Clinical trial results:
A Phase 1/2 Open-label Study of the Safety, Tolerability, Pharmacokinetics, Pharmacodynamic and Preliminary Efficacy of BMN 701 (GILT-tagged Recombinant human GAA) in Patients with Late-onset Pompe Disease

Summary

EudraCT number	2010-023561-22
Trial protocol	GB DE
Global end of trial date	06 March 2013

Results information

Result version number	v1 (current)
This version publication date	04 April 2018
First version publication date	04 April 2018

Trial information

Trial identification

Sponsor protocol code	POM-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01230801
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., +01 415-455-7448, slava.titov@bmrn.com
Scientific contact	BMN701 Clinical Program Management, BioMarin Europe Ltd., +01 415-455-7448, slava.titov@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	03 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 March 2013
Global end of trial reached?	Yes
Global end of trial date	06 March 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of the study are:
• To evaluate the safety and tolerability of BMN 701

Protection of trial subjects:

The Investigator supplied the following FDA or region-appropriate Regulatory Authority approved products and/or medications (generic or branded) to be used, as needed, for IP reconstitution or pre-medication to prevent or minimize infusion-associated reactions (IARs), with costs reimbursed by BioMarin:
• Sterile water for reconstitution of IP.
• 0.9% sodium chloride solution.
• diphenhydramine or other antihistamine preparations.
• acetaminophen or other anti-pyretic preparations.
• methylprednisolone sodium succinate or other corticosteroid preparations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 December 2010
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: 4
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	United States: 9
Worldwide total number of subjects	22
EEA total number of subjects	9

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)	22
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

22 subjects were enrolled.

Pre-assignment

Screening details:

Subjects aged 13 years or older with late-onset Pompe disease were selected to participate in this study, if they (or their legal guardian) had provided written informed consent, were enzyme replacement therapy naïve, and met requirements for muscular and pulmonary function. Subjects were required to be at least 18 years old in Germany and France.

Period 1

Period 1 title	0-24 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	BMN701-5 mg/kg
Investigational medicinal product name	BMN 701
Investigational medicinal product code	BMN 701
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

5 mg/kg, it is for intravenous use

Arm title	10 mg/kg

Arm description:

10 mg/kg

Arm type	BMN701-10 mg/kg
Investigational medicinal product name	BMN 701
Investigational medicinal product code	BMN 701
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

10 mg/kg, it is for intravenous use

Arm title	20 mg/kg

Arm description:

20 mg/kg

Arm type	BMN701-20 mg/kg
Investigational medicinal product name	BMN 701
Investigational medicinal product code	BMN 701
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:
20 mg/kg, it is for intravenous use

Number of subjects in period 1	5 mg/kg	10 mg/kg	20 mg/kg
Started	3	3	16
Completed	3	3	15
Not completed	0	0	1
Physician decision	-	-	1

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	16
Age categorical Units: Subjects			
18-65	3	3	16
Age continuous Units: Years			
arithmetic mean	51.7	42.3	50.1
standard deviation	± 6.81	± 12.90	± 5.37
Gender categorical Units: Subjects			
Female	0	2	6
Male	3	1	10

Reporting group values	Total		
Number of subjects	22		
Age categorical Units: Subjects			
18-65	22		
Age continuous Units: Years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	8		
Male	14		

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	intent to treat
Subject analysis set type	Intention-to-treat
Subject analysis set description: It includes all enrolled subjects	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description: The safety population includes all enrolled subjects treated with at least 1 dose of study drug.	

Primary: Adverse Events

End point title	Adverse Events[1]
End point description:	
End point type	Primary
End point timeframe: 0-24 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: Please see Adverse event section below for further details.

End point values	5 mg/kg	10 mg/kg	20 mg/kg	Safety Population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	3	3	16	22
Units: measureble	3	3	15	21

Statistical analyses

No statistical analyses for this end point

Secondary: Baseline Six Minutes Walk Test

End point title	Baseline Six Minutes Walk Test
End point description:	
End point type	Secondary

End point timeframe:
baseline

End point values	5 mg/kg	10 mg/kg	20 mg/kg	intent to treat
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	3	3	16	22
Units: meter				
arithmetic mean (standard deviation)	334 (± 227.12)	360 (± 51.4)	354.5 (± 156.94)	352.5 (± 151.05)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline at week 6 - Six Minutes Walk Test

End point title	Change from baseline at week 6 - Six Minutes Walk Test

End point description:

End point type	Secondary

End point timeframe:
6 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	intent to treat
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	2	3	16	21
Units: meter				
arithmetic mean (standard deviation)	-2.5 (± 23.33)	-30.3 (± 56.5)	19.8 (± 35.11)	10.5 (± 40.08)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline at week 12 - Six Minutes Walk Test

End point title	Change from baseline at week 12 - Six Minutes Walk Test

End point description:

End point type	Secondary

End point timeframe:
12 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	intent to treat
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)	31.2 (± 78.81)	-13.7 (± 8.04)	11.1 (± 42.67)	10.4 (± 45.32)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline at week 18 - Six Minutes Walk Test

End point title	Change from baseline at week 18 - Six Minutes Walk Test

End point description:

End point type	Secondary

End point timeframe:

18 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	intent to treat
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)	43.3 (± 89.44)	-79 (± 104.61)	16.4 (± 55.09)	6.6 (± 73.43)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline at week 24 - Six Minutes Walk Test

End point title	Change from baseline at week 24 - Six Minutes Walk Test

End point description:

End point type	Secondary

End point timeframe:

24 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	intent to treat
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	3	3	16	22
Units: meter				
arithmetic mean (standard deviation)	36 (± 76.02)	-42.7 (± 12.57)	22.3 (± 54.23)	15.3 (± 56.97)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Baseline Percent Predicted Upright Forced Vital Capacity

End point title	Baseline Percent Predicted Upright Forced Vital Capacity

End point description:

End point type	Other pre-specified

End point timeframe:
baseline

End point values	5 mg/kg	10 mg/kg	20 mg/kg	intent to treat
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	3	3	16	22
Units: percent				
arithmetic mean (standard deviation)	69.3 (± 19.73)	67.3 (± 26.58)	58.1 (± 18.42)	60.9 (± 19.21)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from baseline at week 6 - Percent Predicted Upright Forced Vital Capacity

End point title	Change from baseline at week 6 - Percent Predicted Upright Forced Vital Capacity

End point description:

End point type	Other pre-specified

End point timeframe:
6 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	intent to treat
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	2	3	16	21
Units: percent				
arithmetic mean (standard deviation)	4 (± 4.24)	-2 (± 2.65)	0.4 (± 3.3)	0.4 (± 3.46)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from baseline at week 12 - Percent Predicted Upright Forced Vital Capacity

End point title	Change from baseline at week 12 - Percent Predicted Upright Forced Vital Capacity

End point description:

End point type	Other pre-specified

End point timeframe:

12 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	intent to treat
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	3	3	16	22
Units: percent				
arithmetic mean (standard deviation)	-2.6 (± 9.5)	-3.7 (± 2.89)	1.6 (± 4.35)	0.3 (± 5.25)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from baseline at week 18 - Percent Predicted Upright Forced Vital Capacity

End point title	Change from baseline at week 18 - Percent Predicted Upright Forced Vital Capacity

End point description:

End point type	Other pre-specified

End point timeframe:

18 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	intent to treat
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)	1.5 (± 4.09)	0.3 (± 3.06)	1.2 (± 4.49)	1.1 (± 4.1)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from baseline at week 24 - Percent Predicted Upright Forced Vital Capacity

End point title	Change from baseline at week 24 - Percent Predicted Upright Forced Vital Capacity

End point description:

End point type	Other pre-specified

End point timeframe:

24 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	intent to treat
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	3	3	16	22
Units: percent				
arithmetic mean (standard deviation)	1 (± 2.65)	-1.7 (± 3.06)	1.2 (± 3.89)	0.8 (± 3.65)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Baseline Percent Predicted Supine Forced Vital Capacity

End point title	Baseline Percent Predicted Supine Forced Vital Capacity

End point description:

End point type	Other pre-specified

End point timeframe:

baseline

End point values	5 mg/kg	10 mg/kg	20 mg/kg	intent to treat
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	3	3	13	19
Units: percent				
arithmetic mean (standard deviation)	36.7 (± 17.95)	47.7 (± 32.58)	46.3 (± 21.93)	45 (± 22.1)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from baseline at week 6 - Percent Predicted Supine Forced Vital Capacity

End point title	Change from baseline at week 6 - Percent Predicted Supine Forced Vital Capacity

End point description:

End point type	Other pre-specified

End point timeframe:

6 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	intent to treat
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	2	3	13	18
Units: percent				
arithmetic mean (standard deviation)	2.1 (± 1.2)	-1.3 (± 4.04)	-0.8 (± 4.86)	-0.6 (± 4.44)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from baseline at week 12 - Percent Predicted Supine Forced Vital Capacity

End point title	Change from baseline at week 12 - Percent Predicted Supine Forced Vital Capacity

End point description:

End point type	Other pre-specified

End point timeframe:

12 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	intent to treat
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)	0.3 (± 4.22)	-4.7 (± 2.89)	3.3 (± 3.87)	1.5 (± 4.7)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from baseline at week 18 - Percent Predicted Supine Forced Vital Capacity

End point title	Change from baseline at week 18 - Percent Predicted Supine Forced Vital Capacity

End point description:

End point type	Other pre-specified

End point timeframe:

18 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	intent to treat
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)	1.3 (± 1.53)	-1.3 (± 6.66)	2.3 (± 3.14)	1.5 (± 3.7)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from baseline at week 24 - Percent Predicted Supine Forced Vital Capacity

End point title	Change from baseline at week 24 - Percent Predicted Supine Forced Vital Capacity

End point description:

End point type	Other pre-specified

End point timeframe:

24 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	intent to treat
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	3	3	13	19
Units: percent				
arithmetic mean (standard deviation)	2 (± 3)	-3.3 (± 5.51)	1.1 (± 4.42)	0.5 (± 4.53)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Baseline Percent Predicted Upright Maximum Expiratory Pressure

End point title	Baseline Percent Predicted Upright Maximum Expiratory Pressure

End point description:

End point type	Other pre-specified

End point timeframe:

baseline

End point values	5 mg/kg	10 mg/kg	20 mg/kg	intent to treat
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	0[2]	3	16	19
Units: percent				
arithmetic mean (standard deviation)	()	31.1 (± 6.64)	36.3 (± 15.46)	35.5 (± 14.42)

Notes:

[2] - no patient has data

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from baseline at week 6 - Percent Predicted Upright Maximum Expiratory Pressure

End point title	Change from baseline at week 6 - Percent Predicted Upright Maximum Expiratory Pressure

End point description:

End point type	Other pre-specified

End point timeframe:

6 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	intent to treat
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	0[3]	3	16	19
Units: percent				
arithmetic mean (standard deviation)	()	6.8 (± 4.06)	3.2 (± 5.38)	3.8 (± 5.27)

Notes:

[3] - None of patients has baseline data

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from baseline at week 12 - Percent Predicted Upright Maximum Expiratory Pressure

End point title	Change from baseline at week 12 - Percent Predicted Upright Maximum Expiratory Pressure

End point description:

End point type	Other pre-specified

End point timeframe:

12 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	intent to treat
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	0[4]	3	16	19
Units: percent				
arithmetic mean (standard deviation)	()	1.4 (± 4.53)	2.2 (± 8.68)	2 (± 8.07)

Notes:

[4] - None of patients has baseline data

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from baseline at week 18 - Percent Predicted Upright Maximum Expiratory Pressure

End point title	Change from baseline at week 18 - Percent Predicted Upright Maximum Expiratory Pressure

End point description:

End point type	Other pre-specified

End point timeframe:

18 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	intent to treat
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	0[5]	3	15	18
Units: percent				
arithmetic mean (standard deviation)	()	1.2 (± 2.06)	6.9 (± 7.21)	6 (± 6.94)

Notes:

[5] - None of patients has baseline data

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from baseline at week 24 - Percent Predicted Upright Maximum Expiratory Pressure

End point title	Change from baseline at week 24 - Percent Predicted Upright Maximum Expiratory Pressure

End point description:

End point type	Other pre-specified

End point timeframe:

24 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	intent to treat
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	0[6]	3	16	19
Units: percent				
arithmetic mean (standard deviation)	()	2.5 (± 10.4)	5.2 (± 8.25)	4.8 (± 8.36)

Notes:

[6] - None of patients has baseline data

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Baseline Percent Predicted Upright Maximum Inspiratory Pressure

End point title	Baseline Percent Predicted Upright Maximum Inspiratory Pressure

End point description:

End point type	Other pre-specified

End point timeframe:

baseline

End point values	5 mg/kg	10 mg/kg	20 mg/kg	intent to treat
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	0[7]	3	16[8]	19
Units: percent				
arithmetic mean (standard deviation)	()	39.5 (± 21.87)	40.5 (± 25.01)	40.3 (± 23.97)

Notes:

[7] - None of patients has baseline data

[8] - None of patients has baseline data

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from baseline at week 6 - Percent Predicted Upright Maximum Inspiratory Pressure

End point title	Change from baseline at week 6 - Percent Predicted Upright Maximum Inspiratory Pressure

End point description:

End point type	Other pre-specified

End point timeframe:

6 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	intent to treat
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	0[9]	3	16	19
Units: percent				
arithmetic mean (standard deviation)	()	1.7 (± 1.46)	5.3 (± 9.8)	4.7 (± 9.06)

Notes:

[9] - None of patients has baseline data

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from baseline at week 12 - Percent Predicted Upright Maximum Inspiratory Pressure

End point title	Change from baseline at week 12 - Percent Predicted Upright Maximum Inspiratory Pressure

End point description:

End point type	Other pre-specified

End point timeframe:

12 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	intent to treat
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	0[10]	3	16	19
Units: percent				
arithmetic mean (standard deviation)	()	3.4 (± 6.74)	11.4 (± 10.92)	10.1 (± 10.65)

Notes:

[10] - None of patients has baseline data

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from baseline at week 18 - Percent Predicted Upright Maximum Inspiratory Pressure

End point title	Change from baseline at week 18 - Percent Predicted Upright Maximum Inspiratory Pressure

End point description:

End point type	Other pre-specified

End point timeframe:

18 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	intent to treat
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	0[11]	3	15	18
Units: percent				
arithmetic mean (standard deviation)	()	2.9 (± 11.77)	14.5 (± 14.48)	12.6 (± 14.45)

Notes:

[11] - None of patients has baseline data

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from baseline at week 24 - Percent Predicted Upright Maximum Inspiratory Pressure

End point title	Change from baseline at week 24 - Percent Predicted Upright Maximum Inspiratory Pressure

End point description:

End point type	Other pre-specified

End point timeframe:

24 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	intent to treat
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	0[12]	3	16	19
Units: percent				
arithmetic mean (standard deviation)	()	0.7 (± 6.69)	11.1 (± 8.31)	9.5 (± 8.81)

Notes:

[12] - None of patients has baseline data

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Baseline Upright Maximum Ventilatory Volume

End point title	Baseline Upright Maximum Ventilatory Volume

End point description:

End point type	Other pre-specified

End point timeframe:

baseline

End point values	5 mg/kg	10 mg/kg	20 mg/kg	intent to treat
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	0[13]	3	16	19
Units: litre(s)				
arithmetic mean (standard deviation)	()	76 (± 41.04)	67.6 (± 25.9)	68.9 (± 27.5)

Notes:

[13] - None of patients has baseline data

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from baseline at week 6 - Upright Maximum Ventilatory Volume

End point title	Change from baseline at week 6 - Upright Maximum Ventilatory Volume

End point description:

End point type	Other pre-specified

End point timeframe:

6 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	intent to treat
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	0[14]	3	16	19
Units: litre(s)				
arithmetic mean (standard deviation)	()	-1 (± 0.35)	1.5 (± 11.1)	1.1 (± 10.18)

Notes:

[14] - None of patients has baseline data

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from baseline at week 12 - Upright Maximum Ventilatory Volume

End point title	Change from baseline at week 12 - Upright Maximum Ventilatory Volume

End point description:

End point type	Other pre-specified

End point timeframe:

12 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	intent to treat
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	0[15]	3	16	19
Units: litre(s)				
arithmetic mean (standard deviation)	()	-1.1 (± 2.73)	3.8 (± 11.64)	3 (± 10.82)

Notes:

[15] - None of patients has baseline data

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from baseline at week 18 - Upright Maximum Ventilatory Volume

End point title	Change from baseline at week 18 - Upright Maximum Ventilatory Volume

End point description:

End point type	Other pre-specified

End point timeframe:

18 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	intent to treat
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	0[16]	3	15	18
Units: litre(s)				
arithmetic mean (standard deviation)	()	-3.9 (± 2.86)	4.7 (± 10.89)	3.3 (± 10.46)

Notes:

[16] - None of patients has baseline data

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from baseline at week 24 - Upright Maximum Ventilatory Volume

End point title	Change from baseline at week 24 - Upright Maximum Ventilatory Volume

End point description:

End point type	Other pre-specified

End point timeframe:

24 weeks

End point values	5 mg/kg	10 mg/kg	20 mg/kg	intent to treat
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	0[17]	3	15	18
Units: litre(s)				
arithmetic mean (standard deviation)	()	-0.7 (± 9.1)	2.3 (± 10.71)	1.8 (± 10.28)

Notes:

[17] - None of patients has baseline data

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

32 weeks (27 days of screening and baseline measurements + 24 weeks of treatment + 20 days of follow-up)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

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	0 / 3 (0.00%)	0 / 3 (0.00%)	4 / 16 (25.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
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			
Hypersensitivity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
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 / 16 (6.25%)
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 / 16 (93.75%)
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	5	0	1
Haematoma			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Hot flush			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	3 / 16 (18.75%)
occurrences (all)	0	0	5
Hypotension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Pallor			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	0	2
Poor venous access			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Systolic hypertension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Venous thrombosis			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Application site erythema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Chest discomfort			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	5 / 16 (31.25%)
occurrences (all)	6	2	6
Chills			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	3 / 16 (18.75%)
occurrences (all)	0	1	3
Fatigue			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Feeling cold			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Feeling hot			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	3 / 16 (18.75%)
occurrences (all)	0	0	3
Infusion site discomfort			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Local swelling			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	2
Malaise			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	0	3
Non-cardiac chest pain			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Oedema peripheral			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	3 / 16 (18.75%)
occurrences (all)	0	0	3
Pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Tenderness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Thirst			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Vaccination site inflammation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Vessel puncture site bruise			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Vaginal haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	2 / 16 (12.50%)
occurrences (all)	1	1	2
Dyspnoea			

subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	5 / 16 (31.25%)
occurrences (all)	0	2	10
Dyspnoea exertional			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Hypopnoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Laryngeal oedema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Nasal congestion			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Oropharyngeal pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	3 / 16 (18.75%)
occurrences (all)	1	0	3
Pharyngeal oedema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Respiratory distress			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Throat irritation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Confusional state			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1

Depression			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Depressive symptom			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Nervousness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	0	2
Investigations			
Blood glucose decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Body temperature increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Cardiac murmur			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Complement factor decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Respiratory rate increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	5
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Arthropod bite			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Contusion			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	3 / 16 (18.75%)
occurrences (all)	1	1	4
Fall			

subjects affected / exposed	1 / 3 (33.33%)	3 / 3 (100.00%)	3 / 16 (18.75%)
occurrences (all)	2	5	4
Infusion related reaction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	0	2
Laceration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Post procedural haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Procedural pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Bundle branch block right			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Palpitations			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	3 / 16 (18.75%)
occurrences (all)	0	1	4
Sinus tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	4 / 16 (25.00%)
occurrences (all)	0	2	16
Nervous system disorders			
Disturbance in attention			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Dizziness			

subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	6 / 16 (37.50%)
occurrences (all)	0	1	9
Headache			
subjects affected / exposed	1 / 3 (33.33%)	2 / 3 (66.67%)	6 / 16 (37.50%)
occurrences (all)	2	8	27
Hypoaesthesia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Lethargy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Paraesthesia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Tremor			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	3 / 16 (18.75%)
occurrences (all)	0	0	4
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Vision blurred			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	0	2
Abdominal distension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	2
Abdominal pain upper			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	0	2
Abdominal tenderness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	0	2
Diarrhoea			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	4 / 16 (25.00%)
occurrences (all)	1	0	5
Dry mouth			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Dyspepsia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Dysphagia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Epigastric discomfort			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Gastritis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Haemorrhoids			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	8 / 16 (50.00%)
occurrences (all)	0	0	15
Rectal haemorrhage			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Retching			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Tongue discolouration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	5 / 16 (31.25%)
occurrences (all)	1	1	9
Skin and subcutaneous tissue disorders			
Cold sweat			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	2
Dermatitis allergic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Eczema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	0	2
Hyperhidrosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	2
Pruritus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	0	4
Rash			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	4 / 16 (25.00%)
occurrences (all)	0	0	5
Rash erythematous			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Rash maculo-papular			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1

Rash pruritic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 16 (6.25%)
occurrences (all)	0	1	4
Skin discolouration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Urticaria			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 16 (6.25%)
occurrences (all)	0	1	13
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Back pain			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	2 / 16 (12.50%)
occurrences (all)	4	0	3
Joint swelling			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Muscle spasms			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Neck pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	2	0	1
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	3 / 16 (18.75%)
occurrences (all)	0	0	4
Infections and infestations			
Candida infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1

Laryngitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Localised infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Lower respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	0	2
Nasopharyngitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	2 / 16 (12.50%)
occurrences (all)	2	0	3
Sinusitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Tooth abscess			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	0	2
Urinary tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Hyperglycaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Hyperphagia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Hypoglycaemia			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	14 / 16 (87.50%)
occurrences (all)	0	0	41
Lactic acidosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 August 2009	The purposes of Amendment 1 were to: • Add a final study visit (end of study assessment) at approximately 30 days after the last infusion. • Modify enrollment of dose-escalation cohorts such that: o The first patient of each dose level would complete Visit 2 (Day 14) safety assessments before enrolling the second patient, and the second patient would complete Visit 2 (Day 14) safety assessments prior to enrolling the third patient. o Dose escalation to the next dose level would occur after completion of the Week 12 Visit of the third subject in the lower dose cohort. • Specify enrollment of patients under 18 years of age would be deferred until at least two adult patients had completed the Visit 2 (Day 14) assessments. • Clarify that up to 3 subjects who are withdrawn for any reason prior to completion of all scheduled infusions could be replaced if enrollment into the study was ongoing. • Add a height assessment at Week 12 for patients less than 18 years of age.
19 January 2011	The purposes of Amendment 2 were to: • Convert the protocol from the ZyStor style, including the following: changed from the ZyStor protocol template to the BioMarin clinical protocol template; changed the protocol number from "ZS0l-Al-09-00l" to "POM-00l"; changed the study drug name from "ZC-70l" to "BMN 701". • Change from a Phase 1 to Phase 1/2. • Increase the number of sites from "1-2" to "approximately 15". • Change the number of subjects to be enrolled from "10" to "approximately 30" and extended the study period from 12 weeks to 24 weeks • Eliminate the following assessment tools: the 10-meter walk test; the home diary for collection of safety data; the LifeShirt diary system for collection of 24-hour plethysmography data. • Expand the age range of eligible subjects from 13 to 50 years to 13 years of age or older. • Add the option of a whole blood assay option for diagnosis of Pompe Disease before or during the Screening Period for endogenous GAA activity < 75% of the lower limit of the normal adult range reported by the testing laboratory. • Restrict enrollment to subjects who were naïve to ERT with rhGAA; previous version had provided eligibility for subjects who had not received ERT with GAA within 30 days prior to Screening initiation. • Clarify and reorder several exclusion criteria, eg, those involving childbearing potential and other sexual considerations. • Remove the exclusion of subjects with a major congenital anomaly other than Pompe disease from entering the study. • Add an exclusion criterion dealing with diabetes or diseases known to cause hypoglycemia. • Delete condition-specific exclusion criteria 4, 6, 7, and 8 and replaced them with the last 2 exclusion criteria in the current protocol. • Add MEP, MIP, and MVV at the time points where FVC was measured (except at Screening) • Add QMT of the arm and leg. • Add measurement of urinary tetrasaccharide. • Add lipase and thyroid screening to clinical laboratory tests performed.
29 March 2011	The purposes of Amendment 3 were to: • Change from completion of 12 weeks of treatment to 8 weeks between cohorts • Change the period of time required between dosing 2 subjects within the same cohort from 2 weeks to 1 week • Change the following inclusion criterion from "Subject has ≥ 40% and < 80% predicted upright FVC during the Screening Period" to "Subject has ≥ 30% predicted upright FVC and either < 80% predicted upright FVC or > 10% reduction in supine FVC compared to upright FVC during the Screening Period"

10 May 2011	The purposes of Amendment 4 were to: • Change the inclusion criteria guidance on period of contraceptive use from 'at least 30 days', to 'at least 4 months following last dose of BMN 701'. This change was made in response to the UK Regulatory Authority (MHRA) recommendation that, in the absence of reproductive toxicology data and given the long half-life of BMN 701, a duration covering a whole spermatogenic cycle and five half-lives was appropriate. • Creatine kinase was restored to the blood chemistry analytes listed, having been inadvertently deleted in Protocol Amendments 2 and 3.
09 March 2012	The purposes of Amendment 5 were to: • Add information for a second clinical drug lot of BMN 701. • Clarify in the schedule of events table that a subject's weight from the previous clinic visit could be used to calculate BMN 701 infusion dosage on the day before or on the day of infusion. • Add testing of C3, C4, and CH50 at the time of a hypersensitivity reaction. In addition, plasma was obtained every 4 weeks for storage for testing of C3, C4, and CH50 and other possible immunologic and inflammatory markers in the event a subject experienced a hypersensitivity reaction. • Add assays of IGF analytes (IGF-I, IGF-II, and IGFBP3) in serum samples being collected at study visits. • Remove the Week 12 chest X-ray requirement. • Remove the Week 12 ECG requirement. • Remove the requirement for dosing of 2 adults prior to dosing of children. • Broaden language regarding requirement to use FDA approved medications to allow for use of medications approved by the local competent health authority. • Add option to increase BMN 701 infusion time as required. • Add option to use anti-inflammatory medications (eg, ibuprofen) as an infusion pretreatment at the Investigator's discretion. • Revise administration of 6MWT to note that portions of the 6MWT could be videotaped to assess gait abnormalities. Subject identities would be protected by obscuring the facial area in the videos. • Add language clarifying that, along with antibody testing, immune and cytokine testing was performed every 4 weeks. • Change the population of subjects who would undergo PK sampling from all subjects to all subjects in the 5 and 10 mg/kg cohorts and up to approximately 8 subjects in the 20 mg/kg cohort.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported