



## Clinical trial results:

### A Multicenter, Multinational, Open-Label, Extension Study to Evaluate the Long-Term Efficacy and Safety of BMN 110 in Patients with Mucopolysaccharidosis IVA (Morquio A Syndrome)

#### Summary

EudraCT number	2010-021048-16
Trial protocol	GB
Global end of trial date	11 July 2014

#### Results information

Result version number	v1 (current)
This version publication date	02 December 2018
First version publication date	02 December 2018

#### Trial information

##### Trial identification

Sponsor protocol code	MOR-100
-----------------------	---------

##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01242111
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?	Yes

Notes:

---

**Results analysis stage**

---

Analysis stage	Final
Date of interim/final analysis	23 December 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 July 2014
Global end of trial reached?	Yes
Global end of trial date	11 July 2014
Was the trial ended prematurely?	No

Notes:

---

**General information about the trial**

---

Main objective of the trial:

To evaluate the long-term safety and efficacy of weekly infusions of 2.0 mg/kg of BMN 110, administered to subjects with mucopolysaccharidosis (MPS) IVA.

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	22 November 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

---

**Population of trial subjects**

---

**Subjects enrolled per country**

Country: Number of subjects enrolled	United Kingdom: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

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)	18
Adolescents (12-17 years)	2
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0
-------------------	---

## Subject disposition

### Recruitment

Recruitment details:

MOR-100 is an extension study of MOR-002 conducted at 5 study centers in the United Kingdom (UK).

### Pre-assignment

Screening details:

Of the 20 subjects enrolled into MOR-002, 18 subjects completed the study and 17 subjects continued receiving BMN 110 throughout the entire study duration of MOR-100.

### Period 1

Period 1 title	Overall (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
------------------	-----------------------

Arm description:

BMN110 at 2.0 mg/kg/week intravenous infusion, over a period of approximately 4 hours per infusion, for up to 168 weeks

Arm type	Experimental
Investigational medicinal product name	BMN 110
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, over a period of approximately 4 hours per infusion

<b>Number of subjects in period 1</b>	BMN110 2.0 mg/kg/week
Started	20
Completed	17
Not completed	3
Consent withdrawn by subject	1
Adverse event, non-fatal	1
MOR-100 Follow-up Consent Refusal	1

## Baseline characteristics

### Reporting groups

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

Reporting group description:

BMN110 at 2.0 mg/kg/week intravenous infusion, over a period of approximately 4 hours per infusion, for up to 168 weeks

Reporting group values	BMN110 2.0 mg/kg/week	Total	
Number of subjects	20	20	
Age categorical			
Units: Subjects			
>=4 to <8	10	10	
>=8 to <10	5	5	
>=10 to <=18	5	5	
Age continuous			
Units: years			
arithmetic mean	8.4	-	
standard deviation	± 2.9	-	
Gender categorical			
Units: Subjects			
Female	8	8	
Male	12	12	
Race			
Units: Subjects			
Asian	9	9	
White	9	9	
Other	2	2	
Ethnicity			
Units: Subjects			
Not Hispanic or Latino	20	20	
Region of Enrollment			
Units: Subjects			
United Kingdom	20	20	
MOR-002 Baseline : Urine Keratan Sulfate			
Units: ug/mg			
arithmetic mean	26.4	-	
standard deviation	± 12.04	-	
MOR-002 Baseline : Maximum Voluntary Ventilation			
Units: L/min			
arithmetic mean	31.7	-	
standard deviation	± 30.45	-	
MOR-002 Baseline : Forced Vital Capacity			
Units: litre			
arithmetic mean	0.9	-	
standard deviation	± 0.86	-	



## End points

### End points reporting groups

Reporting group title	BMN110 2.0 mg/kg/week
Reporting group description:	
BMN110 at 2.0 mg/kg/week intravenous infusion, over a period of approximately 4 hours per infusion, for up to 168 weeks	

### Primary: Number of subjects with adverse events (AEs)

End point title	Number of subjects with adverse events (AEs) <sup>[1]</sup>
End point description:	
Safety population includes all subjects who received any amount of study drug in MOR-002 or MOR-100, and includes 2 subjects who discontinued treatment in MOR-002 at study Week 11 while receiving BMN 110 at 0.1 mg/kg/week and 1 subject who discontinued treatment during the MOR-002 continuation period, as well as all subjects in MOR-100.	
SAE (Serious Adverse Event). AE (CTCAE) Grade: 1=Mild, 2=Moderate, 3=Severe or Undesirable, 4=Life Threatening or Debilitating.	
End point type	Primary
End point timeframe:	
Up to Week 168	

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: No statistical analysis done for safety endpoints.

End point values	BMN110 2.0 mg/kg/week			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Participants				
Any AE—Grade 1	1			
Any AE—Grade 2	5			
Any AE—Grade 3	12			
Any AE—Grade 4	2			
Any Study Drug-Related AE—Grade 1	6			
Any Study Drug-Related AE—Grade 2	10			
Any Study Drug-Related AE—Grade 3	2			
Any Study Drug-Related AE—Grade 4	1			
Any SAE—Grade 1	0			
Any SAE—Grade 2	6			
Any SAE—Grade 3	11			
Any SAE—Grade 4	2			
Any Study Drug-Related SAE—Grade 1	0			
Any Study Drug-Related SAE—Grade 2	6			
Any Study Drug-Related SAE—Grade 3	2			
Any Study Drug-Related SAE—Grade 4	1			
Any AE Leading to Study Discontinuation—Grade 4	1			
Any AE Leading to Permanent Drug Disc—Grade 4	1			
Death	0			

## Statistical analyses

No statistical analyses for this end point

### Primary: Change From Baseline in Endurance as Measured by the 6-minute Walk Test During the Pilot Trial (MOR-002) and Current Extension Trial (MOR-100)

End point title	Change From Baseline in Endurance as Measured by the 6-minute Walk Test During the Pilot Trial (MOR-002) and Current Extension Trial (MOR-100) <sup>[2]</sup>
-----------------	---

End point description:

As a measure of endurance, a 6-minute walk test (6MWT) was performed according to the American Thoracic Society Guidelines. Patients were instructed to walk as far as possible in 6 minutes. The analysis was based on observed cases

Intent-to-Treat (ITT) population includes all subjects who enrolled in the study. Two patients were either physically (score was designated as 0 m) or developmentally (score was set to missing) unable to perform the 6MWT.

End point type	Primary
----------------	---------

End point timeframe:

Baseline and every 12 weeks for up to 72 weeks during the MOR-002 pilot trial and every 24 weeks for up to 192 weeks during the MOR-100 extension trial

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 analyses are Descriptive statistics for continuous variables consist of mean, standard deviation, median, and range and also include count and percentage for categorical variables.

End point values	BMN110 2.0 mg/kg/week			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Meters				
arithmetic mean (standard deviation)				
MOR-002 Baseline (n=20)	266.9 (± 137.39)			
MOR-002 Week 12 Change from Baseline (n=19)	-20.7 (± 85.95)			
MOR-002 Week 24 Change from Baseline (n=17)	16.3 (± 71.74)			
MOR-002 Week 36 Change from Baseline (n=17)	13.8 (± 63.25)			
MOR-002 Week 48 Change from Baseline (n=17)	-4.8 (± 64.70)			
MOR-002 Week 72 Change from Baseline (n=17)	4.0 (± 87.24)			
MOR-100 Week 0 Change from Baseline (n=16)	15.7 (± 89.00)			
MOR-100 Week 24 Change from Baseline (n=16)	24.5 (± 101.23)			
MOR-100 Week 48 Change from Baseline (n=16)	6.8 (± 98.66)			



MOR-100 Week 72 Change from Baseline (n=17)	-49.8 (± 132.63)			
MOR-100 Week 96 Change from Baseline (n=16)	11.2 (± 85.24)			
MOR-100 Week 120 Change from Baseline (n=16)	4.2 (± 94.09)			
MOR-100 Week 144 Change from Baseline (n=13)	3.1 (± 106.82)			
MOR-100 Week 192 Change from Baseline (n=9)	-37.1 (± 103.96)			

## Statistical analyses

No statistical analyses for this end point

### Primary: Change in Baseline in Endurance as Measured by the 3 Minute Stair Climb During the Pilot Trial (MOR-002) and Current Extension Trial (MOR-100)

End point title	Change in Baseline in Endurance as Measured by the 3 Minute Stair Climb During the Pilot Trial (MOR-002) and Current Extension Trial (MOR-100) <sup>[3]</sup>
-----------------	---

End point description:

In the 3-minute Stair Climb Test (3MSCT), patients walked up stairs that have a railing, which could be used for support, for 3 minutes, with the number of stairs climbed recorded. The test result was the number of steps climbed per minute. The analysis was based on observed cases.

ITT population. One patient was developmentally unable to perform the 3MSCT and the test scores were set to missing.

End point type	Primary
----------------	---------

End point timeframe:

Baseline and every 12 weeks for up to 72 weeks during the MOR-002 pilot trial and every 24 weeks for up to 192 weeks during the MOR-100 extension trial

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: Statistical analyses are Descriptive statistics for continuous variables consist of mean, standard deviation, median, and range and also include count and percentage for categorical variables.

<b>End point values</b>	BMN110 2.0 mg/kg/week			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: stairs/min				
arithmetic mean (standard deviation)				
MOR-002 Baseline (n=20)	38.9 (± 25.39)			
MOR-002 Week 12 Change from Baseline (n=19)	0.3 (± 14.07)			
MOR-002 Week 24 Change from Baseline (n=17)	6.1 (± 8.66)			
MOR-002 Week 36 Change from Baseline (n=17)	7.8 (± 13.69)			
MOR-002 Week 48 Change from Baseline (n=17)	9.7 (± 14.42)			
MOR-002 Week 72 Change from Baseline (n=17)	9.7 (± 13.91)			
MOR-100 Week 0 Change from Baseline (n=16)	12.7 (± 13.96)			

MOR-100 Week 24 Change from Baseline (n=16)	13.4 (± 17.07)			
MOR-100 Week 48 Change from Baseline (n=16)	6.6 (± 16.87)			
MOR-100 Week 72 Change from Baseline (n=16)	-1.4 (± 21.11)			
MOR-100 Week 96 Change from Baseline (n=16)	9.9 (± 18.84)			
MOR-100 Week 120 Change from Baseline (n=16)	6.2 (± 14.41)			
MOR-100 Week 144 Change from Baseline (n=12)	5.4 (± 11.93)			
MOR-100 Week 192 Change from Baseline (n=7)	-0.2 (± 10.34)			

## Statistical analyses

No statistical analyses for this end point

### Primary: Percent Change From Baseline in Urine Keratan Sulfate (uKS) Levels During the Pilot Trial (MOR-002) and Current Extension Trial (MOR-100)

End point title	Percent Change From Baseline in Urine Keratan Sulfate (uKS) Levels During the Pilot Trial (MOR-002) and Current Extension Trial (MOR-100) <sup>[4]</sup>
-----------------	--

End point description:

Percent change was calculated (Week X value - baseline value)/baseline value\*100%.

ITT population.

End point type	Primary
----------------	---------

End point timeframe:

Baseline and every 12 weeks for up to 72 weeks during the MOR-002 pilot trial and every 24 weeks for up to 168 weeks during the MOR-100 extension trial

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: Statistical analyses are Descriptive statistics for continuous variables consist of mean, standard deviation, median, and range and also include count and percentage for categorical variables.

End point values	BMN110 2.0 mg/kg/week			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Percentage change				
arithmetic mean (standard deviation)				
MOR-002 Wk 12 Percent Change from Baseline (n=19)	-23.2 (± 19.04)			
MOR-002 Wk 24 Percent Change from Baseline (n=18)	-27.9 (± 17.92)			
MOR-002 Wk 36 Percent Change from Baseline (n=18)	-40.6 (± 20.16)			
MOR-002 Wk 48 Percent Change from Baseline (n=18)	-35.9 (± 13.09)			
MOR-002 Wk 60 Percent Change from Baseline (n=16)	-31.4 (± 17.51)			
MOR-002 Wk 72 Percent Change from Baseline (n=17)	-32.2 (± 17.10)			

MOR-100 Wk 0 Percent Change from Baseline (n=17)	-30.0 (± 19.23)			
MOR-100 Wk 24 Percent Change from Baseline (n=17)	-43.6 (± 19.56)			
MOR-100 Wk 48 Percent Change from Baseline (n=16)	-41.9 (± 19.29)			
MOR-100 Wk 72 Percent Change from Baseline (n=12)	-36.4 (± 36.70)			
MOR-100 Wk 96 Percent Change from Baseline (n=17)	-49.7 (± 19.93)			
MOR-100 Wk 120 Percent Change from Baseline (n=16)	-49.3 (± 22.28)			
MOR-100 Wk 144 Percent Change from Baseline (n=16)	-56.6 (± 19.54)			
MOR-100 Wk 168 Percent Change from Baseline (n=15)	-58.9 (± 16.02)			

## Statistical analyses

No statistical analyses for this end point

### Primary: Percent Change From Baseline in Respiratory Function Test MVV During the Pilot Trial (MOR-002) and Current Extension Trial (MOR-100)

End point title	Percent Change From Baseline in Respiratory Function Test MVV During the Pilot Trial (MOR-002) and Current Extension Trial (MOR-100) <sup>[5]</sup>
-----------------	---

End point description:

MVV (Maximum Voluntary Ventilation).

ITT population. The analysis was based on observed cases.

End point type	Primary
----------------	---------

End point timeframe:

Baseline and every 12 weeks for up to 72 weeks during the MOR-002 pilot trial and every 24 weeks for up to 192 weeks during the MOR-100 extension trial

Notes:

[5] - 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 analyses are Descriptive statistics for continuous variables consist of mean, standard deviation, median, and range and also include count and percentage for categorical variables.

End point values	BMN110 2.0 mg/kg/week			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Percentage change				
arithmetic mean (standard deviation)				
MOR-002 Wk 12 Percent Change from Baseline (n=14)	9.9 (± 21.29)			
MOR-002 Wk 24 Percent Change from Baseline (n=13)	11.0 (± 21.48)			
MOR-002 Wk 36 Percent Change from Baseline (n=14)	10.5 (± 17.43)			
MOR-002 Wk 48 Percent Change from Baseline (n=12)	18.1 (± 23.54)			
MOR-002 Wk 72 Percent Change from Baseline (n=14)	18.4 (± 20.77)			

MOR-100 Wk 0 Percent Change from Baseline (n=13)	11.1 (± 16.44)			
MOR-100 Wk 24 Percent Change from Baseline (n=13)	9.8 (± 22.25)			
MOR-100 Wk 48 Percent Change from Baseline (n=12)	3.5 (± 17.78)			
MOR-100 Wk 72 Percent Change from Baseline (n=13)	10.1 (± 27.83)			
MOR-100 Wk 96 Percent Change from Baseline (n=12)	-4.9 (± 35.53)			
MOR-100 Wk 120 Percent Change from Baseline (n=13)	-3.3 (± 28.35)			
MOR-100 Wk 144 Percent Change from Baseline (n=11)	-3.5 (± 34.61)			
MOR-100 Wk 192 Percent Change from Baseline (n=6)	28.2 (± 38.78)			

## Statistical analyses

No statistical analyses for this end point

### Primary: Percent Change From Baseline in Respiratory Function Test FVC During the Pilot Trial (MOR-002) and Current Extension Trial (MOR-100)

End point title	Percent Change From Baseline in Respiratory Function Test FVC During the Pilot Trial (MOR-002) and Current Extension Trial (MOR-100) <sup>[6]</sup>
-----------------	---

End point description:

FVC (Forced Vital Capacity).

ITT population. The analysis was based on observed cases.

End point type	Primary
----------------	---------

End point timeframe:

Baseline and every 12 weeks for up to 72 weeks during the MOR-002 pilot trial and every 24 weeks for up to 192 weeks during the MOR-100 extension trial

Notes:

[6] - 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 analyses are Descriptive statistics for continuous variables consist of mean, standard deviation, median, and range and also include count and percentage for categorical variables.

End point values	BMN110 2.0 mg/kg/week			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Percentage change				
arithmetic mean (standard deviation)				
MOR-002 Wk 12 Percent Change from Baseline (n=18)	3.4 (± 10.85)			
MOR-002 Wk 24 Percent Change from Baseline (n=16)	0.2 (± 16.60)			
MOR-002 Wk 36 Percent Change from Baseline (n=16)	10.7 (± 20.81)			
MOR-002 Wk 48 Percent Change from Baseline (n=14)	11.2 (± 17.11)			
MOR-002 Wk 72 Percent Change from Baseline (n=16)	12.5 (± 14.88)			

MOR-100 Wk 0 Percent Change from Baseline (n=15)	11.8 (± 14.97)			
MOR-100 Wk 24 Percent Change from Baseline (n=14)	15.3 (± 16.31)			
MOR-100 Wk 48 Percent Change from Baseline (n=13)	15.8 (± 16.56)			
MOR-100 Wk 72 Percent Change from Baseline (n=15)	16.1 (± 21.96)			
MOR-100 Wk 96 Percent Change from Baseline (n=14)	14.8 (± 17.36)			
MOR-100 Wk 120 Percent Change from Baseline (n=16)	22.8 (± 21.14)			
MOR-100 Wk 144 Percent Change from Baseline (n=12)	17.5 (± 24.32)			
MOR-100 Wk 192 Percent Change from Baseline (n=7)	18.6 (± 30.98)			

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to Week 168

Adverse event reporting additional description:

Safety population.

Assessment type	Systematic
-----------------	------------

### Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	16.1
--------------------	------

### Reporting groups

Reporting group title	BMN110
-----------------------	--------

Reporting group description:

Safety population.

Serious adverse events	BMN110		
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 20 (95.00%)		
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 / 20 (5.00%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Procedural pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skull fracture			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Jugular vein distension			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Poor venous access			
subjects affected / exposed	8 / 20 (40.00%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Supraventricular tachycardia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tachycardia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Abscess drainage			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

Bone operation			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Knee operation			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Central venous catheterisation			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Medical device implantation			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Medical device removal			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Orthopaedic procedure			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cervical cord compression			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Gait disturbance			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		



Infusion site inflammation			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infusion site reaction			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Malaise			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Type I hypersensitivity			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary oedema			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sleep apnoea syndrome			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Rash maculo-papular			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Panic attack			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Knee deformity			
subjects affected / exposed	6 / 20 (30.00%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abscess limb			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Catheter site infection				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infusion site infection				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lobar pneumonia				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	2 / 20 (10.00%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Otitis media				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory syncytial virus infection				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia mycoplasmal				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Viral infection				

subjects affected / exposed	2 / 20 (10.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	<b>BMN110</b>		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 20 (100.00%)		
Vascular disorders			
Flushing			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	6		
Hot flush			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Poor venous access			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	6		
Hypotension			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Hypertension			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	6		
Thrombosis			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Surgical and medical procedures			
Catheter removal			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Cautery to nose			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Central venous catheterisation			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Ear tube insertion			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Medical device removal			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	4		
Thrombectomy			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Application site reaction			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Application site vesicles			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Catheter site erythema			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	9		
Catheter site extravasation			
subjects affected / exposed	7 / 20 (35.00%)		
occurrences (all)	12		
Catheter site inflammation			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Catheter site rash			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Catheter site pain			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	5		
Catheter site oedema			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Catheter site swelling			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	6		
Catheter site scab			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Catheter site related reaction			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Chest pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Chills			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Device expulsion			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Device dislocation			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Device connection issue			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Device leakage			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Device malfunction			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Device occlusion			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Extravasation			

subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Fatigue			
subjects affected / exposed	7 / 20 (35.00%)		
occurrences (all)	11		
Feeling hot			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Influenza like illness			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Gait disturbance			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Infusion site pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Infusion site erythema			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Infusion site extravasation			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Infusion site reaction			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	3		
Injection site reaction			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Medical device complication			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	4		
Malaise			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	8		
Local swelling			

subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Medical device site reaction			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	6 / 20 (30.00%)		
occurrences (all)	12		
Pyrexia			
subjects affected / exposed	16 / 20 (80.00%)		
occurrences (all)	101		
Vaccination site pain			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Seasonal allergy			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	8		
Reproductive system and breast disorders			
Balanitis			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Genital ulceration			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Dysmenorrhoea			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Menorrhagia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Penile pain			



subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Scrotal erythema			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Perineal ulceration			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Vulvovaginal pruritus			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Cough			
subjects affected / exposed	18 / 20 (90.00%)		
occurrences (all)	81		
Dry throat			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Dysphonia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Dyspnoea			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	5		
Dyspnoea exertional			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Nasal congestion			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Epistaxis			

subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	12		
Nasal obstruction			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	6		
Pharyngeal disorder			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	15 / 20 (75.00%)		
occurrences (all)	31		
Pharyngeal erythema			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Pharyngeal oedema			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Productive cough			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Rales			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Respiratory failure			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Rhinitis allergic			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	6		
Sleep apnoea syndrome			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Wheezing			

subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	6		
Tachypnoea			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Anxiety			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Aspiration joint			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Blood cholesterol increased			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Blood immunoglobulin G decreased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Blood immunoglobulin E increased			
subjects affected / exposed	6 / 20 (30.00%)		
occurrences (all)	6		
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Blood pressure systolic increased			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Blood sodium increased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Body temperature increased			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	6		
Breath sounds abnormal			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Cardiac murmur			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Computerised tomogram			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Electrocardiogram T wave amplitude decreased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Liver palpable subcostal			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Eosinophil percentage increased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Eosinophil count increased			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Nuclear magnetic resonance imaging spinal			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Oxygen saturation decreased			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	3		
Nuclear magnetic resonance imaging			
subjects affected / exposed	6 / 20 (30.00%)		
occurrences (all)	8		
Protein total abnormal			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Respiratory rate increased			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Protein urine			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Ultrasound scan abnormal			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Weight increased			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	4		
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	5		
Arthropod sting			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Contusion			
subjects affected / exposed	6 / 20 (30.00%)		
occurrences (all)	8		
Ear injury			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Excoriation			

subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	4		
Eye contusion			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Fall			
subjects affected / exposed	8 / 20 (40.00%)		
occurrences (all)	20		
Face injury			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Head injury			
subjects affected / exposed	8 / 20 (40.00%)		
occurrences (all)	14		
Injury			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Infusion related reaction			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Laceration			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Ligament sprain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Limb injury			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	4		
Lip injury			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Neck injury			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Post procedural complication			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Periorbital contusion			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Occupational exposure to radiation			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Procedural headache			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Scar			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Procedural vomiting			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Procedural pain			
subjects affected / exposed	7 / 20 (35.00%)		
occurrences (all)	7		
Scratch			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Skeletal injury			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Sunburn			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Thermal burn			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Upper limb fracture			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Wound complication			

subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Congenital, familial and genetic disorders Congenital heart valve disorder subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Cardiac disorders Aortic valve incompetence subjects affected / exposed occurrences (all)  Diastolic dysfunction subjects affected / exposed occurrences (all)  Mitral valve disease subjects affected / exposed occurrences (all)  Mitral valve incompetence subjects affected / exposed occurrences (all)  Pulmonary valve incompetence subjects affected / exposed occurrences (all)  Tachycardia subjects affected / exposed occurrences (all)  Tricuspid valve incompetence subjects affected / exposed occurrences (all)	3 / 20 (15.00%) 3  1 / 20 (5.00%) 1  2 / 20 (10.00%) 2  3 / 20 (15.00%) 3  3 / 20 (15.00%) 3  3 / 20 (15.00%) 6  3 / 20 (15.00%) 3		
Nervous system disorders Areflexia subjects affected / exposed occurrences (all)  Ageusia subjects affected / exposed occurrences (all)  Cervical cord compression	1 / 20 (5.00%) 1  1 / 20 (5.00%) 1		



subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Clonus			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	4		
Lethargy			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	5		
Headache			
subjects affected / exposed	16 / 20 (80.00%)		
occurrences (all)	100		
Dizziness			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	7		
Migraine			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Neuralgia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Spinal cord compression			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Reflexes abnormal			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	5		
Eosinophilia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		

Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Deafness			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Ear canal erythema			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Deafness neurosensory			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Ear discomfort			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Ear disorder			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Ear pain			
subjects affected / exposed	12 / 20 (60.00%)		
occurrences (all)	41		
Ear pruritus			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Hyperacusis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Hypoacusis			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	4		
Middle ear disorder			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Otorrhoea			

subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Motion sickness			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	9		
Tinnitus			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Tympanic membrane perforation			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Tympanic membrane hyperaemia			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Tympanic membrane disorder			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Eye disorders			
Conjunctivitis			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	4		
Dry eye			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Eye discharge			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Eye pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Eye pruritus			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Eye swelling			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		

Ocular hyperaemia subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Eyelid cyst subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Gastrointestinal disorders			
Abdominal discomfort subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2		
Abdominal pain upper subjects affected / exposed occurrences (all)	11 / 20 (55.00%) 33		
Abdominal pain subjects affected / exposed occurrences (all)	12 / 20 (60.00%) 27		
Constipation subjects affected / exposed occurrences (all)	5 / 20 (25.00%) 5		
Dental caries subjects affected / exposed occurrences (all)	3 / 20 (15.00%) 5		
Dental plaque subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Dyspepsia subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Diarrhoea subjects affected / exposed occurrences (all)	12 / 20 (60.00%) 28		
Faecal incontinence subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 2		
Gastrooesophageal reflux disease			

subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Gingival hyperpigmentation			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Glossodynia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Haematemesis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Lip disorder			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Mouth ulceration			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Lip pain			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	8		
Retching			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Tongue discolouration			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Tooth deposit			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Tooth disorder			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Toothache			

subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	8		
Vomiting			
subjects affected / exposed	16 / 20 (80.00%)		
occurrences (all)	92		
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Dermatitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Dermatitis contact			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Dermatitis diaper			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	6		
Eczema			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Erythema			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	43		
Eczema asteatotic			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Lichen planus			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Miliaria			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Onychomadesis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Pain of skin			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Pigmentation disorder			
subjects affected / exposed	6 / 20 (30.00%)		
occurrences (all)	14		
Petechiae			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Papule			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Rash			
subjects affected / exposed	11 / 20 (55.00%)		
occurrences (all)	34		
Psoriasis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	3		
Pruritus			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	11		
Rash erythematous			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Rash generalised			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Rash maculo-papular			

subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	35		
Skin depigmentation			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Skin discolouration			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Skin mass			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	4		
Skin exfoliation			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Skin disorder			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	5		
Urticaria			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	53		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Polyuria			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Incontinence			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	3		
Enuresis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	3		
Urinary incontinence			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		



Endocrine disorders			
Autoimmune thyroiditis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Atlantoaxial instability			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Arthralgia			
subjects affected / exposed	12 / 20 (60.00%)		
occurrences (all)	58		
Axillary mass			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	9 / 20 (45.00%)		
occurrences (all)	17		
Bursitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Joint stiffness			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Joint instability			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Joint swelling			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Knee deformity			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Mobility decreased			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	6		
Muscle spasms			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	3		
Muscular weakness			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Myalgia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	16 / 20 (80.00%)		
occurrences (all)	75		
Neck pain			
subjects affected / exposed	8 / 20 (40.00%)		
occurrences (all)	12		
Pain in jaw			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Catheter site infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Eye infection			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Ear infection			
subjects affected / exposed	6 / 20 (30.00%)		
occurrences (all)	15		

Fungal infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Fungal skin infection			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Furuncle			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	4		
Gingivitis			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Gastroenteritis viral			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Helminthic infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Herpes simplex			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Herpes zoster			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Impetigo			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	3		
Infection			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Influenza			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Localised infection			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		

Lice infestation			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Nail infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Molluscum contagiosum			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Lower respiratory tract infection			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	8		
Nasopharyngitis			
subjects affected / exposed	17 / 20 (85.00%)		
occurrences (all)	53		
Otitis externa			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Otitis media			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Paronychia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Oral candidiasis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Postoperative wound infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Pharyngitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Rash pustular			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		

Skin infection			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Rhinitis			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	8		
Subcutaneous abscess			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Tinea pedis			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	4		
Tonsillitis			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	5		
Upper respiratory tract infection			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	5		
Urinary tract infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Varicella			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Viral infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Wound infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Appetite disorder			

subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Decreased appetite			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Hypercholesterolaemia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Dehydration			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Vitamin D deficiency			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 July 2010	<p>1. Removed text that the study may be terminated if the study drug becomes commercially available. Rationale: The United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA) stated that commercial availability of BMN 110 is not an appropriate scientific endpoint and should be deleted.</p> <p>2. The frequency of X-rays of the lumbar spine and lower extremity has been reduced from every 48 weeks to every 18 months from the previous examination. For subjects completing an Early Termination Visit (ETV), X-rays of the lumbar spine and lower extremity will be performed if the previous set was at least 12-18 months prior to ETV. Rationale: The frequency of the X-rays should be decreased to limit radiation exposure, particularly as the population includes children.</p> <p>3. Language has been added to describe views of cervical spine, lumbar spine, and lower extremity X-rays. Rationale: A description of X-ray views is included for clarity.</p> <p>4. Minor changes have been made for clarity and consistency throughout the protocol.</p>
16 March 2011	<p>1. Infusion reaction (IR) has been more specifically termed infusion-associated-reaction (IAR). In addition, the definition of IAR has been modified to include a more thorough description of potential symptoms, and to be inclusive of all reactions occurring after the onset of the infusion, within one day following the end of the infusion, regardless of the investigator's assessment of relatedness to study drug administration.</p> <p>2. Immunogenicity testing, in the event of a severe IAR or an IAR requiring cessation of infusion, was revised to include complement component 4 (C4). CH50 was deleted from testing. No blood draws were added or eliminated.</p> <p>3. Text has been added to further describe the Allergic Reaction Review Board (ARRB). The ARRB will serve as a consultant to the clinical team and medical monitor. The ARRB may make recommendations regarding the appropriate management of IARs.</p> <p>4. Duplicate testing for the 6-minute walk (6MW) and 3-meter stair climb (3MSC) tests was eliminated.</p> <p>5. The schedule for obtaining cervical spine radiographs was lengthened to every 72 weeks, similar to the schedule for obtaining lumbar spine and lower extremity radiographs.</p> <p>6. The lower extremity radiographs will only be performed for patients <math>\leq 20</math> years old.</p> <p>7. Corneal clouding examinations were added as part of the physical examination at the Baseline and Every 12 week assessments.</p> <p>8. Removed the option for patients, who enrolled and participated in MOR-004, to enroll in this long-term extension study and added participation in MOR-004 as an exclusion criterion.</p> <p>9. Additional immunogenicity, total IgE, urine keratan sulfate, and urine creatinine assessments have been added during the time of the transition from Phase 1/2 to Phase 3 products.</p> <p>10. Minor changes have been made throughout the protocol to improve the clarity and consistency of the protocol, update contact information for the Medical Monitor, and to include updated information from the ongoing MOR-002 study.</p>

21 June 2013	<ol style="list-style-type: none"> <li>1. An internal Data Monitoring Committee (DMC) has been added to act in an advisory capacity to monitor the safety of BMN 110 in patients who participate in MOR-100.</li> <li>2. Language regarding oversight by the Allergic Reaction Review Board (ARRB) has been modified.</li> <li>3. The frequency and extent of study assessments have been changed.</li> <li>4. Time windows were added to vital signs assessments to decrease the number of minor protocol deviations and improve study site compliance without posing any material risk to patient safety.</li> <li>5. The dose rationale and study background information were updated to include the results from the Phase 3 studies, MOR-004 and MOR-005.</li> <li>6. Language was added permitting biomarker, pharmacogenetic, and pharmacodynamics testing of leftover research samples, and pharmacogenetic analysis to confirm diagnosis of MPS IVA in patients who had not had genetic testing previously. The testing in all cases was intended to permit a better understanding of the correlation between genotype and the varying patient responses to BMN 110.</li> <li>7. Language regarding study drug administration was modified to make it clear that subjects did not have to return to an infusion center for dosing, thereby opening up the possibility of home infusion.</li> </ol>
30 January 2014	<p>A summary of major changes covered by Amendment 4 to the protocol is provided below.</p> <ol style="list-style-type: none"> <li>1. A patient-reported outcomes (PRO) questionnaire and validated health utility scores (HUS) score (EQ-5D-5L) have been added to the study.</li> </ol> <p>Rationale: Patient Reported Outcomes (PRO) and Health Utility Scores (HUS) are essential tools to assess the overall effectiveness of a drug on disease burden as observed and experienced by patients and/or caregivers. PRO and HUS data will be collected at a single visit utilizing a health questionnaire and a validated HUS score (EQ5D-5L). Information on perceived disease burden at a given time point and at that point compared with the past will be collected to analyze the changes in disease burden during treatment over a period of 4 years or more.</p>

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported