



## Clinical trial results:

### A Phase 1/2 Open-Label Dose-Escalation Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Efficacy of Intracerebroventricular BMN 190 in Patients with Late-Infantile Neuronal Ceroid Lipofuscinosis (CLN2) Disease

#### Summary

EudraCT number	2012-005430-11
Trial protocol	GB DE IT
Global end of trial date	30 November 2015

#### Results information

Result version number	v1 (current)
This version publication date	30 June 2019
First version publication date	30 June 2019

#### Trial information

##### Trial identification

Sponsor protocol code	190-201
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01907087
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)	EMA-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	27 April 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 November 2015
Global end of trial reached?	Yes
Global end of trial date	30 November 2015
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 safety and tolerability of BMN 190 administered to subjects with CLN2 by an implanted intracerebroventricular (ICV) reservoir and cannula.

To evaluate effectiveness using a CLN2-specific rating scale score in comparison with natural history data after 12 months of treatment.

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	13 September 2013
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	United Kingdom: 3
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	United States: 3
Worldwide total number of subjects	24
EEA total number of subjects	21

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:

This study was conducted at 5 clinic sites in Germany, Italy, United Kingdom and United States.

### Pre-assignment

Screening details:

Of the 24 subjects enrolled to study, 23 subjects remained on treatment through the end of the study.

### Period 1

Period 1 title	All Participants Intervention (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	No
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<b>Arm title</b>	Dose Escalation Period - Cohort 1
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Arm description:

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

Subjects 1 to 3 (Cohort 1) assigned to the 30mg dose, then escalated to 100mg and 300mg after data review.

Arm type	Experimental
Investigational medicinal product name	BMN 190
Investigational medicinal product code	
Other name	recombinant human tripeptidyl peptidase 1 (rhTPP1)
Pharmaceutical forms	Infusion
Routes of administration	Intracerebroventricular use

Dosage and administration details:

All study subjects administered BMN 190 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.

Subjects 1 to 3 (Cohort 1) assigned to the 30mg dose, then escalated to 100mg and 300mg after data review.

<b>Arm title</b>	Dose Escalation Period - Cohort 2
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Arm description:

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

Subjects 4 to 6 (Cohort 2) assigned to the 100mg dose, then escalated to 300mg after data review.

Arm type	Experimental
Investigational medicinal product name	BMN 190
Investigational medicinal product code	
Other name	recombinant human tripeptidyl peptidase 1 (rhTPP1)
Pharmaceutical forms	Infusion
Routes of administration	Intracerebroventricular use

Dosage and administration details:

All study subjects administered BMN 190 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.

Subjects 4 to 6 (Cohort 2) assigned to the 100mg dose, then escalated to 300mg after data review.

<b>Arm title</b>	Dose Escalation Period - Cohort 3
Arm description:	
All study subjects administered BMN 190 by continuous Intracerebroventricular (ICV) infusion at 2.5mL/hr for approximately 4hrs every 14 days in the morning after a fast of at least 2hrs.	
Subjects 7 to 10 (Cohort 3) assigned to the 300mg dose.	
Arm type	Experimental
Investigational medicinal product name	BMN 190
Investigational medicinal product code	
Other name	recombinant human tripeptidyl peptidase 1 (rhTPP1)
Pharmaceutical forms	Infusion
Routes of administration	Intracerebroventricular use

Dosage and administration details:

All study subjects administered BMN 190 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.

Subjects 7 to 10 (Cohort 3) assigned to the 300mg dose.

<b>Arm title</b>	Stable Dose Period - Stable Dose Only
Arm description:	
All study subjects administered BMN 190 by continuous Intracerebroventricular (ICV) infusion at 2.5mL/hr for approximately 4hrs every 14 days in the morning after a fast of at least 2hrs.	
Of 9 subjects from Dose Escalation cohorts rolling over into the 48-week Stable Dose Period with 14 subjects enrolled directly, counting 23 during this Stable Dose Period, all subjects were administered BMN 190 infusions of 300 mg for 48 weeks.	
Arm type	Experimental
Investigational medicinal product name	BMN 190
Investigational medicinal product code	
Other name	recombinant human tripeptidyl peptidase 1 (rhTPP1)
Pharmaceutical forms	Infusion
Routes of administration	Intracerebroventricular use

Dosage and administration details:

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

Of 9 subjects from Dose Escalation cohorts rolling over into the 48-week Stable Dose Period with 14 subjects enrolled directly, counting 23 during this Stable Dose Period, all subjects were administered BMN 190 infusions of 300 mg for 48 weeks.

<b>Number of subjects in period 1</b>	Dose Escalation Period - Cohort 1	Dose Escalation Period - Cohort 2	Dose Escalation Period - Cohort 3
Started	3	3	4
Completed	3	3	3
Not completed	0	0	1
Withdrew consent	-	-	1

<b>Number of subjects in period 1</b>	Stable Dose Period - Stable Dose Only
Started	23
Completed	23
Not completed	0
Withdrew consent	-



## Baseline characteristics

### Reporting groups

Reporting group title	All Participants Intervention
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Reporting group description: -

Reporting group values	All Participants Intervention	Total	
Number of subjects	24	24	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	4.3 ± 1.24	-	
Gender categorical Units: Subjects			
Female	15	15	
Male	9	9	
Race Units: Subjects			
Asian	1	1	
White	23	23	
Ethnicity Units: Subjects			
Hispanic or Latino	1	1	
Not Hispanic or Latino	23	23	

## End points

### End points reporting groups

Reporting group title	Dose Escalation Period - Cohort 1
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Reporting group description:

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

Subjects 1 to 3 (Cohort 1) assigned to the 30mg dose, then escalated to 100mg and 300mg after data review.

Reporting group title	Dose Escalation Period - Cohort 2
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Reporting group description:

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

Subjects 4 to 6 (Cohort 2) assigned to the 100mg dose, then escalated to 300mg after data review.

Reporting group title	Dose Escalation Period - Cohort 3
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Reporting group description:

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

Subjects 7 to 10 (Cohort 3) assigned to the 300mg dose.

Reporting group title	Stable Dose Period - Stable Dose Only
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Reporting group description:

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

Of 9 subjects from Dose Escalation cohorts rolling over into the 48-week Stable Dose Period with 14 subjects enrolled directly, counting 23 during this Stable Dose Period, all subjects were administered BMN 190 infusions of 300 mg for 48 weeks.

Subject analysis set title	300 mg BMN 190
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

The intent-to-treat (ITT) population comprises all study subjects who received any amount of study drug and report any efficacy results, excluding one subject who withdrew from the study after a single infusion of study drug. The defined ITT population has 23 enrolled subjects that received > 1 dose of study drug.

### Primary: Motor-Language (ML) Scale Score During 300 mg Dosing Period

End point title	Motor-Language (ML) Scale Score During 300 mg Dosing Period <sup>[1]</sup>
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End point description:

Intent-to-treat (ITT) population

The progression of ceroid lipofuscinosis (CLN2) disease was assessed using adapted motor and language domains of the Hamburg rating scale (ML scale score). Motor and Language are each 0 - 3 point subscales in which 3 represents best function and 0 represents loss of function. The sum of the motor and language scores (ML score, 0-6 points) was used to evaluate the loss of function.

End point type	Primary
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End point timeframe:

Baseline, Week 49/Last Assessment

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: The primary endpoint is a responder analysis based on the ITT population: absence of an unreversed two-point decline or score of zero in CLN2 score by Week 48 (Study Day 340 relative to first 300 mg infusion). The study met the primary endpoint with 20 of 23 (87%) subjects responding

compared to an expected response rate of 50% ( $p = 0.0002$ ).

A 'response' is defined as the absence of an unreversed two-point decline or score of 0 in the 0-to-6 point CLN2 score at 48 weeks.

<b>End point values</b>	300 mg BMN 190			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: unit on scale				
arithmetic mean (standard deviation)				
Baseline	3.5 ( $\pm 1.20$ )			
Last Recorded Observation	3.1 ( $\pm 1.41$ )			
Change from Baseline to Last Recorded Observation	-0.4 ( $\pm 0.84$ )			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage Change From Baseline of Magnetic Resonance Imaging (MRI) at Week 49 During 300 mg Dosing Period: Whole Brain Volume

End point title	Percentage Change From Baseline of Magnetic Resonance Imaging (MRI) at Week 49 During 300 mg Dosing Period: Whole Brain Volume			
End point description:	ITT Population			
	Percentage changes in whole brain volume from the ITT population for the 300 mg dosing period			
End point type	Secondary			
End point timeframe:	Baseline, Week 49			

<b>End point values</b>	300 mg BMN 190			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: percentage change from baseline				
arithmetic mean (standard deviation)	-4.4 ( $\pm 8.46$ )			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage Change From Baseline of Magnetic Resonance Imaging (MRI) at Week 49 During 300 mg Dosing Period: Volume of Total Grey Matter

End point title	Percentage Change From Baseline of Magnetic Resonance Imaging (MRI) at Week 49 During 300 mg Dosing Period:			
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End point description:

ITT Population

Percentage changes in volume of total grey matter from the ITT population for the 300 mg dosing period

End point type Secondary

End point timeframe:

Baseline, Week 49

<b>End point values</b>	300 mg BMN 190			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Percentage change from baseline				
arithmetic mean (standard deviation)	-9.7 ( $\pm$ 8.08)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage Change From Baseline of Magnetic Resonance Imaging (MRI) at Week 49 During 300 mg Dosing Period: Total White Matter Volume

End point title Percentage Change From Baseline of Magnetic Resonance Imaging (MRI) at Week 49 During 300 mg Dosing Period: Total White Matter Volume

End point description:

ITT Population

Percentage changes in total white matter volume from the ITT population for the 300 mg dosing period

End point type Secondary

End point timeframe:

Baseline, Week 49

<b>End point values</b>	300 mg BMN 190			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: percentage change from baseline				
arithmetic mean (standard deviation)	-4.2 ( $\pm$ 9.58)			

### Statistical analyses

No statistical analyses for this end point

**Secondary: Percentage Change From Baseline of Magnetic Resonance Imaging (MRI) at Week 49 During 300 mg Dosing Period: Volume of Cerebrospinal Fluid**

End point title	Percentage Change From Baseline of Magnetic Resonance Imaging (MRI) at Week 49 During 300 mg Dosing Period: Volume of Cerebrospinal Fluid
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End point description:

ITT population

Percentage changes in volume of cerebrospinal fluid from the ITT population for the 300 mg dosing period

End point type	Secondary
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End point timeframe:

Baseline, Week 49

<b>End point values</b>	300 mg BMN 190			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: percentage change from baseline				
arithmetic mean (standard deviation)	3.6 (± 15.3)			

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Percentage Change From Baseline of Magnetic Resonance Imaging (MRI) at Week 49 During 300 mg Dosing Period: Whole Brain Apparent Diffusion Coefficient**

End point title	Percentage Change From Baseline of Magnetic Resonance Imaging (MRI) at Week 49 During 300 mg Dosing Period: Whole Brain Apparent Diffusion Coefficient
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End point description:

ITT Population

Percentage changes in whole brain apparent diffusion coefficient from the ITT population for the 300 mg dosing period

End point type	Secondary
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End point timeframe:

Baseline, Week 49

<b>End point values</b>	300 mg BMN 190			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Percentage change from baseline				
arithmetic mean (standard deviation)	0.02 (± 0.023)			

## **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 85 weeks (60 weeks + 6 months safety follow up)

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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### Reporting groups

Reporting group title	Adverse Events
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Reporting group description: -

Serious adverse events	Adverse Events		
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 24 (66.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Subdural haematoma			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Epilepsy			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences causally related to treatment / all	0 / 2		
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		
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		
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	6 / 24 (25.00%)		
occurrences causally related to treatment / all	8 / 8		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Dental caries			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
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			
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		
Infections and infestations			

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			
Gastroenteritis				
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			
Pharyngitis				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pharyngitis bacterial				
subjects affected / exposed	2 / 24 (8.33%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	0 / 1			
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			
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			
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		

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

<b>Non-serious adverse events</b>	Adverse Events		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 24 (100.00%)		
General disorders and administration site conditions			
Developmental delay			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		
Feeling jittery			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	4		
Gait disturbance			
subjects affected / exposed	7 / 24 (29.17%)		
occurrences (all)	7		
Needle issue			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	13 / 24 (54.17%)		
occurrences (all)	87		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	6		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 24 (20.83%)		
occurrences (all)	8		
Psychiatric disorders			

Abnormal behaviour subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 3		
Agitation subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2		
Insomnia subjects affected / exposed occurrences (all)	4 / 24 (16.67%) 4		
Irritability subjects affected / exposed occurrences (all)	4 / 24 (16.67%) 5		
Sleep disorder subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 4		
Investigations CSF test abnormal subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2		
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	6 / 24 (25.00%) 11		
Head injury subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 3		
Laceration subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 4		
Procedural pain subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2		
Cardiac disorders Bradycardia subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2		

Nervous system disorders			
Atonic seizures			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	4		
Drop attacks			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Dystonia			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	4		
Epilepsy			
subjects affected / exposed	11 / 24 (45.83%)		
occurrences (all)	87		
Extensor plantar response			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	4		
Generalised tonic-clonic seizure			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	3		
Headache			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	7		
Hypotonia			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Language disorder			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Myoclonus			
subjects affected / exposed	7 / 24 (29.17%)		
occurrences (all)	14		
Partial seizures			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	3		
Petit mal epilepsy			

subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2		
Pleocytosis subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 3		
Seizure subjects affected / exposed occurrences (all)	14 / 24 (58.33%) 110		
Seizure cluster subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 4		
Tremor subjects affected / exposed occurrences (all)	4 / 24 (16.67%) 4		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 3		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 4		
Constipation subjects affected / exposed occurrences (all)	7 / 24 (29.17%) 10		
Diarrhoea subjects affected / exposed occurrences (all)	4 / 24 (16.67%) 5		
Dysphagia subjects affected / exposed occurrences (all)	4 / 24 (16.67%) 6		
Toothache subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2		
Vomiting			

subjects affected / exposed occurrences (all)	11 / 24 (45.83%) 20		
<b>Skin and subcutaneous tissue disorders</b>			
<b>Dermatitis contact</b>			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	3		
<b>Rash</b>			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	3		
<b>Urticaria</b>			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
<b>Infections and infestations</b>			
<b>Conjunctivitis</b>			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
<b>Gastroenteritis</b>			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	4		
<b>Nasopharyngitis</b>			
subjects affected / exposed	7 / 24 (29.17%)		
occurrences (all)	9		
<b>Oral herpes</b>			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	4		
<b>Pharyngitis</b>			
subjects affected / exposed	5 / 24 (20.83%)		
occurrences (all)	6		
<b>Respiratory tract infection</b>			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
<b>Rhinitis</b>			
subjects affected / exposed	5 / 24 (20.83%)		
occurrences (all)	7		
<b>Tonsillitis</b>			

subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 3		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	10 / 24 (41.67%) 17		
Urinary tract infection subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 3		
Viral infection subjects affected / exposed occurrences (all)	5 / 24 (20.83%) 7		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 May 2013	<p>Amendment 1:</p> <ol style="list-style-type: none"><li>1. To permit sufficient study drug clearance, based on nonclinical data, the follow-up visit was changed from 4 weeks to 6 months.</li><li>2. To ensure additional precaution for subject safety, during the first dosing cohort, at least 72 hours must have elapsed between the first and second subjects.</li><li>3. To require antihistamine pretreatment, it was clarified that an antipyretic medication may not be substituted but may be added, if appropriate.</li><li>4. To be consistent with European ethics committee recommendations, subjects 16 years of age or older were excluded from study participation.</li><li>5. To add a precautionary measure for this pediatric study population, females of child-bearing potential were excluded from study participation.</li></ol>
26 July 2013	<p>Amendment 2:</p> <ol style="list-style-type: none"><li>1. Added rationale for investigational drug infusion volume and rate.</li><li>2. Added statement regarding subject sedation during infusion at the discretion of the investigator.</li><li>3. Added statement regarding monitoring for epileptic seizure during infusion and for interrupting infusion at the discretion of the investigator.</li><li>4. For safety variables, removed head circumference assessment and replaced "length" with "height" assessment in complete physical exam.</li><li>5. Added statements regarding procedure for evaluating status of ICV access device on a regular basis. Specifically, "Surgical implantation of an ICV access device will take place prior to study drug administration. The investigator will evaluate the patency, location, and skin integrity of the reservoir at each study drug administration. At the discretion of the investigator and/or neurosurgeon, the ICV access device may be replaced during the clinical study."</li></ol>
07 July 2014	<p>Amendment 3:</p> <ol style="list-style-type: none"><li>1. The schedule for Magnetic resonance imaging (MRI) during the Stable Dose Period for quantitative analysis was changed be done at four time points: Baseline or Week 1 in the Stable Dose Period, and at Weeks 9, 25, and 49 in the Stable Dose Period. A screening MRI was required prior to ICV access device placement for anatomic localization. If sedation or anesthesia were required for this image sequence, the ICV access device placement would occur in the same period.</li><li>2. All adapted CLN2 scale assessments were videotaped at all site visits where the adapted CLN2 scale assessments are done.</li><li>3. For the post-implantation, first dose, and dose-escalation visits, subjects were monitored for 48 hours after infusions (with a minimum of 24 hours in the pediatric intensive care unit [PICU], and the remaining time on an inpatient ward). A follow-up phone call was also conducted within 24 hours after inpatient discharge.</li><li>4. Planned enrollment in the study was changed from 22 to "approximately 22" subjects.</li><li>5. Language was added concerning the collection of device-related adverse events (AEs) prior to the first administration of study drug.</li><li>6. Language was added detailing the risks of intracerebroventricular drug administration.</li><li>7. It was clarified that all Screening procedures are to be completed <math>\leq 3</math> days prior to the ICV access device implant surgery.</li><li>8. Baseline total and drug-specific IgE assessment was added.</li></ol>

08 August 2014	Amendment 4: 1. Device-related AE reporting requirements were amended to include all infusion system components that come into contact with BMN 190. 2. Subjects and their caregivers were given written instructions following ICV placement providing details about signs and symptoms of potential device complications or failure.
24 September 2014	Amendment 5: 1. Device-related AE reporting requirements were amended to include all infusion system components. 2. Language was clarified that, for Stable Dose Period visits, subjects would be closely monitored in an inpatient setting for up to 48 hours following each infusion, but could be discharged after 24 hours if medically stable and if no safety issues were observed.

Notes:

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported