin in safety database based on medical sig. Inv. assessed AE as not related to BMN190;however,due to absence of alternative etiological factors & strong temporal relationship,BioMarin conservatively assessed AE to be possibly related to BMN190 as SUSAR.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	BMN 190-203

Reporting group description:

Safety population : All enrolled participants (N = 14) had an ICV reservoir implanted and were included in the Safety Population.

One AE of atrioventricular block was considered as non-serious event per clinical database and excluded form SAE.

Serious adverse events	BMN 190-203		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 14 (85.71%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Propionibacteriu m test positive			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Periorbital haematoma			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Pleocytosis			

subjects affected / exposed	1 / 14 (7.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Status epilepticus				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Complication of device insertion				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Medical device site haematoma				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Medical device site irritation				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	4 / 14 (28.57%)			
occurrences causally related to treatment / all	1 / 7			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Anaphylactic reaction				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypersensitivity				
subjects affected / exposed	2 / 14 (14.29%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			

Ear and labyrinth disorders			
Deafness unilateral			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Dental caries			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Dysphagia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal fistula			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Adenoidal hypertrophy			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Coronavirus infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Escherichia urinary tract infection			

subjects affected / exposed	1 / 14 (7.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	2 / 14 (14.29%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Mycoplasma infection				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rhinitis				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rhinovirus infection				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				

subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device leakage			
subjects affected / exposed	1 / 14 (7.14%)		
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 190-203		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 14 (100.00%)		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	12 / 14 (85.71%)		
occurrences (all)	62		
Asthenia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Chills			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		

Complication of device insertion subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Gait disturbance subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 2		
Malaise subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Medical device site haematoma subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Medical device site irritation subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Medical device site swelling subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Pain subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	4 / 14 (28.57%) 20		
Anaphylactic reaction subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Drug hypersensitivity subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Seasonal allergy subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Reproductive system and breast disorders			

Vaginal discharge			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 14 (28.57%)		
occurrences (all)	9		
Adenoidal hypertrophy			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Epistaxis			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	8		
Nasal congestion			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	4		
Hypoxia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Respiratory disorder			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Rhinitis allergic			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Stridor			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Psychiatric disorders			

Insomnia			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Sleep disorder			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Attention deficit/hyperactivity disorder			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Irritability			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Product issues			
Device leakage			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	4		
Needle issue			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	3		
Device breakage			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Device malfunction			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Investigations			
Viral test positive			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Body temperature increased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	4		
CSF red blood cell count positive			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Electrocardiogram abnormal			

subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Electroencephalogram abnormal			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Hepatic enzyme increased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Human rhinovirus test positive			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Propionibacterium test positive			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Respiratory syncytial virus test			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Respirovirus test positive			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	4 / 14 (28.57%)		
occurrences (all)	8		
Medication monitoring error			
subjects affected / exposed	4 / 14 (28.57%)		
occurrences (all)	4		
Foreign body			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	3		
Skin abrasion			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	3		
Eyelid contusion			

subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Fall			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Foot fracture			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Head injury			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Laceration			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Periorbital haematoma			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Periorbital haemorrhage			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Procedural pain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Congenital, familial and genetic disorders			
Bicuspid aortic valve			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Talipes			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Cardiac disorders			
Atrioventricular block second degree			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Nervous system disorders			

Extensor plantar response subjects affected / exposed occurrences (all)	7 / 14 (50.00%) 7			
Generalised tonic-clonic seizure subjects affected / exposed occurrences (all)	6 / 14 (42.86%) 18			
Atonic seizures subjects affected / exposed occurrences (all)	3 / 14 (21.43%) 4			
Dystonia subjects affected / exposed occurrences (all)	3 / 14 (21.43%) 3			
Partial seizures subjects affected / exposed occurrences (all)	3 / 14 (21.43%) 28			
Seizure subjects affected / exposed occurrences (all)	3 / 14 (21.43%) 8			
Speech disorder developmental subjects affected / exposed occurrences (all)	3 / 14 (21.43%) 3			
Dyskinesia subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 34			
Epilepsy subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 3			
Tremor subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2			
Athetosis subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1			
Febrile convulsion subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 2			

Headache subjects affected / exposed occurrences (all) Language disorder subjects affected / exposed occurrences (all) Myoclonic epilepsy subjects affected / exposed occurrences (all) Partial seizures with secondary generalisation subjects affected / exposed occurrences (all) Petit mal epilepsy subjects affected / exposed occurrences (all) Pleocytosis subjects affected / exposed occurrences (all) Seizure cluster subjects affected / exposed occurrences (all) Status epilepticus subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 2 1 / 14 (7.14%) 2 1 / 14 (7.14%) 4 1 / 14 (7.14%) 2 1 / 14 (7.14%) 3 1 / 14 (7.14%) 1 1 / 14 (7.14%) 1 1 / 14 (7.14%) 1		
Ear and labyrinth disorders Deafness unilateral subjects affected / exposed occurrences (all) Ear haemorrhage subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1 1 / 14 (7.14%) 1		
Eye disorders Visual impairment subjects affected / exposed occurrences (all) Dry eye	2 / 14 (14.29%) 2		

subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Eye movement disorder			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	11		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	5 / 14 (35.71%)		
occurrences (all)	7		
Dysphagia			
subjects affected / exposed	4 / 14 (28.57%)		
occurrences (all)	5		
Constipation			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	3		
Abdominal pain			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Dental caries			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	5		
Stomatitis			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Aphthous ulcer			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Gastrointestinal fistula			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		

Toothache			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	4		
Dermatitis atopic			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Eczema			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Rash generalised			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Rash macular			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Urinary retention			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Pain in jaw			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Infections and infestations			
Upper respiratory tract infection			

subjects affected / exposed	12 / 14 (85.71%)			
occurrences (all)	26			
Gastroenteritis				
subjects affected / exposed	7 / 14 (50.00%)			
occurrences (all)	10			
Influenza				
subjects affected / exposed	4 / 14 (28.57%)			
occurrences (all)	6			
Corona virus infection				
subjects affected / exposed	3 / 14 (21.43%)			
occurrences (all)	4			
Rhinitis				
subjects affected / exposed	3 / 14 (21.43%)			
occurrences (all)	5			
Viral upper respiratory tract infection				
subjects affected / exposed	3 / 14 (21.43%)			
occurrences (all)	4			
Bronchitis				
subjects affected / exposed	2 / 14 (14.29%)			
occurrences (all)	3			
Otitis media				
subjects affected / exposed	2 / 14 (14.29%)			
occurrences (all)	2			
Parainfluenzae virus infection				
subjects affected / exposed	2 / 14 (14.29%)			
occurrences (all)	2			
Tonsillitis				
subjects affected / exposed	2 / 14 (14.29%)			
occurrences (all)	2			
Ear infection				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	1			
Escherichia urinary tract infection				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	2			
Exanthema subitum				

subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	1			
Fungal skin infection				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	1			
Hordeolum				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	3			
Infection				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	1			
Laryngitis				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	1			
Mycoplasma infection				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	1			
Otitis externa				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	1			
Paronychia				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	1			
Pharyngitis				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	1			
Pharyngotonsillitis				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	1			
Pneumonia				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	3			
Pneumonia chlamydial				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	1			
Pyelonephritis				

subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Pyuria			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Respiratory tract infection viral			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Rhinovirus infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Rotavirus infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Urinary tract infection bacterial			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Viral infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hypernatraemia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 January 2017	Implemented following agreed measures from modified BMN 190 paediatric investigation plan as set out in European Medicines Agency decision(P/0248/2016)dated 05 September 2016. This global protocol amendment superseded the previously implemented original & US-specific versions of protocol: o Added secondary study objective to assess serial CSF & plasma PK on Day 1,& Weeks 25, 49, & 97 to characterize the PK profile at the recommended doses o Added secondary study objective to assess time to disease manifestation for asymptomatic participants to better characterize the development of symptoms not captured by change in the CLN2 ML scale o Per Agency request, removed inclusion criterion requiring the participant to have at least 1 sibling with confirmed CLN2 disease who was enrolled in Study 190-201 o Added inclusion criterion requiring abstinence or a highly effective method of contraception while participating in the study & until 6 months after the study has been completed(or withdrawal from the study) o Modified BMN 190 dosing plan from 300mg administered every 14 days(+/-3 days)to dosing every 14 days (+/-3 days) according to the participant's age: ▪ birth to <6 months:100mg ▪ 6 months to <1 year:150mg ▪ 1 year to <2 years:200mg(first 4 doses),300 mg(subsequent doses) ▪ >=2 years:300mg This change was implemented in order to describe dosing for participants who may be enrolled & are younger than 2 years of age o Changed timing of Hamburg CLN2 disease rating scale administration from once every 12 weeks to once every 4 weeks in order to have more frequent assessments of clinical function; the complete Hamburg CLN2 scale(motor, language, vision, & seizure subscales)will be administered for each assessment. Rating scale assessments will be videotaped every 12 weeks o Added follow-up plan that all participants will be offered participation in a follow-up registry that will assess long-term safety & efficacy of BMN 190 for patients
17 March 2017	o Clarified that vital signs (SBP, DBP, heart rate, respiration rate, and temperature) will be measured within 30 (±5) minutes before infusion start (or restart), every 30 (±5 minutes) during infusion, 0.5 hours (±5 minutes), 1 hour (±5 minutes), and 4 hours (±15 minutes) after infusion end, and then every 4 hours (±15 minutes) for the next 16 hours. o In order to collect more accurate blood pressure measurements, added that blood pressure will be measured in the upper arm using an appropriately sized blood pressure cuff. If the participant's blood pressure is abnormal (as compared to site-specific reference ranges), a manual blood pressure will be obtained by a trained healthcare professional. o Added that in participants with present or past bradycardia, conduction disorders, or with structural heart disease, an ECG (12-lead) (heart rate, rhythm, intervals, axis, conduction defects, and anatomic abnormalities) will be performed within 30 minutes before the start of infusion (±5 minutes), at 2 hours (±15 minutes) during infusion, within 15 (±5) minutes after infusion end, and 12 hours (±3 hours) after infusion end for each study drug administration. o Clarified that a standard ECG (12-lead) will be performed at the first infusion and every 24 weeks thereafter within 15 (±5) minutes after infusion end. o Added cardiovascular and ECG adverse events as AESI that require reporting to BioMarin Pharmacovigilance (BPV), irrespective of severity, seriousness, or causality within 24 hours of a study site awareness. o Clarified that in the event that the ICV device is replaced, the next infusion will occur at least 14 days and no more than 28 days after surgery. o Added dose selection rationale supporting the uniform infusion rate of 2.5 mL/hour for all participants, thus requiring shorter total infusion times for participants administered doses lower than 300 mg.

05 May 2017	Implemented Regulatory Agency recommendation to increase ECG monitoring to further characterize possible acute cardiac effects of BMN 190; and to enroll at least 5 participants < 2 years of age. Significant changes were as follows: o For the first infusion of BMN 190, continuous ECG monitoring (3- or 5-lead) will be performed for all participants. The ECG should begin 15 (± 5) minutes prior to infusion start, continue through infusion of BMN 190, and end after infusion of flushing solution. In the event that the participant has already received the first infusion of BMN 190, the next infusion will be monitored as above. If a 12-lead ECG is required during this time, continuous monitoring should be interrupted in order to obtain the 12-lead ECG. o Revised 12-lead ECG assessment to occur 30 (± 5) minutes after infusion end for all participants to provide adequate time for the infusion of flushing solution and completion of telemetry prior to the 12-lead ECG assessment. o Added requirement that at least 5 participants < 2 years of age are enrolled. o 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) should also be returned.
20 October 2017	Extended the study duration from 96 to 144 weeks and clarified study procedures during the extended study duration. Significant changes were as follows: o Modified the study duration to 144 weeks globally. The 48-week increase in treatment was implemented to increase the power of the study to show a treatment benefit for the study drug and to obtain additional safety data. o Revised Schedule of Events to indicate study procedures that will be performed from Week 96 to 144. o Frequency of complete physical examination changed from every 24 weeks to every 48 weeks to decrease burden to the participants. The frequency of the brief physical exam remains unchanged (every 2 weeks). o Updates were made to the immunogenicity assessment section to include serum neutralizing antibodies (Nab) sample collection. This change was made in response to Regulatory Agency request to evaluate the presence of neutralizing antibodies to BMN 190 in serum. No changes are being made to the frequency or schedule of assessments.
17 December 2018	o Added clarification that for participants who do not participate in an extension study or registry after last dose of study drug, 4-week device safety follow-up visit & 6-month safety follow-up visit will capture information regarding ongoing events at the time of last dose or new events related to study drug o Added that central laboratories(or a central reviewer)will be used to evaluate EEG scans in order to standardize review & data presentation, & limit siteassociated variability o Added CLN2 disease rating scale assessment to 4-week device safety follow-up visit & 6-month safety follow-up visit in order to ascertain whether there were any functional changes associated with any reported adverse events o Removed Infant-Toddler Quality of Life Questionnaire in order to decrease study burden & in acknowledgement that other Quality of Life questionnaires administered may be more relevant to this patient population o Removed EQ-5D-5L Questionnaire in order to decrease study burden & in acknowledgement that other Quality of Life questionnaires administered may be more relevant to this patient population o Clarified that EEGs should be performed every 24 weeks, including end of treatment visit o Added updated information that material degradation of ICV device reservoir has occurred after approximately 105 perforations of ICV device in benchtop testing, & has been observed in clinical trials with approximately 4 years of BMN 190 administration. Access device replacement should be considered prior to 4 years of regular administration of BMN 190; with decision made on an individual participant level based on medical judgment of investigator o Assessment of height & body weight has been changed from every 48 weeks to every 24 weeks to permit additional monitoring of growth milestones o Clarified that, in event of a device-related AE where device & its components should be returned to BioMarin for further testing, infusion pump does not need to be returned

05 February 2019	Corrected an error in Protocol 190-203 Amendment 5 in which "Ophthalmology Assessments" (Baseline/First Infusion, Q48W, Study Completion/Early Termination) was inadvertently removed from the Schedule of Events (Table 9.1.1) and Study Procedures (Section 12). Ophthalmologic assessments for the 190-203 protocol should continue to be performed before the first infusion and every 48 weeks for the duration of the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported