Clinical trial results:
A Long-Term Study for Extended BMN 701Treatment of Patients with Pompe Disease who have Participated in a BMN 701 Study

Summary

EudraCT number	2011-001805-28
Trial protocol	GB DE
Global end of trial date	09 September 2016

Results information

Result version number	v1 (current)
This version publication date	28 September 2017
First version publication date	28 September 2017

Trial information

Trial identification

Sponsor protocol code	POM-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01435772
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	BioMarin Pharmaceutical Inc.
Sponsor organisation address	105 Digital Drive, Novato, United States, 94949
Public contact	BMN701 Clinical Program Management, BioMarin Europe Ltd., +44 0782455 2081, POMPE@bmrn.com
Scientific contact	BMN701 Clinical Program Management, BioMarin Europe Ltd., +44 0782455 2081, POMPE@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	28 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 September 2016
Global end of trial reached?	Yes
Global end of trial date	09 September 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of the study are:
• To provide long-term, ongoing, treatment to patients who have participated in a BMN 701 clinical trial.
• To evaluate the long-term safety and tolerability both during and following BMN 701 administration;

• To determine the anti-BMN 701 antibody response to BMN 701
• To determine the anti-IGF-I and anti-IGF-II antibody response to BMN 701.

Protection of trial subjects:

The DMC reviewed the study data on a schedule defined in the DMC Charter, and offered advice on whether or not to proceed with, modify, or terminate study enrollment on the basis of toxicity. Meetings of the DMC were convened at the discretion of the DMC Chair or the Study Medical Officer.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 August 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	Australia: 6
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	21
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)	0

Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	21
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Individuals eligible to participate in this study met all of the following criteria:
Have participated in a prior BMN 701 clinical development study;
Have been diagnosed with late-onset Pompe disease, based on the entry criteria of a prior BMN 701 study.

There were no screening failures

Period 1

Period 1 title	0-144 weeks (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	5 mg/kg

Arm description:

5 mg/kg

Arm type	Experimental
Investigational medicinal product name	BMN 701
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

BMN 701 at doses of 5 mg/kg, 10 mg/kg, or 20 mg/kg for IV administration over approximately 1.5 to 4 hours qow over repeatable 24-week treatment cycles.

Arm title	10 mg/kg

Arm description:

10 mg/kg

Arm type	Experimental
Investigational medicinal product name	BMN 701
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

BMN 701 at doses of 5 mg/kg, 10 mg/kg, or 20 mg/kg for IV administration over approximately 1.5 to 4 hours qow over repeatable 24-week treatment cycles.

Arm title	20 mg/kg

Arm description:

20 mg/kg

Arm type	Experimental

Investigational medicinal product name	BMN 701
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

BMN 701 at doses of 5 mg/kg, 10 mg/kg, or 20 mg/kg for IV administration over approximately 1.5 to 4 hours qow over repeatable 24-week treatment cycles.

Number of subjects in period 1	5 mg/kg	10 mg/kg	20 mg/kg
Started	3	3	15
Completed	2	2	10
Not completed	1	1	5
Consent withdrawn by subject	-	1	3
Adverse event	1	-	2

Baseline characteristics

Reporting groups	
Reporting group title	5 mg/kg
Reporting group description: 5 mg/kg	
Reporting group title	10 mg/kg
Reporting group description: 10 mg/kg	
Reporting group title	20 mg/kg
Reporting group description: 20 mg/kg	

Reporting group values	5 mg/kg	10 mg/kg	20 mg/kg
Number of subjects	3	3	15
Age categorical Units: Subjects			
18-65	3	3	15
Age continuous Units: Years			
arithmetic mean	52.3	42.7	50.1
standard deviation	± 6.66	± 13.05	± 5.28
Gender categorical Units: Subjects			
Female	0	2	6
Male	3	1	9

Reporting group values	Total		
Number of subjects	21		
Age categorical Units: Subjects			
18-65	21		
Age continuous Units: Years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	8		
Male	13		

End points

End points reporting groups

Reporting group title	5 mg/kg
Reporting group description: 5 mg/kg	
Reporting group title	10 mg/kg
Reporting group description: 10 mg/kg	
Reporting group title	20 mg/kg
Reporting group description: 20 mg/kg	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description: The Full Analysis Set (FAS) includes all 21 subjects enrolled in POM-002 who received at least 1 dose (or a partial dose) of BMN 701.	

Primary: Anti-BMN 701 Antibody Response(Positive) to BMN 701 at Day 1

End point title	Anti-BMN 701 Antibody Response(Positive) to BMN 701 at Day 1[1]
End point description:	
End point type	Primary
End point timeframe: 0-144 weeks	

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: The study was terminated because BioMarin decided to end the overall development program based on competing corporate priorities. The study was not terminated for efficacy or safety reasons.

End point values	5 mg/kg	10 mg/kg	20 mg/kg	Full Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	2	1	12	15
Units: number	2	1	11	14

Statistical analyses

No statistical analyses for this end point

Primary: Anti-BMN 701 Antibody Response(Positive) to BMN 701 at Week 144

End point title	Anti-BMN 701 Antibody Response(Positive) to BMN 701 at Week 144[2]
End point description:	
End point type	Primary

End point timeframe:

0-144 weeks

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: The study was terminated because BioMarin decided to end the overall development program based on competing corporate priorities. The study was not terminated for efficacy or safety reasons.

End point values	5 mg/kg	10 mg/kg	20 mg/kg	Full Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	2	2	10	14
Units: Number	2	2	10	14

Statistical analyses

No statistical analyses for this end point

Primary: Anti-IGF-I Antibody Response(Positive) to BMN 701 at Baseline

End point title	Anti-IGF-I Antibody Response(Positive) to BMN 701 at

End point description:

End point type	Primary

End point timeframe:

0-144 weeks

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The study was terminated because BioMarin decided to end the overall development program based on competing corporate priorities. The study was not terminated for efficacy or safety reasons.

End point values	5 mg/kg	10 mg/kg	20 mg/kg	Full Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	3	3	15	21
Units: Number	0	2	0	2

Statistical analyses

No statistical analyses for this end point

Primary: Anti-IGF-I Antibody Response(Positive) to BMN 701 at Week 144

End point title	Anti-IGF-I Antibody Response(Positive) to BMN 701 at Week 144[4]

End point description:

End point type	Primary

End point timeframe:

0-144 weeks

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The study was terminated because BioMarin decided to end the overall development program based on competing corporate priorities. The study was not terminated for efficacy or safety reasons.

End point values	5 mg/kg	10 mg/kg	20 mg/kg	Full Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	2	2	10	14
Units: Number	0	1	5	6

Statistical analyses

No statistical analyses for this end point

Primary: Anti-IGF-II Antibody Response(Positive) to BMN 701 at Baseline

End point title	Anti-IGF-II Antibody Response(Positive) to BMN 701 at Baseline[5]

End point description:

End point type	Primary

End point timeframe:

0-144 weeks

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The study was terminated because BioMarin decided to end the overall development program based on competing corporate priorities. The study was not terminated for efficacy or safety reasons.

End point values	5 mg/kg	10 mg/kg	20 mg/kg	Full Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	3	3	15	21
Units: Number	1	2	2	5

Statistical analyses

No statistical analyses for this end point

Primary: Anti-IGF-II Antibody Response(Positive) to BMN 701 at Week 144

End point title	Anti-IGF-II Antibody Response(Positive) to BMN 701 at Week 144[6]

End point description:

End point type	Primary

End point timeframe:

0-144 weeks

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The study was terminated because BioMarin decided to end the overall development program based on competing corporate priorities. The study was not terminated for efficacy or safety reasons.

End point values	5 mg/kg	10 mg/kg	20 mg/kg	Full Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	2	2	10	14
Units: Number	0	2	7	9

Statistical analyses

No statistical analyses for this end point

Secondary: Baseline - Percent Predicted MIP

End point title	Baseline - Percent Predicted MIP

End point description:

End point type	Secondary

End point timeframe:

0-144 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	Full Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	0[7]	3	15	18
Units: percent				
arithmetic mean (standard deviation)	()	39.53 (± 21.868)	40.2 (± 25.863)	40.09 (± 24.641)

Notes:

[7] - NA

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 144 - Percent Predicted MIP

End point title	Change from Baseline to Week 144 - Percent Predicted MIP

End point description:

End point type	Secondary

End point timeframe:

0-144 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	Full Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	0[8]	2	11	13
Units: percent				
arithmetic mean (standard deviation)	()	21.21 (± 14.537)	18.48 (± 18.599)	18.89 (± 17.518)

Notes:
[8] - NA

Statistical analyses

No statistical analyses for this end point

Secondary: Baseline - Percent Predicted MEP

End point title	Baseline - Percent Predicted MEP

End point description:

End point type	Secondary

End point timeframe:
0-144 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	Full Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	0[9]	3	15	18
Units: percent				
arithmetic mean (standard deviation)	()	31.07 (± 6.641)	36.7 (± 15.939)	35.76 (± 14.801)

Notes:
[9] - NA

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 144 - Percent Predicted MEP

End point title	Change from Baseline to Week 144 - Percent Predicted MEP

End point description:

End point type	Secondary

End point timeframe:
0-144 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	Full Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	0[10]	2	11	13
Units: percent				
arithmetic mean (standard deviation)	()	-0.28 (± 5.841)	5.11 (± 16.395)	4.28 (± 15.197)

Notes:

[10] - NA

Statistical analyses

No statistical analyses for this end point

Secondary: Baseline - 6 Minutes Walk Test

End point title	Baseline - 6 Minutes Walk Test

End point description:

End point type	Secondary

End point timeframe:

0-144 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	Full Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	3	3	15	21
Units: meter				
arithmetic mean (standard deviation)	334 (± 227.119)	360 (± 51.403)	363.8 (± 157.818)	359 (± 151.553)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 144 - 6 Minutes Walk Test

End point title	Change from Baseline to Week 144 - 6 Minutes Walk Test

End point description:

End point type	Secondary

End point timeframe:

0-144 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	Full Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	3	2	11	16
Units: meter				
arithmetic mean (standard deviation)	-36 (± 90.508)	-120.75 (± 67.529)	9.5 (± 77.572)	-15.31 (± 86.181)

Statistical analyses

No statistical analyses for this end point

Secondary: Baseline - Maximum Voluntary Ventilation (MVV)

End point title	Baseline - Maximum Voluntary Ventilation (MVV)

End point description:

End point type	Secondary

End point timeframe:

0-144 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	Full Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	0[11]	3	15	18
Units: L/min				
arithmetic mean (standard deviation)	()	76 (± 41.037)	68.08 (± 26.74)	69.4 (± 28.217)

Notes:

[11] - NA

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline at Week 144 - Maximum Voluntary Ventilation (MVV)

End point title	Change from Baseline at Week 144 - Maximum Voluntary Ventilation (MVV)

End point description:

End point type	Secondary

End point timeframe:

0-144 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	Full Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	0[12]	2	11	13
Units: L/min				
arithmetic mean (standard deviation)	()	13.5 (± 13.435)	2.24 (± 11.635)	3.97 (± 12.073)

Notes:

[12] - NA

Statistical analyses

No statistical analyses for this end point

Secondary: Baseline - Percent Predicted Upright FVC

End point title	Baseline - Percent Predicted Upright FVC

End point description:

End point type	Secondary

End point timeframe:

0-144 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	Full Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	3	3	15	21
Units: Percent				
arithmetic mean (standard deviation)	69.33 (± 19.732)	67.33 (± 26.577)	57.13 (± 18.677)	60.33 (± 19.518)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 144 - Percent Predicted Upright FVC

End point title	Change from Baseline to Week 144 - Percent Predicted Upright FVC

End point description:

End point type	Secondary

End point timeframe:

0-144 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	Full Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	3	2	11	16
Units: percent				
arithmetic mean (standard deviation)	-8.33 (± 7.095)	-0.5 (± 4.95)	-2 (± 8)	-3 (± 7.633)

Statistical analyses

No statistical analyses for this end point

Secondary: Baseline - Percent Predicted Supine FVC

End point title	Baseline - Percent Predicted Supine FVC

End point description:

End point type	Secondary

End point timeframe:

0-144 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	Full Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	3	3	12	18
Units: percent				
arithmetic mean (standard deviation)	36.67 (± 17.954)	47.67 (± 32.578)	44.25 (± 21.55)	43.56 (± 21.794)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 144 - Percent Predicted Supine FVC

End point title	Change from Baseline to Week 144 - Percent Predicted Supine FVC

End point description:

End point type	Secondary

End point timeframe:

0-144 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	Full Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	3	2	7	12
Units: percent				
arithmetic mean (standard deviation)	-4.33 (± 9.452)	4.5 (± 26.163)	-3.43 (± 6.901)	-2.33 (± 10.714)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 144 - Urine Tetrasaccharide

End point title	Change from Baseline to Week 144 - Urine Tetrasaccharide

End point description:

21 patients analyzed for this endpoint transitioned from the POM-001 protocol. The baseline data use to calculate the change from baseline Urine Tetrasaccharide was derived from the POM-001 study.

End point type	Secondary

End point timeframe:

0-144 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	Full Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	0[13]	2	10	12
Units: mmol/mol				
arithmetic mean (standard deviation)	()	-0.2 (± 3.394)	-1.07 (± 0.975)	-0.93 (± 1.393)

Notes:

[13] - NA

Statistical analyses

No statistical analyses for this end point

Secondary: Baseline - IGF-I

End point title	Baseline - IGF-I

End point description:

End point type	Secondary

End point timeframe:

0-144 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	Full Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	0[14]	0[15]	11	11
Units: nmol/L				
arithmetic mean (standard deviation)	()	()	20.26 (± 6.465)	20.26 (± 6.465)

Notes:

[14] - NA

[15] - NA

Statistical analyses

No statistical analyses for this end point

Secondary: Week 144 - IGF-I

End point title	Week 144 - IGF-I

End point description:

End point type	Secondary

End point timeframe:

0-144 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	Full Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	2	2	11	15
Units: nmol/L				
arithmetic mean (standard deviation)	26.98 (± 1.379)	18.4 (± 7.078)	17.62 (± 5.878)	18.97 (± 6.247)

Statistical analyses

No statistical analyses for this end point

Secondary: Baseline - IGF-II

End point title	Baseline - IGF-II

End point description:

End point type	Secondary

End point timeframe:

0-144 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	Full Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	0[16]	1	6	7
Units: nmol/L				
arithmetic mean (standard deviation)	()	702 (± 0)	496.83 (± 113.417)	526.14 (± 129.355)

Notes:

[16] - 20 mg/kg dose group suggested the most efficacious activity compared to other dose groups studied.

Statistical analyses

No statistical analyses for this end point

Secondary: Week 144 - IGF-II

End point title	Week 144 - IGF-II

End point description:

End point type	Secondary

End point timeframe:

0-144 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	Full Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	3	2	11	11
Units: nmol/L				
arithmetic mean (standard deviation)	467.67 (± 117.142)	559.5 (± 140.714)	698.82 (± 228.948)	639.75 (± 216.405)

Statistical analyses

No statistical analyses for this end point

Secondary: Baseline - IGFBP3

End point title	Baseline - IGFBP3

End point description:

End point type	Secondary

End point timeframe:

0-144 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	Full Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	0[17]	0[18]	11	11
Units: nmol/L				
arithmetic mean (standard deviation)	()	()	150.45 (± 23.914)	150.45 (± 23.914)

Notes:

[17] - 20 mg/kg dose group suggested the most efficacious activity compared to other dose groups studied.

[18] - 20 mg/kg dose group suggested the most efficacious activity compared to other dose groups studied.

Statistical analyses

No statistical analyses for this end point

Secondary: Week 144 - IGFBP3

End point title	Week 144 - IGFBP3

End point description:

End point type	Secondary

End point timeframe:

0-144 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	Full Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	3	2	11	16
Units: nmol/L				
arithmetic mean (standard deviation)	157.33 (± 41.477)	209 (± 39.598)	146.64 (± 33.587)	156.44 (± 39.05)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Study Period	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	5 mg/kg
Reporting group description: -	
Reporting group title	10 mg/kg
Reporting group description: -	
Reporting group title	20 mg/kg
Reporting group description: -	

Serious adverse events	5 mg/kg	10 mg/kg	20 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 3 (66.67%)	1 / 3 (33.33%)	7 / 15 (46.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 15 (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
Cardiac disorders			
Cardiac failure acute			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactoid reaction			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic respiratory failure			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 15 (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
Respiratory failure			

subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 15 (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
Stridor			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Prerenal failure			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
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			
Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 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	5 mg/kg	10 mg/kg	20 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	3 / 3 (100.00%)	15 / 15 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Vascular disorders			
Flushing			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	4 / 15 (26.67%)
occurrences (all)	0	0	8
Haematoma			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Hot flush			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	4 / 15 (26.67%)
occurrences (all)	1	1	4
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	3 / 15 (20.00%)
occurrences (all)	0	0	6
Hypotension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	3 / 15 (20.00%)
occurrences (all)	0	0	6
Pallor			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	3
General disorders and administration site conditions			
Application site erythema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Catheter site erythema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Catheter site inflammation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Catheter site pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Chest discomfort			

subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	5 / 15 (33.33%)
occurrences (all)	1	0	19
Chest pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Chills			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	3 / 15 (20.00%)
occurrences (all)	0	0	5
Discomfort			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Extravasation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	8 / 15 (53.33%)
occurrences (all)	18	0	16
Feeling abnormal			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Feeling cold			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	2 / 15 (13.33%)
occurrences (all)	0	1	10
Feeling hot			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	3 / 15 (20.00%)
occurrences (all)	0	1	7
Feeling of body temperature change			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Gait disturbance			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Influenza like illness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Infusion site extravasation			

subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Infusion site pain			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Infusion site swelling			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Malaise			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	4 / 15 (26.67%)
occurrences (all)	1	0	5
Non-cardiac chest pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	2 / 15 (13.33%)
occurrences (all)	0	1	2
Oedema peripheral			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	3 / 15 (20.00%)
occurrences (all)	0	0	8
Pain			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	2	0	2
Peripheral swelling			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	3 / 15 (20.00%)
occurrences (all)	1	1	3
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Temperature intolerance			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Tenderness			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Vessel puncture site bruise			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			

Seasonal allergy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Chronic respiratory failure			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Cough			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	3 / 15 (20.00%)
occurrences (all)	0	0	8
Dyspnoea			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	9 / 15 (60.00%)
occurrences (all)	1	0	26
Epistaxis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Hypoxia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Nasal congestion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Oropharyngeal pain			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	5 / 15 (33.33%)
occurrences (all)	1	2	12
Paranasal sinus hypersecretion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Pleuritic pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Productive cough			

subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Pulmonary congestion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Rales			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Respiratory failure			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Tachypnoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	40
Wheezing			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	4
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Confusional state			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	2 / 15 (13.33%)
occurrences (all)	2	1	2
Mood swings			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Nervousness			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	4 / 15 (26.67%)
occurrences (all)	4	1	6
Restlessness			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	2 / 15 (13.33%)
occurrences (all)	1	0	2

Sleep terror			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Product issues			
Device occlusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Investigations			
Ammonia increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Bacterial test positive			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Blood calcium decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Blood glucose decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	7 / 15 (46.67%)
occurrences (all)	0	0	14
Blood immunoglobulin E increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Cardiac murmur			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Complement factor increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Lipase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Pulmonary physical examination abnormal			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Troponin increased			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Tryptase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 3 (66.67%)	1 / 3 (33.33%)	6 / 15 (40.00%)
occurrences (all)	5	1	9
Epicondylitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Eye contusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Fall			
subjects affected / exposed	3 / 3 (100.00%)	2 / 3 (66.67%)	7 / 15 (46.67%)
occurrences (all)	22	5	26
Head injury			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Joint injury			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Laceration			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Muscle contusion			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Muscle strain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Post procedural contusion			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Post procedural haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Procedural pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	2 / 15 (13.33%)
occurrences (all)	2	0	2
Skin abrasion			
subjects affected / exposed	2 / 3 (66.67%)	1 / 3 (33.33%)	1 / 15 (6.67%)
occurrences (all)	5	1	1
Skin wound			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Tendon injury			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Thermal burn			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Tooth fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	3
Wound			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Cardiac failure			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Diastolic dysfunction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1

Left ventricular hypertrophy			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Sinus tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	3 / 15 (20.00%)
occurrences (all)	0	0	4
Tachycardia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	5 / 15 (33.33%)
occurrences (all)	1	1	49
Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Burning sensation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	2 / 15 (13.33%)
occurrences (all)	0	1	2
Dizziness			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	8 / 15 (53.33%)
occurrences (all)	1	5	11
Headache			
subjects affected / exposed	2 / 3 (66.67%)	1 / 3 (33.33%)	9 / 15 (60.00%)
occurrences (all)	7	4	30
Hypoaesthesia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	3 / 15 (20.00%)
occurrences (all)	1	1	3
Lethargy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Migraine			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Paraesthesia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Presyncope			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Restless legs syndrome			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Sciatica			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Sinus headache			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Tremor			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Tunnel vision			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Iron deficiency anaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Tinnitus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Vertigo positional			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Eye disorders			

Blindness transient			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Ocular hyperaemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Visual impairment			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	1 / 15 (6.67%)
occurrences (all)	1	1	3
Abdominal distension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	3
Abdominal pain lower			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Abdominal pain upper			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	3 / 15 (20.00%)
occurrences (all)	1	1	5
Abdominal tenderness			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	3 / 15 (20.00%)
occurrences (all)	0	0	4
Dental caries			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Diarrhoea			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	7 / 15 (46.67%)
occurrences (all)	0	0	13
Dyspepsia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Flatulence			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	3 / 15 (20.00%)
occurrences (all)	0	0	3
Irritable bowel syndrome			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	3
Nausea			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	6 / 15 (40.00%)
occurrences (all)	1	1	29
Painful defaecation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Rectal haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Salivary hypersecretion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Tooth loss			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	5
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	3 / 15 (20.00%)
occurrences (all)	0	0	4
Hepatobiliary disorders			

Cholelithiasis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Cold sweat			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	3 / 15 (20.00%)
occurrences (all)	0	0	3
Decubitus ulcer			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Dermal cyst			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 15 (0.00%)
occurrences (all)	4	0	0
Erythema			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	3 / 15 (20.00%)
occurrences (all)	1	1	4
Hyperhidrosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	4 / 15 (26.67%)
occurrences (all)	0	0	14
Night sweats			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	2 / 15 (13.33%)
occurrences (all)	2	0	3
Rash			
subjects affected / exposed	1 / 3 (33.33%)	2 / 3 (66.67%)	1 / 15 (6.67%)
occurrences (all)	1	5	1
Rash macular			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Rash papular			

subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Rash pruritic			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	0 / 15 (0.00%)
occurrences (all)	2	1	0
Rosacea			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Skin lesion			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Skin mass			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Skin ulcer			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Urticaria			
subjects affected / exposed	3 / 3 (100.00%)	1 / 3 (33.33%)	2 / 15 (13.33%)
occurrences (all)	8	1	3
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	2 / 15 (13.33%)
occurrences (all)	0	1	2
Renal impairment			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Endocrine disorders			
Androgen deficiency			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 3 (66.67%)	1 / 3 (33.33%)	7 / 15 (46.67%)
occurrences (all)	8	1	18
Back pain			

subjects affected / exposed	3 / 3 (100.00%)	1 / 3 (33.33%)	7 / 15 (46.67%)
occurrences (all)	6	1	10
Bursitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Flank pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Groin pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Intervertebral disc protrusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Joint swelling			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Muscle spasms			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	3 / 15 (20.00%)
occurrences (all)	1	0	9
Muscle twitching			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Muscular weakness			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	2 / 15 (13.33%)
occurrences (all)	1	0	2
Musculoskeletal chest pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Musculoskeletal discomfort			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Musculoskeletal pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	2 / 15 (13.33%)
occurrences (all)	1	0	3
Myalgia			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	3 / 15 (20.00%)
occurrences (all)	0	0	4
Neck pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	3 / 15 (20.00%)
occurrences (all)	0	0	4
Osteopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	8 / 15 (53.33%)
occurrences (all)	1	1	14
Spinal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Tendonitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Infections and infestations			
Blister infected			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Bronchitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Ear infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Fungal infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Gastroenteritis viral			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Herpes simplex			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 15 (0.00%)
occurrences (all)	3	0	0

Influenza			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	3 / 15 (20.00%)
occurrences (all)	1	0	3
Lower respiratory tract infection			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	4 / 15 (26.67%)
occurrences (all)	1	1	9
Lower respiratory tract infection viral			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Nasopharyngitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	4 / 15 (26.67%)
occurrences (all)	0	1	7
Rhinitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	2 / 15 (13.33%)
occurrences (all)	1	0	2
Sinusitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 3 (33.33%)	2 / 3 (66.67%)	7 / 15 (46.67%)
occurrences (all)	3	6	11
Urinary tract infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 15 (6.67%)
occurrences (all)	0	2	1
Viral infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 15 (6.67%)
occurrences (all)	0	2	2
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Glucose tolerance impaired			

subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Hyperglycaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Hyperkalaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Hypoglycaemia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	14 / 15 (93.33%)
occurrences (all)	19	30	106
Iron deficiency			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 March 2012	-Pharmacokinetic assessments have been added to Week 24 (or at time of early discontinuation) for transition patients in POM-002. Additional assessments (hematology, chemistry panel, lipase, and a brief physical examination) have been added to Week -2, Day of transition, and Weeks +2 and +4 for the transition patients. -Testing of C3, C4, and CH50 at the time of an infusion-associated reaction (IAR) has been added. In addition, serum will be obtained every 6 weeks for storage for testing of C3, C4, and CH50 and other possible immunologic and inflammatory markers in the event a patient experiences an IAR. -Added option to increase BMN 701 infusion time as required. -Added option to use anti-inflammatory medications (e.g., ibuprofen) as an infusion pretreatment at the Investigator's discretion. -Added assays of insulin-like growth factor (IGF) analytes (IGF-I, IGF-II, and IGFBP3) in serum samples being collected at study visits.
07 December 2012	-Optional desensitization regimen has been added to provide an additional treatment option for patients who experience infusion-associated reactions (IARs) that meet certain criteria. -Study size has been changed from 30-45 patients to approximately 22 patients initially, and the number of sites participating from 20 to approximately 12 initially. -The primary study objectives have been modified to include evaluation of the long-term safety and tolerability both during and following BMN 701 administration.
12 August 2013	-An additional requirement has been added that equipment (including epinephrine) for emergency resuscitation be readily available during infusions of BMN 701. -If a patient experiences a severe IAR or an IAR requiring cessation of the BMN 701 infusion, blood is to be drawn for additional antibody assessments 4 hours (± 15 minutes) after the cessation of the infusion instead of "shortly" after the cessation of the infusion. -A new exploratory objective has been added to study biochemical, molecular, cellular, and genetic/genomic aspects relevant to Pompe disease from blood and urine samples obtained from patients in the study. -Laboratory testing for hemoglobin A1c levels has been added at the Week 12, Week 24, Termination, and 4-Week Post-Dose Follow-Up Visits.
15 May 2015	-During the Transition Period visits where PK sampling is performed, an additional PK timepoint has been added at 4 hours post-infusion completion. In addition, glucose monitoring has been added at all post-completion timepoints (0.25, 0.5, 1, 2, 3, 4, 6, and 8 hours). -Clarified that urine tetrasaccharide and blood samples for evaluation of anti-drug antibodies will be done at the Week 24 assessment visit following the Transition Period to the new BMN 701 drug product. -Stopping criteria concerning hypoglycemia have been added. -The possible length of the study has been increased from 240 weeks (10 cycles) to 480 weeks (20 cycles).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated because BioMarin decided to end the overall development program based on competing corporate priorities. The study was not terminated for efficacy or safety reasons.

Notes: