Clinical trial results:
An Exploratory Study of the Safety and Efficacy of Prophylactic Immunomodulatory Treatment in Myozyme®-Naive, CRIM(-) Patients With Infantile-onset Pompe Disease

Summary

EudraCT number	2015-000584-14
Trial protocol	Outside EU/EEA
Global end of trial date	27 March 2013

Results information

Result version number	v1 (current)
This version publication date	23 May 2016
First version publication date	25 June 2015

Trial information

Trial identification

Sponsor protocol code	AGLU03807, MSC12862

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00701129
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Genzyme Corporation
Sponsor organisation address	500 Kendall Street, Cambridge, United States, 02142
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 April 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 March 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objectives were to assess the efficacy of a prophylactic immunomodulatory regimen given prior to first treatment with alglucosidase alfa, as assessed by anti-recombinant human acid alpha-glucosidase (anti-rhGAA) antibody titers, and antibodies that inhibit the activity and/or uptake of alglucosidase alfa; to evaluate the clinical benefit as measured by overall survival, ventilator-free survival, left ventricular mass index (LVMI), gross motor function and development, disability index and the incidence of adverse events (AEs), serious adverse events (SAEs), and clinical laboratory abnormalities.

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of pediatric subjects. The parent(s) or guardian(s) as well as the children were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time. In addition to the consent form for the parent(s)/guardian(s), an assent form in child-appropriate language was provided and explained to the child. Repeated invasive procedures were minimized. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. A topical anesthesia may have been used to minimize distress and discomfort.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	01 October 2009
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	United States: 4
Worldwide total number of subjects	4
EEA total number of subjects	0

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)	4
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study was conducted at 2 centres in the United States of America between October 01, 2009 and March 27, 2013.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Alglucosidase Alfa

Arm description:

Alglucosidase alfa was given every other week (qow) or every week (qw) beginning from Day 0 to a minimum of 18 months or if the subject was less than (<) 6 months of age at the time of enrollment, until the subject was 2 years of age, along with methotrexate for 3 consecutive days qow beginning from Day 0 to Week 6 (9 doses) and rituximab qw beginning from Day -1 to Week 4 (4 doses) as per local prescribing information. An additional 4-week cycle of rituximab (up to 4 additional doses) and 6-week cycle of methotrexate (up to 9 additional doses) may have been administered within the first 6 months of the study as per local prescribing information.

Arm type	Experimental
Investigational medicinal product name	Alglucosidase Alfa
Investigational medicinal product code	
Other name	Myozyme®
Pharmaceutical forms	Powder and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

20 mg/kg

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

375 mg/m^2

Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.4 mg/kg

Number of subjects in period 1	Alglucosidase Alfa
Started	4
Full Analysis Set (FAS)	4
Completed	2
Not completed	2
Death	2

Baseline characteristics

Reporting groups	
Reporting group title	Alglucosidase Alfa
Reporting group description:	
Alglucosidase alfa was given every other week (qow) or every week (qw) beginning from Day 0 to a minimum of 18 months or if the subject was less than (<) 6 months of age at the time of enrollment, until the subject was 2 years of age, along with methotrexate for 3 consecutive days qow beginning from Day 0 to Week 6 (9 doses) and rituximab qw beginning from Day -1 to Week 4 (4 doses) as per local prescribing information. An additional 4-week cycle of rituximab (up to 4 additional doses) and 6-week cycle of methotrexate (up to 9 additional doses) may have been administered within the first 6 months of the study as per local prescribing information.	

Reporting group values	Alglucosidase Alfa	Total	
Number of subjects	4	4	
Age categorical Units: Subjects			
Less Than or Equal to (=<) 6 Months	2	2	
Greater Than (>) 6 Months	2	2	
Gender categorical Units: Subjects			
Female	3	3	
Male	1	1	
Race Units: Subjects			
Black	2	2	
White	1	1	
White, Black	1	1	
Ethnicity Units: Subjects			
Hispanic	2	2	
Non Hispanic	2	2	
Number of Subjects With Anti-Recombinant Human Acid Alfa-glucosidase (Anti-rhGAA) Immunoglobulin G			
As all subjects were treatment naïve, it was expected that no subject would be Anti-rhGAA immunoglobulin G (IgG) antibody positive at baseline.			
Units: Subjects			
Negative	4	4	
Positive	0	0	
Number of Subjects With Normal/Abnormal Left Ventricular Mass (LVM) Z-Score			
LVM Z-Score was assessed by echocardiography (ECHO). LVM Z-Score: an indicator of degree of standard deviations from mean in a normal distribution. Negative values indicate a smaller LVM than mean and values higher than 0 indicate a larger LVM than mean. Normal range is -2 to 2; values <-2 or >2 indicate abnormal score.			
Units: Subjects			
Normal	0	0	
Abnormal	4	4	
Number of Subjects With			

Normal/Abnormal LVM Index			
LVM Index was assessed by echocardiography (ECHO). LVM index: an index value derived by normalizing LVM by body surface area. LVM index provides evidence of cardiomyopathy. LVM index values <65 gram per square meter (g/m^2) were considered as normal and LVM index values >=65 g/m^2 were considered as abnormal.			
Units: Subjects			
Normal	0	0	
Abnormal	4	4	
Number of Subjects With Ventilator Use Units: Subjects			
Yes	3	3	
No	1	1	
Gross Motor Disability Assessed by Gross Motor Function Measure-88 (GMFM-88)			
GMFM-88:an 88-item measure to detect gross motor function; consists of 5 categories: lying and rolling; sitting; crawling and kneeling; standing; walking, running and jumping. Each item is scored on a 4-point Likert scale(0=cannot do; 1=initiates [<10% of the task]; 2=partially completes [10% to <100% of the task]; 3=task completion). Score for each dimension is expressed as a percentage of maximum score for that dimension. Total score=sum of percentage scores for each dimension divided by number of dimensions. Total score range: 0% to 100%, where higher scores indicate better motor functions.			
Units: percentage of maximum total score			
median	5.1		
full range (min-max)	0.39 to 7.49	-	
Motor Development Status Assessed by Alberta Infantile Motor Scale (AIMS)			
AIMS:58-item in 4 subscales: prone; supine; sitting; and standing. Each item is scored as observed/not observed. Item in observed range create a motor window. Subscale scores are calculated by giving child 1 point for observed items within motor window in addition to being given 1 point for all less mature items before motor window. AIMS total score=sum of scores for 58 items, range: 0-58,higher score=more mature motor development. Score was then compared with age-equivalent peers from normative sample and equivalence level age (in months) is reported. Here, number of subjects analyzed = 3.			
Units: months			
median	0		
full range (min-max)	0 to 1.37	-	
Disability Index-Pompe Pediatric Evaluation of Disability Inventory-Functional Skills:Mobility (n=4)			
All items of original Pompe Pediatric Evaluation of Disability Inventory (Pompe –PEDI) (197 functional skill in 3 domains:self-care;mobility;social function) and additional items in functional skills,mobility was self-care . Each domain consists of 2 subdomains: functional skill performance, caregiver assistance scale. Norm-based scoring was developed for additional items, and scoring for PEDI have been adjusted to reflect additional normative data collected for Pompe PEDI. Total score range for each domain (mean of subdomains) and subdomain=0-100;higher score=high capability.			
Units: units on a scale			
median	4.5		
full range (min-max)	0 to 18.4	-	
Disability Index-Pompe PEDI-Functional Skills: SelfCare (n=4) Units: units on a scale			
median	14.4		
full range (min-max)	4.9 to 16.1	-	
Disability Index-Pompe PEDI-Functional Skills: Social Function (n=1) Units: units on a scale			
median	10.5		
full range (min-max)	10.5 to 10.5	-	

Disability Index-Pompe PEDI-Caregiver Assistance: Mobility (n=2) Units: units: units on a scale median full range (min-max)	 0 0 to 0	 -	
Disability Index-Pompe PEDI-Caregiver Assistance: Self-Care (n=2) Units: units: units on a scale median full range (min-max)	 0 0 to 0	 -	
Disability Index-Pompe PEDI-Caregiver Assistance: Social Function (n=2) Units: units: units on a scale median full range (min-max)	 0 0 to 0	 -	

End points

End points reporting groups

Reporting group title	Alglucosidase Alfa

Reporting group description:

Alglucosidase alfa was given every other week (qow) or every week (qw) beginning from Day 0 to a minimum of 18 months or if the subject was less than (<) 6 months of age at the time of enrollment, until the subject was 2 years of age, along with methotrexate for 3 consecutive days qow beginning from Day 0 to Week 6 (9 doses) and rituximab qw beginning from Day -1 to Week 4 (4 doses) as per local prescribing information. An additional 4-week cycle of rituximab (up to 4 additional doses) and 6-week cycle of methotrexate (up to 9 additional doses) may have been administered within the first 6 months of the study as per local prescribing information.

Primary: Change From Baseline in Number of Subjects With Anti-Recombinant Human Acid Alfa-glucosidase (Anti-rhGAA) Immunoglobulin G (IgG) Antibody at End of Study

End point title	Change From Baseline in Number of Subjects With Anti-Recombinant Human Acid Alfa-glucosidase (Anti-rhGAA) Immunoglobulin G (IgG) Antibody at End of Study[1]

End point description:

Serum samples from subjects were analyzed for the presence of anti-rhGAA IgG antibodies. End of study (EOS) refers to the last post baseline observation during study period (up to Week 79). FAS population included all enrolled subjects who signed informed consent and received at least 1 dose of alglucosidase alfa.

End point type	Primary

End point timeframe:

Baseline, End of Study (up to Week 79 or early termination)

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: As the analysis was descriptive, no statistical analysis is provided.

End point values	Alglucosidase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: subjects				
Baseline - Negative; EOS - Positive	2			
Baseline - Negative; EOS - Negative	2			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Recombinant Human Acid Alfa-glucosidase (rhGAA) Inhibitory Antibody at End of Study

End point title	Number of Subjects With Recombinant Human Acid Alfa-glucosidase (rhGAA) Inhibitory Antibody at End of Study[2]

End point description:

Subjects with positive anti-rhGAA IgG antibody were assessed for the presence of inhibitory antibodies

(inhibition of enzyme activity and inhibition of enzyme uptake). Enzyme-linked immunosorbent assay (ELISA) was used to measure inhibition of rhGAA enzymatic activity in vitro and a cell-based assay was used to measure the inhibition of the uptake of rhGAA in normal fibroblast cells by flow cytometry. FAS population included all enrolled subjects who signed informed consent and received at least 1 dose of alglucosidase alfa. Here, number of subjects analyzed = subjects with positive anti-rhGAA IgG antibody.

End point type	Primary

End point timeframe:

End of study (up to Week 79)

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: As the analysis was descriptive, no statistical analysis is provided.

End point values	Alglucosidase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: subjects				
Inhibition of Enzyme Activity	0			
Inhibition of Enzyme Uptake	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects Who Survived at End of Study

End point title	Number of Subjects Who Survived at End of Study[3]

End point description:

FAS population included all enrolled subjects who signed informed consent and received at least 1 dose of alglucosidase alfa.

End point type	Primary

End point timeframe:

Baseline up to End of study (Week 79)

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: As the analysis was descriptive, no statistical analysis is provided.

End point values	Alglucosidase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: subjects	2			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Normal/Abnormal Left Ventricular Mass (LVM) Z-Score and LVM Index at End of Study

End point title	Number of Subjects With Normal/Abnormal Left Ventricular Mass (LVM) Z-Score and LVM Index at End of Study[4]

End point description:

LVM Z-score and LVM index were assessed by ECHO. LVM Z-Score provides an indicator of degree of standard deviations from the mean in a normal distribution. Negative values indicate a smaller LVM than mean and values higher than 0 indicate a larger LVM than the mean. The normal range for LVM Z-Score is -2 to 2. Values <-2 or >2 indicate abnormal LVM Z-Score. LVM index is an index value derived by normalizing LVM by body surface area. LVM index provides evidence of cardiomyopathy. LVM index values <65 gram per meter^2 (g/m^2) were considered as normal and LVM index values >=65 g/m^2 were considered as abnormal. End of study refers to the last post baseline observation during study period (up to Week 79). FAS population included all enrolled subjects who signed informed consent and received at least 1 dose of alglucosidase alfa.

End point type	Primary

End point timeframe:

End of study (up to Week 79 or early termination)

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: As the analysis was descriptive, no statistical analysis is provided.

End point values	Alglucosidase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: subjects				
LVM Z-score: Normal	3			
LVM Z-score: Abnormal	1			
LVM index: Normal	2			
LVM index: Abnormal	2			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Ventilator Use at End of Study

End point title	Number of Subjects With Ventilator Use at End of Study[5]

End point description:

Number of subjects who had ventilator support at end of study was reported. End of study refers to the last post baseline observation during study period (up to Week 79). FAS population included all enrolled subjects who signed informed consent and received at least 1 dose of alglucosidase alfa.

End point type	Primary

End point timeframe:

End of study (up to Week 79 or early termination)

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: As the analysis was descriptive, no statistical analysis is provided.

End point values	Alglucosidase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: subjects				
Yes	3			
No	1			

Statistical analyses

No statistical analyses for this end point

Primary: Gross Motor Disability Assessed by Gross Motor Function Measure-88 (GMFM-88) at End of Study

End point title	Gross Motor Disability Assessed by Gross Motor Function Measure-88 (GMFM-88) at End of Study[6]

End point description:

GMFM-88 is an 88-item measure to detect gross motor function. Consist of 5 categories: lying and rolling; sitting; crawling and kneeling; standing; walking, running and jumping. Each item is scored on a 4-point Likert scale (0=cannot do; 1=initiates [<10% of the task]; 2=partially completes [10% to <100% of the task]; 3=task completion). Score for each dimension is expressed as a percentage of the maximum score for that dimension. Total score is obtained by adding percentage scores for each dimension and dividing sum by total number of dimensions. Total score ranges from 0% -100%, where higher scores indicate better motor functions. Total score of <7.5% demonstrates gross motor disability. End of study refers to last post baseline observation during study period (up to Week 79). FAS population included all enrolled subjects who signed informed consent and received at least 1 dose of alglucosidase alfa. Here, numbers of subjects analyzed = subjects with end of study GMFM-88 assessment.

End point type	Primary

End point timeframe:

End of study (up to Week 79 or early termination)

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: As the analysis was descriptive, no statistical analysis is provided.

End point values	Alglucosidase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: percentage of maximum total score				
median (full range (min-max))	8.24 (6.76 to 89.8)			

Statistical analyses

No statistical analyses for this end point

Primary: Motor Development Status Assessed by Alberta Infantile Motor Scale (AIMS) at End of Study

End point title	Motor Development Status Assessed by Alberta Infantile Motor

	Scale (AIMS) at End of Study[7]

End point description:

AIMS: 58-item reliable and valid measure of motor development for infants at risk for motor delay. It assesses infant movement in 4 positions (subscales): prone (reciprocal crawling);supine (moving hands to feet);sitting (sitting with arm support);standing (pulls to stand). For each subscale, items were scored as "observed" or "not observed". Item in observed range create motor window. Subscale scores are calculated by giving the child credit (1 point) for observed items within motor window in addition to being given credit (1 point) for all of less mature items before motor window. Total score was calculated by summing scores for 58 items (range: 0-58). Higher score=more mature motor development. Score was then compared with age-equivalent peers from normative sample and equivalence level age (months) is reported. End of study: last post baseline observation during study period (up to Week 79). FAS population. Numbers of subjects analyzed = subjects with end of study AIMS assessment.

End point type	Primary

End point timeframe:

End of study (up to Week 79 or early termination)

Notes:

[7] - 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: As the analysis was descriptive, no statistical analysis is provided.

End point values	Alglucosidase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: months				
median (full range (min-max))	1.09 (1 to 14.5)			

Statistical analyses

No statistical analyses for this end point

Primary: Disability Index Assessed by the Pompe Pediatric Evaluation of Disability Inventory (Pompe PEDI) at End of Study

End point title	Disability Index Assessed by the Pompe Pediatric Evaluation of Disability Inventory (Pompe PEDI) at End of Study[8]

End point description:

Pompe PEDI is disease specific version to assess functional capabilities and performance in children with Pompe (2 months-adolescence). It consists of (197 functional skill in 3 domains: self-care; mobility; and social function) and additional items in functional skills, mobility and self-care were clinically relevant functional. Each domain consisted of 2 subdomains: functional skill performance and caregiver assistance scale. Norm-based scoring was for additional items, and scoring algorithms for PEDI have been adjusted to reflect additional normative data collected for Pompe PEDI. Total score range for each domain (mean of subdomains) and subdomain ranges (0-100), where higher score indicates high capability. End of study was last post baseline observation during study period (up to Week 79). FAS population. Here, number of subject analyzed = number of subjects with end of study Pompe PEDI assessment and n = number of subjects with end of study assessment of specified category.

End point type	Primary

End point timeframe:

End of study (up to Week 79 or early termination)

Notes:

[8] - 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: As the analysis was descriptive, no statistical analysis is provided.

End point values	Alglucosidase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: units on a scale				
median (full range (min-max))				
Functional Skills: Mobility Score (n=3)	25.1 (23.2 to 56)			
Functional Skills: Self-Care Score (n=3)	39.3 (37 to 55.2)			
Functional Skills: Social Function Score (n=3)	46.2 (40.4 to 46.8)			
Caregiver Assistance: Mobility Score (n=3)	20.3 (20.3 to 31.9)			
Caregiver Assistance: Self-Care Score (n=2)	28.7 (20.1 to 37.2)			
Caregiver Assistance: Social Function Score (n=3)	48.5 (20.4 to 53.1)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose of study drug up to end of study (up to Week 79)

Adverse event reporting additional description:

In the event a single subject has experienced both serious and non-serious form of the same adverse event (AE), subject has been included in numerator of both AE tables. Analysis was performed on the safety population: all subjects who received at least 1 dose of alglucosidase alfa. AEs are listed independent of relationship to treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Alglucosidase Alfa

Reporting group description:

Alglucosidase alfa was given every other week (qow) or every week (qw) beginning from Day 0 to a minimum of 18 months or if the subject was less than (<) 6 months of age at the time of enrollment, until the subject was 2 years of age, along with methotrexate for 3 consecutive days qow beginning from Day 0 to Week 6 (9 doses) and rituximab qw beginning from Day -1 to Week 4 (4 doses) as per local prescribing information. An additional 4-week cycle of rituximab (up to 4 additional doses) and 6-week cycle of methotrexate (up to 9 additional doses) may have been administered within the first 6 months of the study as per local prescribing information.

Serious adverse events	Alglucosidase Alfa		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 4 (75.00%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events			
Investigations			
Pulse Absent			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Injury, poisoning and procedural complications			
Feeding Tube Complication			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Torus Fracture			

subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Vena Cava Thrombosis			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Bradycardia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac Arrest			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiopulmonary Failure			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
General disorders and administration site conditions			
Disease Progression			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

Ear and labyrinth disorders			
Tympanic Membrane Disorder			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Dyspnoea			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Laryngeal Stenosis			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory Distress			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Muscle Contracture			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Tracheitis			

subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Serratia Sepsis			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Clostridium Difficile Colitis			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Fluid Imbalance			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Alglucosidase Alfa		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Fibroma			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Vascular disorders			
Vena Cava Thrombosis			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Flushing			

subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	2		
Hypotension			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Pallor			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Surgical and medical procedures			
Post Procedural Drainage			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
Gastrointestinal Tube Removal			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Catheter Site Discharge			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Catheter Site Rash			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
Device Occlusion			
subjects affected / exposed	3 / 4 (75.00%)		
occurrences (all)	6		
Catheter Site Pruritus			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Face Oedema			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Device Dislocation			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Catheter Site Erythema			

subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	3		
Catheter Site Erosion			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Catheter Site Related Reaction			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Intentional Medical Device Removal By Subject			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	7		
Medical Device Complication			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	2		
Oedema Peripheral			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	3		
Pyrexia			
subjects affected / exposed	4 / 4 (100.00%)		
occurrences (all)	16		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	3		
Bronchospasm			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Bronchial Secretion Retention			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	2		
Aspiration			

subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Acute Respiratory Failure				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Rhinitis Allergic				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Atelectasis				
subjects affected / exposed	2 / 4 (50.00%)			
occurrences (all)	3			
Respiratory Distress				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	2			
Pneumothorax				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Pneumonia Aspiration				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Diaphragm Muscle Weakness				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	2			
Increased Bronchial Secretion				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	2			
Diaphragmatic Disorder				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Dyspnoea				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	2			
Laryngeal Stenosis				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	2			
Rhinorrhoea				

subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	6		
Wheezing			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	5		
Tachypnoea			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	3		
Investigations			
Blood Culture Positive			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Blood Creatine Phosphokinase Mb Increased			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
Alanine Aminotransferase Increased			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
Band Neutrophil Percentage Increased			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Aspartate Aminotransferase Increased			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	4		
Antibiotic Resistant Staphylococcus Test Positive			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		

Blood Chloride Decreased				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Clostridium Test Positive				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	3			
Body Temperature Increased				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Blood Sodium Decreased				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Blood Pressure Increased				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Blood Immunoglobulin G Increased				
subjects affected / exposed	2 / 4 (50.00%)			
occurrences (all)	2			
Blood Potassium Decreased				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Blood Lactate Dehydrogenase Increased				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Blood Iron Decreased				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Blood Potassium Increased				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Occult Blood Positive				
subjects affected / exposed	2 / 4 (50.00%)			
occurrences (all)	3			
Neutrophil Percentage Increased				

subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Neutrophil Count Decreased				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Eosinophil Percentage Increased				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Lymphocyte Percentage Decreased				
subjects affected / exposed	2 / 4 (50.00%)			
occurrences (all)	2			
Heart Rate Irregular				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Heart Rate Decreased				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Moraxella Test Positive				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Weight Decreased				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Urine Output Decreased				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Urinary Hexose Tetrasaccharide Increased				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Oxygen Saturation Decreased				
subjects affected / exposed	2 / 4 (50.00%)			
occurrences (all)	6			
Specific Gravity Urine Increased				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			

Respiratory Rate Increased subjects affected / exposed occurrences (all)	 1 / 4 (25.00%) 1			
Respiratory Rate Decreased subjects affected / exposed occurrences (all)	 1 / 4 (25.00%) 1			
Protein Total Decreased subjects affected / exposed occurrences (all)	 1 / 4 (25.00%) 1			
Reticulocyte Percentage Increased subjects affected / exposed occurrences (all)	 1 / 4 (25.00%) 1			
White Blood Cell Count Decreased subjects affected / exposed occurrences (all)	 1 / 4 (25.00%) 1			
White Blood Cell Count Increased subjects affected / exposed occurrences (all)	 1 / 4 (25.00%) 2			
Injury, poisoning and procedural complications				
Spinal Compression Fracture subjects affected / exposed occurrences (all)	 1 / 4 (25.00%) 1			
Procedural Site Reaction subjects affected / exposed occurrences (all)	 1 / 4 (25.00%) 1			
Procedural Pain subjects affected / exposed occurrences (all)	 2 / 4 (50.00%) 3			
Overdose subjects affected / exposed occurrences (all)	 1 / 4 (25.00%) 1			
Lip Injury subjects affected / exposed occurrences (all)	 1 / 4 (25.00%) 1			
Laceration				

subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Burns Second Degree			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Medication Error			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Torus Fracture			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
Extrasystoles			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Cyanosis			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Tachycardia			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
Nervous system disorders			
Clonus			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Lymphadenopathy			

subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Anaemia			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	4		
Ear and labyrinth disorders			
Tympanic Membrane Disorder			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	3		
Eye disorders			
Eyelid Ptosis			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Conjunctivitis			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Periorbital Oedema			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 4 (75.00%)		
occurrences (all)	10		
Anorectal Disorder			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Anal Sphincter Atony			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	4		
Retching			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	4		
Duodenogastric Reflux			

subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Flatulence			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Gastritis			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Haematemesis			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Haematochezia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Teething			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	3 / 4 (75.00%)		
occurrences (all)	6		
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
Excessive Granulation Tissue			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	3		
Drug Eruption			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Eczema			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Dermatitis Contact			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		

Dermatitis Diaper				
subjects affected / exposed	3 / 4 (75.00%)			
occurrences (all)	8			
Rash Papular				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Rash Erythematous				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Rash Macular				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	2			
Hair Colour Changes				
subjects affected / exposed	2 / 4 (50.00%)			
occurrences (all)	3			
Rash				
subjects affected / exposed	3 / 4 (75.00%)			
occurrences (all)	12			
Palmar-Plantar Erythrodysaesthesia Syndrome				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Macule				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Hyperhidrosis				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Papule				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	2			
Swelling Face				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences (all)	1			
Skin Ulcer				

subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	2		
Red Man Syndrome			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Skin Hypopigmentation			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	2		
Skin Hyperpigmentation			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Skin Exfoliation			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
Skin Irritation			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Muscle Contracture			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	2		
Muscle Spasms			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Osteopenia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Infections and infestations			
Catheter Site Cellulitis			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Body Tinea			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Clostridium Difficile Colitis			

subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	4		
Candidiasis			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Serratia Infection			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Sepsis			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Otitis Media Acute			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Otitis Media			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Oral Candidiasis			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Impetigo			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Urinary Tract Infection Enterococcal			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	2		
Tracheitis			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
Viral Infection			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Metabolism and nutrition disorders			

Dehydration subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1		
Vitamin D Deficiency subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 March 2008	Clarified rituximab dosing for subjects smaller than average. Clarified that a central cardiologist reviews the ECG and ECHO data for consistency, while a local cardiologist reviews the ECG and ECHO data for safety and clinical management of the subject. Clarified baseline assessments for consistency with Study AGLU03707. Clarified timeline for performing plasmapheresis. Clarified that infusion-associated reactions are related only to alglucosidase alfa for the purposes of the study.
29 July 2008	Clarified that a second cycle of immunomodulatory therapy can only be administered within the first 6 months of study participation. Clarified source of biopsy sample for Western Blot analysis. Allowed enrolment at non-US sites. Clarified source of prescribing information. Added stopping rule for fatal or life-threatening reaction to plasmapheresis/plasma exchange.
01 October 2009	Removed plasmapheresis globally from the protocol as it had been determined that the frequency of administration allowed by the protocol would not be clinically meaningful for the subject population. Clarified that historical CRIM testing results were acceptable. Added details on the indication for IVIG administration. Clarified the risks associated with IVIG therapy. Added NCI/CTCAE grading to the associated severity category throughout the protocol. Expanded criteria for removing a subject from the study to include receipt of interventions or procedures that may impact the efficacy or safety of the required study assessments and treatments. Added new information on delayed onset of AEs related to rituximab administration. Clarified that subjects are fully evaluated for clinical stability and lack of acute illness prior to dosing. Clarified requirements for GAA mutation analysis. Added details on optional port-a-catheter. Clarified procedures for evaluating clinically significant changes in ECG findings and subsequent documentation of AEs.
24 May 2010	Allowed increased alglucosidase alfa dose frequency. Clarified processes for an enrolled subject later found to be CRIM-positive on Western Blot analysis. Clarified that an Investigator should determine exclusion criteria on a case-by-case basis. Clarified that the GMFM-88 is utilized rather than the GMFM-66.

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.

Due to the small number of subjects assessed in this study the results must be interpreted with caution.

Notes: