



## 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 |
|-----------------------|--------------------|

##### 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 |
|------------------------------|-----|

|                  |  |
|------------------|--|
| <b>Arm title</b> | Alglucosidase Alfa 4000 L material (Non-US subjects) |
|------------------|--|

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) |
|------------------|---|

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<br>4000 L material<br>(Non-US subjects) | Algucosidase Alfa<br>160 L material (US<br>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) |
|-----------------------|---|

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.

| 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<br>Units: Subjects                                      |   |  |       |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 0.3<br>± 0  | 0.5<br>± 0.28                                  | -     |
| Gender categorical<br>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:<br>Algucosidase alfa 4000 L material for 52 weeks. |   |
| Reporting group title   | Algucosidase Alfa 160 L material (US subjects)      |
| Reporting group description:<br>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:<br>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:<br>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 |
|-----------------|---|

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 |
|----------------|-----------|

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 |
|-----------------|---|

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                         | Alglucosidase Alfa 4000 L material (Non-US subjects) | Alglucosidase 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 "Alglucosidase 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 |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

### Reporting groups

|                       |   |
|-----------------------|---|
| Reporting group title | Alglucosidase Alfa 160 L material (US subjects) |
|-----------------------|---|

Reporting group description:

Alglucosidase alfa 160 L material for 52 weeks.

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

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<br>160 L material (US<br>subjects) | Alglucosidase Alfa<br>4000 L material<br>(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<br>subjects affected / exposed<br>occurrences (all)   | 2 / 3 (66.67%)<br>2  | 0 / 1 (0.00%)<br>0   |  |
| Cardiac Failure Congestive<br>subjects affected / exposed<br>occurrences (all)  | 1 / 3 (33.33%)<br>1  | 0 / 1 (0.00%)<br>0   |  |
| Cardiomyopathy<br>subjects affected / exposed<br>occurrences (all)  | 1 / 3 (33.33%)<br>1  | 0 / 1 (0.00%)<br>0   |  |
| Nodal Rhythm<br>subjects affected / exposed<br>occurrences (all)  | 1 / 3 (33.33%)<br>1  | 0 / 1 (0.00%)<br>0   |  |
| Nervous system disorders<br>Nystagmus<br>subjects affected / exposed<br>occurrences (all)   | 1 / 3 (33.33%)<br>1  | 0 / 1 (0.00%)<br>0   |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)   | 1 / 3 (33.33%)<br>1  | 0 / 1 (0.00%)<br>0   |  |
| Ear and labyrinth disorders<br>Middle Ear Effusion<br>subjects affected / exposed<br>occurrences (all)  | 1 / 3 (33.33%)<br>1  | 0 / 1 (0.00%)<br>0   |  |
| Gastrointestinal disorders<br>Abdominal Pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Vomiting<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0<br><br>1 / 3 (33.33%)<br>1<br><br>1 / 3 (33.33%)<br>4 | 1 / 1 (100.00%)<br>1<br><br>0 / 1 (0.00%)<br>0<br><br>0 / 1 (0.00%)<br>0 |  |
| Skin and subcutaneous tissue disorders<br>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