Clinical trial results:
A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multinational Clinical Study to Evaluate the Efficacy and Safety of 2.0 mg/kg/week and 2.0 mg/kg/every other week BMN 110 in Patients with Mucopolysaccharidosis IVA (Morquio A Syndrome)

Summary

EudraCT number	2010-020198-18
Trial protocol	GB NL FR DE PT IT NO DK
Global end of trial date	23 August 2012

Results information

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

Trial information

Trial identification

Sponsor protocol code	MOR-004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01275066
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	BioMarin Pharmaceutical Inc.
Sponsor organisation address	105 Digital Drive, Novato, United States, CA 94949
Public contact	Clinical Trials Information, BioMarin Pharmaceutical Inc., clinicaltrials@bmrn.com
Scientific contact	Clinical Trials Information, BioMarin Pharmaceutical Inc., clinicaltrials@bmrn.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000973-PIP01-10
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 August 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 August 2012
Global end of trial reached?	Yes
Global end of trial date	23 August 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the ability of 2.0 mg/kg/week BMN 110 and 2.0 mg/kg/qow BMN 110 compared with placebo to enhance endurance in patients with MPS IVA, as measured by an increase in the number of meters walked in the 6MW test from baseline to Week 24.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 February 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	Argentina: 2
Country: Number of subjects enrolled	Brazil: 21
Country: Number of subjects enrolled	Canada: 14
Country: Number of subjects enrolled	Colombia: 6
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	France: 20
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	Japan: 6
Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	Qatar: 2
Country: Number of subjects enrolled	Saudi Arabia: 7
Country: Number of subjects enrolled	Taiwan: 5
Country: Number of subjects enrolled	United Kingdom: 23
Country: Number of subjects enrolled	United States: 33
Country: Number of subjects enrolled	Korea, Republic of: 7

Worldwide total number of subjects	176
EEA total number of subjects	73

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)	93
Adolescents (12-17 years)	47
Adults (18-64 years)	36
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 33 study centers in 17 countries.

Pre-assignment

Screening details:

Total of 204 patients screened, 177 randomized and 175 subjects completed the study. One subject was excluded before treatment due to unconfirmed diagnosis of Mucopolysaccharidosis IVA (MPS IVA).

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Intravenous infusion of placebo solution at a volume equivalent to that needed for 2.0 mg/kg dose of BMN 110 administered over a period of approximately 4 hours once a week.

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

Dosage and administration details:

Intravenous infusion of placebo solution at a volume equivalent to that needed for 2.0 mg/kg dose of BMN 110 administered over a period of approximately 4 hours once a week.

Arm title	BMN110 2.0 mg/kg/Qow

Arm description:

Intravenous infusion of BMN 110 at a dose of 2.0 mg/kg administered over a period of approximately 4 hours every other week and infusions of placebo on alternating weeks.

Arm type	Experimental
Investigational medicinal product name	BMN 110
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous infusion of BMN 110 at a dose of 2.0 mg/kg administered over a period of approximately 4 hours every other week and infusions of placebo on alternating weeks.

Arm title	BMN110 2.0 mg/kg/Week

Arm description:

Intravenous infusion of BMN 110 at a dose of 2.0 mg/kg administered over a period of approximately 4 hours once a week.

Arm type	Experimental

Investigational medicinal product name	BMN 110
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous infusion of BMN 110 at a dose of 2.0 mg/kg administered over a period of approximately 4 hours once a week.

Number of subjects in period 1	Placebo	BMN110 2.0 mg/kg/Qow	BMN110 2.0 mg/kg/Week
Started	59	59	58
Completed	59	59	57
Not completed	0	0	1
Consent withdrawn by subject	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Intravenous infusion of placebo solution at a volume equivalent to that needed for 2.0 mg/kg dose of BMN 110 administered over a period of approximately 4 hours once a week.	

Reporting group title	BMN110 2.0 mg/kg/Qow
Reporting group description:	
Intravenous infusion of BMN 110 at a dose of 2.0 mg/kg administered over a period of approximately 4 hours every other week and infusions of placebo on alternating weeks.	
Reporting group title	BMN110 2.0 mg/kg/Week
Reporting group description:	
Intravenous infusion of BMN 110 at a dose of 2.0 mg/kg administered over a period of approximately 4 hours once a week.	

Reporting group values	Placebo	BMN110 2.0 mg/kg/Qow	BMN110 2.0 mg/kg/Week
Number of subjects	59	59	58
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	15.0	15.3	13.1
standard deviation	± 11.30	± 10.79	± 8.10
Gender categorical Units: Subjects			
Female	32	25	32
Male	27	34	26
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	13	16	9
Not Hispanic or Latino	46	43	49
Race Units: Subjects			
Asian	11	15	14
Black or African American	0	2	2
White	44	35	36
Other	4	7	6
Walk Category Units: Subjects			
<= 200m	23	24	23
> 200m	36	35	35
Normalized Urine Keratan Sulfate			
Baseline			
Units: ug/mg			
arithmetic mean	26.1	28.6	26.9
standard deviation	± 15.43	± 21.17	± 14.11

Reporting group values	Total		
Number of subjects	176		
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	89		
Male	87		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	38		
Not Hispanic or Latino	138		
Race Units: Subjects			
Asian	40		
Black or African American	4		
White	115		
Other	17		
Walk Category Units: Subjects			
<= 200m	70		
> 200m	106		
Normalized Urine Keratan Sulfate			
Baseline			
Units: ug/mg arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Intravenous infusion of placebo solution at a volume equivalent to that needed for 2.0 mg/kg dose of BMN 110 administered over a period of approximately 4 hours once a week.

Reporting group title	BMN110 2.0 mg/kg/Qow

Reporting group description:

Intravenous infusion of BMN 110 at a dose of 2.0 mg/kg administered over a period of approximately 4 hours every other week and infusions of placebo on alternating weeks.

Reporting group title	BMN110 2.0 mg/kg/Week

Reporting group description:

Intravenous infusion of BMN 110 at a dose of 2.0 mg/kg administered over a period of approximately 4 hours once a week.

Primary: Change From Baseline in Endurance as Measured by the 6-minute Walk Test

End point title	Change From Baseline in Endurance as Measured by the 6-minute Walk Test

End point description:

Intention to treat (ITT) population consist of all subjects who were randomized to study treatment and received at least one dose of study drug.

Two missing outcomes at Week 24 were imputed using method of multiple imputation.

End point type	Primary

End point timeframe:

Baseline to Week 24

End point values	Placebo	BMN110 2.0 mg/kg/Qow	BMN110 2.0 mg/kg/Week	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59	59	58	
Units: Meters				
arithmetic mean (standard deviation)				
Baseline	211.9 (± 69.88)	205.7 (± 81.19)	203.9 (± 76.32)	
Week 24	225.4 (± 83.22)	219.9 (± 87.60)	240.0 (± 86.61)	
Change from Baseline to Week 24	13.5 (± 50.63)	14.2 (± 40.82)	36.0 (± 58.11)	

Statistical analyses

Statistical analysis title	Placebo vs BMN110 2.0 mg/kg/Week
Comparison groups	Placebo v BMN110 2.0 mg/kg/Week

Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0174
Method	ANCOVA

Statistical analysis title	Placebo vs BMN110 2.0 mg/kg/Qow
Comparison groups	Placebo v BMN110 2.0 mg/kg/Qow
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9542
Method	ANCOVA

Secondary: Change From Baseline in Endurance as Measured by the 3-minute Stair Climb Test

End point title	Change From Baseline in Endurance as Measured by the 3-minute Stair Climb Test
End point description: ITT population.	
End point type	Secondary
End point timeframe: Baseline to Week 24	

End point values	Placebo	BMN110 2.0 mg/kg/Qow	BMN110 2.0 mg/kg/Week	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59	59	58	
Units: Stairs/minute				
arithmetic mean (standard deviation)				
Baseline	30.0 (± 14.05)	27.1 (± 15.8)	29.6 (± 16.44)	
Week 24	33.6 (± 18.36)	30.4 (± 17.77)	34.3 (± 18.7)	
Change from Baseline to Week 24	3.6 (± 8.51)	3.2 (± 10.29)	4.7 (± 7.99)	

Statistical analyses

Statistical analysis title	Placebo vs BMN110 2.0 mg/kg/Week
Comparison groups	Placebo v BMN110 2.0 mg/kg/Week

Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4935
Method	ANCOVA

Statistical analysis title	Placebo vs BMN110 2.0 mg/kg/Qow
Comparison groups	BMN110 2.0 mg/kg/Qow v Placebo
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7783
Method	ANCOVA

Secondary: Percent Change From Baseline in Normalized Urine Keratan Sulfate

End point title	Percent Change From Baseline in Normalized Urine Keratan Sulfate

End point description:

ITT population. Normalized urine keratan sulfate is calculated as urine keratan sulfate divided by urine creatinine.

Nine missing outcomes at Week 24 were imputed using method of multiple imputation.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Placebo	BMN110 2.0 mg/kg/Qow	BMN110 2.0 mg/kg/Week	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59	59	58	
Units: ug/mg				
arithmetic mean (standard deviation)				
Percent Change From Baseline	-3.6 (± 27.41)	-35.3 (± 20.74)	-43.7 (± 22.29)	

Statistical analyses

Statistical analysis title	Placebo vs BMN110 2.0 mg/kg/Week
Comparison groups	Placebo v BMN110 2.0 mg/kg/Week

Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Statistical analysis title	Placebo vs BMN110 2.0 mg/kg/Qow
Comparison groups	Placebo v BMN110 2.0 mg/kg/Qow
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to Week 24	
Adverse event reporting additional description:	
Safety Population: Consisted of all subjects who received any study drug (either BMN 110 or placebo).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	BMN110 2.0 mg/kg/Qow
Reporting group description: -	
Reporting group title	BMN110 2.0 mg/kg/Week
Reporting group description: -	

Serious adverse events	Placebo	BMN110 2.0 mg/kg/Qow	BMN110 2.0 mg/kg/Week
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 59 (3.39%)	4 / 59 (6.78%)	9 / 58 (15.52%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Surgical and medical procedures			
Suture removal			
subjects affected / exposed	0 / 59 (0.00%)	1 / 59 (1.69%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cervical cord compression			
subjects affected / exposed	1 / 59 (1.69%)	0 / 59 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Infusion site pain			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 59 (1.69%)	0 / 59 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 59 (0.00%)	1 / 59 (1.69%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Dengue fever			
subjects affected / exposed	0 / 59 (0.00%)	1 / 59 (1.69%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media			

subjects affected / exposed	0 / 59 (0.00%)	1 / 59 (1.69%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	2 / 58 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	BMN110 2.0 mg/kg/Qow	BMN110 2.0 mg/kg/Week
Total subjects affected by non-serious adverse events			
subjects affected / exposed	57 / 59 (96.61%)	59 / 59 (100.00%)	56 / 58 (96.55%)
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 59 (1.69%)	4 / 59 (6.78%)	3 / 58 (5.17%)
occurrences (all)	1	6	3
Hypertension			
subjects affected / exposed	4 / 59 (6.78%)	4 / 59 (6.78%)	3 / 58 (5.17%)
occurrences (all)	13	18	6
Hypotension			
subjects affected / exposed	1 / 59 (1.69%)	2 / 59 (3.39%)	3 / 58 (5.17%)
occurrences (all)	1	3	3
Flushing			
subjects affected / exposed	0 / 59 (0.00%)	1 / 59 (1.69%)	5 / 58 (8.62%)
occurrences (all)	0	1	7
Poor venous access			
subjects affected / exposed	4 / 59 (6.78%)	1 / 59 (1.69%)	3 / 58 (5.17%)
occurrences (all)	8	1	4
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	17 / 59 (28.81%)	22 / 59 (37.29%)	25 / 58 (43.10%)
occurrences (all)	29	35	47
Fatigue			
subjects affected / exposed	15 / 59 (25.42%)	8 / 59 (13.56%)	9 / 58 (15.52%)
occurrences (all)	24	10	17
Chills			
subjects affected / exposed	1 / 59 (1.69%)	6 / 59 (10.17%)	6 / 58 (10.34%)
occurrences (all)	1	7	7
Infusion site extravasation			
subjects affected / exposed	2 / 59 (3.39%)	4 / 59 (6.78%)	2 / 58 (3.45%)
occurrences (all)	2	4	2
Infusion site pain			
subjects affected / exposed	0 / 59 (0.00%)	4 / 59 (6.78%)	4 / 58 (6.90%)
occurrences (all)	0	7	4
Oedema peripheral			
subjects affected / exposed	2 / 59 (3.39%)	4 / 59 (6.78%)	1 / 58 (1.72%)
occurrences (all)	2	6	1
Non-cardiac chest pain			
subjects affected / exposed	0 / 59 (0.00%)	3 / 59 (5.08%)	1 / 58 (1.72%)
occurrences (all)	0	3	1
Puncture site pain			
subjects affected / exposed	2 / 59 (3.39%)	3 / 59 (5.08%)	1 / 58 (1.72%)
occurrences (all)	2	3	1
Device occlusion			
subjects affected / exposed	1 / 59 (1.69%)	2 / 59 (3.39%)	3 / 58 (5.17%)
occurrences (all)	1	2	4
Chest discomfort			
subjects affected / exposed	0 / 59 (0.00%)	1 / 59 (1.69%)	3 / 58 (5.17%)
occurrences (all)	0	1	3
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 59 (1.69%)	4 / 59 (6.78%)	3 / 58 (5.17%)
occurrences (all)	1	7	3
Reproductive system and breast disorders			

Dysmenorrhoea			
subjects affected / exposed	2 / 59 (3.39%)	3 / 59 (5.08%)	1 / 58 (1.72%)
occurrences (all)	2	3	1
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	7 / 59 (11.86%)	9 / 59 (15.25%)	12 / 58 (20.69%)
occurrences (all)	8	12	14
Cough			
subjects affected / exposed	21 / 59 (35.59%)	17 / 59 (28.81%)	16 / 58 (27.59%)
occurrences (all)	28	29	20
Dyspnoea			
subjects affected / exposed	3 / 59 (5.08%)	6 / 59 (10.17%)	7 / 58 (12.07%)
occurrences (all)	4	8	12
Nasal congestion			
subjects affected / exposed	5 / 59 (8.47%)	5 / 59 (8.47%)	5 / 58 (8.62%)
occurrences (all)	8	7	7
Rhinorrhoea			
subjects affected / exposed	4 / 59 (6.78%)	4 / 59 (6.78%)	5 / 58 (8.62%)
occurrences (all)	6	9	5
Asthma			
subjects affected / exposed	0 / 59 (0.00%)	3 / 59 (5.08%)	1 / 58 (1.72%)
occurrences (all)	0	3	1
Epistaxis			
subjects affected / exposed	3 / 59 (5.08%)	2 / 59 (3.39%)	3 / 58 (5.17%)
occurrences (all)	5	2	3
Tonsillar hypertrophy			
subjects affected / exposed	3 / 59 (5.08%)	0 / 59 (0.00%)	0 / 58 (0.00%)
occurrences (all)	3	0	0
Throat irritation			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	3 / 58 (5.17%)
occurrences (all)	0	0	4
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 59 (0.00%)	2 / 59 (3.39%)	3 / 58 (5.17%)
occurrences (all)	0	2	3
Investigations			

Oxygen saturation decreased			
subjects affected / exposed	6 / 59 (10.17%)	7 / 59 (11.86%)	6 / 58 (10.34%)
occurrences (all)	19	8	10
Blood pressure diastolic increased			
subjects affected / exposed	2 / 59 (3.39%)	3 / 59 (5.08%)	2 / 58 (3.45%)
occurrences (all)	5	4	2
Blood pressure systolic increased			
subjects affected / exposed	2 / 59 (3.39%)	3 / 59 (5.08%)	1 / 58 (1.72%)
occurrences (all)	5	16	1
Body temperature increased			
subjects affected / exposed	2 / 59 (3.39%)	2 / 59 (3.39%)	4 / 58 (6.90%)
occurrences (all)	10	2	24
Respiratory rate increased			
subjects affected / exposed	3 / 59 (5.08%)	1 / 59 (1.69%)	1 / 58 (1.72%)
occurrences (all)	3	1	1
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 59 (1.69%)	4 / 59 (6.78%)	0 / 58 (0.00%)
occurrences (all)	1	5	0
Head injury			
subjects affected / exposed	0 / 59 (0.00%)	3 / 59 (5.08%)	2 / 58 (3.45%)
occurrences (all)	0	3	2
Ligament sprain			
subjects affected / exposed	3 / 59 (5.08%)	0 / 59 (0.00%)	0 / 58 (0.00%)
occurrences (all)	3	0	0
Cardiac disorders			
Tricuspid valve incompetence			
subjects affected / exposed	3 / 59 (5.08%)	7 / 59 (11.86%)	4 / 58 (6.90%)
occurrences (all)	3	7	4
Mitral valve incompetence			
subjects affected / exposed	4 / 59 (6.78%)	3 / 59 (5.08%)	3 / 58 (5.17%)
occurrences (all)	4	3	3
Tachycardia			
subjects affected / exposed	6 / 59 (10.17%)	2 / 59 (3.39%)	3 / 58 (5.17%)
occurrences (all)	7	6	8
Pulmonary valve incompetence			

subjects affected / exposed	2 / 59 (3.39%)	1 / 59 (1.69%)	3 / 58 (5.17%)
occurrences (all)	2	1	3
Nervous system disorders			
Headache			
subjects affected / exposed	21 / 59 (35.59%)	24 / 59 (40.68%)	24 / 58 (41.38%)
occurrences (all)	38	52	69
Dizziness			
subjects affected / exposed	3 / 59 (5.08%)	4 / 59 (6.78%)	7 / 58 (12.07%)
occurrences (all)	3	6	10
Paraesthesia			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	3 / 58 (5.17%)
occurrences (all)	0	0	6
Somnolence			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	3 / 58 (5.17%)
occurrences (all)	0	0	3
Hyperreflexia			
subjects affected / exposed	3 / 59 (5.08%)	1 / 59 (1.69%)	0 / 58 (0.00%)
occurrences (all)	6	3	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	5 / 59 (8.47%)	8 / 59 (13.56%)	3 / 58 (5.17%)
occurrences (all)	6	11	3
Eye disorders			
Corneal opacity			
subjects affected / exposed	1 / 59 (1.69%)	0 / 59 (0.00%)	5 / 58 (8.62%)
occurrences (all)	1	0	5
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	21 / 59 (35.59%)	21 / 59 (35.59%)	26 / 58 (44.83%)
occurrences (all)	42	44	61
Nausea			
subjects affected / exposed	12 / 59 (20.34%)	14 / 59 (23.73%)	18 / 58 (31.03%)
occurrences (all)	13	22	37
Diarrhoea			
subjects affected / exposed	7 / 59 (11.86%)	12 / 59 (20.34%)	12 / 58 (20.69%)
occurrences (all)	8	14	14
Abdominal pain			

subjects affected / exposed	5 / 59 (8.47%)	8 / 59 (13.56%)	14 / 58 (24.14%)
occurrences (all)	5	14	23
Abdominal pain upper			
subjects affected / exposed	5 / 59 (8.47%)	4 / 59 (6.78%)	9 / 58 (15.52%)
occurrences (all)	6	4	22
Abdominal discomfort			
subjects affected / exposed	1 / 59 (1.69%)	3 / 59 (5.08%)	2 / 58 (3.45%)
occurrences (all)	1	4	4
Dyspepsia			
subjects affected / exposed	4 / 59 (6.78%)	1 / 59 (1.69%)	1 / 58 (1.72%)
occurrences (all)	4	1	1
Flatulence			
subjects affected / exposed	3 / 59 (5.08%)	1 / 59 (1.69%)	0 / 58 (0.00%)
occurrences (all)	4	1	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	5 / 59 (8.47%)	6 / 59 (10.17%)	6 / 58 (10.34%)
occurrences (all)	6	7	9
Urticaria			
subjects affected / exposed	0 / 59 (0.00%)	4 / 59 (6.78%)	4 / 58 (6.90%)
occurrences (all)	0	5	6
Petechiae			
subjects affected / exposed	0 / 59 (0.00%)	3 / 59 (5.08%)	0 / 58 (0.00%)
occurrences (all)	0	3	0
Pruritus			
subjects affected / exposed	2 / 59 (3.39%)	3 / 59 (5.08%)	4 / 58 (6.90%)
occurrences (all)	2	5	4
Eczema			
subjects affected / exposed	3 / 59 (5.08%)	1 / 59 (1.69%)	1 / 58 (1.72%)
occurrences (all)	3	1	2
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	9 / 59 (15.25%)	14 / 59 (23.73%)	9 / 58 (15.52%)
occurrences (all)	13	24	16
Back pain			

subjects affected / exposed	6 / 59 (10.17%)	10 / 59 (16.95%)	7 / 58 (12.07%)
occurrences (all)	7	17	10
Arthralgia			
subjects affected / exposed	17 / 59 (28.81%)	9 / 59 (15.25%)	10 / 58 (17.24%)
occurrences (all)	27	14	14
Musculoskeletal stiffness			
subjects affected / exposed	1 / 59 (1.69%)	3 / 59 (5.08%)	0 / 58 (0.00%)
occurrences (all)	1	3	0
Neck pain			
subjects affected / exposed	0 / 59 (0.00%)	3 / 59 (5.08%)	5 / 58 (8.62%)
occurrences (all)	0	5	6
Osteopenia			
subjects affected / exposed	3 / 59 (5.08%)	3 / 59 (5.08%)	0 / 58 (0.00%)
occurrences (all)	3	3	0
Musculoskeletal pain			
subjects affected / exposed	3 / 59 (5.08%)	2 / 59 (3.39%)	3 / 58 (5.17%)
occurrences (all)	4	2	4
Myalgia			
subjects affected / exposed	0 / 59 (0.00%)	1 / 59 (1.69%)	3 / 58 (5.17%)
occurrences (all)	0	1	4
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	9 / 59 (15.25%)	12 / 59 (20.34%)	10 / 58 (17.24%)
occurrences (all)	12	13	11
Upper respiratory tract infection			
subjects affected / exposed	9 / 59 (15.25%)	10 / 59 (16.95%)	10 / 58 (17.24%)
occurrences (all)	14	13	15
Gastroenteritis			
subjects affected / exposed	4 / 59 (6.78%)	8 / 59 (13.56%)	7 / 58 (12.07%)
occurrences (all)	4	10	8
Viral infection	Additional description: Safety population		
subjects affected / exposed	1 / 59 (1.69%)	6 / 59 (10.17%)	3 / 58 (5.17%)
occurrences (all)	1	6	3
Influenza			
subjects affected / exposed	3 / 59 (5.08%)	5 / 59 (8.47%)	2 / 58 (3.45%)
occurrences (all)	4	5	3

Otitis media			
subjects affected / exposed	4 / 59 (6.78%)	5 / 59 (8.47%)	9 / 58 (15.52%)
occurrences (all)	4	6	10
Rhinitis			
subjects affected / exposed	6 / 59 (10.17%)	4 / 59 (6.78%)	5 / 58 (8.62%)
occurrences (all)	8	8	8
Viral upper respiratory tract infection			
subjects affected / exposed	3 / 59 (5.08%)	4 / 59 (6.78%)	2 / 58 (3.45%)
occurrences (all)	5	5	4
Pharyngitis			
subjects affected / exposed	7 / 59 (11.86%)	3 / 59 (5.08%)	4 / 58 (6.90%)
occurrences (all)	7	3	4
Ear infection			
subjects affected / exposed	1 / 59 (1.69%)	2 / 59 (3.39%)	5 / 58 (8.62%)
occurrences (all)	1	2	5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 October 2010	•Study design modified to include a third treatment arm(2.0mg/kg/every other week) •Total number of patients increased from 120(60 patients per treatment arm) to 162 •Number of study centers increased from approximately 20 to approximately 40 •Randomization stratification factors were revised. Stratification by age group(5-11,12-18&≥19yrs old)was added. Randomization will be stratified by screening 6MW test categories(≤200m&>200m)& age group •PK sample size revised from 60(30 per treatment arm) to 54(18 per treatment arm) •PK time point at 180 min after start of infusion deleted & a new PK time point at 180 min post infusion added •PK assessment at Week 1 deleted.PK assessment for Week 23 moved to Week 22 •Immunogenicity testing deleted at Week 1&23 •Definition of infusion associated reaction(IAR) modified to include more thorough description of potential symptoms & to be inclusive of all reactions occurring after onset of infusion/within 1day following end of infusion regardless of investigator's assessment of whether or not event was related to study drug administration •Immunogenicity testing in event of a severe IAR/IAR requiring cessation of infusion revised to include C4. CH50 deleted from testing •Allergic Reaction Review Board(ARRB) added to review severe/serious infusion associated reactions •Thyroid panel moved from Baseline to Screening •Schedule for 6MW test & 3MSC test revised from every 6 wks to every 12 wks •Cervical spine & lumbar spine radiographs deleted from Week 24&Early Termination Visit(ETV) •Audiometry examinations added to Baseline & Week 24 assessments for selected sites. Change in hearing assessments will be evaluated as a tertiary objective •Echocardiogram assessments will include evaluation for presence/absence of valve stenosis/regurgitation & clinical significance at Screening & Week 24 •Corneal clouding examinations added as part of physical examination at Screening, Week 12&Week 24 assessments

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported