



## Clinical trial results:

### A Phase 2, Open-label, Multinational Study to Evaluate the Efficacy and Safety of BMN 110 in Patients with Mucopolysaccharidosis IVA (Morquio A Syndrome) Who Have Limited Ambulation

#### Summary

EudraCT number	2011-005703-33
Trial protocol	DE GB
Global end of trial date	22 October 2014

#### Results information

Result version number	v1 (current)
This version publication date	13 December 2018
First version publication date	13 December 2018

#### Trial information

##### Trial identification

Sponsor protocol code	MOR-006
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01697319
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	BioMarin Pharmaceutical Inc.
Sponsor organisation address	105 Digital Drive, Novato, United States, CA 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-000973-PIP01-10
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

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**Results analysis stage**

Analysis stage	Final
Date of interim/final analysis	21 April 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 October 2014
Global end of trial reached?	Yes
Global end of trial date	22 October 2014
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

Main objective of the trial:

To evaluate the effect of 2.0 mg/kg/week BMN 110 (as defined by the domains of upper extremity function and dexterity, mobility, pain, and self care and functional abilities) in a patient population that has limited ambulation.

Protection of trial subjects:

The study was conducted in accordance with the principles of the Declaration of Helsinki including amendments in force up to and including the time the study was conducted. The study was conducted in compliance with the International Conference on Harmonisation E6 Guideline for Good Clinical Practice, and is compliant with the European Union Clinical Trial Directive 2001/20/EC. The study was also conducted in compliance with the United States Food and Drug Administration regulations in 21 Code of Federal Regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 August 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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**Population of trial subjects****Subjects enrolled per country**

Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	United States: 6
Country: Number of subjects enrolled	Germany: 6
Worldwide total number of subjects	16
EEA total number of subjects	10

Notes:

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**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)	1
Adolescents (12-17 years)	6

Adults (18-64 years)	9
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 7 study centers in 3 countries.

### Pre-assignment

Screening details:

Subject enrolled were 16 and 1 subject withdrew from study before treatment. Treatment received subjects were 15 and 12 completed the study.

### Period 1

Period 1 title	BMN 110 2.0 mg/kg/week (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

### Arms

<b>Arm title</b>	BMN110 2.0 mg/kg/week
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Arm description:

BMN110 2.0 mg/kg/week intravenous infusion (approximately 4 hours) for an initial treatment phase of 48 weeks and an extension treatment phase of up to an additional 96 weeks.

Arm type	Experimental
Investigational medicinal product name	BMN110
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

BMN110 2.0 mg/kg/week intravenous infusion (approximately 4 hours) for an initial treatment phase of 48 weeks and an extension treatment phase of up to an additional 96 weeks.

<b>Number of subjects in period 1<sup>[1]</sup></b>	BMN110 2.0 mg/kg/week
Started	15
Completed	12
Not completed	3
Consent withdrawn by subject	1
Serious Adverse Events	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Subject enrolled were 16 and 1 subject withdrew from study before treatment. Treatment received subjects were 15 and 12 completed the study.

## Baseline characteristics

### Reporting groups

Reporting group title	BMN110 2.0 mg/kg/week
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Reporting group description:

BMN110 2.0 mg/kg/week intravenous infusion (approximately 4 hours) for an initial treatment phase of 48 weeks and an extension treatment phase of up to an additional 96 weeks.

Reporting group values	BMN110 2.0 mg/kg/week	Total	
Number of subjects	15	15	
Age categorical			
Units: Subjects			
5 - 11	1	1	
12 - 18	8	8	
>= 19	6	6	
Age continuous			
Units: Years			
arithmetic mean	20.8	-	
standard deviation	± 8.67	-	
Gender categorical			
Units: Subjects			
Female	6	6	
Male	9	9	
Race			
Units: Subjects			
Asian	2	2	
Black or African American	1	1	
White	11	11	
Other	1	1	
Ethnicity			
Units: Subjects			
Hispanic or Latino	3	3	
Not Hispanic or Latino	12	12	
Functional Dexterity Test-Dominant Hand			
Units: number of pegs/minute			
arithmetic mean	13.3	-	
standard deviation	± 10.86	-	
Functional Dexterity Test-Non-Dominant Hand			
Units: pegs/minute			
arithmetic mean	13.2	-	
standard deviation	± 12.49	-	
25-Foot Walk Test			
Units: Feet/Minute			
arithmetic mean	21.3	-	
standard deviation	± 31.18	-	
Urine Keratan Sulfate			
Urine Keratan Sulfate (n=14)			

Units: ug/mg			
arithmetic mean	16.5		
standard deviation	± 8.91	-	

## End points

### End points reporting groups

Reporting group title	BMN110 2.0 mg/kg/week
Reporting group description:	
BMN110 2.0 mg/kg/week intravenous infusion (approximately 4 hours) for an initial treatment phase of 48 weeks and an extension treatment phase of up to an additional 96 weeks.	

### Primary: Percent Change From Baseline in Speed as Measured in Functional Dexterity Test (FDT)

End point title	Percent Change From Baseline in Speed as Measured in Functional Dexterity Test (FDT) <sup>[1]</sup>
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End point description:

FDT assesses the ability to use the hand in daily tasks. The test involves turning 16 wooden pegs over as quickly as possible on a hardwood pegboard with one hand requiring a three-jaw chuck prehension pattern between the fingers and thumb within a two-minute time limit. Hand function is evaluated by how fast a patient can turn over pegs in the given time limit, i.e. speed (number of pegs/minute).

Modified intent-to-treat (mITT) population included all subjects who received at least one dose of study medication.

End point type	Primary
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End point timeframe:

Up to 96 weeks

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 sample size of the study was not determined by statistical power consideration since no statistical hypotheses were posed.

End point values	BMN110 2.0 mg/kg/week			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: % of change				
arithmetic mean (standard deviation)				
Week 12: Dominant Hand (n=15)	-2.9 (± 41.37)			
Week 24: Dominant Hand (n=15)	1.8 (± 45.60)			
Week 36: Dominant Hand (n=14)	11.2 (± 48.21)			
Week 48: Dominant Hand (n=13)	23.1 (± 53.88)			
Week 72: Dominant Hand (n=9)	37.2 (± 54.94)			
Week 96: Dominant Hand (n=3)	22.5 (± 42.21)			
Week 12: Non-dominant Hand (n=14)	11.5 (± 36.84)			
Week 24: Non-dominant Hand (n=14)	13.8 (± 32.54)			
Week 36: Non-dominant Hand (n=13)	9.3 (± 20.55)			
Week 48: Non-dominant Hand (n=12)	6.0 (± 35.78)			
Week 72: Non-dominant Hand (n=8)	49.3 (± 126.26)			
Week 96: Non-dominant Hand (n=2)	-2.0 (± 2.83)			

## Statistical analyses

No statistical analyses for this end point

### Primary: Change From Baseline in Strength as Assessed by Grip Test

End point title	Change From Baseline in Strength as Assessed by Grip Test <sup>[2]</sup>
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End point description:

A grip-strength dynamometer was used to measure grip strength of dominant and non-dominant hands in the forearm and wrist supported position.

mITT population.

End point type	Primary
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End point timeframe:

Up to Week 96

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: The sample size of the study was not determined by statistical power consideration since no statistical hypotheses were posed.

End point values	BMN110 2.0 mg/kg/week			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Kg				
arithmetic mean (standard deviation)				
Baseline (n=10)	1.3 (± 0.90)			
Week 12: Dominant Hand (n=10)	0.1 (± 0.90)			
Week 24: Dominant Hand (n=10)	0.1 (± 0.89)			
Week 36: Dominant Hand (n=8)	-0.1 (± 0.87)			
Week 48: Dominant Hand (n=9)	-0.3 (± 0.90)			
Week 72: Dominant Hand (n=6)	-0.1 (± 0.33)			
Week 96: Dominant Hand (n=3)	0.3 (± 0.23)			
Week 12: Non-dominant Hand (n=10)	0.1 (± 0.66)			
Week 24: Non-dominant Hand (n=10)	-0.0 (± 0.70)			
Week 36: Non-dominant Hand (n=8)	0.0 (± 0.73)			
Week 48: Non-dominant Hand (n=9)	-0.1 (± 0.66)			
Week 72: Non-dominant Hand (n=6)	0.1 (± 0.79)			
Week 96: Non-dominant Hand (n=3)	0.4 (± 0.87)			

## Statistical analyses

No statistical analyses for this end point

### Primary: Percent Change From Baseline in Speed as Measured in Timed 25-Foot Walk Test (25FWT)

End point title	Percent Change From Baseline in Speed as Measured in Timed 25-Foot Walk Test (25FWT) <sup>[3]</sup>
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End point description:

The 25FWT is an assessment of mobility and leg function performance based on a timed 25-foot walk. The subject was directed to one end of a clearly marked 25-foot course and was instructed to walk 25 feet as quickly as possible, but safely. The time was calculated from the initiation of the instruction to start and ended when the subject reached the 25-foot mark. The task was immediately administered



again by having the subject walk back the same distance. Subjects could use assistive devices when doing this task. In addition, subjects could “walk” on their knees if this was their usual method of ambulation. The score for the 25FWT was the average of the two completed attempts.

mITT population.

End point type	Primary
End point timeframe:	
Up to Week 72	

Notes:

[3] - 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 sample size of the study was not determined by statistical power consideration since no statistical hypotheses were posed.

<b>End point values</b>	BMN110 2.0 mg/kg/week			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: % of change				
arithmetic mean (standard deviation)				
Week 24 (n=8)	95.7 (± 142.37)			
Week 48 (n=7)	53.5 (± 102.74)			
Week 72 (n=4)	48.3 (± 145.01)			

## Statistical analyses

No statistical analyses for this end point

## Primary: Change from Baseline in Strength as Assessed by Pinch Test

End point title	Change from Baseline in Strength as Assessed by Pinch Test <sup>[4]</sup>
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End point description:

A pinch meter was used to measure pinch strength of dominant and non-dominant hands in the forearm and wrist supported position. Each subject was tested with the elbow at 90°, the forearm neutral, and the wrist in neutral deviation.

mITT population.

For Pinch Dominant Hand Week 96 One observation only.

End point type	Primary
End point timeframe:	
Up to Week 96	

Notes:

[4] - 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 sample size of the study was not determined by statistical power consideration since no statistical hypotheses were posed.

<b>End point values</b>	BMN110 2.0 mg/kg/week			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Kg				
arithmetic mean (standard deviation)				
Baseline: Dominant Hand (n=10)	0.6 (± 0.36)			
Week 12: Dominant Hand (n=9)	0.0 (± 0.26)			
Week 24: Dominant Hand (n=9)	-0.1 (± 0.32)			
Week 36: Dominant Hand (n=8)	-0.0 (± 0.22)			
Week 48: Dominant Hand (n=9)	-0.0 (± 0.30)			
Week 72: Dominant Hand (n=7)	-0.1 (± 0.23)			
Week 96: Dominant Hand (n=1)	-0.6 (± 0)			
Baseline: Non Dominant Hand (n=10)	0.5 (± 0.39)			
Week 12: Non-dominant Hand (n=9)	0.1 (± 0.21)			
Week 24: Non-dominant Hand (n=9)	-0.0 (± 0.18)			
Week 36: Non-dominant Hand (n=8)	0.0 (± 0.19)			
Week 48: Non-dominant Hand (n=9)	0.0 (± 0.27)			
Week 72: Non-dominant Hand (n=7)	-0.1 (± 0.31)			
Week 96: Non-dominant Hand (n=2)	-0.3 (± 0.36)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change From Baseline in Normalized Urine Keratan Sulfate (uKS)

End point title	Percent Change From Baseline in Normalized Urine Keratan Sulfate (uKS)
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End point description:

Urinary keratan sulfate and urinary creatinine were measured through quantitative analysis. Urine Keratan Sulfate (uKS) is normalized to creatinine.

mITT population.

End point type	Secondary
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End point timeframe:

Up to Week 96

<b>End point values</b>	BMN110 2.0 mg/kg/week			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: % of change				
arithmetic mean (standard deviation)				
Week 24 (n=15)	-47.7 (± 15.4)			
Week 48 (n=15)	-43.4 (± 24.82)			
Week 72(n=9)	-45.5 (± 19.67)			

Week 96 (n=3)	-48.3 (± 24.13)			
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### 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 Week 144

Adverse event reporting additional description:

Safety population.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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### Reporting groups

Reporting group title	BMN110 2.0 mg/kg/week
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Reporting group description: -

Serious adverse events	BMN110 2.0 mg/kg/week		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 15 (46.67%)		
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 / 15 (6.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Poor venous access			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Central venous catheterisation			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cervical cord compression			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Bone disorder			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Otitis media			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia bacterial			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia mycoplasmal			
subjects affected / exposed	1 / 15 (6.67%)		
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>	BMN110 2.0 mg/kg/week		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 15 (100.00%)		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pallor			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Poor venous access			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
General disorders and administration site conditions			

Catheter site pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Device occlusion			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Chest pain			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Extravasation			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Face oedema			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	5		
Feeling cold			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Influenza like illness			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Infusion site extravasation			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Infusion site pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	3		
Injection site pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Infusion site reaction			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	5		

Localised oedema			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Medical device pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Nodule			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Non-cardiac chest pain			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	5		
Oedema peripheral			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	9 / 15 (60.00%)		
occurrences (all)	26		
Pain			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	5		
Immune system disorders			
Allergy to arthropod bite			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Anaphylactic reaction			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Anaphylactoid reaction			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hypersensitivity			



subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Reaction to colouring			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Seasonal allergy			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	3		
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Cough			
subjects affected / exposed	6 / 15 (40.00%)		
occurrences (all)	15		
Dyspnoea			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	4		
Hypoxia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Nasal congestion			
subjects affected / exposed	5 / 15 (33.33%)		
occurrences (all)	10		
Nasal obstruction			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	14		
Respiratory failure			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Restrictive pulmonary disease			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Rhinorrhoea			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Tachypnoea			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Sinus congestion			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Throat irritation			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Wheezing			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	3		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Depressed mood			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Restlessness			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Blood bilirubin increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Body temperature increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Blood glucose increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Electrocardiogram PR prolongation			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
QRS axis abnormal			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Weight increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Chillblains			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Fall			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	3		
Heat exhaustion			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Limb injury			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Tooth fracture			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Sinus tachycardia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Tachycardia			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Nervous system disorders			
Burning sensation			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Clonus			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Dizziness			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	10		
Hypoaesthesia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	3		
Headache			
subjects affected / exposed	11 / 15 (73.33%)		
occurrences (all)	42		
Lethargy			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	3		
Somnolence			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Ear pain			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	3		
Ear disorder			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Otorrhoea			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Eye disorders			
Corneal opacity			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Dry eye			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Eye disorder			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Eye pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Eye pruritus			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Eyelid cyst			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Eyelid pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Lacrimation increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	3		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	3		
Abdominal pain upper			
subjects affected / exposed	6 / 15 (40.00%)		
occurrences (all)	12		
Abdominal pain			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	7		
Constipation			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Gastritis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	7 / 15 (46.67%)		
occurrences (all)	28		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	7 / 15 (46.67%)		
occurrences (all)	19		
Vomiting			
subjects affected / exposed	6 / 15 (40.00%)		
occurrences (all)	29		

Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Dermatitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Dermatitis allergic			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pigmentation disorder			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	6		
Pruritus generalised			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Rash follicular			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Skin disorder			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Renal and urinary disorders			

Nephrolithiasis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	3		
Dysuria			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 15 (33.33%)		
occurrences (all)	28		
Back pain			
subjects affected / exposed	5 / 15 (33.33%)		
occurrences (all)	16		
Flank pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Musculoskeletal chest pain			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Musculoskeletal pain			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	5		
Myalgia			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	8		
Neck pain			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Pubic pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	5 / 15 (33.33%)		
occurrences (all)	8		
Sensation of heaviness			



subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Tenosynovitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Cystitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Ear infection			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	5		
Eye infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Hordeolum			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Lower respiratory tract infection			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	4		
Otitis externa fungal			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Otitis media			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		

Nasopharyngitis			
subjects affected / exposed	9 / 15 (60.00%)		
occurrences (all)	19		
Periodontitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pulpitis dental			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Respiratory tract infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	3		
Sinusitis			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	4		
Skin candida			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	7 / 15 (46.67%)		
occurrences (all)	14		
Subcutaneous abscess			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	6		
Viral infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 March 2013	<p>Other than protocol clarifications and administrative changes, the following items were revised:</p> <ol style="list-style-type: none"><li>1. An extension treatment phase was added to the existing protocol, to permit subjects to continue to receive study drug past the completion of the initial treatment phase without enrolling in a new study.</li><li>2. The sleep study was extended to include all eligible subjects, with no minimum or maximum cap on enrollment.</li><li>3. Cardiopulmonary exercise testing (CPET) and plasma keratan sulfate (KS) collection were removed from the study. CPET was removed because, due to the required limitations on ambulatory capacity as an enrollment criterion for the study, none of the enrolled subjects were physically capable of performing the CPET testing. Plasma KS was removed based on findings from other BMN 110 studies which showed no meaningful results from the test.</li><li>4. Certain assessments (genu valgum, kyphosis, radius length) were removed from the standard physical examination.</li><li>5. Changes were made to the language surrounding collection of biomarkers of bone and cartilage metabolism, as well as language surrounding the timing of collection of drug-specific IgE following a possible hypersensitivity reaction, to make the language in MOR-006 consistent with other BMN 110 study protocols.</li></ol>
12 June 2013	<p>Other than protocol clarifications and administrative changes, the following items were revised:</p> <ol style="list-style-type: none"><li>1. Language regarding imaging scans at the termination visits was clarified to make it clear that subjects at that visit needed to receive either a cervical spine radiograph or an MRI (not both), and that DXA would not be performed at the termination visit for the extension phase.</li><li>2. Background information was updated to include the results from the Phase 3 studies, MOR-004 and MOR-005, as well as additional updated safety information. In addition, the rationale for the 2.0 mg/kg/week dose was updated based on the results of MOR-004 and MOR-005.</li><li>3. An interim CSR, to be completed when all subjects have completed Week 48, was added.</li><li>4. The list of BMN 110 excipients was updated to reflect those included in the Phase 3/commercial formulation.</li><li>5. The Allergic Reaction Review Board (ARRB) language was modified; ARRB approval was no longer required in order to determine what (if any) blood sampling should be performed in response to possible hypersensitivity reactions. This change was made based on experience in other BMN 110 studies.</li></ol>

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

The study was terminated after all subjects had the opportunity to complete the initial treatment phase (Week 48 visit). The N is reduced beyond Week 48 due to the staggered accrual and efficacy reporting.

Notes: