

**Clinical trial results:****An Exploratory Study of the Safety and Efficacy of Immune Tolerance Induction (ITI) in Subjects with Pompe Disease Who Have Previously Received Myozyme****Summary**

EudraCT number	2015-000583-34
Trial protocol	Outside EU/EEA
Global end of trial date	18 February 2020

Results information

Result version number	v1 (current)
This version publication date	08 August 2020
First version publication date	08 August 2020

Trial information**Trial identification**

Sponsor protocol code	AGLU03707_MSC12817
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00701701
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Genzyme, a Sanofi company
Sponsor organisation address	50 Binney St, Cambridge, MA, 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	22 January 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	18 February 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety of ITI regimens, as assessed by 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 minimised. 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 minimise distress and discomfort.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 December 2008
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: 3
Country: Number of subjects enrolled	Israel: 1
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)	2
Children (2-11 years)	2

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:

The study was conducted in 2 countries. A total of 5 subjects were screened between 14 December 2008 and 17 August 2010 (dates when first subject and last subject signed informed consent), of which one subject died before enrollment.

Pre-assignment

Screening details:

A total of 4 subjects were included and treated in this study. Subjects were assigned to either Regimen A or Regimen B.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Regimen A: Alglucosidase alfa and Cyclophosphamide

Arm description:

Subjects exhibiting clinical decline since starting alglucosidase alfa (Myozyme®) therapy and had inhibitory antibodies and/or a sustained high recombinant human acid alpha-glucosidase (rhGAA) antibody titer (defined as at least 2 titers greater than or equal to (\geq) 25,600 obtained at least 1 month apart), regardless of their cross-reacting immunologic material (CRIM) status, were assigned to Regimen A. Subjects received alglucosidase alfa (Myozyme®) Intravenous (IV) infusion of 20 milligram per kilogram (mg/kg) every other week (qow) for a minimum of 18 months or, until the subject reaches the age of 2 years (if the subject was less than (<6) months of age at the time of enrolment). In addition, cyclophosphamide 250 milligram per square meter (mg/m^2) IV infusion was administered every 4 weeks after Myozyme® infusion for 6 months.

Arm type	Experimental
Investigational medicinal product name	Alglucosidase alfa
Investigational medicinal product code	
Other name	Myozyme®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Alglucosidase alfa (Myozyme®) 20 mg/kg IV infusion qow. Alglucosidase alfa (Myozyme®) was infused in a dedicated IV line. The length of infusion was approximately 3.5 to 4 hours for a dose of 20 mg/kg.

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

Dosage and administration details:

Cyclophosphamide 250 mg/m^2 administered IV every 4 weeks.

Arm title	Regimen B: Alglucosidase alfa, Rituximab and Methotrexate
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Arm description:

CRIM-negative subjects were assigned to Regimen B if they either (1) exhibited clinical decline since starting alglucosidase alfa (Myozyme®) therapy and did not have inhibitory antibodies and/or a sustained rhGAA antibody titer (defined as at least 2 titers $\geq 25,600$ obtained at least 1 month apart), or (2) did not exhibit clinical decline since starting alglucosidase alfa (Myozyme®) therapy, regardless of their anti-rhGAA or inhibitory antibody status. Regimen B subjects with CRIM-negative status received alglucosidase alfa (Myozyme®) IV infusion of 20 mg/kg qow for a minimum of 18 months or, until subject reaches the age of 2 years (if subject was <6 months of age at time of

rituximab 375 mg/m² IV was administered weekly beginning the day after Myozyme® infusion for 4 weeks (an optional 2nd cycle might be administered at the discretion of the investigator) and biweekly methotrexate 15 mg/m² subcutaneous on the day after Myozyme® infusion for 6 months.

Arm type	Experimental
Investigational medicinal product name	Alglucosidase alfa
Investigational medicinal product code	
Other name	Myozyme®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Alglucosidase alfa (Myozyme®) 20 mg/kg IV infusion qow. Alglucosidase alfa (Myozyme®) was infused in a dedicated IV line. The length of infusion was approximately 3.5 to 4 hours for a dose of 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:

Rituximab 375 mg/m² IV administered weekly.

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

Dosage and administration details:

Methotrexate 15 mg/m² subcutaneous every other week.

Number of subjects in period 1	Regimen A: Alglucosidase alfa and Cyclophosphamide	Regimen B: Alglucosidase alfa, Rituximab and Methotrexate
Started	1	3
Completed	1	1
Not completed	0	2
Consent withdrawn by subject	-	1
Adverse Event	-	1

Baseline characteristics

Reporting groups

Reporting group title	Regimen A: Alglucosidase alfa and Cyclophosphamide
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Reporting group description:

Subjects exhibiting clinical decline since starting alglucosidase alfa (Myozyme®) therapy and had inhibitory antibodies and/or a sustained high recombinant human acid alpha-glucosidase (rhGAA) antibody titer (defined as at least 2 titers greater than or equal to (\geq) 25,600 obtained at least 1 month apart), regardless of their cross-reacting immunologic material (CRIM) status, were assigned to Regimen A. Subjects received alglucosidase alfa (Myozyme®) Intravenous (IV) infusion of 20 milligram per kilogram (mg/kg) every other week (qow) for a minimum of 18 months or, until the subject reaches the age of 2 years (if the subject was less than (<6) months of age at the time of enrolment). In addition, cyclophosphamide 250 milligram per square meter (mg/m²) IV infusion was administered every 4 weeks after Myozyme® infusion for 6 months.

Reporting group title	Regimen B: Alglucosidase alfa, Rituximab and Methotrexate
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Reporting group description:

CRIM-negative subjects were assigned to Regimen B if they either (1) exhibited clinical decline since starting alglucosidase alfa (Myozyme®) therapy and did not have inhibitory antibodies and/or a sustained rhGAA antibody titer (defined as at least 2 titers \geq 25,600 obtained at least 1 month apart), or (2) did not exhibit clinical decline since starting alglucosidase alfa (Myozyme®) therapy, regardless of their anti-rhGAA or inhibitory antibody status. Regimen B subjects with CRIM-negative status received alglucosidase alfa (Myozyme®) IV infusion of 20 mg/kg qow for a minimum of 18 months or, until subject reaches the age of 2 years (if subject was <6 months of age at time of enrolment). In addition, rituximab 375 mg/m² IV was administered weekly beginning the day after Myozyme® infusion for 4 weeks (an optional 2nd cycle might be administered at the discretion of the investigator) and biweekly methotrexate 15 mg/m² subcutaneous on the day after Myozyme® infusion

Reporting group values	Regimen A: Alglucosidase alfa and Cyclophosphamide	Regimen B: Alglucosidase alfa, Rituximab and Methotrexate	Total
Number of subjects	1	3	4
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	2	2
Children (2-11 years)	1	1	2
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	0	2	2
Male	1	1	2

End points

End points reporting groups

Reporting group title	Regimen A: Alglucosidase alfa and Cyclophosphamide
Reporting group description:	
Subjects exhibiting clinical decline since starting alglucosidase alfa (Myozyme®) therapy and had inhibitory antibodies and/or a sustained high recombinant human acid alpha-glucosidase (rhGAA) antibody titer (defined as at least 2 titers greater than or equal to (\geq) 25,600 obtained at least 1 month apart), regardless of their cross-reacting immunologic material (CRIM) status, were assigned to Regimen A. Subjects received alglucosidase alfa (Myozyme®) Intravenous (IV) infusion of 20 milligram per kilogram (mg/kg) every other week (qow) for a minimum of 18 months or, until the subject reaches the age of 2 years (if the subject was less than ($<$ 6) months of age at the time of enrolment). In addition, cyclophosphamide 250 milligram per square meter (mg/m^2) IV infusion was administered every 4 weeks after Myozyme® infusion for 6 months.	
Reporting group title	Regimen B: Alglucosidase alfa, Rituximab and Methotrexate
Reporting group description:	
CRIM-negative subjects were assigned to Regimen B if they either (1) exhibited clinical decline since starting alglucosidase alfa (Myozyme®) therapy and did not have inhibitory antibodies and/or a sustained rhGAA antibody titer (defined as at least 2 titers \geq 25,600 obtained at least 1 month apart), or (2) did not exhibit clinical decline since starting alglucosidase alfa (Myozyme®) therapy, regardless of their anti-rhGAA or inhibitory antibody status. Regimen B subjects with CRIM-negative status received alglucosidase alfa (Myozyme®) IV infusion of 20 mg/kg qow for a minimum of 18 months or, until subject reaches the age of 2 years (if subject was $<$ 6 months of age at time of enrolment). In addition, rituximab 375 mg/m^2 IV was administered weekly beginning the day after Myozyme® infusion for 4 weeks (an optional 2nd cycle might be administered at the discretion of the investigator) and biweekly methotrexate 15 mg/m^2 subcutaneous on the day after Myozyme® infusion	

Primary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) ^[1]
End point description:	
An AE was defined as any undesirable physical, psychological, or behavioral effect experienced by subject during his/her participation in an investigational study, in conjunction with the use of the drug or biologic, whether or not product-related. TEAEs were defined as AEs that occurred or worsened during the on-treatment period (time from the start of investigational medicinal product [IMP] administration up to 18 months). SAE was any AE that resulted in any of the following outcomes: death, was life-threatening, required or prolonged inpatient hospitalisation, persistent or significant disability/incapacity; congenital anomaly; or important medical events that may jeopardise the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above; new invasive ventilator use. Analysis was performed on safety set that included subjects who received at least 1 dose of alglucosidase alfa in the study.	
End point type	Primary
End point timeframe:	
From baseline up to 18 months	

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 endpoint was descriptive in nature, no statistical analysis was provided.

End point values	Regimen A: Alglucosidase alfa and Cyclophosphamide	Regimen B: Alglucosidase alfa, Rituximab and Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	3		

Units: subject				
number (not applicable)				
Any TEAE	1	3		
Any Treatment-emergent SAE	1	3		
Any TEAE leading to withdrawal	0	1		
Any TEAE leading to death	0	1		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Anti-Recombinant Human Acid Alpha-glucosidase (Anti-rhGAA) Immunoglobulin G (IgG) Antibodies at Month 18

End point title	Number of Subjects With Anti-Recombinant Human Acid Alpha-glucosidase (Anti-rhGAA) Immunoglobulin G (IgG) Antibodies at Month 18
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End point description:

Serum samples from subjects were planned to be analysed for the presence of anti-rhGAA IgG antibodies. Analysis was performed on Full Analysis Set (FAS) which included subjects who signed informed consent, completed all baseline assessments, and received at least 1 dose of alglucosidase alfa. Here, "99999" was used as space fillers and signifies that data were not summarised for this exploratory end-point due to low number of enrollment of subjects.

End point type	Other pre-specified
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End point timeframe:

Month 18

End point values	Regimen A: Alglucosidase alfa and Cyclophosphamide	Regimen B: Alglucosidase alfa, Rituximab and Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	3		
Units: subjects				
number (not applicable)	99999	99999		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Recombinant Human Acid Alpha-glucosidase (rhGAA) Inhibitory Antibody at Month 18

End point title	Number of Subjects With Recombinant Human Acid Alpha-glucosidase (rhGAA) Inhibitory Antibody at Month 18
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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. Analysis was performed on FAS. Here, "99999" was used as space fillers and signifies that data were not summarised for this exploratory end-point due to low number of enrollment of subjects.

End point type	Other pre-specified
End point timeframe:	
Month 18	

End point values	Regimen A: Alglucosidase alfa and Cyclophospha mide	Regimen B: Alglucosidase alfa, Rituximab and Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	3		
Units: subjects				
number (not applicable)				
Inhibition of enzyme activity	99999	99999		
Inhibition of enzyme uptake	99999	99999		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Overall Survival (OS)

End point title	Overall Survival (OS)
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End point description:

Overall Survival was defined as the time interval from the date of first study drug administration to the date of death due to any cause. Analysis was performed on FAS. Here, "99999" was used as space fillers and signifies that data were not summarised for this exploratory end-point due to low number of enrollment of subjects.

End point type	Other pre-specified
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End point timeframe:

From randomisation until death or study cut-off whichever comes earlier (up to 18 months)

End point values	Regimen A: Alglucosidase alfa and Cyclophospha mide	Regimen B: Alglucosidase alfa, Rituximab and Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	3		
Units: month				
median (full range (min-max))	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Ventilator Use

End point title | Number of Subjects With Ventilator Use

End point description:

Number of subjects requiring ventilator support were planned to be reported. Analysis was performed on FAS. Here, "99999" was used as space fillers and signifies that data were not summarised for this exploratory end-point and only individual subject listings were generated due to low number of enrollment of subjects.

End point type | Other pre-specified

End point timeframe:

From baseline up to 18 months

End point values	Regimen A: Alglucosidase alfa and Cyclophospha mide	Regimen B: Alglucosidase alfa, Rituximab and Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	3		
Units: subjects				
number (not applicable)	99999	99999		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Left Ventricular Mass (LVM) Z-Score and LVM Index

End point title | Left Ventricular Mass (LVM) Z-Score and LVM Index

End point description:

LVM Z-score and LVM index were assessed by echocardiograms (ECHOs). LVM Z-Score is an indicator of degree of standard deviations from the mean in a normal distribution. The normal range for LVM Z-Score is -2 to 2. Values <-2 or >2 indicate abnormal LVM Z-Score. Values less than 0 (negative values) indicated a smaller LVM than mean and values higher than 0 indicate a larger LVM than the mean. LVM index is an index value derived by normalising LVM by body surface area. LVM index provides evidence of cardiomyopathy. LVM index values <65 gram per meter² (g/m²) were considered as normal and LVM index values ≥65 g/m² were considered as abnormal. Analysis was performed on FAS. Here, "99999" was used as space fillers and signifies that data were not summarised for this exploratory end-point due to low number of enrollment of subjects.

End point type | Other pre-specified

End point timeframe:

From baseline up to 18 months

End point values	Regimen A: Alglucosidase alfa and Cyclophospha mide	Regimen B: Alglucosidase alfa, Rituximab and Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	3		
Units: subjects				
number (not applicable)				
LVM Z-score	99999	99999		
LVM index	99999	99999		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Gross Motor Disability Assessed by Gross Motor Function Measure-88 (GMFM-88) Score

End point title	Gross Motor Disability Assessed by Gross Motor Function Measure-88 (GMFM-88) Score
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End point description:

GMFM-88 is an 88-item measure to detect gross motor function. It consists of 5 categories: lying and rolling; sitting; crawling and kneeling; standing; and 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). The score for each dimension is expressed as a percentage of the maximum score for that dimension. Total score is obtained by adding the percentage scores for each dimension and dividing the sum by the total number of dimensions. Total score ranges from 0% to 100%, where higher scores indicate better motor functions. A total score of <7.5% demonstrates gross motor disability. Analysis was performed on FAS. Here, "99999" was used as space fillers and signifies that data were not summarised for this exploratory end-point due to low number of enrollment of subjects.

End point type	Other pre-specified
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End point timeframe:

From baseline up to 18 months

End point values	Regimen A: Alglucosidase alfa and Cyclophospha mide	Regimen B: Alglucosidase alfa, Rituximab and Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	3		
Units: percentage of total score				
number (not applicable)	99999	99999		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Motor Development Status Assessed by Alberta Infantile Motor Scale (AIMS) Score

End point title	Motor Development Status Assessed by Alberta Infantile Motor Scale (AIMS) Score
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End point description:

AIMS is a 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); and standing (pulls to stand).For each subscale, items are scored as "observed" or "not observed". Item in observed range create a motor window. When scoring, subscale scores are calculated by giving child credit (1 point) for observed items within motor window in addition to being given credit (1 point) for all of the less mature items before motor window. AIMS total score is calculated by summing scores for 58 items and ranges from 0-58, with higher score indicating more mature motor development. Analysis was performed on FAS. Here, "99999" was used as space fillers and signifies that data were not summarised for this exploratory end-point due to low number of enrollment of subjects.

End point type	Other pre-specified
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End point timeframe:

From baseline up to 18 months

End point values	Regimen A: Alglucosidase alfa and Cyclophospha mide	Regimen B: Alglucosidase alfa, Rituximab and Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	3		
Units: score on a scale				
number (not applicable)	99999	99999		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Disability Index Assessed by the Pompe Pediatric Evaluation of Disability Inventory (Pompe PEDI) Score

End point title	Disability Index Assessed by the Pompe Pediatric Evaluation of Disability Inventory (Pompe PEDI) Score
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End point description:

Pompe PEDI: assesses functional capabilities and performance in children with Pompe disease from 2 months through adolescence. It consists of all items of original PEDI (197 functional skill items in 3 domains:self-care; mobility; and social function) and additional items in functional skills, mobility, and self-care domains to reflect clinically relevant functional skills. Each domain consisted of 2 subdomains: functional skill performance and caregiver assistance scale. Norm-based scoring was developed for these 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 subdomains ranges from 0-100, higher score indicated higher capability. Analysis was performed on FAS. Here, "99999" was used as space fillers and signifies that data were not summarised for this exploratory end-point due to low number of enrollment of subjects.

End point type	Other pre-specified
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End point timeframe:

From baseline up to 18 months

End point values	Regimen A: Alglucosidase alfa and Cyclophospha mide	Regimen B: Alglucosidase alfa, Rituximab and Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	3		
Units: score on a scale				
number (not applicable)	99999	99999		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs were collected from first IMP administration up to 18 months.

Adverse event reporting additional description:

Reported AEs and deaths are treatment-emergent adverse events that are AEs that developed/worsened and deaths that occurred during the 'on treatment period' (time from first IMP administration until 18 months). Analysis was performed on safety population.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.1
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Reporting groups

Reporting group title	Regimen A: Alglucosidase alfa and Cyclophosphamide
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Reporting group description:

Subjects exhibiting clinical decline since starting alglucosidase alfa (Myozyme®) therapy and had inhibitory antibodies and/or a sustained high rhGAA antibody titer (defined as at least 2 titers $\geq 25,600$ obtained at least 1 month apart), regardless of their CRIM status, were assigned to Regimen A. Subjects received alglucosidase alfa (Myozyme®) IV infusion of 20 mg/kg qow for a minimum of 18 months or, until the subject reaches the age of 2 years (if the subject was less than (<6) months of age at the time of enrolment). In addition, cyclophosphamide 250 mg/m² IV infusion was administered every 4 weeks after Myozyme® infusion for 6 months.

Reporting group title	Regimen B: Alglucosidase alfa, Rituximab and Methotrexate
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Reporting group description:

CRIM-negative subjects were assigned to Regimen B if they either (1) exhibited clinical decline since starting alglucosidase alfa (Myozyme®) therapy and did not have inhibitory antibodies and/or a sustained rhGAA antibody titer (defined as at least 2 titers $\geq 25,600$ obtained at least 1 month apart), or (2) did not exhibit clinical decline since starting alglucosidase alfa (Myozyme®) therapy, regardless of their anti-rhGAA or inhibitory antibody status. Regimen B subjects with CRIM-negative status received alglucosidase alfa (Myozyme®) IV infusion of 20 mg/kg qow for a minimum of 18 months or, until subject reaches the age of 2 years (if subject was <6 months of age at time of enrolment). In addition, rituximab 375 mg/m² IV was administered weekly beginning the day after Myozyme® infusion for 4 weeks (an optional 2nd cycle might be administered at the discretion of the investigator) and biweekly methotrexate 15 mg/m² subcutaneous on the day after Myozyme® infusion

Serious adverse events	Regimen A: Alglucosidase alfa and Cyclophosphamide	Regimen B: Alglucosidase alfa, Rituximab and Methotrexate	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	3 / 3 (100.00%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Investigations			
Blood Pressure Decreased			
subjects affected / exposed	1 / 1 (100.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen Saturation Decreased			

subjects affected / exposed	1 / 1 (100.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcus Test Positive			
subjects affected / exposed	0 / 1 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Pallor			
subjects affected / exposed	1 / 1 (100.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial Thrombosis			
subjects affected / exposed	1 / 1 (100.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Hypertrophy			
subjects affected / exposed	1 / 1 (100.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyanosis			
subjects affected / exposed	1 / 1 (100.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertrophic Cardiomyopathy			
subjects affected / exposed	1 / 1 (100.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Neutropenia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General Physical Health Deterioration			
subjects affected / exposed	0 / 1 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 1 (100.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 1 (100.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	1 / 1 (100.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 1 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercapnia			
subjects affected / exposed	1 / 1 (100.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			

subjects affected / exposed	0 / 1 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Increased Upper Airway Secretion			
subjects affected / exposed	1 / 1 (100.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Distress			
subjects affected / exposed	0 / 1 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Failure			
subjects affected / exposed	0 / 1 (0.00%)	2 / 3 (66.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Cold Sweat			
subjects affected / exposed	1 / 1 (100.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	1 / 1 (100.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 1 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia			

subjects affected / exposed	1 / 1 (100.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Streptococcal			
subjects affected / exposed	0 / 1 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Viral			
subjects affected / exposed	0 / 1 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 1 (100.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 1 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Regimen A: Alglucosidase alfa and Cyclophosphamide	Regimen B: Alglucosidase alfa, Rituximab and Methotrexate	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	3 / 3 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 1 (100.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Hypotension			
subjects affected / exposed	1 / 1 (100.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Phlebitis			

subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 2	0 / 3 (0.00%) 0	
General disorders and administration site conditions			
Catheter Site Phlebitis			
subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 2	0 / 3 (0.00%) 0	
Medical Device Complication			
subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 2	0 / 3 (0.00%) 0	
Oedema Peripheral			
subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 1	0 / 3 (0.00%) 0	
Pain			
subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 3 (33.33%) 1	
Pyrexia			
subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 10	2 / 3 (66.67%) 10	
Thrombosis In Device			
subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 3 (33.33%) 1	
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 3 (33.33%) 1	
Atelectasis			
subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 1	0 / 3 (0.00%) 0	
Cough			
subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 3 (33.33%) 2	
Dyspnoea			
subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 1	0 / 3 (0.00%) 0	
Haemoptysis			

subjects affected / exposed	0 / 1 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Hypoxia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	3	
Increased Bronchial Secretion			
subjects affected / exposed	1 / 1 (100.00%)	0 / 3 (0.00%)	
occurrences (all)	3	0	
Increased Upper Airway Secretion			
subjects affected / exposed	0 / 1 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Pleural Effusion			
subjects affected / exposed	1 / 1 (100.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Pneumonia Aspiration			
subjects affected / exposed	1 / 1 (100.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Pneumonitis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Pneumothorax			
subjects affected / exposed	0 / 1 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Pulmonary Oedema			
subjects affected / exposed	0 / 1 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Respiratory Distress			
subjects affected / exposed	1 / 1 (100.00%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Rhinorrhoea			
subjects affected / exposed	1 / 1 (100.00%)	1 / 3 (33.33%)	
occurrences (all)	2	1	
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 1 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	

Insomnia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Restlessness			
subjects affected / exposed	1 / 1 (100.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	3	
Blood Creatine Phosphokinase Mb Increased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	3	
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	2	
Blood Immunoglobulin M Increased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Blood Magnesium Decreased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Blood Potassium Decreased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	2	
Body Temperature Increased			
subjects affected / exposed	0 / 1 (0.00%)	3 / 3 (100.00%)	
occurrences (all)	0	10	
Heart Rate Increased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	4	
Lymphocyte Count Decreased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Lymphocyte Percentage Decreased			

subjects affected / exposed	0 / 1 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Muscle Enzyme Increased			
subjects affected / exposed	1 / 1 (100.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Neutrophil Count Decreased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Neutrophil Percentage Increased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Oxygen Saturation Decreased			
subjects affected / exposed	1 / 1 (100.00%)	1 / 3 (33.33%)	
occurrences (all)	3	1	
Urine Output Decreased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	2	
White Blood Cell Count Decreased			
subjects affected / exposed	0 / 1 (0.00%)	2 / 3 (66.67%)	
occurrences (all)	0	2	
White Blood Cells Urine Positive			
subjects affected / exposed	0 / 1 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Arthropod Bite			
subjects affected / exposed	0 / 1 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	2	
Excoriation			
subjects affected / exposed	0 / 1 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Feeding Tube Complication			
subjects affected / exposed	1 / 1 (100.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Thermal Burn			

subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 3 (33.33%) 1	
Tracheal Haemorrhage subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 3 (33.33%) 1	
Cardiac disorders Bradycardia subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 5	0 / 3 (0.00%) 0	
Tachycardia subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 3 (33.33%) 3	
Ventricular Hypertrophy subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 3 (33.33%) 1	
Nervous system disorders Clonus subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 3 (33.33%) 1	
Hypokinesia subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	2 / 3 (66.67%) 2	
Blood and lymphatic system disorders Leukocytosis subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 3 (33.33%) 1	
Ear and labyrinth disorders Conductive Deafness subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 3 (33.33%) 2	
Deafness Bilateral subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 3 (33.33%) 1	
Mixed Deafness subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 3 (33.33%) 1	
Eye disorders			

Conjunctivitis subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 3 (33.33%) 2	
Gastrointestinal disorders			
Abdominal Distension subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 1	0 / 3 (0.00%) 0	
Constipation subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 5	1 / 3 (33.33%) 1	
Diarrhoea subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 3 (33.33%) 2	
Faecaloma subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 2	0 / 3 (0.00%) 0	
Faeces Hard subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 3	0 / 3 (0.00%) 0	
Nausea subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 1	0 / 3 (0.00%) 0	
Retching subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 3 (33.33%) 1	
Vomiting subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 4	1 / 3 (33.33%) 1	
Skin and subcutaneous tissue disorders			
Decubitus Ulcer subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 1	0 / 3 (0.00%) 0	
Dermatitis Diaper subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 3 (33.33%) 1	
Erythema			

subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 1	1 / 3 (33.33%) 1	
Papule subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 3 (33.33%) 1	
Pruritus subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 1	0 / 3 (0.00%) 0	
Rash subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 3 (33.33%) 2	
Red Man Syndrome subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 3 (33.33%) 1	
Skin Discolouration subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 3 (33.33%) 1	
Skin Exfoliation subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 3 (33.33%) 1	
Skin Irritation subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 3 (33.33%) 1	
Skin Swelling subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 3 (33.33%) 3	
Urticaria subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 2	2 / 3 (66.67%) 6	
Renal and urinary disorders			
Hydronephrosis subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 1	0 / 3 (0.00%) 0	
Oliguria subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 2	0 / 3 (0.00%) 0	

Urinary Retention subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 5	0 / 3 (0.00%) 0	
Musculoskeletal and connective tissue disorders Joint Contracture subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 3 (33.33%) 1	
Infections and infestations Bacterial Tracheitis subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 3 (33.33%) 1	
Otitis Media subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	3 / 3 (100.00%) 3	
Otitis Media Acute subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	2 / 3 (66.67%) 2	
Pharyngitis subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 1	0 / 3 (0.00%) 0	
Pneumonia subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 1	0 / 3 (0.00%) 0	
Staphylococcal Bacteraemia subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 1	0 / 3 (0.00%) 0	
Tracheitis subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 3 (33.33%) 1	
Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	2 / 3 (66.67%) 7	
Urinary Tract Infection subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 3 (33.33%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 August 2008	Following changes were made: Allowed enrollment at non-US sites; clarified that a second cycle of immunomodulatory therapy can only be administered within the first 6 months of study participation; clarified that infusion-associated reactions are related only to alglucosidase alfa for the purposes of the study.
19 March 2009	Following changes were made: Allowed subjects to be assigned to either ITI regimen based on their qualifications for a given regimen, and thereby address the greater number of cross-reacting immunologic material (CRIM)-negative subjects being identified by sites; allowed for CRIM testing, thereby minimising testing procedures for subjects while still ensuring consistency in testing standards, and ensured that sites receive the results; clarified the subjects who should receive intravenous immunoglobulin (IVIG) and the risks associated with IVIG therapy; clarified that subjects must have received at least 1 dose of alglucosidase alfa prior to enrollment, in place of a 6-month alglucosidase alfa treatment period.
01 October 2009	Following changes were made: Clarified that a central cardiologist reviews the electrocardiogram and echocardiogram data for consistency, while a local cardiologist reviews the ECG and ECHO data for safety and clinical management of the subject; 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; added National Cancer Institute Common Terminology Criteria for Adverse Events grading to the associated severity category throughout the protocol; added details on the indication for IVIG administration; 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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
26 August 2013	Since Food and Drug Administration (FDA) feedback on post-marketing commitment (PMC) was pending, with FDA's acknowledgement further enrollment of subjects were stopped; and the Study was deemed terminated after receiving FDA acknowledgment of PMC fulfillment on 18 Feb 2020.	-

Notes:

Limitations and caveats

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

Due to low number of enrolment and exploratory nature of endpoints, only safety data were summarised and reported.

Notes: