Clinical trial results:
A Phase 1/2, Multicenter, Open-Label, Dose-Escalation Study to Evaluate the Safety, Tolerability, and Efficacy of BMN 110 in Subjects with Mucopolysaccharidosis IVA (Morquio Syndrome)

Summary

EudraCT number	2008-007365-23
Trial protocol	GB
Global end of trial date	09 February 2011

Results information

Result version number	v1 (current)
This version publication date	25 July 2018
First version publication date	25 July 2018

Trial information

Trial identification

Sponsor protocol code	MOR-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00884949
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)	EMEA-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	24 October 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 February 2011
Global end of trial reached?	Yes
Global end of trial date	09 February 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety of weekly infusions of BMN 110 administered in escalating doses to subjects with 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 Harmonization 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	08 April 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United 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)	16
Adolescents (12-17 years)	4
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Twenty patients were enrolled in the study. This sample size was determined based upon the small number of sites and the rarity of the disease. The 12 male and 8 female patients ranged in age from 4 to 16 years. Due to the heterogeneity of the disease, patients had wide variation in their functional impairment and organ system involvement.

Pre-assignment

Screening details:

Screening was to take place within 14 days prior to Baseline. The informed consent was to be completed and signed prior to any screening procedures.

Period 1

Period 1 title	Period 1 (weeks 1-12): 0.1 mg/kg/week
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	BMN 110 0.1 mg/kg/week

Arm description: -

Arm type	Experimental
Investigational medicinal product name	BMN 110
Investigational medicinal product code	
Other name	recombinant human N-acetylgalactosamine-6-sulfatase
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

BMN 110, was administered weekly as a 4- to 5-hour intravenous infusion over three consecutive 12-week dose-escalating intervals.

Number of subjects in period 1	BMN 110 0.1 mg/kg/week
Started	20
Completed	18
Not completed	2
Consent withdrawn by subject	1
Adverse event, non-fatal	1

Period 2

Period 2 title	Period 2: Weeks 13-24: 1.0 mg/kg/week
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms	
Arm title	BMN 110 1.0 mg/kg/week
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	BMN 110
Investigational medicinal product code	
Other name	recombinant human N-acetylgalactosamine-6-sulfatase
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

BMN 110, was administered weekly as a 4- to 5-hour intravenous infusion over three consecutive 12-week dose-escalating intervals.

Number of subjects in period 2	BMN 110 1.0 mg/kg/week
Started	18
Completed	18

Period 3	
Period 3 title	Period 3: Weeks 25-36: 2.0 mg/kg/week
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms	
Arm title	BMN 110 2.0 mg/kg/week
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	BMN 110
Investigational medicinal product code	
Other name	recombinant human N-acetylgalactosamine-6-sulfatase
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

BMN 110, was administered weekly as a 4- to 5-hour intravenous infusion over three consecutive 12-week dose-escalating intervals.

Number of subjects in period 3	BMN 110 2.0 mg/kg/week
Started	18
Completed	18

Period 4	
Period 4 title	Period 4: Continuation Period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	BMN 110 1.0 mg/kg/week (Continuation)

Arm description: -

Arm type	Experimental
Investigational medicinal product name	BMN 110
Investigational medicinal product code	
Other name	recombinant human N-acetylgalactosamine-6-sulfatase
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

BMN 110, was administered weekly as a 4- to 5-hour intravenous infusion over three consecutive 12-week dose-escalating intervals.

Number of subjects in period 4	BMN 110 1.0 mg/kg/week (Continuation)
Started	18
Completed	18

Baseline characteristics

Reporting groups

Reporting group title	Period 1 (weeks 1-12): 0.1 mg/kg/week

Reporting group description: -

Reporting group values	Period 1 (weeks 1-12): 0.1 mg/kg/week	Total	
Number of subjects	20	20	
Age categorical Units: Subjects			
>=4 to <8 years	10	10	
>=8 to <10 years	6	6	
>=10 to <=18 years	4	4	
Age continuous Units: years			
arithmetic mean	8.0		
standard deviation	± 2.89	-	
Gender categorical Units: Subjects			
Female	8	8	
Male	12	12	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	
Not Hispanic or Latino	20	20	
Unknown or Not Reported	0	0	
Race/Ethnicity Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	9	9	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	9	9	
Other	2	2	
Maximum Voluntary Ventilation (MVV) Units: L/min			
arithmetic mean	31.7		
standard deviation	± 30.45	-	
Forced Vital Capacity (FVC) Units: Liter			
arithmetic mean	0.9		
standard deviation	± 0.86	-	

End points

End points reporting groups

Reporting group title	BMN 110 0.1 mg/kg/week
Reporting group description: -	
Reporting group title	BMN 110 1.0 mg/kg/week
Reporting group description: -	
Reporting group title	BMN 110 2.0 mg/kg/week
Reporting group description: -	
Reporting group title	BMN 110 1.0 mg/kg/week (Continuation)
Reporting group description: -	
Subject analysis set title	Entire Study: BMN 110
Subject analysis set type	Full analysis
Subject analysis set description:	
Entire Study period includes both Dose-Escalation Period and Continuation Period.	

Primary: Number of subjects with Treatment Emergent Adverse Events (TEAEs)

End point title	Number of subjects with Treatment Emergent Adverse Events (TEAEs)[1]
End point description:	
Safety Population.	
End point type	Primary
End point timeframe:	
Up to Week 84 (Continuation Period)	

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 was performed for Safety Evaluation (Adverse Event).

End point values	BMN 110 0.1 mg/kg/week	BMN 110 1.0 mg/kg/week	BMN 110 2.0 mg/kg/week	BMN 110 1.0 mg/kg/week (Continuation)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	18	18	18
Units: Participants				
Any AEs	18	18	17	17
Any Study Drug-Related AEs	12	10	7	8
Any SAEs	6	2	8	6
Any Study Drug-Related SAEs	2	1	2	1
Any AEs During Infusion	15	13	10	15
Any SAEs During Infusion	5	0	1	1
Any AEs Causing Study Discontinuation	1	0	0	0
Any Study Drug-Related AE Causing Study Discont.	1	0	0	0
AEs Causing Permanent Study Drug Discontinuation	1	0	0	0
Drug-Related AE Causing Permanent StudyDrug Discon	1	0	0	0
Any SAEs Causing Study Discontinuation	1	0	0	0
Any SAEs Causing Permanent Study Drug Discont.	1	0	0	0
Study Drug-Related SAE Causing Study Discont.	1	0	0	0

StudyDrug-Related SAE Causing Permanent DrugDiscon	1	0	0	0
Death	0	0	0	0

End point values	Entire Study: BMN 110			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: Participants				
Any AEs	20			
Any Study Drug-Related AEs	14			
Any SAEs	14			
Any Study Drug-Related SAEs	4			
Any AEs During Infusion	17			
Any SAEs During Infusion	6			
Any AEs Causing Study Discontinuation	1			
Any Study Drug-Related AE Causing Study Discont.	1			
AEs Causing Permanent Study Drug Discontinuation	1			
Drug-Related AE Causing Permanent StudyDrug Discon	1			
Any SAEs Causing Study Discontinuation	1			
Any SAEs Causing Permanent Study Drug Discont.	1			
Study Drug-Related SAE Causing Study Discont.	1			
StudyDrug-Related SAE Causing Permanent DrugDiscon	1			
Death	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in 6MWT

End point title	Change From Baseline in 6MWT

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.

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. The analysis was based on observed cases.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 36, 48, and 72

End point values	Entire Study: BMN 110			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: Meters				
arithmetic mean (standard deviation)				
Baseline	266.9 (± 137.39)			
Week 12 Change from Baseline (n=19)	-20.7 (± 85.95)			
Week 24 Change from Baseline (n=17)	16.3 (± 71.74)			
Week 36 Change from Baseline (n=17)	13.8 (± 63.25)			
Week 48 Change from Baseline (n=17)	-4.8 (± 64.70)			
Week 72 Change from Baseline (n=17)	4.0 (± 87.24)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in 3MSCT

End point title	Change From Baseline in 3MSCT

End point description:

Change from baseline in the 3-minute Stair Climb Test. 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.

ITT population. One patient was developmentally unable to perform the 3MSCT and the test scores were set to missing. The analysis was based on observed cases.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 36, 48 and 72

End point values	Entire Study: BMN 110			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: Steps/min				
arithmetic mean (standard deviation)				
Baseline	38.9 (± 25.39)			
Week 12 Change from Baseline (n=19)	0.3 (± 14.07)			
Week 24 Change from Baseline (n=17)	6.1 (± 8.66)			
Week 36 Change from Baseline (n=17)	7.8 (± 13.69)			
Week 48 Change from Baseline (n=17)	9.7 (± 14.42)			
Week 72 Change from Baseline (n=17)	9.7 (± 13.91)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Change From Baseline in Urine Keratan Sulfate (uKS)

End point description:

Change was calculated as: Week X value - baseline value)/baseline value

ITT population.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 36 and 72

End point values	Entire Study: BMN 110			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: ug/mg				
arithmetic mean (standard deviation)				
Baseline (n=20)	26.4 (± 12.04)			
Week 12 (n=19)	20.3 (± 7.63)			
Week 24 (n=18)	19.6 (± 5.40)			
Week 36 (n=18)	15.7 (± 4.10)			
Week 72 (n=17)	18.7 (± 5.63)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Maximum Voluntary Ventilation (MVV)

End point title	Percent Change From Baseline in Maximum Voluntary Ventilation (MVV)

End point description:

ITT population.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 36 and 72

End point values	Entire Study: BMN 110			
Subject group type	Subject analysis set			
Number of subjects analysed	18[2]			
Units: Percentage of MVV				
arithmetic mean (standard deviation)				
Week 12 Percent Change from Baseline (n=14)	9.9 (± 21.29)			

Week 24 Percent Change from Baseline (n=13)	11.0 (± 21.48)			
Week 36 Percent Change from Baseline (n=14)	10.5 (± 17.43)			
Week 72 Percent Change from Baseline (n=14)	18.4 (± 20.77)			

Notes:

[2] - Two patients were either physically or developmentally unable to perform.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Forced Vital Capacity (FVC)

End point title	Percent Change From Baseline in Forced Vital Capacity (FVC)

End point description:

ITT population.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 36 and 72

End point values	Entire Study: BMN 110			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: Percentage of FVC				
arithmetic mean (standard deviation)				
Week 12 Percent Change from Baseline (n=18)	3.4 (± 10.85)			
Week 24 Percent Change from Baseline (n=16)	0.2 (± 16.60)			
Week 36 Percent Change from Baseline (n=16)	10.7 (± 20.82)			
Week 72 Percent Change from Baseline (n=16)	12.5 (± 14.88)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to Week 84 (Continuation Period)	
Adverse event reporting additional description:	
Safety Population.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups	
Reporting group title	Dose Escalation (weeks 1-12): BMN 110 0.1 mg/kg/week
Reporting group description:	
BMN 110 0.1 mg/kg/week (4- to 5-hour intravenous infusion weekly) in Dose-Escalation Period (weeks 1-12)	
Reporting group title	Dose Escalation (weeks 13-24): BMN 110 1.0 mg/kg/week
Reporting group description:	
BMN 110 1.0 mg/kg/week (4- to 5-hour intravenous infusion weekly) in Dose-Escalation Period (weeks 13-24)	
Reporting group title	Dose Escalation (weeks 25-36): BMN 110 2.0 mg/kg/week
Reporting group description:	
BMN 110 2.0 mg/kg/week (4- to 5-hour intravenous infusion weekly) in Dose-Escalation Period (weeks 25-36)	
Reporting group title	Continuation Period (weeks 36-48): BMN 110 1.0 mg/kg/week
Reporting group description:	
Subjects continuing on treatment after the Dose-Escalation period will receive BMN 110 1.0 mg/kg/week (4- to 5-hour intravenous infusion weekly) for 36 to 48 weeks.	
Reporting group title	Entire Study
Reporting group description:	
Entire Study period includes both Dose-Escalation Period and Continuation Period.	

Serious adverse events	Dose Escalation (weeks 1-12): BMN 110 0.1 mg/kg/week	Dose Escalation (weeks 13-24): BMN 110 1.0 mg/kg/week	Dose Escalation (weeks 25-36): BMN 110 2.0 mg/kg/week
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 20 (30.00%)	2 / 18 (11.11%)	8 / 18 (44.44%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Road traffic accident			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			

Poor venous access			
subjects affected / exposed	3 / 20 (15.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Abscess drainage			
subjects affected / exposed	1 / 20 (5.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheterisation venous			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	3 / 18 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Gait disturbance			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Type I hypersensitivity			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash generalised			

subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Knee deformity			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	2 / 18 (11.11%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess limb			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Implant site infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Lower respiratory tract infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media			
subjects affected / exposed	2 / 20 (10.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Continuation Period (weeks 36-48): BMN 110 1.0 mg/kg/week	Entire Study	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 18 (33.33%)	14 / 20 (70.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Road traffic accident			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Poor venous access			
subjects affected / exposed	1 / 18 (5.56%)	4 / 20 (20.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Abscess drainage			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheterisation venous			

subjects affected / exposed	0 / 18 (0.00%)	3 / 20 (15.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Gait disturbance			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Type I hypersensitivity			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash generalised			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Knee deformity			

subjects affected / exposed	2 / 18 (11.11%)	5 / 20 (25.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implant site infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	2 / 18 (11.11%)	3 / 20 (15.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	0 / 18 (0.00%)	2 / 20 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Dose Escalation (weeks 1-12): BMN 110 0.1 mg/kg/week	Dose Escalation (weeks 13-24): BMN 110 1.0 mg/kg/week	Dose Escalation (weeks 25-36): BMN 110 2.0 mg/kg/week
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 20 (90.00%)	18 / 18 (100.00%)	17 / 18 (94.44%)
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 20 (0.00%)	2 / 18 (11.11%)	1 / 18 (5.56%)
occurrences (all)	0	2	1
Hot flush			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Hypotension			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Poor venous access			
subjects affected / exposed	3 / 20 (15.00%)	1 / 18 (5.56%)	1 / 18 (5.56%)
occurrences (all)	0	1	0
Surgical and medical procedures			
Cautery to nose			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Induction of anaesthesia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Catheterisation venous			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	3 / 18 (16.67%)
occurrences (all)	0	0	3
Abscess drainage			

subjects affected / exposed	1 / 20 (5.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
General disorders and administration site conditions			
Application site vesicles			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Catheter site erythema			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Catheter site pain			
subjects affected / exposed	3 / 20 (15.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	3	1	0
Chills			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Extravasation			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Feeling hot			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Gait disturbance			
subjects affected / exposed	2 / 20 (10.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	2	0	0
Implant site erythema			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Implant site extravasation			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Implant site rash			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			

subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Infusion site erythema			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Infusion site inflammation			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Infusion site oedema			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Injection site pain			
subjects affected / exposed	0 / 20 (0.00%)	2 / 18 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Injection site reaction			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Malaise			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	6 / 20 (30.00%)	9 / 18 (50.00%)	5 / 18 (27.78%)
occurrences (all)	6	12	8
Infusion related reaction			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Hypersensitivity			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Type I hypersensitivity			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0

Reproductive system and breast disorders			
Balanitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Penile pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 20 (5.00%)	5 / 18 (27.78%)	3 / 18 (16.67%)
occurrences (all)	1	7	3
Dry throat			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	2
Oropharyngeal pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Pharyngeal oedema			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Productive cough			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Rales			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Wheezing			

subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Blood immunoglobulin E increased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Blood immunoglobulin G decreased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Blood sodium increased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Cardiac murmur			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Computerised tomogram			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Echocardiogram abnormal			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Electrocardiogram T wave amplitude decreased			

subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Eosinophil count increased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Nuclear magnetic resonance imaging			
subjects affected / exposed	1 / 20 (5.00%)	2 / 18 (11.11%)	0 / 18 (0.00%)
occurrences (all)	1	2	0
Oxygen saturation decreased			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	3	0
Protein total abnormal			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Respiratory rate increased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Weight increased			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Arthropod sting			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Contusion			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Device migration			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Excoriation			

subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Eye injury			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Face injury			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	2 / 20 (10.00%)	0 / 18 (0.00%)	2 / 18 (11.11%)
occurrences (all)	3	0	2
Head injury			
subjects affected / exposed	2 / 20 (10.00%)	1 / 18 (5.56%)	1 / 18 (5.56%)
occurrences (all)	3	2	1
Injury			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Joint injury			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Medical device complication			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Mouth injury			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Procedural pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Procedural vomiting			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Thermal burn			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Road traffic accident			

subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Mitral valve disease			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Tachycardia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Ageusia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Clonus			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	2 / 20 (10.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Headache			
subjects affected / exposed	4 / 20 (20.00%)	2 / 18 (11.11%)	1 / 18 (5.56%)
occurrences (all)	8	3	8
Lethargy			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Spinal cord compression			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 20 (0.00%)	2 / 18 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Deafness neurosensory			

subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Ear canal erythema			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Ear disorder			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Ear pain			
subjects affected / exposed	1 / 20 (5.00%)	1 / 18 (5.56%)	1 / 18 (5.56%)
occurrences (all)	1	2	3
External ear disorder			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Hyperacusis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Hypoacusis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Inner ear disorder			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Motion sickness			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Otorrhoea			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Tinnitus			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0

Eye discharge			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Eyelid cyst			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 20 (15.00%)	1 / 18 (5.56%)	1 / 18 (5.56%)
occurrences (all)	3	2	3
Abdominal pain upper			
subjects affected / exposed	4 / 20 (20.00%)	1 / 18 (5.56%)	3 / 18 (16.67%)
occurrences (all)	8	2	6
Constipation			
subjects affected / exposed	1 / 20 (5.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Dental caries			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 20 (0.00%)	2 / 18 (11.11%)	3 / 18 (16.67%)
occurrences (all)	0	2	4
Faecal incontinence			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Glossodynia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	1 / 20 (5.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Retching			

subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Salivary gland enlargement			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	1 / 20 (5.00%)	2 / 18 (11.11%)	1 / 18 (5.56%)
occurrences (all)	1	2	1
Vomiting			
subjects affected / exposed	2 / 20 (10.00%)	7 / 18 (38.89%)	4 / 18 (22.22%)
occurrences (all)	3	7	6
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	1 / 20 (5.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Skin and subcutaneous tissue disorders			
Dermatitis diaper			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Dry skin			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Erythema			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Petechiae			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Psoriasis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Rash			

subjects affected / exposed	1 / 20 (5.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Rash generalised			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Rash maculo-papular			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Rash papular			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	3	0
Rash pruritic			
subjects affected / exposed	1 / 20 (5.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Skin disorder			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Skin lesion			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Skin ulcer			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Drug eruption			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Enuresis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Incontinence			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	3	0
Urinary incontinence			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0

Endocrine disorders			
Autoimmune thyroiditis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 20 (15.00%)	3 / 18 (16.67%)	0 / 18 (0.00%)
occurrences (all)	3	4	0
Back pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Bursitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Mobility decreased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Muscular weakness			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	4 / 20 (20.00%)	3 / 18 (16.67%)	1 / 18 (5.56%)
occurrences (all)	6	3	1
Pain in jaw			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Catheter site infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	1

Ear infection			
subjects affected / exposed	1 / 20 (5.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Gastroenteritis viral			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Helminthic infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Impetigo			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Lice infestation			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Localised infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	0
Nail infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	2 / 20 (10.00%)	3 / 18 (16.67%)	1 / 18 (5.56%)
occurrences (all)	3	3	1
Otitis externa			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Pharyngitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0

Rhinitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Skin infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Subcutaneous abscess			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Tinea pedis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Tonsillitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Varicella			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Otitis media			
subjects affected / exposed	2 / 20 (10.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Abscess limb			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Implant site infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Pneumonia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Eye infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	0 / 20 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Hypercholesterolaemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Continuation Period (weeks 36-48): BMN 110 1.0 mg/kg/week	Entire Study	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 18 (94.44%)	20 / 20 (100.00%)	
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 18 (5.56%)	3 / 20 (15.00%)	
occurrences (all)	1	4	
Hot flush			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Hypotension			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Poor venous access			
subjects affected / exposed	1 / 18 (5.56%)	5 / 20 (25.00%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Cautery to nose			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Induction of anaesthesia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Catheterisation venous			
subjects affected / exposed	0 / 18 (0.00%)	3 / 20 (15.00%)	
occurrences (all)	0	3	
Abscess drainage			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
General disorders and administration			

site conditions				
Application site vesicles				
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)		
occurrences (all)	1	1		
Catheter site erythema				
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)		
occurrences (all)	1	2		
Catheter site pain				
subjects affected / exposed	0 / 18 (0.00%)	3 / 20 (15.00%)		
occurrences (all)	0	4		
Chills				
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)		
occurrences (all)	0	1		
Extravasation				
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)		
occurrences (all)	0	2		
Feeling hot				
subjects affected / exposed	1 / 18 (5.56%)	2 / 20 (10.00%)		
occurrences (all)	1	2		
Gait disturbance				
subjects affected / exposed	0 / 18 (0.00%)	2 / 20 (10.00%)		
occurrences (all)	0	2		
Implant site erythema				
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)		
occurrences (all)	4	4		
Implant site extravasation				
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)		
occurrences (all)	0	1		
Implant site rash				
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)		
occurrences (all)	1	1		
Influenza like illness				
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)		
occurrences (all)	0	1		
Infusion site erythema				

subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	2	
Infusion site inflammation			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Infusion site oedema			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Injection site pain			
subjects affected / exposed	0 / 18 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Injection site reaction			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Malaise			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	2	3	
Pyrexia			
subjects affected / exposed	10 / 18 (55.56%)	14 / 20 (70.00%)	
occurrences (all)	20	46	
Infusion related reaction			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Hypersensitivity			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Type I hypersensitivity			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			

Balanitis			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Penile pain			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	10 / 18 (55.56%)	13 / 20 (65.00%)	
occurrences (all)	18	29	
Dry throat			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Dyspnoea			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Epistaxis			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Nasal congestion			
subjects affected / exposed	1 / 18 (5.56%)	3 / 20 (15.00%)	
occurrences (all)	1	4	
Oropharyngeal pain			
subjects affected / exposed	4 / 18 (22.22%)	6 / 20 (30.00%)	
occurrences (all)	4	6	
Pharyngeal oedema			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Productive cough			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Rales			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Wheezing			

subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Blood immunoglobulin E increased			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Blood immunoglobulin G decreased			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Blood sodium increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Cardiac murmur			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Computerised tomogram			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Echocardiogram abnormal			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Electrocardiogram T wave amplitude decreased			

subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Eosinophil count increased			
subjects affected / exposed	1 / 18 (5.56%)	2 / 20 (10.00%)	
occurrences (all)	1	2	
Nuclear magnetic resonance imaging			
subjects affected / exposed	4 / 18 (22.22%)	6 / 20 (30.00%)	
occurrences (all)	4	7	
Oxygen saturation decreased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	3	
Protein total abnormal			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Respiratory rate increased			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Weight increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Arthropod sting			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Contusion			
subjects affected / exposed	2 / 18 (11.11%)	2 / 20 (10.00%)	
occurrences (all)	2	4	
Device migration			
subjects affected / exposed	2 / 18 (11.11%)	2 / 20 (10.00%)	
occurrences (all)	2	3	
Excoriation			

subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Eye injury			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Face injury			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	2	2	
Fall			
subjects affected / exposed	1 / 18 (5.56%)	5 / 20 (25.00%)	
occurrences (all)	2	7	
Head injury			
subjects affected / exposed	1 / 18 (5.56%)	4 / 20 (20.00%)	
occurrences (all)	1	7	
Injury			
subjects affected / exposed	1 / 18 (5.56%)	2 / 20 (10.00%)	
occurrences (all)	1	2	
Joint injury			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Medical device complication			
subjects affected / exposed	2 / 18 (11.11%)	2 / 20 (10.00%)	
occurrences (all)	2	2	
Mouth injury			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Procedural pain			
subjects affected / exposed	2 / 18 (11.11%)	2 / 20 (10.00%)	
occurrences (all)	2	2	
Procedural vomiting			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Thermal burn			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Road traffic accident			

subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Cardiac disorders			
Mitral valve disease			
subjects affected / exposed	0 / 18 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Tachycardia			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Nervous system disorders			
Ageusia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Clonus			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Dizziness			
subjects affected / exposed	0 / 18 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	3	
Headache			
subjects affected / exposed	6 / 18 (33.33%)	9 / 20 (45.00%)	
occurrences (all)	16	35	
Lethargy			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Spinal cord compression			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 18 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Deafness neurosensory			

subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Ear canal erythema			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Ear disorder			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Ear pain			
subjects affected / exposed	5 / 18 (27.78%)	5 / 20 (25.00%)	
occurrences (all)	10	16	
External ear disorder			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Hyperacusis			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Hypoacusis			
subjects affected / exposed	1 / 18 (5.56%)	2 / 20 (10.00%)	
occurrences (all)	1	2	
Inner ear disorder			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Motion sickness			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Otorrhoea			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Tinnitus			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 18 (5.56%)	2 / 20 (10.00%)	
occurrences (all)	1	2	

Eye discharge			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Eyelid cyst			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 18 (5.56%)	4 / 20 (20.00%)	
occurrences (all)	2	10	
Abdominal pain upper			
subjects affected / exposed	4 / 18 (22.22%)	8 / 20 (40.00%)	
occurrences (all)	4	20	
Constipation			
subjects affected / exposed	1 / 18 (5.56%)	3 / 20 (15.00%)	
occurrences (all)	1	3	
Dental caries			
subjects affected / exposed	2 / 18 (11.11%)	2 / 20 (10.00%)	
occurrences (all)	2	2	
Diarrhoea			
subjects affected / exposed	1 / 18 (5.56%)	6 / 20 (30.00%)	
occurrences (all)	2	8	
Faecal incontinence			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Glossodynia			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Nausea			
subjects affected / exposed	2 / 18 (11.11%)	3 / 20 (15.00%)	
occurrences (all)	3	5	
Retching			

subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Salivary gland enlargement			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Toothache			
subjects affected / exposed	1 / 18 (5.56%)	4 / 20 (20.00%)	
occurrences (all)	1	5	
Vomiting			
subjects affected / exposed	12 / 18 (66.67%)	13 / 20 (65.00%)	
occurrences (all)	26	42	
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	1 / 18 (5.56%)	2 / 20 (10.00%)	
occurrences (all)	1	3	
Skin and subcutaneous tissue disorders			
Dermatitis diaper			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Dry skin			
subjects affected / exposed	1 / 18 (5.56%)	2 / 20 (10.00%)	
occurrences (all)	1	2	
Erythema			
subjects affected / exposed	2 / 18 (11.11%)	2 / 20 (10.00%)	
occurrences (all)	2	2	
Petechiae			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Psoriasis			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Rash			

subjects affected / exposed	3 / 18 (16.67%)	4 / 20 (20.00%)	
occurrences (all)	4	6	
Rash generalised			
subjects affected / exposed	2 / 18 (11.11%)	3 / 20 (15.00%)	
occurrences (all)	1	3	
Rash maculo-papular			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	3	3	
Rash papular			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	3	
Rash pruritic			
subjects affected / exposed	1 / 18 (5.56%)	3 / 20 (15.00%)	
occurrences (all)	2	4	
Skin disorder			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	2	2	
Skin lesion			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Skin ulcer			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Drug eruption			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Renal and urinary disorders			
Enuresis			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Incontinence			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	3	
Urinary incontinence			
subjects affected / exposed	2 / 18 (11.11%)	2 / 20 (10.00%)	
occurrences (all)	2	2	

Endocrine disorders			
Autoimmune thyroiditis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 18 (22.22%)	8 / 20 (40.00%)	
occurrences (all)	4	11	
Back pain			
subjects affected / exposed	3 / 18 (16.67%)	4 / 20 (20.00%)	
occurrences (all)	4	5	
Bursitis			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Mobility decreased			
subjects affected / exposed	1 / 18 (5.56%)	3 / 20 (15.00%)	
occurrences (all)	1	3	
Muscular weakness			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Neck pain			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Pain in extremity			
subjects affected / exposed	5 / 18 (27.78%)	11 / 20 (55.00%)	
occurrences (all)	5	15	
Pain in jaw			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Catheter site infection			
subjects affected / exposed	0 / 18 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	1	

Ear infection			
subjects affected / exposed	3 / 18 (16.67%)	5 / 20 (25.00%)	
occurrences (all)	4	6	
Gastroenteritis viral			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Helminthic infection			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Impetigo			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	3	3	
Infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Lice infestation			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	2	
Localised infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Lower respiratory tract infection			
subjects affected / exposed	2 / 18 (11.11%)	3 / 20 (15.00%)	
occurrences (all)	2	2	
Nail infection			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Nasopharyngitis			
subjects affected / exposed	4 / 18 (22.22%)	8 / 20 (40.00%)	
occurrences (all)	6	13	
Otitis externa			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Pharyngitis			
subjects affected / exposed	2 / 18 (11.11%)	2 / 20 (10.00%)	
occurrences (all)	2	2	

Rhinitis			
subjects affected / exposed	2 / 18 (11.11%)	2 / 20 (10.00%)	
occurrences (all)	2	2	
Skin infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Subcutaneous abscess			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Tinea pedis			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Tonsillitis			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Varicella			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Otitis media			
subjects affected / exposed	0 / 18 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Abscess limb			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Implant site infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Pneumonia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Eye infection			
subjects affected / exposed	1 / 18 (5.56%)	2 / 20 (10.00%)	
occurrences (all)	1	2	
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Hypercholesterolaemia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 February 2009	1. The original study design was a 2-part study with a 36-week Dose-Escalation Period and an optional Extension Period lasting until the investigational product is commercially available or the study is terminated. In this amendment, the 36-week Dose-Escalation Period remains the same, but the Extension Period has been replaced with an optional bridging period of 36 weeks (referred to as the Continuation Period) that allows for the minimum time required to transition patients to a separate long-term treatment protocol and avoid any interruption to treatment. The total duration of this study will be 72 weeks of treatment for each subject (36-week Dose-Escalation Period plus an optional 36-week Continuation Period). 2. In the Extension Period, subjects were to be treated with an initial dose of 1.0 mg/kg/week with possible dose adjustment after analysis of the data from the Dose-Escalation Period. The protocol has been amended so that subjects who opt to continue treatment after the Dose-Escalation Period will be treated at a dose of 1.0 mg/kg/week; no dose adjustments will be made based on data analysis. 3. An Interim Analysis plan was incorporated to analyze the following three parameters at each dose level: safety (adverse events and laboratory analyses), total drug exposure as determined by PK assessments, and the percent reduction from Baseline in plasma and/or urine KS concentrations. This interim analysis will occur after the last patient completes the 36-week Dose-Escalation period and will be used to determine an optimal dose for a separate long-term treatment protocol. The following additional changes were made: 4. The design of the Dose-Escalation period was clarified to be a within-patient dose escalation. 5. The inclusion criteria for confirming diagnosis of MPS IVA was clarified to include results of molecular genetic testing. 6. Minor editorial changes were made for clarity and consistency throughout the protocol.
08 September 2009	1. Treatment prior to administration of study drug has been added. a. For all subjects, pretreatment with appropriate doses of anti-histamine and anti-pyretic will be administered prior to infusion of study drug. Non-sedating antihistamines, such as cetirizine or loratadine, are preferred. b. For subjects who have a history of infusion reactions or other risk factors (eg, history of allergies), a sedating antihistamine (eg, diphenhydramine or chlorpheniramine) may be administered, and premedication with additional agents such as H2 blockers, montelukast sodium, or steroids may be considered. 2. To mitigate the risk of infusion reactions (IRs), the study drug infusion rate information has been revised; additional details have been added. The increase in infusion rate has been slowed, with gradual rate increases every 15 minutes. The minimum infusion duration remains approximately 4 hours. 3. Information regarding the management of allergic reactions (Section 10.3) and site-specific guidelines have been added (Section 24.2) to provide further guidance regarding the management of hypersensitivity reactions. 4. Information regarding an independent Allergic Reaction Review Board (ARRB) has been added. The ARRB will review severe or serious IRs during the study. 5. For subjects who have a severe IR or experience an IR requiring cessation of infusion, additional blood samples will be taken to assess for CH50, total immunoglobulin E (IgE), and serum tryptase level. In addition, a sample will be obtained for testing of drug specific antibody levels. The Schedule of Events (Table 2.1.1) and Study Procedures (Section 12) have been revised to incorporate the additional sampling. 6. Safety information has been updated in the Summary of Overall Risks and Benefits (Section 7.5). Information regarding a subject who experienced a serious adverse event of Type I hypersensitivity during the study has been added. 7. Minor changes have been made for clarity and consistency

01 July 2010	The following additional measures with regard to managing and monitoring subject safety: 1. Extended the Continuation Period to allow up to 12 additional weeks on a subject- by-subject basis until enrollment in the long-term open label treatment study (MOR-100) is available or the subject decides to discontinue. This will extend the total duration of the study from 72 weeks up to a maximum of 84 weeks. 2. Allow subjects who discontinue receiving study drug to remain in the study. Rationale: There is little information available on the natural history of MPS IVA. Allowing these subjects to remain on study and continue to perform study assessments will help to characterize the progression of MPS IVA once enzyme replacement therapy is discontinued. Ongoing collection of clinical assessment data in subjects off therapy will allow a more complete understanding of the relative clinical impact of therapy. The safety burden of continued assessments is anticipated to be minimal. 3. Additional blood may be taken when subjects experience infusion reactions. Rationale: To allow further characterization of possibly related adverse events, including serious adverse events, the Investigator may need to order additional safety related laboratory testing. Capturing this data will improve understanding of these events and help to better define the risks of treatment with enzyme replacement therapy for all MPS IVA patients. 4. Guidance for the allowed number of missed infusions during the Continuation Period has been added. Rationale: Guidance to investigators is needed regarding missed infusions during the final 48 weeks of the study (Continuation Period). Guidelines are based on knowledge from related therapies while ensuring latitude for an individual subject. 5. Updated Section 7.2 (Nonclinical Studies). Rationale: To accurately report new nonclinical information since previous amendment. 6. Updated Sections 7.5 (Summary of Overall Risks and Benefits) and 7.5.1 (Infus

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported