Clinical trial results:
A Phase 3 Switchover Study of the Efficacy and Safety of BMN 701 (GILT-tagged Recombinant Human GAA) and Long-Term Study for Extended Treatment in rhGAA Exposed Subjects with Late-onset Pompe Disease

Summary

EudraCT number	2013-001768-48
Trial protocol	GB BE DE IT PT AT
Global end of trial date	12 September 2016

Results information

Result version number	v1 (current)
This version publication date	14 October 2017
First version publication date	14 October 2017

Trial information

Trial identification

Sponsor protocol code	701-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01924845
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, smccarthy@bmrn.com
Scientific contact	BMN701 Clinical Program Management, BioMarin Europe Ltd., +44 0782455 2081, smccarthy@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	30 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 September 2016
Global end of trial reached?	Yes
Global end of trial date	12 September 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to determine if treatment with BMN 701 results in an increase in MIP measured at the mouth by the Mueller maneuver from Baseline to Week 24 in subjects with late-onset Pompe disease previously treated with rhGAA.

The primary objective of the extension period of the study is to evaluate the long-term safety and efficacy of BMN 701 in subjects with late-onset Pompe disease previously treated with rhGAA.

Protection of trial subjects:

An independent Data Monitoring Committee (DMC) acted in an advisory capacity to monitor safety in subjects who participated in Study 701-301. The DMC included at least one allergist/immunologist and may have also provided guidance on management of hypersensitivity reactions.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 March 2014
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	Belgium: 1
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	24
EEA total number of subjects	17

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	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Individuals who met any of the following exclusion criteria were not eligible to participate in the study: Use of any investigational product or investigational medical device within 4 weeks prior to Screening; Required noninvasive ventilatory support while awake and in the upright position; Had a diagnosis of diabetes.

Period 1

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

Arms

Arm title	BMN 701 20 mg/kg

Arm description:

BMN 701 20 mg/kg

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

Dosage and administration details:

BMN 701 20 mg/kg for IV administration over approximately 4 hours every 2 weeks over a 24-week Treatment Period (total of 13 doses), and every 2 weeks over a 240-week Extension Period (up to 120 additional doses).

Number of subjects in period 1	BMN 701 20 mg/kg
Started	24
Completed	18
Not completed	6
Consent withdrawn by subject	2
Adverse event, non-fatal	3
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	BMN 701 20 mg/kg
Reporting group description:	
BMN 701 20 mg/kg	

Reporting group values	BMN 701 20 mg/kg	Total	
Number of subjects	24	24	
Age categorical Units: Subjects			
18-65	22	22	
> 65	2	2	
Age continuous Units: Years			
arithmetic mean	47.9		
standard deviation	± 13.27	-	
Gender categorical Units: Subjects			
Female	12	12	
Male	12	12	

End points

End points reporting groups

Reporting group title	BMN 701 20 mg/kg
Reporting group description: BMN 701 20 mg/kg	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description: Full Analysis Set	

Primary: Baseline Percent Predicted MIP

End point title	Baseline Percent Predicted MIP[1]
End point description:	
End point type	Primary
End point timeframe: Baseline	

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. Patients

End point values	BMN 701 20 mg/kg	Full Analysis Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	18	18		
Units: percent				
arithmetic mean (standard deviation)	50 (± 17.5)	50 (± 17.5)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline to Week 24 - Percent Predicted MIP

End point title	Change from Baseline to Week 24 - Percent Predicted MIP[2]
End point description:	
End point type	Primary
End point timeframe: 0-24 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. Patients

End point values	BMN 701 20 mg/kg	Full Analysis Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	18	18		
Units: percent				
arithmetic mean (standard deviation)	2.2 (± 8.3)	2.2 (± 8.3)		

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:

Baseline

End point values	BMN 701 20 mg/kg	Full Analysis Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	18	18		
Units: percent				
arithmetic mean (standard deviation)	38.9 (± 12.3)	38.9 (± 12.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 24 - Percent Predicted MEP

End point title	Change from Baseline to Week 24 - Percent Predicted MEP

End point description:

End point type	Secondary

End point timeframe:

0-24 Weeks

End point values	BMN 701 20 mg/kg	Full Analysis Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	18	18		
Units: percent				
arithmetic mean (standard deviation)	3.1 (± 8.7)	3.1 (± 8.7)		

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	BMN 701 20 mg/kg	Full Analysis Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	17	17		
Units: meter				
arithmetic mean (standard deviation)	345.8 (± 95.3)	345.8 (± 95.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 24 - Six Minutes Walk Test

End point title	Change from Baseline to Week 24 - Six Minutes Walk Test

End point description:

End point type	Secondary

End point timeframe:

0-24 Weeks

End point values	BMN 701 20 mg/kg	Full Analysis Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	17	17		
Units: meter				
arithmetic mean (standard deviation)	26.1 (± 40.6)	26.1 (± 40.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Baseline Percent Predicted FVC Upright

End point title	Baseline Percent Predicted FVC Upright

End point description:

End point type	Secondary

End point timeframe:

Baseline

End point values	BMN 701 20 mg/kg	Full Analysis Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	18	18		
Units: percent				
arithmetic mean (standard deviation)	60.7 (± 15.1)	60.7 (± 15.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 24 - Percent Predicted FVC Upright

End point title	Change from Baseline to Week 24 - Percent Predicted FVC Upright

End point description:

End point type	Secondary

End point timeframe:

0-24 Weeks

End point values	BMN 701 20 mg/kg	Full Analysis Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	18	18		
Units: percent				
arithmetic mean (standard deviation)	-3.7 (± 4.4)	-3.7 (± 4.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Non-serious AEs

End point title	Non-serious AEs

End point description:

End point type	Secondary

End point timeframe:

0-24 weeks

End point values	BMN 701 20 mg/kg	Full Analysis Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	24	24		
Units: number	23	23		

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	BMN 701 20 mg/kg

Reporting group description: -

Serious adverse events	BMN 701 20 mg/kg		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 24 (41.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			

subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Erythema nodosum			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypoglycaemia			

subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	BMN 701 20 mg/kg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 24 (95.83%)		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	5 / 24 (20.83%)		
occurrences (all)	6		
Infusion related reaction			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Vascular disorders			
Hypotension			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		
Cardiac disorders			
Palpitations			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	5		
Nervous system disorders			
Dizziness			
subjects affected / exposed	8 / 24 (33.33%)		
occurrences (all)	12		
Headache			
subjects affected / exposed	13 / 24 (54.17%)		
occurrences (all)	50		
Lethargy			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Tremor			

subjects affected / exposed occurrences (all)	4 / 24 (16.67%) 5		
General disorders and administration site conditions Chest discomfort subjects affected / exposed occurrences (all) Chills subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all)	 2 / 24 (8.33%) 3 4 / 24 (16.67%) 6 5 / 24 (20.83%) 8 2 / 24 (8.33%) 2		
Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all) Abdominal distension subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 2 / 24 (8.33%) 2 2 / 24 (8.33%) 2 2 / 24 (8.33%) 3 5 / 24 (20.83%) 8 8 / 24 (33.33%) 22 4 / 24 (16.67%) 7		
Respiratory, thoracic and mediastinal disorders			

Dyspnoea subjects affected / exposed occurrences (all)	6 / 24 (25.00%) 12		
Dyspnoea exertional subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 4		
Nasal congestion subjects affected / exposed occurrences (all)	4 / 24 (16.67%) 4		
Nasal obstruction subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 3		
Oropharyngeal pain subjects affected / exposed occurrences (all)	5 / 24 (20.83%) 5		
Skin and subcutaneous tissue disorders Cold sweat subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 3		
Hyperhidrosis subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2		
Pruritus subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 4		
Rash subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 5		

Back pain subjects affected / exposed occurrences (all)	5 / 24 (20.83%) 12		
Musculoskeletal pain subjects affected / exposed occurrences (all)	4 / 24 (16.67%) 4		
Myalgia subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 5		
Neck pain subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2		
Pain in extremity subjects affected / exposed occurrences (all)	5 / 24 (20.83%) 6		
Infections and infestations Lower respiratory tract infection subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 4		
Nasopharyngitis subjects affected / exposed occurrences (all)	4 / 24 (16.67%) 5		
Pharyngitis subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2		
Viral infection subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 3		
Metabolism and nutrition disorders Hypoglycaemia subjects affected / exposed occurrences (all)	16 / 24 (66.67%) 165		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 October 2013	Change in forced vital capacity (FVC) upright from Baseline to Week 24 has been changed from a tertiary endpoint to a secondary endpoint. The measurements of IGF-1, IGF-2, and IGF-BP3 will now be performed at the same visits as the immunogenicity assessments (Baseline and Weeks 2, 4, 8, 12, 16, 20, and 24) instead of at Baseline, Week 12 and Week 24 as previously scheduled. The repeated measures analysis of MIP (and likewise of the secondary efficacy endpoints) has been replaced with an analysis of covariance (ANCOVA) approach. Separate assessments of the 6MWT are now used for Screening (to determine eligibility) vs. Baseline (used for statistical analysis). It has been emphasized that Baseline, not Screening, values will be used to calculate the change values used in statistical analyses. The use of antihistamines in the desensitization protocol has been clarified as optional. The use of any form of ventilatory assistance will now be captured as part of the assessment of concomitant medications before study and at each study visit. The Borg scale, rather than the modified Borg scale, will now be used. The patient-reported outcome (PRO) instruments have been removed as Appendices to the protocol. The collection of exploratory blood and urine samples has been clarified as an optional assessment. Administrative updates have been made to improve consistency and clarity.
03 February 2014	An extension phase of up to 240 weeks has been added to the study. The neutralizing antibody for BMN 701 activity has been removed. Sleep assessments and analyses have been added to the study. References to a "light meal" to be eaten prior to BMN 701 infusions have been changed to a "meal." The Week 12 magnetic resonance imaging (MRI) assessment has been removed. Chest X-rays taken within 12 months of study enrollment will now satisfy the requirement for a Screening chest X-ray (previously the X-ray must have been within 2 months of study enrollment). The requirement for both a posterior-anterior (PA) and lateral chest X-ray views has been removed. A PA view alone will suffice. The Baseline genomic sampling will be tested looking for angiotensin converting enzyme (ACE) polymorphisms. The collection of exploratory blood and urine samples has been clarified a required assessment; the genetic/genomic testing of these samples is optional. Language regarding assessments which may be necessary upon transition of the product to a new clinical lot has been added. Administrative updates have been made to improve consistency and clarity.
16 April 2014	The interval of assessment between the pulmonary function tests and the 6-minute walk test (6MWT) has been reduced from 2 hours to 30 minutes, the interval between consecutive 6MWTs has been reduced to a minimum of one hour, and the interval between the 6MWT and the Quick Motor Function Test (QMFT) has been reduced from 4 hours to 1 hour. The QMFT assessments have been removed from the Week 6 and Week 18 visits. The post-infusion observation time has been reduced from 3 hours to 2 hours. The Screening window may be extended, upon approval by the Medical Monitor. The window for last rhGAA administration prior to the start of treatment BMN 701 has been changed from 14-28 days to 10-31 days. The window for assessment of GAA activity following an rhGAA treatment has been reduced from ≥ 14 days to ≥ 12 days. The timing of pharmacokinetic (PK) assessments for subjects receiving the complete PK analysis has been changed to remove the 8 hour post-infusion collection timepoint and add a timepoint 5 hours post-infusion, with the final collection at 6 hours. Administrative updates have been made to improve consistency and clarity.

23 April 2015	The anticipated number of patients in the study has been increased to up to approximately 70. An additional pharmacokinetic (PK) and immunogenicity assessment visit has been added to the Transition Period (after the subject starts to receive study drug from the new clinical lot). Subjects in the complete PK cohort will also have complete PK testing at weeks 12 and 24 following the clinical lot transition. Blood glucose monitoring has been added to the transition period visits. The sleep study inclusion criteria have been modified. Visit windows (± 7 days) have been added to each of the visits during the Extension Period. Language was added to make it clear that all infusions should be administered with a minimum of 7 days between consecutive infusions. Language regarding PK sampling at the time of infusion end has been modified to change "prior to line flush" to "after all the drug has infused, including that within the tubing". Language regarding "infusion-associated" reactions has been changed to reference "hypersensitivity" reactions. Clarified what was meant by the need to have ACLS-certified personnel and emergency equipment "readily available" during infusions. Clarified that the Appendix 1 guidance for medical management of subjects with hypoglycemia are intended as a suggested course of action, not a requirement. Added language to allow for discretionary home blood glucose monitoring. Reference to subjects transitioning to a new clinical lot prior to Week 24 of the study have been removed. Section 7 has been updated to reflect the latest information available in the Investigator's Brochure. The Appendix 1 hypoglycemia management guidelines have been updated to provide more complete guidance. The adverse event reporting language has been updated to clarify that all AEs with severity of grade 3 or higher should be reported as serious AEs, and conform with BioMarin's internal processes. The identity of the medical monitor has been updated.
15 April 2016	Expanded inclusion criteria to permit enrollment of subjects aged 12-17. Added as an exclusion criterion the need for invasive ventilatory support to exclude subjects with invasive ventilator support based on complete respiratory muscle paralysis. Added as an exclusion criterion moderate to severe respiratory or cardiac disease not related to Pompe, including, but not limited to, symptomatic asthma, angina, congestive heart failure, or chronic obstructive pulmonary disease (COPD), causing respiratory and functional limitations requiring concurrent treatment. Added as an exclusion criterion a history of limb fracture which impairs ambulation at the time of consent. Added as an exclusion criterion the concurrent use of smoking tobacco within 6 months prior to study enrollment due to significant comorbid conditions not related to LOPD that would limit ability to adequately ascertain efficacy of reveglucosidase alfa on respiratory function and endurance. Subjects who have experienced reductions in blood glucose with CTCAE severity ≥ grade 2 or AEs of "hypoglycemia" or "blood glucose decreased" during the Treatment Period should have glucose monitoring during Extension Period infusions at the same intervals indicated for the initial 24-week Treatment Period (every 30 minutes) until 12 weeks have passed without hypoglycemia more severe than CTCAE grade 1. At that point, monitoring may return to every 1 hour (±10 minutes) after the start of the infusion, for at least 2 hours following completion of the infusion. Clarified that the subject's blood glucose level must be stable and ≥72 mg/dL (≥4.0 mmol/L) on the last two measurements prior to discharge. Clarified that blood glucose must be within normal limits (≥ 72 mg/dL [≥ 4.0 mmol/L]) before the infusion may be started.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported