



Clinical trial results:

A Randomized, Double-Blind, Pilot Study of the Safety and Physiological Effects of Two Doses of BMN 110 in Patients with Mucopolysaccharidosis IVA (Morquio A Syndrome)

Summary

EudraCT number	2011-005682-20
Trial protocol	DE GB
Global end of trial date	20 November 2014

Results information

Result version number	v1 (current)
This version publication date	06 December 2017
First version publication date	06 December 2017

Trial information

Trial identification

Sponsor protocol code	MOR-008
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01609062
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)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 March 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	20 November 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To evaluate the safety of 2.0 and 4.0 mg/kg/week BMN 110 administered for 27 weeks

The primary objective for extending the Phase 2 study is:

- To evaluate the long-term safety of 2.0 and 4.0 mg/kg/week BMN 110 in patients 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 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 Federal Regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 May 2012
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	Canada: 6
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	United States: 14
Worldwide total number of subjects	25
EEA total number of subjects	5

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)	14
Adolescents (12-17 years)	8
Adults (18-64 years)	3
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

After providing Informed Consent, subjects were screened for eligibility over a 3-week period.

Period 1

Period 1 title	Primary Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Arms

Are arms mutually exclusive?	Yes
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Arm title	BMN110 2.0 mg/kg/week
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	Elosulfase alfa
Investigational medicinal product code	BMN110
Other name	Vimizim, recombinant human N-acetylgalactosamine-6-sulfatase
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Weekly IV infusions of BMN 110 2.0 mg/kg/week for 27 consecutive weeks (Week 0 through Week 26). Each infusion was administered over a period of approximately 4 hours.

Arm title	BMN110 4.0 mg/kg/week
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	Elosulfase alfa
Investigational medicinal product code	BMN110
Other name	Vimizim, recombinant human N-acetylgalactosamine-6-sulfatase
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Weekly IV infusions of BMN 110 4.0 mg/kg/week for 27 consecutive weeks (Week 0 through Week 26). Each infusion was administered over a period of approximately 4 hours.

Number of subjects in period 1	BMN110 2.0 mg/kg/week	BMN110 4.0 mg/kg/week
Started	15	10
Completed	15	10

Period 2	
Period 2 title	Extension Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	BMN110 2.0 mg/kg/week

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Elosulfase alfa
Investigational medicinal product code	BMN110
Other name	Vimizim, recombinant human N-acetylgalactosamine-6-sulfatase
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Weekly IV infusions of BMN 110 2.0 mg/kg/week for 27 consecutive weeks (Week 0 through Week 26). Each infusion was administered over a period of approximately 4 hours.

Arm title	BMN110 4.0 mg/kg/week
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	Elosulfase alfa
Investigational medicinal product code	BMN110
Other name	Vimizim, recombinant human N-acetylgalactosamine-6-sulfatase
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Weekly IV infusions of BMN 110 4.0 mg/kg/week for 27 consecutive weeks (Week 0 through Week 26). Each infusion was administered over a period of approximately 4 hours.

Number of subjects in period 2	BMN110 2.0 mg/kg/week	BMN110 4.0 mg/kg/week
Started	15	10
Completed	0	0
Not completed	15	10
Anticipated Surgery	-	1
Pregnancy	1	-
Study Terminated by Sponsor	14	9

Baseline characteristics

Reporting groups

Reporting group title	BMN110 2.0 mg/kg/week
Reporting group description: -	
Reporting group title	BMN110 4.0 mg/kg/week
Reporting group description: -	

Reporting group values	BMN110 2.0 mg/kg/week	BMN110 4.0 mg/kg/week	Total
Number of subjects	15	10	25
Age categorical Units: Subjects			
7 - 11	9	5	14
12 - 18	3	5	8
>= 19	3	0	3
Age continuous Units: Years			
arithmetic mean	14.9	12	-
standard deviation	± 9.32	± 3.16	-
Gender categorical Units: Subjects			
Female	12	4	16
Male	3	6	9
Distance Walked in Six Minutes Units: meters			
arithmetic mean	369.6	376.3	-
standard deviation	± 89.19	± 69.98	-
Three Minute Stair Climb Rate Units: steps/minute			
arithmetic mean	65.5	64.2	-
standard deviation	± 21.42	± 23.32	-
Normalized Urine Keratan Sulfate Units: ug/mg			
arithmetic mean	16.4	18.8	-
standard deviation	± 15.23	± 9.03	-
Respiratory Function Test MVV Units: L/min			
arithmetic mean	42.2	57.2	-
standard deviation	± 22.81	± 33.83	-
Respiratory Function Test FVC Units: Liter			
arithmetic mean	1.9	1.8	-
standard deviation	± 1.21	± 1.15	-
Cardiopulmonary Exercise Testing (CPET) - Duration of Exercise Units: min			
arithmetic mean	8	7.1	-
standard deviation	± 2.63	± 1.42	-
Cardiopulmonary Exercise Testing			

(CPET) - Peak Workload Units: Watts arithmetic mean standard deviation	43.5 ± 29.88	35.8 ± 17.2	-
Cardiopulmonary Exercise Testing (CPET) - O2 Pulse Units: VE/VCO2 arithmetic mean standard deviation	4.9 ± 2.63	4.7 ± 1.06	-
Cardiopulmonary Exercise Testing (CPET) - Aerobic Efficiency Units: mL/watt arithmetic mean standard deviation	12.8 ± 3.87	14.1 ± 1.47	-
Cardiopulmonary Exercise Testing (CPET) - Peak VO2 Units: mL/min arithmetic mean standard deviation	848.3 ± 487.45	724.6 ± 220.7	-
Muscle Strength Testing - Knee Extension Test Units: N*m arithmetic mean standard deviation	31.6 ± 16.97	23.9 ± 22.29	-
Muscle Strength Testing - Knee Flexion Test Units: N*m arithmetic mean standard deviation	20.2 ± 15.07	18.9 ± 14.51	-
Muscle Strength Testing - Elbow Flexion Test Units: N*m arithmetic mean standard deviation	9.6 ± 7.61	12.3 ± 10.94	-

Subject analysis sets

Subject analysis set title	Modified Intent-to-Treat
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All subjects who were randomized to study treatment, received at least one dose of study drug, and had at least one post-treatment observation. The primary efficacy analyses for all efficacy endpoints were based on the modified ITT population and data were analyzed according to the treatment assigned at randomization.

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects who received one or more doses of study drug

Reporting group values	Modified Intent-to-Treat	Safety Population	
Number of subjects	25	25	
Age categorical Units: Subjects			
7 - 11	14	14	

12 - 18	8	8	
>= 19	3	3	

Age continuous Units: Years arithmetic mean standard deviation	13.7 ± 7.52	13.7 ± 7.52	
Gender categorical Units: Subjects			
Female	16	16	
Male	9	9	
Distance Walked in Six Minutes Units: meters arithmetic mean standard deviation	372.2 ± 80.55	372.2 ± 80.55	
Three Minute Stair Climb Rate Units: steps/minute arithmetic mean standard deviation	65 ± 21.73	65 ± 21.73	
Normalized Urine Keratan Sulfate Units: ug/mg arithmetic mean standard deviation	17.4 ± 12.96	17.4 ± 12.96	
Respiratory Function Test MVV Units: L/min arithmetic mean standard deviation	49 ± 28.65	49 ± 28.65	
Respiratory Function Test FVC Units: Liter arithmetic mean standard deviation	1.9 ± 1.16	1.9 ± 1.16	
Cardiopulmonary Exercise Testing (CPET) - Duration of Exercise Units: min arithmetic mean standard deviation	7.7 ± 2.29	7.7 ± 2.29	
Cardiopulmonary Exercise Testing (CPET) - Peak Workload Units: Watts arithmetic mean standard deviation	40.9 ± 25.94	40.9 ± 25.94	
Cardiopulmonary Exercise Testing (CPET) - O2 Pulse Units: VE/VCO2 arithmetic mean standard deviation	4.9 ± 2.18	4.9 ± 2.18	
Cardiopulmonary Exercise Testing (CPET) - Aerobic Efficiency Units: mL/watt arithmetic mean standard deviation	13.3 ± 3.21	13.3 ± 3.21	
Cardiopulmonary Exercise Testing (CPET) - Peak VO2			

Units: mL/min arithmetic mean standard deviation	807.1 ± 412.6	807.1 ± 412.6	
Muscle Strength Testing - Knee Extension Test Units: N*m arithmetic mean standard deviation	28.5 ± 19.22	28.5 ± 19.22	
Muscle Strength Testing - Knee Flexion Test Units: N*m arithmetic mean standard deviation	19.7 ± 14.55	19.7 ± 14.55	
Muscle Strength Testing - Elbow Flexion Test Units: N*m arithmetic mean standard deviation	10.6 ± 8.86	10.6 ± 8.86	

End points

End points reporting groups

Reporting group title	BMN110 2.0 mg/kg/week
Reporting group description: -	
Reporting group title	BMN110 4.0 mg/kg/week
Reporting group description: -	
Reporting group title	BMN110 2.0 mg/kg/week
Reporting group description: -	
Reporting group title	BMN110 4.0 mg/kg/week
Reporting group description: -	
Subject analysis set title	Modified Intent-to-Treat
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: All subjects who were randomized to study treatment, received at least one dose of study drug, and had at least one post-treatment observation. The primary efficacy analyses for all efficacy endpoints were based on the modified ITT population and data were analyzed according to the treatment assigned at randomization.	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description: All subjects who received one or more doses of study drug	

Primary: Serious Adverse Events

End point title	Serious Adverse Events ^[1]
End point description: No statistical analysis performed for this endpoint as it is descriptive analysis	
End point type	Primary
End point timeframe: Entire Study Period, up to 192 weeks or ETV (early termination visit)	
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 performed for this endpoint as it is descriptive analysis	

End point values	BMN110 2.0 mg/kg/week	BMN110 4.0 mg/kg/week	Safety Population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	15	10	25	
Units: Subjects	3	2	5	

Statistical analyses

No statistical analyses for this end point

Primary: Non Serious Adverse Events

End point title	Non Serious Adverse Events ^[2]
End point description: No statistical analysis performed for this endpoint as it is descriptive analysis	

End point type	Primary
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End point timeframe:

Entire Study Period, up to 192 weeks or ETV (early termination visit)

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: No statistical analysis performed for this endpoint as it is descriptive analysis

End point values	BMN110 2.0 mg/kg/week	BMN110 4.0 mg/kg/week	Safety Population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	15	10	25	
Units: Subjects	15	10	25	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 12 in Distance Walked in Six Minutes - Modified ITT Population

End point title	Change from Baseline to Week 12 in Distance Walked in Six Minutes - Modified ITT Population
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End point description:

Change from baseline in metres in 6-minute Walk Test. 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.

End point type	Secondary
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End point timeframe:

Baseline to Week 12

End point values	BMN110 2.0 mg/kg/week	BMN110 4.0 mg/kg/week	Modified Intent-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	15	10	25	
Units: metres				
arithmetic mean (standard deviation)	14.7 (± 30.9)	-8.9 (± 83.52)	5.3 (± 57.55)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 24 in Distance Walked in Six Minutes - Modified ITT Population

End point title	Change from Baseline to Week 24 in Distance Walked in Six Minutes - Modified ITT Population
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End point description:

Change from baseline in metres in 6-minute Walk Test. 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.

End point type	Secondary
End point timeframe:	
Baseline to Week 24	

End point values	BMN110 2.0 mg/kg/week	BMN110 4.0 mg/kg/week	Modified Intent-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	15	10	25	
Units: metres				
arithmetic mean (standard deviation)	-13 (\pm 54.12)	0.1 (\pm 34.7)	-7.8 (\pm 46.94)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 52 in Distance Walked in Six Minutes - Modified ITT Population

End point title	Change from Baseline to Week 52 in Distance Walked in Six Minutes - Modified ITT Population
End point description:	
Change from baseline in metres in 6-minute Walk Test. 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.	
End point type	Secondary
End point timeframe:	
Baseline to Week 52	

End point values	BMN110 2.0 mg/kg/week	BMN110 4.0 mg/kg/week	Modified Intent-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	14	10	24	
Units: metres				
arithmetic mean (standard deviation)	9 (\pm 48.41)	31.8 (\pm 54.56)	18.5 (\pm 51.19)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 12 in Average Three Minute Stair Climb

Rate - Modified ITT Population

End point title	Change from Baseline to Week 12 in Average Three Minute Stair Climb Rate - Modified ITT Population
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End point description:

Change from baseline 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.

End point type	Secondary
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End point timeframe:

Baseline to Week 12

End point values	BMN110 2.0 mg/kg/week	BMN110 4.0 mg/kg/week	Modified Intent-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	15	10	25	
Units: stairs/min				
arithmetic mean (standard deviation)	-3.7 (± 13.16)	1.7 (± 11.28)	-1.5 (± 12.49)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 24 in Average Three Minute Stair Climb Rate - Modified ITT Population

End point title	Change from Baseline to Week 24 in Average Three Minute Stair Climb Rate - Modified ITT Population
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End point description:

Change from baseline 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.

End point type	Secondary
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End point timeframe:

Baseline to Week 24

End point values	BMN110 2.0 mg/kg/week	BMN110 4.0 mg/kg/week	Modified Intent-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	14	10	24	
Units: stairs/min				
arithmetic mean (standard deviation)	-2.2 (± 11.01)	12.5 (± 15.26)	3.9 (± 14.65)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 52 in Average Three Minute Stair Climb Rate - Modified ITT Population

End point title	Change from Baseline to Week 52 in Average Three Minute Stair Climb Rate - Modified ITT Population
End point description:	Change from baseline 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.
End point type	Secondary
End point timeframe:	Baseline to Week 52

End point values	BMN110 2.0 mg/kg/week	BMN110 4.0 mg/kg/week	Modified Intent-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	15	10	25	
Units: stairs/min				
arithmetic mean (standard deviation)	-4.4 (\pm 9.82)	10 (\pm 16.88)	1.3 (\pm 14.66)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline to Week 12 in Respiratory Function Test MVV - Modified ITT Population

End point title	Percent Change From Baseline to Week 12 in Respiratory Function Test MVV - Modified ITT Population
End point description:	Respiratory Function was assessed by spirometry in accordance with American Thoracic Society standards. Percent Change from Baseline in Maximum Voluntary Ventilation (MVV).
End point type	Secondary
End point timeframe:	Baseline to Week 12

End point values	BMN110 2.0 mg/kg/week	BMN110 4.0 mg/kg/week	Modified Intent-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	12	10	22	
Units: % change				
arithmetic mean (standard deviation)	12.8 (\pm 21.77)	32.4 (\pm 140.73)	21.7 (\pm 94)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline to Week 24 in Respiratory Function Test MVV - Modified ITT Population

End point title	Percent Change From Baseline to Week 24 in Respiratory Function Test MVV - Modified ITT Population
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End point description:

Respiratory Function was assessed by spirometry in accordance with American Thoracic Society standards.

Percent Change from Baseline in Maximum Voluntary Ventilation (MVV).

End point type	Secondary
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End point timeframe:

Baseline to Week 24

End point values	BMN110 2.0 mg/kg/week	BMN110 4.0 mg/kg/week	Modified Intent-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	11	10	21	
Units: % change				
arithmetic mean (standard deviation)	8.8 (± 17.2)	-0.6 (± 27)	4.3 (± 22.34)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline to Week 52 in Respiratory Function Test MVV - Modified ITT Population

End point title	Percent Change From Baseline to Week 52 in Respiratory Function Test MVV - Modified ITT Population
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End point description:

Respiratory Function was assessed by spirometry in accordance with American Thoracic Society standards.

Percent Change from Baseline in Maximum Voluntary Ventilation (MVV).

End point type	Secondary
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End point timeframe:

Baseline to Week 52

End point values	BMN110 2.0 mg/kg/week	BMN110 4.0 mg/kg/week	Modified Intent-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	12	10	22	
Units: % change				
arithmetic mean (standard deviation)	2.2 (± 41.24)	-17.8 (± 38.61)	-6.9 (± 40.43)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline to Week 12 in Respiratory Function Test FVC - Modified ITT Population

End point title	Percent Change From Baseline to Week 12 in Respiratory Function Test FVC - Modified ITT Population
End point description: Respiratory Function was assessed by spirometry in accordance with American Thoracic Society standards. Percent Change from Baseline in Maximum Voluntary Ventilation (MVV).	
End point type	Secondary
End point timeframe: Baseline to Week 12	

End point values	BMN110 2.0 mg/kg/week	BMN110 4.0 mg/kg/week	Modified Intent-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	14	10	24	
Units: % change				
arithmetic mean (standard deviation)	1.7 (± 8.77)	3.2 (± 10.63)	2.3 (± 9.39)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline to Week 24 in Respiratory Function Test FVC - Modified ITT Population

End point title	Percent Change From Baseline to Week 24 in Respiratory Function Test FVC - Modified ITT Population
End point description: Respiratory Function was assessed by spirometry in accordance with American Thoracic Society standards. Percent Change from Baseline in Forced Vital Capacity (FVC).	
End point type	Secondary
End point timeframe: Baseline to Week 24	

End point values	BMN110 2.0 mg/kg/week	BMN110 4.0 mg/kg/week	Modified Intent-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	14	10	24	
Units: % change				
arithmetic mean (standard deviation)	3.4 (± 9.01)	13 (± 16.3)	7.4 (± 13.16)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline to Week 52 in Respiratory Function Test FVC - Modified ITT Population

End point title	Percent Change From Baseline to Week 52 in Respiratory Function Test FVC - Modified ITT Population
End point description:	Respiratory Function was assessed by spirometry in accordance with American Thoracic Society standards. Percent Change from Baseline in Forced Vital Capacity (FVC).
End point type	Secondary
End point timeframe:	Baseline to Week 52

End point values	BMN110 2.0 mg/kg/week	BMN110 4.0 mg/kg/week	Modified Intent-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	15	10	25	
Units: % change				
arithmetic mean (standard deviation)	4.8 (± 12.68)	15.1 (± 15.94)	8.9 (± 14.69)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline to Week 12 in Normalized Urine Keratan Sulfate - Modified ITT Population

End point title	Percent Change from Baseline to Week 12 in Normalized Urine Keratan Sulfate - Modified ITT Population
End point description:	Urinary KS was measured by a quantitative method and normalized using the sample urinary creatinine measurement.
End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	BMN110 2.0 mg/kg/week	BMN110 4.0 mg/kg/week	Modified Intent-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	14	9	23	
Units: % change				
arithmetic mean (standard deviation)	-27.6 (± 25.1)	-50.9 (± 14)	-36.7 (± 24.07)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline to Week 24 in Normalized Urine Keratan Sulfate - Modified ITT Population

End point title	Percent Change from Baseline to Week 24 in Normalized Urine Keratan Sulfate - Modified ITT Population
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End point description:

Urinary KS was measured by a quantitative method and normalized using the sample urinary creatinine measurement.

End point type	Secondary
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End point timeframe:

Baseline to Week 24

End point values	BMN110 2.0 mg/kg/week	BMN110 4.0 mg/kg/week	Modified Intent-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	14	9	23	
Units: % change				
arithmetic mean (standard deviation)	-37.4 (± 23.21)	-55.5 (± 12.62)	-44.5 (± 21.39)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline to Week 52 in Normalized Urine Keratan Sulfate - Modified ITT Population

End point title	Percent Change from Baseline to Week 52 in Normalized Urine Keratan Sulfate - Modified ITT Population
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End point description:

Urinary KS was measured by a quantitative method and normalized using the sample urinary creatinine measurement.

End point type	Secondary
End point timeframe:	
Baseline to Week 52	

End point values	BMN110 2.0 mg/kg/week	BMN110 4.0 mg/kg/week	Modified Intent-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	10	5	15	
Units: % change				
arithmetic mean (standard deviation)	-20.5 (\pm 36.95)	-52.8 (\pm 5.74)	-31.3 (\pm 33.69)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 25 in Cardiopulmonary Exercise Testing (CPET) - Duration of Exercise - Modified ITT Population

End point title	Change from Baseline to Week 25 in Cardiopulmonary Exercise Testing (CPET) - Duration of Exercise - Modified ITT Population
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End point description:

Subjects performed maximal incremental exercise testing using an electronically braked upright cycle ergometer. Cycle ergometry is a method of CPET that may be feasible in subjects who have orthopedic, peripheral vascular, or neurological limitations that restrict weight bearing.

End point type	Secondary
End point timeframe:	
Baseline to Week 25	

End point values	BMN110 2.0 mg/kg/week	BMN110 4.0 mg/kg/week	Modified Intent-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	10	5	15	
Units: minutes				
arithmetic mean (standard deviation)	0.8 (\pm 0.88)	1.1 (\pm 1.43)	0.9 (\pm 1.05)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 52 in Cardiopulmonary Exercise Testing

(CPET) - Duration of Exercise - Modified ITT Population

End point title	Change from Baseline to Week 52 in Cardiopulmonary Exercise Testing (CPET) - Duration of Exercise - Modified ITT Population
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End point description:

Subjects performed maximal incremental exercise testing using an electronically braked upright cycle ergometer. Cycle ergometry is a method of CPET that may be feasible in subjects who have orthopedic, peripheral vascular, or neurological limitations that restrict weight bearing.

End point type	Secondary
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End point timeframe:

Baseline to Week 52

End point values	BMN110 2.0 mg/kg/week	BMN110 4.0 mg/kg/week	Modified Intent-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	10	5	15	
Units: minutes				
arithmetic mean (standard deviation)	0.6 (\pm 1.34)	0.7 (\pm 1.46)	0.6 (\pm 1.33)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline to Week 25 in Cardiopulmonary Exercise Testing (CPET) - Peak Workload - Modified ITT Population

End point title	Percent Change from Baseline to Week 25 in Cardiopulmonary Exercise Testing (CPET) - Peak Workload - Modified ITT Population
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End point description:

Subjects performed maximal incremental exercise testing using an electronically braked upright cycle ergometer. Cycle ergometry is a method of CPET that may be feasible in subjects who have orthopedic, peripheral vascular, or neurological limitations that restrict weight bearing.

End point type	Secondary
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End point timeframe:

Baseline to Week 25

End point values	BMN110 2.0 mg/kg/week	BMN110 4.0 mg/kg/week	Modified Intent-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	10	5	15	
Units: % change				
arithmetic mean (standard deviation)	23.6 (\pm 20.87)	38.4 (\pm 44.66)	28.5 (\pm 30.04)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline to Week 52 in Cardiopulmonary Exercise Testing (CPET) - Peak Workload - Modified ITT Population

End point title	Percent Change from Baseline to Week 52 in Cardiopulmonary Exercise Testing (CPET) - Peak Workload - Modified ITT Population
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End point description:

Subjects performed maximal incremental exercise testing using an electronically braked upright cycle ergometer. Cycle ergometry is a method of CPET that may be feasible in subjects who have orthopedic, peripheral vascular, or neurological limitations that restrict weight bearing.

End point type	Secondary
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End point timeframe:

Baseline to Week 52

End point values	BMN110 2.0 mg/kg/week	BMN110 4.0 mg/kg/week	Modified Intent-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	10	5	15	
Units: % change				
arithmetic mean (standard deviation)	24.7 (± 26.17)	13 (± 22.69)	20.8 (± 24.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline to Week 25 in Cardiopulmonary Exercise Testing (CPET) - O2 Pulse - Modified ITT Population

End point title	Percent Change from Baseline to Week 25 in Cardiopulmonary Exercise Testing (CPET) - O2 Pulse - Modified ITT Population
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End point description:

Subjects performed maximal incremental exercise testing using an electronically braked upright cycle ergometer. Cycle ergometry is a method of CPET that may be feasible in subjects who have orthopedic, peripheral vascular, or neurological limitations that restrict weight bearing.

End point type	Secondary
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End point timeframe:

Baseline to Week 25

End point values	BMN110 2.0 mg/kg/week	BMN110 4.0 mg/kg/week	Modified Intent-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	10	5	15	
Units: % change				
arithmetic mean (standard deviation)	6.8 (± 14.17)	13.5 (± 17.65)	9 (± 15.13)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline to Week 52 in Cardiopulmonary Exercise Testing (CPET) - O2 Pulse - Modified ITT Population

End point title	Percent Change from Baseline to Week 52 in Cardiopulmonary Exercise Testing (CPET) - O2 Pulse - Modified ITT Population
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End point description:

Subjects performed maximal incremental exercise testing using an electronically braked upright cycle ergometer. Cycle ergometry is a method of CPET that may be feasible in subjects who have orthopedic, peripheral vascular, or neurological limitations that restrict weight bearing.

End point type	Secondary
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End point timeframe:

Baseline to Week 52

End point values	BMN110 2.0 mg/kg/week	BMN110 4.0 mg/kg/week	Modified Intent-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	9	5	14	
Units: % change				
arithmetic mean (standard deviation)	7.6 (± 27.89)	2 (± 31.74)	5.6 (± 28.22)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline to Week 25 in Cardiopulmonary Exercise Testing (CPET) - Aerobic Efficiency - Modified ITT Population

End point title	Percent Change from Baseline to Week 25 in Cardiopulmonary Exercise Testing (CPET) - Aerobic Efficiency - Modified ITT Population
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End point description:

Subjects performed maximal incremental exercise testing using an electronically braked upright cycle ergometer. Cycle ergometry is a method of CPET that may be feasible in subjects who have orthopedic, peripheral vascular, or neurological limitations that restrict weight bearing.

End point type	Secondary
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End point timeframe:

Baseline to Week 25

End point values	BMN110 2.0 mg/kg/week	BMN110 4.0 mg/kg/week	Modified Intent-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	9	5	14	
Units: % change				
arithmetic mean (standard deviation)	-8.9 (± 15.41)	-6 (± 8.29)	-7.9 (± 13.02)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline to Week 52 in Cardiopulmonary Exercise Testing (CPET) - Aerobic Efficiency - Modified ITT Population

End point title	Percent Change from Baseline to Week 52 in Cardiopulmonary Exercise Testing (CPET) - Aerobic Efficiency - Modified ITT Population
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End point description:

Subjects performed maximal incremental exercise testing using an electronically braked upright cycle ergometer. Cycle ergometry is a method of CPET that may be feasible in subjects who have orthopedic, peripheral vascular, or neurological limitations that restrict weight bearing.

End point type	Secondary
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End point timeframe:

Baseline to Week 52

End point values	BMN110 2.0 mg/kg/week	BMN110 4.0 mg/kg/week	Modified Intent-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	9	4	13	
Units: % change				
arithmetic mean (standard deviation)	-7.5 (± 28.39)	-9.8 (± 33.14)	-8.2 (± 28.52)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 25 in Peak Force in Muscle Strength Testing - Knee Extension Test - Modified ITT Population

End point title	Change from Baseline to Week 25 in Peak Force in Muscle Strength Testing - Knee Extension Test - Modified ITT Population
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End point description:

Peak Force in the muscle strength testing using the knee extension test

End point type	Secondary
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End point timeframe:

Baseline to Week 25

End point values	BMN110 2.0 mg/kg/week	BMN110 4.0 mg/kg/week	Modified Intent-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	15	10	25	
Units: newton metres				
arithmetic mean (standard deviation)	-0.6 (± 9.76)	5.2 (± 7.63)	1.7 (± 9.26)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 52 in Peak Force in Muscle Strength Testing - Knee Extension Test - Modified ITT Population

End point title	Change from Baseline to Week 52 in Peak Force in Muscle Strength Testing - Knee Extension Test - Modified ITT Population
End point description:	Peak Force in the muscle strength testing using the knee extension test
End point type	Secondary
End point timeframe:	Baseline to Week 52

End point values	BMN110 2.0 mg/kg/week	BMN110 4.0 mg/kg/week	Modified Intent-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	13	9	22	
Units: newton metres				
arithmetic mean (standard deviation)	3.3 (± 6.88)	6.7 (± 8.87)	4.7 (± 7.74)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline to Week 25 in Peak Force in Muscle Strength Testing - Knee Flexion Test - Modified ITT Population

End point title	Percent Change from Baseline to Week 25 in Peak Force in Muscle Strength Testing - Knee Flexion Test - Modified ITT Population
End point description:	Peak Force in the muscle strength testing using the knee flexion test
End point type	Secondary

End point timeframe:

Baseline to Week 25

End point values	BMN110 2.0 mg/kg/week	BMN110 4.0 mg/kg/week	Modified Intent-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	14	10	24	
Units: % change				
arithmetic mean (standard deviation)	-4.2 (± 24.83)	9.4 (± 44.87)	1.5 (± 34.39)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline to Week 52 in Peak Force in Muscle Strength Testing - Knee Flexion Test - Modified ITT Population

End point title	Percent Change from Baseline to Week 52 in Peak Force in Muscle Strength Testing - Knee Flexion Test - Modified ITT Population
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End point description:

Peak Force in the muscle strength testing using the knee flexion test

End point type	Secondary
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End point timeframe:

Baseline to Week 52

End point values	BMN110 2.0 mg/kg/week	BMN110 4.0 mg/kg/week	Modified Intent-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	12	9	21	
Units: % change				
arithmetic mean (standard deviation)	-10.8 (± 22.72)	8.2 (± 41.57)	-2.7 (± 32.69)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline to Week 25 in Peak Force in Muscle Strength Testing - Elbow Flexion Test - Modified ITT Population

End point title	Percent Change from Baseline to Week 25 in Peak Force in Muscle Strength Testing - Elbow Flexion Test - Modified ITT Population
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End point description:

Peak Force in the muscle strength testing using the elbow flexion test

Percent Change from Baseline to Week 52 in Peak Force in Muscle Strength Testing - Elbow Flexion Test - Modified ITT Population

End point type	Secondary
End point timeframe:	
Baseline to Week 25	

End point values	BMN110 2.0 mg/kg/week	BMN110 4.0 mg/kg/week	Modified Intent-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	12	7	19	
Units: % change				
arithmetic mean (standard deviation)	12 (± 55.42)	17.7 (± 41.82)	14.1 (± 49.67)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline to Week 52 in Peak Force in Muscle Strength Testing - Elbow Flexion Test - Modified ITT Population

End point title	Percent Change from Baseline to Week 52 in Peak Force in Muscle Strength Testing - Elbow Flexion Test - Modified ITT Population			
End point description:	Peak Force in the muscle strength testing using the elbow flexion test			
End point type	Secondary			
End point timeframe:	Baseline to Week 52			

End point values	BMN110 2.0 mg/kg/week	BMN110 4.0 mg/kg/week	Modified Intent-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	10	6	16	
Units: % change				
arithmetic mean (standard deviation)	49.7 (± 86.83)	50.7 (± 59.81)	50.1 (± 75.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 12 in Pain Intensity measured using the

Adolescent Paediatric Pain Tool (APPT) - Modified ITT Population

End point title	Change from Baseline to Week 12 in Pain Intensity measured using the Adolescent Paediatric Pain Tool (APPT) - Modified ITT Population
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End point description:

The APPT is a validated, multidimensional tool to evaluate pain in children, adolescents, and young adults. The complete APPT is measured in three parts - Part 1 of the APPT scale determines the subject's pain locations using a body template. Part 2 of the APPT scale determines the intensity of the pain using a 10 cm visual analog scale (VAS) with the lowest point of the scale (0) labeled No Pain and the highest point on the scale (10) labeled Worst Possible Pain. Intermediate regions of the scale were labeled with 3 intermediate descriptors (Little Pain, Medium Pain, and Large Pain). Part 3 of the APPT scale characterizes the pain by tracking the number and percentage of words selected by subjects to describe their pain from a total of 57 choices. Part 2 corresponds most closely to other typically used pain scales (based on VAS) and for this reason the results from Part 2 are presented here.

End point type	Secondary
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End point timeframe:

Baseline to Week 12

End point values	BMN110 2.0 mg/kg/week	BMN110 4.0 mg/kg/week	Modified Intent-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	12	9	21	
Units: scale units				
arithmetic mean (standard deviation)	-2.3 (± 3.37)	-1.2 (± 2.23)	-1.8 (± 2.93)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 24 in Pain Intensity measured using the Adolescent Paediatric Pain Tool (APPT) - Modified ITT Population

End point title	Change from Baseline to Week 24 in Pain Intensity measured using the Adolescent Paediatric Pain Tool (APPT) - Modified ITT Population
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End point description:

The APPT is a validated, multidimensional tool to evaluate pain in children, adolescents, and young adults. The complete APPT is measured in three parts - Part 1 of the APPT scale determines the subject's pain locations using a body template. Part 2 of the APPT scale determines the intensity of the pain using a 10 cm visual analog scale (VAS) with the lowest point of the scale (0) labeled No Pain and the highest point on the scale (10) labeled Worst Possible Pain. Intermediate regions of the scale were labeled with 3 intermediate descriptors (Little Pain, Medium Pain, and Large Pain). Part 3 of the APPT scale characterizes the pain by tracking the number and percentage of words selected by subjects to describe their pain from a total of 57 choices. Part 2 corresponds most closely to other typically used pain scales (based on VAS) and for this reason the results from Part 2 are presented here.

End point type	Secondary
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End point timeframe:

Baseline to Week 24

End point values	BMN110 2.0 mg/kg/week	BMN110 4.0 mg/kg/week	Modified Intent-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	12	8	20	
Units: scale units				
arithmetic mean (standard deviation)	-2.2 (± 3.68)	-1.2 (± 2.87)	-1.8 (± 3.33)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 52 in Pain Intensity measured using the Adolescent Paediatric Pain Tool (APPT) - Modified ITT Population

End point title	Change from Baseline to Week 52 in Pain Intensity measured using the Adolescent Paediatric Pain Tool (APPT) - Modified ITT Population
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End point description:

End point type	Secondary
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End point timeframe:

Baseline to Week 52

End point values	BMN110 2.0 mg/kg/week	BMN110 4.0 mg/kg/week	Modified Intent-to-Treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	11	9	20	
Units: scale units				
arithmetic mean (standard deviation)	-0.8 (± 3.41)	-0.8 (± 3.04)	-0.8 (± 3.17)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Study Period

Adverse event reporting additional description:

None

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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Reporting groups

Reporting group title	BMN110 4.0 mg/kg/week
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Reporting group description: -

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

Serious adverse events	BMN110 4.0 mg/kg/week	BMN110 2.0 mg/kg/week	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 10 (20.00%)	3 / 15 (20.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Surgical and medical procedures			
Medical device removal			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Inflammatory bowel disease			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Enuresis			

subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Knee deformity			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kyphoscoliosis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	BMN110 4.0 mg/kg/week	BMN110 2.0 mg/kg/week	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)	15 / 15 (100.00%)	
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Hot flush			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Hypotension			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	2	
Pallor			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Peripheral coldness			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Surgical and medical procedures			

Catheterisation venous subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Central venous catheterisation subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 15 (6.67%) 1	
Medical device removal subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2	0 / 15 (0.00%) 0	
Tooth extraction subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 2	
General disorders and administration site conditions			
Catheter site pain subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 15 (13.33%) 2	
Chest pain subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 15 (13.33%) 2	
Chills subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 15 (13.33%) 2	
Cyst subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Device malfunction subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Extravasation subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 15 (0.00%) 0	
Face oedema subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 15 (0.00%) 0	
Fatigue			

subjects affected / exposed	2 / 10 (20.00%)	8 / 15 (53.33%)
occurrences (all)	5	12
Influenza like illness		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Infusion site bruising		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Infusion site erythema		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Infusion site extravasation		
subjects affected / exposed	2 / 10 (20.00%)	3 / 15 (20.00%)
occurrences (all)	4	6
Infusion site swelling		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Injection site pain		
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)
occurrences (all)	1	0
Injection site pruritus		
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)
occurrences (all)	2	0
Injection site reaction		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Irritability		
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	3
Local swelling		
subjects affected / exposed	1 / 10 (10.00%)	2 / 15 (13.33%)
occurrences (all)	1	3
Malaise		
subjects affected / exposed	1 / 10 (10.00%)	1 / 15 (6.67%)
occurrences (all)	1	1
Medical device pain		

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Oedema peripheral subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 15 (13.33%) 2	
Pain subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	2 / 15 (13.33%) 2	
Pyrexia subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 9	9 / 15 (60.00%) 24	
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2	0 / 15 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 15 (6.67%) 2	
Cough subjects affected / exposed occurrences (all)	4 / 10 (40.00%) 8	6 / 15 (40.00%) 9	
Dysphonia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Dyspnoea subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	4 / 15 (26.67%) 4	
Epistaxis subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	3 / 15 (20.00%) 5	
Hypoventilation subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Oropharyngeal pain			

subjects affected / exposed occurrences (all)	4 / 10 (40.00%) 6	7 / 15 (46.67%) 11	
Nasal congestion subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2	7 / 15 (46.67%) 9	
Productive cough subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Respiratory distress subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Rhinorrhoea subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 15 (6.67%) 2	
Throat irritation subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2	1 / 15 (6.67%) 1	
Wheezing subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 15 (13.33%) 2	
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 3	2 / 15 (13.33%) 2	
Depression subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 2	
Insomnia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	3 / 15 (20.00%) 3	
Phobia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Investigations			
Blood glucose decreased			

subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Haemoglobin increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Urine output decreased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Urine leukocyte esterase positive			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
White blood cells urine positive			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Weight decreased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Excoriation			
subjects affected / exposed	1 / 10 (10.00%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Fall			
subjects affected / exposed	2 / 10 (20.00%)	2 / 15 (13.33%)	
occurrences (all)	3	2	
Hand fracture			
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Head injury			
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Inadequate analgesia			

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Infusion related reaction subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 15 (0.00%) 0	
Injection related reaction subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 2	
Joint injury subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Laceration subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Ligament sprain subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 15 (0.00%) 0	
Limb crushing injury subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Limb injury subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 15 (13.33%) 2	
Muscle strain subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Procedural pain subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2	5 / 15 (33.33%) 8	
Wound complication subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 15 (0.00%) 0	
Congenital, familial and genetic disorders Pectus carinatum			

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Cardiac disorders			
Bradycardia			
subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Sinus bradycardia			
subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 15 (0.00%) 0	
Tachycardia			
subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2	0 / 15 (0.00%) 0	
Nervous system disorders			
Coordination abnormal			
subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Dizziness			
subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 3	6 / 15 (40.00%) 8	
Dysgeusia			
subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Headache			
subjects affected / exposed occurrences (all)	7 / 10 (70.00%) 44	13 / 15 (86.67%) 89	
Lethargy			
subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Neuralgia			
subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Poor quality sleep			
subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Somnolence			

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 15 (13.33%) 2	
Syncope subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Blood and lymphatic system disorders Lymph node pain subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Ear and labyrinth disorders Ear discomfort subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 15 (0.00%) 0	
Ear pruritus subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Ear pain subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2	2 / 15 (13.33%) 3	
Motion sickness subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 15 (13.33%) 3	
Otorrhoea subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Tinnitus subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Eye disorders Eye pruritus subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Photophobia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Vision blurred			

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 3	
Vitreous floaters subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Gastrointestinal disorders			
Abdominal discomfort subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 3	
Abdominal pain subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 23	6 / 15 (40.00%) 18	
Abdominal pain upper subjects affected / exposed occurrences (all)	4 / 10 (40.00%) 11	4 / 15 (26.67%) 8	
Abdominal pain lower subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Anal pruritus subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Aerophagia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Aphthous stomatitis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 15 (13.33%) 2	
Constipation subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 15 (13.33%) 2	
Diarrhoea subjects affected / exposed occurrences (all)	4 / 10 (40.00%) 10	6 / 15 (40.00%) 21	
Dyspepsia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 6	1 / 15 (6.67%) 1	

Gastroesophageal reflux disease subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Haematochezia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Lip oedema subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Oral pain subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Nausea subjects affected / exposed occurrences (all)	5 / 10 (50.00%) 6	10 / 15 (66.67%) 33	
Swollen tongue subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 15 (0.00%) 0	
Retching subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Vomiting subjects affected / exposed occurrences (all)	5 / 10 (50.00%) 10	11 / 15 (73.33%) 34	
Toothache subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Skin and subcutaneous tissue disorders			
Acne subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 4	1 / 15 (6.67%) 1	
Decubitus ulcer subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Dermatitis allergic			

subjects affected / exposed	1 / 10 (10.00%)	1 / 15 (6.67%)
occurrences (all)	1	1
Dermatitis contact		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Ecchymosis		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Dry skin		
subjects affected / exposed	1 / 10 (10.00%)	1 / 15 (6.67%)
occurrences (all)	2	1
Eczema		
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	2
Erythema		
subjects affected / exposed	2 / 10 (20.00%)	4 / 15 (26.67%)
occurrences (all)	2	9
Nail disorder		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Pruritus		
subjects affected / exposed	1 / 10 (10.00%)	3 / 15 (20.00%)
occurrences (all)	1	6
Rash		
subjects affected / exposed	1 / 10 (10.00%)	6 / 15 (40.00%)
occurrences (all)	3	7
Rash erythematous		
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)
occurrences (all)	1	0
Rash generalised		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Rash pruritic		
subjects affected / exposed	2 / 10 (20.00%)	1 / 15 (6.67%)
occurrences (all)	3	1
Swelling face		

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Urticaria subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	3 / 15 (20.00%) 11	
Renal and urinary disorders			
Dysuria subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Enuresis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 2	
Pollakiuria subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 2	
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	5 / 10 (50.00%) 11	6 / 15 (40.00%) 28	
Back pain subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	6 / 15 (40.00%) 13	
Flank pain subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Elbow deformity subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 15 (6.67%) 1	
Joint swelling subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	2 / 15 (13.33%) 2	
Knee deformity subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 15 (6.67%) 1	
Kyphoscoliosis			

subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Muscle spasms			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Musculoskeletal pain			
subjects affected / exposed	0 / 10 (0.00%)	3 / 15 (20.00%)	
occurrences (all)	0	4	
Musculoskeletal stiffness			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	5	
Osteoarthritis			
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Osteochondrosis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Osteopenia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	4 / 10 (40.00%)	8 / 15 (53.33%)	
occurrences (all)	5	22	
Infections and infestations			
Ear infection			
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	3	
Enterobiasis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	3	

Fungal infection		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Gastroenteritis		
subjects affected / exposed	3 / 10 (30.00%)	2 / 15 (13.33%)
occurrences (all)	5	3
Gastroenteritis viral		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Gastrointestinal infection		
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)
occurrences (all)	1	0
Influenza		
subjects affected / exposed	1 / 10 (10.00%)	4 / 15 (26.67%)
occurrences (all)	1	4
Nasopharyngitis		
subjects affected / exposed	7 / 10 (70.00%)	6 / 15 (40.00%)
occurrences (all)	16	10
Oral herpes		
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)
occurrences (all)	1	0
Otitis media		
subjects affected / exposed	1 / 10 (10.00%)	2 / 15 (13.33%)
occurrences (all)	1	2
Pharyngitis		
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	1
Pharyngitis streptococcal		
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	5
Pneumonia		
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)
occurrences (all)	1	0
Rhinitis		
subjects affected / exposed	2 / 10 (20.00%)	0 / 15 (0.00%)
occurrences (all)	2	0

Sinusitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	5 / 10 (50.00%)	5 / 15 (33.33%)	
occurrences (all)	7	13	
Urinary tract infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 10 (10.00%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Hyperglycaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Hypophosphataemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Increased appetite			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 July 2012	<p>The primary changes for amending the protocol for study MOR-008 (Amendment 1)</p> <ol style="list-style-type: none">1. Language has been changed to permit the Investigator to be unblinded to a patient's treatment assignment without delay, upon their request, in the event of a serious or life-threatening adverse event for which therapy would be determined or significantly altered by knowledge of the treatment assignment. The Investigator does not need to obtain formal written approval of BioMarin's medical monitor prior to unblinding in these circumstances.2. The length of the Screening period has been extended from 14 to 21 days.3. A long-term extension phase has been added to the existing protocol.4. The language for the exclusion criterion concerning cervical spine compression has been modified.5. Language regarding the reporting of adverse events (AEs) and serious adverse events (SAEs), as well as language regarding the collection of additional samples following a severe infusion-associated reaction (IAR), has been clarified for consistency.6. The statement that 100% of the data will be source document verified has been removed.7. The collection and analysis of blood inflammatory markers was removed from this study.8. Additional minor changes have been made to improve clarity and consistency.
02 August 2013	<p>The primary reason for amending the protocol for study MOR-008 (Amendment 2)</p> <ol style="list-style-type: none">1. Dosing in the extension phase of the study has changed to an open-label 2.0 mg/kg weekly.2. The objectives in the extension phase of the study have been updated.3. After Week 96, the visit week schedule has been changed to a 48-week base, and the total length of the extension phase of the study has been changed to 166 weeks (for a total study duration up to 196 weeks).4. The Schedule of Events has been modified to streamline the collection of assessments.5. Plasma glycosaminoglycan (GAG) collection and analysis has been removed from the extension of the study.6. Information regarding previous clinical studies has been updated to include information from the Phase 3 studies, MOR-004 and MOR-005. Safety information has also been updated based on recent updates to the BMN 110 Investigator Brochure7. The BMN 110 excipients have been updated to include only those from the Phase 3/commercial formulation. Excipients found only in the Phase 1/2 drug formulation have been removed.8. The identity and contact information for the medical monitor have been updated.9. Information regarding Case Report Forms and Source Documents has been revised because patient records should be made available for source verification.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

