



## Clinical trial results:

### A Phase 4 Prospective Exploratory Muscle Biopsy, Biomarker, and Imaging Assessment Study in Patients With Late-Onset Pompe Disease Treated With Alglucosidase Alfa

#### Summary

EudraCT number	2010-020611-36
Trial protocol	GB DE NL
Global end of trial date	19 December 2013

#### Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	09 April 2015

#### Trial information

##### Trial identification

Sponsor protocol code	AGLU07310
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01288027
WHO universal trial number (UTN)	-
Other trial identifiers	Secondary identifier: MSC12823

Notes:

#### Sponsors

Sponsor organisation name	Genzyme Corporation
Sponsor organisation address	500 Kendall Street, Cambridge, MA, United States, 02142
Public contact	Sanofi aventis recherche & développement, Trial Transparency Team, Contact-US@Sanofi.com
Scientific contact	Sanofi aventis recherche & développement, Trial Transparency Team, 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?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 March 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	19 December 2013
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate glycogen clearance in muscle tissue samples collected pre and post alglucosidase alfa treatment in subjects with Late-Onset Pompe disease.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency.

Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 July 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	United States: 9
Worldwide total number of subjects	16
EEA total number of subjects	7

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	13
From 65 to 84 years	3
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 11 centres between July 06, 2011 and December 19, 2013.

### Pre-assignment

Screening details:

A total of 20 subjects were screened and 16 subjects were enrolled.

### Period 1

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

### Arms

<b>Arm title</b>	Alglucosidase Alfa
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Arm description:

Alglucosidase alfa every other week for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Alglucosidase Alfa
Investigational medicinal product code	GZ419829
Other name	Myozyme®, Lumizyme®
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Alglucosidase alfa 20 mg/kg.

<b>Number of subjects in period 1</b>	Alglucosidase Alfa
Started	16
Full Analysis Set (FAS)	16
Completed	16

## Baseline characteristics

### Reporting groups

Reporting group title	Alglucosidase Alfa
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Reporting group description:

Alglucosidase alfa every other week for 24 weeks.

Reporting group values	Alglucosidase Alfa	Total	
Number of subjects	16	16	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	51.6		
standard deviation	± 13.69	-	
Gender categorical			
Units: Subjects			
Female	9	9	
Male	7	7	

## End points

### End points reporting groups

Reporting group title	Alglucosidase Alfa
Reporting group description: Alglucosidase alfa every other week for 24 weeks.	

### Primary: Change From Baseline in Tissue Glycogen Content in Quadriceps Muscle Biopsy Samples at Week 26

End point title	Change From Baseline in Tissue Glycogen Content in Quadriceps Muscle Biopsy Samples at Week 26 <sup>[1]</sup>
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End point description:

Tissue glycogen content was measured by quadriceps biopsies as 'percent area of tissue occupied by glycogen'. Analysis was carried out on full analysis set (FAS) population defined as all subjects who received at least one complete infusion of alglucosidase alfa. Here, n = number of subjects with both Baseline and Week 26 assessment of tissue glycogen content.

End point type	Primary
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End point timeframe:

Baseline, Week 26

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: Due to EudraCT format constraint, the statistical analysis could not be provided for single arm study.

End point values	Alglucosidase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: percent area occupied by glycogen				
arithmetic mean (standard deviation)				
Baseline (n=14)	5.3 (± 4.59)			
Change at Week 26 (n=13)	-1.6 (± 4.11)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Glycogen Distribution

End point title	Glycogen Distribution
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End point description:

End point type	Secondary
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End point timeframe:

Baseline, Week 26

<b>End point values</b>	Alglucosidase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[2]</sup>			
Units: subjects				

Notes:

[2] - No quantitative data could be reported for this outcome as the assessment was qualitative in nature.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Muscle Fiber Morphology

End point title	Muscle Fiber Morphology
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End point description:

End point type	Secondary
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End point timeframe:

Baseline, Week 26

<b>End point values</b>	Alglucosidase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[3]</sup>			
Units: subjects				

Notes:

[3] - No quantitative data could be reported for this outcome as the assessment was qualitative in nature.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Lysosomal Inclusions

End point title	Lysosomal Inclusions
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End point description:

End point type	Secondary
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End point timeframe:

Baseline, Week 26

<b>End point values</b>	Alglucosidase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[4]</sup>			
Units: subjects				

Notes:

[4] - No quantitative data could be reported for this outcome as the assessment was qualitative in nature.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change From Baseline in Muscle Involvement Using Mercuri Scoring at Week 26

End point title	Percent Change From Baseline in Muscle Involvement Using Mercuri Scoring at Week 26
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End point description:

Muscle involvement was assessed by T1-weighted magnetic resonance imaging (MRI). T1-weighted MRI data was analyzed using the Mercuri scoring in both legs (Total score = 1-4; where 1=Normal appearance, 2=Mild involvement, 3=Moderate involvement, and 4=Severe involvement). For each subjects, the average for each the upper (thigh) and lower leg was computed for Mercuri grading. Analysis was carried out on FAS population defined as all subjects who received at least one complete infusion of alglucosidase alfa. Here, Number of subjects analyzed= subjects with both Baseline and Week 26 assessment of muscle involvement, n= number of subjects with both Baseline and Week 26 assessment of muscle involvement for specified category.

End point type	Secondary
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End point timeframe:

Baseline, Week 26

<b>End point values</b>	Alglucosidase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: percent change				
arithmetic mean (standard deviation)				
Mercuri Scoring - Upper Leg (n=13)	2.6 (± 9.24)			
Mercuri Scoring - Lower Leg (n=14)	0 (± 0)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change From Baseline in Degree of Fatty Infiltration Using 3-Point 3-Dimensional (3D) Dixon at Week 26

End point title	Percent Change From Baseline in Degree of Fatty Infiltration Using 3-Point 3-Dimensional (3D) Dixon at Week 26
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End point description:

Degree of Fatty Infiltration was assessed by 3-point 3D Dixon acquisition using skeletal muscle MRI in a subset of subjects. Analysis was carried out on FAS population defined as all subjects who received at least one complete infusion of alglucosidase alfa. Here, number of subjects analyzed = number of



subjects with both Baseline and Week 26 assessment of degree of fatty infiltration.

End point type	Secondary
End point timeframe:	
Baseline, Week 26	

<b>End point values</b>	Alglucosidase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: percent change				
arithmetic mean (standard deviation)	2 ( $\pm$ 12.83)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change From Baseline in Disease Activity Using T2 Magnetic Resonance Imaging (MRI) at Week 26

End point title	Percent Change From Baseline in Disease Activity Using T2 Magnetic Resonance Imaging (MRI) at Week 26
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End point description:

Disease activity (inflammation and/or water content within muscles) was quantitatively assessed by T2 MRI values in a subset of subjects. A T2 MRI value of greater than ( $>$ ) 39 millisecond (ms) was defined as abnormal. T2 estimation normally requires an additional acquisition for computing the B1 spatial deviation however, can still be estimated if this acquisition is missing. Analysis was carried out on FAS population defined as all subjects who received at least one complete infusion of alglucosidase alfa. Here Number of subjects analyzed = number of subjects with both baseline and Week 26 assessment of disease activity.

End point type	Secondary
End point timeframe:	
Baseline, Week 26	

<b>End point values</b>	Alglucosidase Alfa			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: percent change				
arithmetic mean (standard deviation)				
T2 with B1	8.1 ( $\pm$ 14.19)			
T2 without B1	7.2 ( $\pm$ 13.58)			

### Statistical analyses



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From signature of the informed consent form up to the final visit (Week 26)

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), individual has been included in numerator of both AE tables. Analysis was performed on the safety population: all subjects who received any amount of aglucosidase alfa. AEs are listed independent of relationship to treatment.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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### Reporting groups

Reporting group title	Aglucosidase Alfa
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Reporting group description:

Aglucosidase alfa intravenous infusion 20 milligram per kilogram (mg/kg) every other week for 24 weeks.

Serious adverse events	Aglucosidase Alfa		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 16 (6.25%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Eye disorders			
Retinal Vascular Thrombosis			
subjects affected / exposed	1 / 16 (6.25%)		
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	Aglucosidase Alfa		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 16 (93.75%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic Naevus			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		

Vascular disorders Hypotension subjects affected / exposed occurrences (all)  Flushing subjects affected / exposed occurrences (all)  Peripheral Coldness subjects affected / exposed occurrences (all)  Thrombosis subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1  2 / 16 (12.50%) 2  1 / 16 (6.25%) 1  1 / 16 (6.25%) 1		
General disorders and administration site conditions Adverse Drug Reaction subjects affected / exposed occurrences (all)  Feeling Cold subjects affected / exposed occurrences (all)  Fatigue subjects affected / exposed occurrences (all)  Influenza Like Illness subjects affected / exposed occurrences (all)  Injection Site Extravasation subjects affected / exposed occurrences (all)  Malaise subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1  1 / 16 (6.25%) 1  2 / 16 (12.50%) 2  1 / 16 (6.25%) 1  1 / 16 (6.25%) 1  1 / 16 (6.25%) 1		
Reproductive system and breast disorders Epididymitis subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		

Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Nasal Congestion			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Oropharyngeal Pain			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Tachypnoea			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Pharyngeal Oedema			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Investigations			
Heart Rate Increased			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Arthropod Bite			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Ligament Sprain			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Procedural Pain			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	3		
Cardiac disorders			

Bradycardia subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	3 / 16 (18.75%) 3		
Muscle Contractions Involuntary subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Headache subjects affected / exposed occurrences (all)	4 / 16 (25.00%) 4		
Paraesthesia subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Sciatica subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Ear and labyrinth disorders Deafness subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Tympanic Membrane Perforation subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Eye disorders Ocular Hyperaemia subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Gastrointestinal disorders Abdominal Discomfort subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Diarrhoea subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2		

Vomiting subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Nausea subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Skin and subcutaneous tissue disorders			
Rash subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2		
Dry Skin subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Urticaria subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Musculoskeletal and connective tissue disorders			
Back Pain subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2		
Arthralgia subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2		
Myalgia subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Muscle Spasms subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Infections and infestations			
Bronchitis subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2		
Ear Infection subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		

Nasopharyngitis			
subjects affected / exposed	5 / 16 (31.25%)		
occurrences (all)	5		
Rhinitis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Subcutaneous Abscess			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Upper Respiratory Tract Infection			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 October 2010	<ul style="list-style-type: none"><li>- Six-minute Walk Test added to Study</li><li>- Post-treatment assessment visit added after Week 24</li><li>- Screening and baseline visit take place on separate days</li><li>- Metabolism and proteomics data to be reported separately from CSR</li><li>- Hand-held dynamometry changed from break technique to make technique</li></ul>
11 March 2011	<ul style="list-style-type: none"><li>- Removed 65 year-old limit for inclusion in Study</li><li>- Removed testing for cardiac hypertrophy</li><li>- Contraception requirement added</li><li>- Multiple techniques for muscle biopsy allowed</li><li>- Allow dose modification in case of AE</li></ul>
30 March 2012	Added electrical impedance myography (EIM) as an additional exploratory assessment at Screening/Baseline and Visits 6, 9, 12, and 15 at a selected subset of sites.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported