Clinical trial results:
A Phase 2, Open-label, Multinational Clinical Study to Evaluate the Safety and Efficacy of BMN 110 in Pediatric Patients Less Than 5 Years of Age with Mucopolysaccharidosis IVA (Morquio A Syndrome)

Summary

EudraCT number	2011-003197-84
Trial protocol	GB IT
Global end of trial date	03 February 2016

Results information

Result version number	v1 (current)
This version publication date	19 August 2017
First version publication date	19 August 2017

Trial information

Trial identification

Sponsor protocol code	MOR-007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01515956
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?	Yes
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	03 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 February 2016
Global end of trial reached?	Yes
Global end of trial date	03 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate safety and tolerability of infusions of BMN 110 at a dose of 2.0 mg/kg/week over a 52-week period in MPS IVA patients less than 5 years of age.
For the extension Phase: To evaluate the long-term safety of BMN 110 at a dose of 2.0 mg/kg/week in patients with MPS IVA less than 5 years of age at enrollment.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 October 2011
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	Italy: 2
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	15
EEA total number of subjects	8

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)	3
Children (2-11 years)	12

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

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening occurred within 14 days prior to Baseline. Informed consent was obtained prior to any Screening procedures.

15 subjects were screened for inclusion, all of whom met the eligibility criteria and were enrolled in the study; there were no screen failures.

Period 1

Period 1 title	Primary Phase
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	BMN110 2.0 mg/kg/week

Arm description:

BMN110 2.0 mg/kg/week for up to 52 weeks

Arm type	BMN110 2.0 mg/kg/week
Investigational medicinal product name	Elosulfase alfa
Investigational medicinal product code	BMN 110
Other name	Vimizim, recombinant human N-acetylgalactosamine-6-sulfatase
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received intravenous (IV) infusions of BMN 110 at a dose of 2.0 mg/kg/week for up to 52 weeks. Each infusion was administered over a period of approximately 4 hours.

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

Period 2

Period 2 title	Extension Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	BMN110 2.0 mg/kg/week

Arm description:

BMN110 2.0 mg/kg/week for up to an additional 156 weeks, in subjects who had completed Period 1 (the initial 52-week treatment phase)

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

Dosage and administration details:

Subjects received intravenous (IV) infusions of BMN 110 at a dose of 2.0 mg/kg/week for up to an additional 156 weeks. Each infusion was administered over a period of approximately 4 hours.

Number of subjects in period 2	BMN110 2.0 mg/kg/week
Started	15
Completed	0
Not completed	15
Consent withdrawn by subject	3
Transferred to Commercial treatment after Wk 105	1
Study Terminated by Sponsor	11

Baseline characteristics

Reporting groups	
Reporting group title	Primary Phase

Reporting group description: -

Reporting group values	Primary Phase	Total	
Number of subjects	15	15	
Age categorical Units: Subjects			
0 to <3 years	7	7	
>=3 to 5 years	8	8	
Age continuous Units: Years			
arithmetic mean	3.1		
standard deviation	± 1.34	-	
Gender categorical Units: Subjects			
Female	8	8	
Male	7	7	
Normalized Urine Keratan Sulfate Units: ug/mg			
arithmetic mean	35.9		
standard deviation	± 12.32	-	
Normalized Standing Height Z-score Units: z-score			
arithmetic mean	-1.6		
standard deviation	± 1.61	-	
Cumulative Growth Rate Z-score Units: z-score			
arithmetic mean	-0.6		
standard deviation	± 0.64	-	

End points

End points reporting groups

Reporting group title	BMN110 2.0 mg/kg/week
Reporting group description:	
BMN110 2.0 mg/kg/week for up to 52 weeks	
Reporting group title	BMN110 2.0 mg/kg/week
Reporting group description:	
BMN110 2.0 mg/kg/week for up to an additional 156 weeks, in subjects who had completed Period 1 (the initial 52-week treatment phase)	

Primary: Safety

End point title	Safety[1]
End point description:	
To evaluate safety and tolerability of infusions of BMN 110 at a dose of 2.0 mg/kg/week over a 52-week period in MPS IVA patients less than 5 years of age.	
End point type	Primary
End point timeframe:	
52-week 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 analyses was specified. Only descriptive statistics would be used.

End point values	BMN110 2.0 mg/kg/week	BMN110 2.0 mg/kg/week		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: none	15	15		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline to Week 52 in Normalized Urine Keratan Sulfate - Efficacy Analysis Set

End point title	Percent Change from Baseline to Week 52 in Normalized Urine Keratan Sulfate - Efficacy Analysis Set
End point description:	
End point type	Secondary
End point timeframe:	
Percent Change from Baseline to Week 52	

End point values	BMN110 2.0 mg/kg/week			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: ug/mg				
arithmetic mean (standard deviation)	-44.3 (± 21.15)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 52 in Normalized Standing Height Z-score - Efficacy Analysis Set

End point title	Change from Baseline to Week 52 in Normalized Standing Height Z-score - Efficacy Analysis Set

End point description:

End point type	Secondary

End point timeframe:

Change from Baseline to Week 52

End point values	BMN110 2.0 mg/kg/week			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: z-score				
arithmetic mean (standard deviation)	-0.4 (± 0.53)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 52 in Cumulative Growth Rate Z-score - Efficacy Analysis Set

End point title	Change from Baseline to Week 52 in Cumulative Growth Rate Z-score - Efficacy Analysis Set

End point description:

End point type	Secondary

End point timeframe:

Change from Baseline to Week 52

End point values	BMN110 2.0 mg/kg/week			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: z-score				
arithmetic mean (standard deviation)	0.2 (± 1.04)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Study Period: All non-serious AEs were recorded from the start of the Week 0 infusion through the end of the study (up to Week 208). All SAEs were
reported from informed consent through the end of the study (up to Week 208)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	BMN110 2.0 mg/kg/week

Reporting group description: -

Serious adverse events	BMN110 2.0 mg/kg/week		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 15 (53.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Congenital, familial and genetic disorders			
Developmental hip dysplasia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Poor venous access			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrospinal fluid leakage			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cervical cord compression			

subjects affected / exposed	4 / 15 (26.67%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Spinal cord oedema			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Medical device complication			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Tonsillar hypertrophy			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Joint instability			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Knee deformity			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Device related infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	BMN110 2.0 mg/kg/week		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 15 (100.00%)		
Vascular disorders			
Flushing			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		

Hot flush				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Hyperaemia				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Hypotension				
subjects affected / exposed	2 / 15 (13.33%)			
occurrences (all)	2			
Poor venous access				
subjects affected / exposed	4 / 15 (26.67%)			
occurrences (all)	6			
Pallor				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Surgical and medical procedures				
Catheter placement				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Central venous catheter removal				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Dental care				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Central venous catheterisation				
subjects affected / exposed	2 / 15 (13.33%)			
occurrences (all)	2			
Ear tube insertion				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Ear tube removal				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Infusion				

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Joint fluid drainage			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Orchidopexy			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
General disorders and administration site conditions			
Catheter site extravasation			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	6		
Catheter site pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Catheter site related reaction			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Chest pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Chills			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Crepitations			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Device difficult to use			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	6		
Gait disturbance			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Implant site haemorrhage			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Infusion site extravasation			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	3		
Injection site hypersensitivity			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Local swelling			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	4		
Mass			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Medical device complication			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Medical device pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Medical device site reaction			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Pain			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Pyrexia			
subjects affected / exposed	15 / 15 (100.00%)		
occurrences (all)	143		
Reproductive system and breast			

disorders			
Balanoposthitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Oedema genital			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Adenoidal hypertrophy			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Allergic respiratory disease			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Asthma			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	11 / 15 (73.33%)		
occurrences (all)	39		
Haemoptysis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Increased upper airway secretion			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Laryngospasm			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Nasal congestion			
subjects affected / exposed	6 / 15 (40.00%)		
occurrences (all)	15		
Nasal obstruction			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Oropharyngeal pain			

subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	23		
Rhinitis allergic			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Rhinorrhoea			
subjects affected / exposed	8 / 15 (53.33%)		
occurrences (all)	20		
Sleep apnoea syndrome			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Sneezing			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	5		
Throat irritation			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Tonsillar hypertrophy			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Wheezing			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Psychiatric disorders			
Agitation			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	3		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Blood bicarbonate decreased			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Body temperature increased			

subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	5		
Breath sounds abnormal			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Heart rate increased			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	11		
Oxygen saturation decreased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Respiratory rate increased			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	10		
Venous pressure decreased			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	5 / 15 (33.33%)		
occurrences (all)	5		
Eye contusion			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Foot fracture			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Fall			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Head injury			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	3		
Infusion related reaction			

subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	3		
Injury corneal			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Laceration			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Limb crushing injury			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Lip injury			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Postoperative fever			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Procedural pain			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Procedural vomiting			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Scar			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Spinal cord injury			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Thermal burn			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Congenital, familial and genetic disorders			
Developmental hip dysplasia			

subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	 4 / 15 (26.67%) 9		
Nervous system disorders Cerebral haematoma subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Hypoaesthesia subjects affected / exposed occurrences (all)	 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1 5 / 15 (33.33%) 13 1 / 15 (6.67%) 2		
Blood and lymphatic system disorders Lymphadenopathy subjects affected / exposed occurrences (all)	 1 / 15 (6.67%) 1		
Ear and labyrinth disorders Aural polyp subjects affected / exposed occurrences (all) Cerumen impaction subjects affected / exposed occurrences (all) Conductive deafness subjects affected / exposed occurrences (all) Deafness subjects affected / exposed occurrences (all) Deafness bilateral	 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1 1 / 15 (6.67%) 2 2 / 15 (13.33%) 2		

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Ear haemorrhage			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Ear pain			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	17		
Hearing impaired			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Middle ear effusion			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Motion sickness			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Otorrhoea			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Eye disorders			
Amblyopia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Astigmatism			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Conjunctivitis			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	5		
Conjunctivitis allergic			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	3		
Corneal opacity			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		

Eye discharge			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	3		
Eye pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Eye swelling			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Keratitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Trichiasis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	4		
Abdominal pain			
subjects affected / exposed	8 / 15 (53.33%)		
occurrences (all)	14		
Abdominal pain upper			
subjects affected / exposed	5 / 15 (33.33%)		
occurrences (all)	14		
Constipation			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Colitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Dental caries			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Diarrhoea			

subjects affected / exposed	11 / 15 (73.33%)		
occurrences (all)	24		
Dyspepsia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Flatulence			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Gastritis			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	3		
Gingival pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Mouth ulceration			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	5		
Oral discomfort			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Oral disorder			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Retching			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Toothache			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Vomiting			
subjects affected / exposed	13 / 15 (86.67%)		
occurrences (all)	59		
Hepatobiliary disorders			

Hepatic function abnormal			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Portal vein thrombosis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Cold sweat			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Blister			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	3		
Dermatitis allergic			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	3		
Dermatitis diaper			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Eczema			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	5		
Erythema			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Petechiae			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	7		
Rash			

subjects affected / exposed	6 / 15 (40.00%)		
occurrences (all)	9		
Rash erythematous			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Skin disorder			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Rash papular			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Skin reaction			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	36		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Haematuria			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pollakiuria			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Vesicoureteric reflux			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 15 (46.67%)		
occurrences (all)	15		
Back pain			

subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Bone pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Joint swelling			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Limb discomfort			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Musculoskeletal stiffness			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Myalgia			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Neck pain			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	5 / 15 (33.33%)		
occurrences (all)	15		
Spinal disorder			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Acute tonsillitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Anal fungal infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		

Bronchitis				
subjects affected / exposed	3 / 15 (20.00%)			
occurrences (all)	7			
Conjunctivitis infective				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Diarrhoea infectious				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Ear infection				
subjects affected / exposed	3 / 15 (20.00%)			
occurrences (all)	4			
Exanthema subitum				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	2			
Fungal skin infection				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Gastroenteritis				
subjects affected / exposed	2 / 15 (13.33%)			
occurrences (all)	3			
Gastroenteritis viral				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	2			
Gingival infection				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Hand-foot-and-mouth disease				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Herpes simplex				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	2			
Hordeolum				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			

Implant site infection				
subjects affected / exposed	3 / 15 (20.00%)			
occurrences (all)	3			
Influenza				
subjects affected / exposed	3 / 15 (20.00%)			
occurrences (all)	3			
Lower respiratory tract infection				
subjects affected / exposed	2 / 15 (13.33%)			
occurrences (all)	4			
Molluscum contagiosum				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	2			
Nasopharyngitis				
subjects affected / exposed	9 / 15 (60.00%)			
occurrences (all)	25			
Oral candidiasis				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Otitis externa				
subjects affected / exposed	2 / 15 (13.33%)			
occurrences (all)	2			
Otitis media				
subjects affected / exposed	5 / 15 (33.33%)			
occurrences (all)	6			
Otitis media acute				
subjects affected / exposed	3 / 15 (20.00%)			
occurrences (all)	6			
Otitis media chronic				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Penile infection				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Pharyngitis				
subjects affected / exposed	2 / 15 (13.33%)			
occurrences (all)	3			

Postoperative wound infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Rash pustular			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	9 / 15 (60.00%)		
occurrences (all)	22		
Skin infection			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Tonsillitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Tooth infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	8 / 15 (53.33%)		
occurrences (all)	52		
Urinary tract infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Viral infection			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Viral rash			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Viral upper respiratory tract infection			
subjects affected / exposed	5 / 15 (33.33%)		
occurrences (all)	8		
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 July 2011	The primary rationale for amending the protocol for Study MOR-007 (Amendment 1) is to include BMN 110 stopping criteria. In addition, Amendment 1 contains other changes as follows: 1. The use of antihistamines and antipyretics prior to study drug infusion was further clarified to address that all patients will be pretreated with an age-appropriate dose of antihistamine medication and antipyretic medications at the discretion of the Investigator due to the risk of paradoxical CNS stimulation or seizures in neonates. 2. The age restriction for the PedsQLTM instrument has been removed, as new parent reports for infants from 0–12 months and 13–24 months have been recently introduced.
23 December 2011	The primary changes for protocol MOR-007 (Amendment 2): 1. Changed Visit window from +/- 4 days to +/-3 days. 2. Added collection of genotype data as part of a patient's medical history. 3. Added collection of the patient's age at the time of Morquio A diagnosis as part of patient's medical history 4. Added measurement of head circumference in all patients at the same time points as other anthropometric measurements 5. Added collection of O2 saturation via pulse oximetry to vital sign collection at all visits 6. Clarified that urinary GAG will be tested in duplicate. 7. Clarified which body parts will be evaluated by dual-emission x-ray absorptiometry (DXA). Where feasible both whole body scan and a lumbar spine DXA scan will be performed. If only one scan will be performed the Investigator should ensure that the same type of scan is performed at both the screening and Week 52 visits. Although the actual scan performed is a whole body scan, for accurate calculation of bone density in this age group the head will be excluded from the analysis. Removed allowance to use a DXA scan at screening taken within the prior 3 months 8. Clarified the inclusion criterion that patients must be <5 years old at the date of the first study-drug infusion 9. Specified that anthropometric measurements will be collected in duplicate (with a 3rd of the first two measurements are outside the specified error range) 10. Added type IIA Collagen N-Propeptide (PIIANP) as an assessment at Baseline, Week 25 and Week 52 11. Added collection of an additional blood sample for plasma KS at Baseline and at weeks 4, 8 and 52 12. Collection of dental samples 13. Updated language on the dilution of BMN110 for children with different weights 14. Clarification that radiologic, echocardiogram, electrocardiogram and magnetic resonance imaging collected and reviewed centrally 15. A post-infusion phone contact was added 16. Change in name and contact of Medical Monitor

27 July 2012	The primary changes for protocol MOR-007 (Amendment 3): 1. A long-term extension phase has been added to the existing protocol. An interim analysis and interim CSR will be performed when the last patient in has reached Week 52. 2. Language surrounding the use of antihistamines and antipyretics has been modified. 3. The second urine collection on the day of infusion has been removed. 4. The statement that 100% of the data will be source document verified has been removed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported