



## Clinical trial results:

### A Phase 3/4, Prospective, Multinational, Open-label, Noninferiority Study of Alglucosidase Alfa Manufactured at the 160 L and 4000 L Scales in Treatment Naïve Patients with Infantile-Onset Pompe Disease

#### Summary

EudraCT number	2011-005595-42
Trial protocol	DE
Global end of trial date	01 December 2014

#### Results information

Result version number	v2 (current)
This version publication date	17 July 2016
First version publication date	12 June 2015
Version creation reason	<ul style="list-style-type: none"><li>• Correction of full data set</li></ul> Clarification of analysis population descriptions for endpoints, of measure in endpoint analysis, and data in endpoints.

#### Trial information

##### Trial identification

Sponsor protocol code	AGLU07510/EFC12722
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01597596
WHO universal trial number (UTN)	-

Notes:

##### Sponsors

Sponsor organisation name	Genzyme Corporation
Sponsor organisation address	500 Kendall Street, 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	26 January 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	01 December 2014
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

The primary objective was to demonstrate the noninferiority of alglucosidase alfa produced at the 4000 L scale to the 160 L scale product in terms of the change from baseline of the left ventricular mass Z-score (LVM-Z) after 52 weeks of treatment.

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	21 August 2012
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: 1
Country: Number of subjects enrolled	United States: 3
Worldwide total number of subjects	4
EEA total number of subjects	1

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:

The study was conducted between 21 August 2012 and 1 December 2014.

### Pre-assignment

Screening details:

A total of 5 subjects were screened and 4 subjects were randomized and treated.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Alglucosidase Alfa 4000 L material (Non-US subjects)
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Arm description:

Alglucosidase alfa 4000 L material for 52 weeks.

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

Dosage and administration details:

20 mg/kg body weight every other week (qow).

<b>Arm title</b>	Alglucosidase Alfa 160 L material (US subjects)
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Arm description:

Alglucosidase alfa 160 L material for 52 weeks.

Arm type	Active comparator
Investigational medicinal product name	Alglucosidase Alfa
Investigational medicinal product code	
Other name	Myozyme
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

20 mg/kg body weight qow.

<b>Number of subjects in period 1</b>	Algucosidase Alfa 4000 L material (Non-US subjects)	Algucosidase Alfa 160 L material (US subjects)
Started	1	3
Treated	1	3
Completed	0	2
Not completed	1	1
Physician decision	-	1
Study Terminated by Sponsor	1	-

## Baseline characteristics

### Reporting groups

Reporting group title	Algucosidase Alfa 4000 L material (Non-US subjects)
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Reporting group description:

Algucosidase alfa 4000 L material for 52 weeks.

Reporting group title	Algucosidase Alfa 160 L material (US subjects)
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Reporting group description:

Algucosidase alfa 160 L material for 52 weeks.

Reporting group values	Algucosidase Alfa 4000 L material (Non-US subjects)	Algucosidase Alfa 160 L material (US subjects)	Total
Number of subjects	1	3	4
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	0.3 ± 0	0.5 ± 0.28	-
Gender categorical Units: Subjects			
Female	0	0	0
Male	1	3	4

## End points

### End points reporting groups

Reporting group title	Algucosidase Alfa 4000 L material (Non-US subjects)
Reporting group description: Algucosidase alfa 4000 L material for 52 weeks.	
Reporting group title	Algucosidase Alfa 160 L material (US subjects)
Reporting group description: Algucosidase alfa 160 L material for 52 weeks.	

### Primary: Change From Baseline in Cardiac Function at Week 52

End point title	Change From Baseline in Cardiac Function at Week 52 <sup>[1]</sup>
End point description: Cardiac function was measured by the left ventricular mass Z-score (LVM-Z). Z-Scores indicate the number of standard deviations (SD) from the mean in a normal distribution. A negative change from baseline indicates a decrease and positive change from baseline indicates an increase in LVM Z-score. The normal range is -2 to 2 and greater than 2 may indicate left ventricular hypertrophy. Analysis was carried out on full analysis population defined as all subjects who receive at least 1 infusion of algucosidase alfa.	
End point type	Primary
End point timeframe: Baseline, Week 52	

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: No statistical analyses for this end point

End point values	Algucosidase Alfa 4000 L material (Non-US subjects)	Algucosidase Alfa 160 L material (US subjects)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 <sup>[2]</sup>	2 <sup>[3]</sup>		
Units: Z Score				
arithmetic mean (standard deviation)	()	-5.06 (± 1.103)		

Notes:

[2] - For this endpoint no subjects were analyzed in this arm at Baseline, and Week 52

[3] - One subject in "Algucosidase Alfa 160 L Material" arm was discontinued from the study at Week 31.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects with Estimated Probability of Survival

End point title	Percentage of Subjects with Estimated Probability of Survival
End point description:	
End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Algucosidase Alfa 4000 L material (Non-US subjects)	Algucosidase Alfa 160 L material (US subjects)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	3		
Units: Percentage of Subjects				
number (not applicable)	100	100		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects with Invasive Ventilator-Free Survival

End point title	Number of Subjects with Invasive Ventilator-Free Survival
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End point description:

Invasive ventilator-free survival is defined as the time during which the subject is alive and not invasively ventilated. Analysis was carried out on full analysis population.

End point type	Secondary
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End point timeframe:

Up to Week 52

End point values	Algucosidase Alfa 4000 L material (Non-US subjects)	Algucosidase Alfa 160 L material (US subjects)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	3		
Units: Number of Subjects				
number (not applicable)	1	2		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Motor Development Status at Week 52

End point title	Change From Baseline in Motor Development Status at Week 52
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End point description:

Motor development status was assessed by the Gross Motor Function Measure - 88 Scale (GMFM-88) total percent scores. 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; walking, running and jumping. Each item was 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 was expressed as a percentage of the maximum score for that dimension. Total score ranges from 0% to 100%, where higher scores indicate better motor functions. Analysis was carried out on full analysis population.

End point type	Secondary
End point timeframe:	
Baseline, Week 52	

End point values	Algucosidase Alfa 4000 L material (Non-US subjects)	Algucosidase Alfa 160 L material (US subjects)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 <sup>[4]</sup>	2 <sup>[5]</sup>		
Units: percentage of maximum total score				
arithmetic mean (standard deviation)	()	48.65 (± 17.183)		

Notes:

[4] - For this endpoint no subjects were analyzed in this arm at Week 52.

[5] - One subject from "Algucosidase Alfa 160 L Material" arm was discontinued from study at Week 31.

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (Week 52) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported adverse events are treatment-emergent adverse events that is AEs that developed/worsened during the 'on treatment period' (the period from the first infusion date to the date that the last data were collected). Analysis was carried out on full analysis population.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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### Reporting groups

Reporting group title	Alglucosidase Alfa 160 L material (US subjects)
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Reporting group description:

Alglucosidase alfa 160 L material for 52 weeks.

Reporting group title	Alglucosidase Alfa 4000 L material (Non-US subjects)
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Reporting group description:

Alglucosidase alfa 4000 L material for 52 weeks.

Serious adverse events	Alglucosidase Alfa 160 L material (US subjects)	Alglucosidase Alfa 4000 L material (Non-US subjects)	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	0 / 1 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Cardiac disorders			
Cardiac Failure			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hypotonia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory Failure			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Oedema			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Adenovirus Infection			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar Pneumonia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis Media Acute			

subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Syncytial Virus Infection			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Alglucosidase Alfa 160 L material (US subjects)	Alglucosidase Alfa 4000 L material (Non-US subjects)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	1 / 1 (100.00%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Infusion Site Erythema			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Device Occlusion			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	3 / 3 (100.00%)	1 / 1 (100.00%)	
occurrences (all)	9	3	
Respiratory, thoracic and mediastinal disorders			
Aspiration			

subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Asthma			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Bronchial Secretion Retention			
subjects affected / exposed	0 / 3 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Nasal Congestion			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
Hypoxia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Pleural Effusion			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Respiratory Disorder			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Investigations			
Oxygen Saturation Decreased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Arthropod Bite			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			

Cardiac Failure subjects affected / exposed occurrences (all)	2 / 3 (66.67%) 2	0 / 1 (0.00%) 0	
Cardiac Failure Congestive subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 1 (0.00%) 0	
Cardiomyopathy subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 1 (0.00%) 0	
Nodal Rhythm subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 1 (0.00%) 0	
Nervous system disorders Nystagmus subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 1 (0.00%) 0	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 1 (0.00%) 0	
Ear and labyrinth disorders Middle Ear Effusion subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 1 (0.00%) 0	
Gastrointestinal disorders Abdominal Pain subjects affected / exposed occurrences (all)  Diarrhoea subjects affected / exposed occurrences (all)  Vomiting subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0  1 / 3 (33.33%) 1  1 / 3 (33.33%) 4	1 / 1 (100.00%) 1  0 / 1 (0.00%) 0  0 / 1 (0.00%) 0	
Skin and subcutaneous tissue disorders Dermatitis Contact			

subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Dermatitis Diaper			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Rash Erythematous			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Rash Pruritic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Urticaria			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Muscle Contracture			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Croup Infectious			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Eye Infection			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Fungal Infection			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Pneumonia			

subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Urinary Tract Infection			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 January 2012	<p>This protocol amendment includes 2 major changes that substantially affect the inclusion criteria for participation in this study. The upper limit of age at the time of the first study infusion was increased from 6 months to 12 months. In addition, the requirement that a subject must have an left ventricular mass index Z-score (LVMI-Z) of greater than 2 was removed.</p> <p>Protocol Synopsis and Abbreviations: Updated to reflect overall changes in protocol.</p> <p>Number of Subjects: expanded the subject population to include subjects without cardiac hypertrophy who met the inclusion criteria. Revised secondary objectives to reflect addition of Alberta Infant Motor Scale (AIMS) for evaluation of changes in motor function in response to enzyme replacement therapy (ERT) over time.</p> <p>Revised tertiary efficacy endpoints to include AIMS as the most appropriate endpoint to assess subjects without cardiac hypertrophy. Assessment was moved from Demographic and Screening Assessments to Efficacy Assessments.</p> <p>Respiratory Function: Updated for clarification. If the subject required mechanical ventilatory support during the study, the start date, stop date, and reasons for each episode of continuous ventilator support would be recorded on the electronic case report form (eCRF) by authorized site personnel.</p> <p>Determination of Sample Size: Updated for clarity.</p> <p>Secondary Efficacy Analyses: Updated for clarity.</p> <p>Schedule of Study Events: Added assessment of AIMS at Week 12, Week 26, and Week 52 as AIMS was the most appropriate endpoint to assess subjects without cardiac hypertrophy.</p>
11 October 2012	<p>This protocol amendment includes 1 major change to the planned analysis of this study. The primary endpoint of this study was change from baseline in cardiac function as measured by left ventricular mass Z-score (LVM-Z) assessed at the end of the 52-week treatment period.</p> <p>- Changed protocol descriptor and protocol title. - Added date of Protocol Amendment 2. - Added Genzyme Europe BV as Sponsor. - Updated Medical Monitor information. - Changed "Global Patient Safety and Risk Management" to "Global Pharmacovigilance and Epidemiology" to reflect recent department name change.- Changed primary objective to indicate that the primary efficacy endpoint was change in left ventricular mass Z-score (LVM-Z) from baseline to Week 52.- Changed all instances of "LVMI-Z" to "LVM-Z" to reflect change in primary efficacy endpoint. - Updated Abbreviations section to add "confidence interval", "Global Pharmacovigilance and Epidemiology" and "noninferiority" and to remove "Global Patient Safety and Risk Management".- Added text to describe Phase 3 or Phase 4 protocol dependent upon country registration status.- Added text to indicate blood testing for cross-reactive immunologic material (CRIM) status was optional and did not had to be repeated if written results were available for testing performed prior to study enrollment.- Amended text to indicate R voltage V6 and S voltage V1 were not required assessments.- Added Sections to provide definitions for "Anaphylactic / Hypersensitivity Reactions" and "Immune Mediated Reactions", respectively. - Revised statistical parameters to correspond with LVM values from Genzyme study AGLU01602/2403.- Revised text to indicate change in analysis planned for clinical laboratory assessments.- Removed stipulation that Data Monitoring Committee be comprised of 4 physicians. Removed Sponsor contact information for Europe as all product handling is now provided by North America office.</p>

Notes:

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## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

None reported