21 November 2013
EMA/26435/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Myozyme

International non-proprietary name: alglucosidase alfa

Procedure No. EMEA/H/C/000636/II/0041

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Genzyme Europe BV submitted to the European Medicines Agency on 31 December 2012 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Myozyme	alglucosidase alfa	See Annex A

The following variation was requested:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH proposed the update of section 4.1 and 5.1 of the SmPC in order to include relevant clinical data from several clinical trials and from other analyses of late-onset Pompe disease patients treated with Myozyme. The Package Leaflet was proposed to be updated accordingly. Also, several small linguistic corrections were proposed for product information annexes of certain languages.

In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 9.0.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.

Rapporteur: Pierre Demolis

1.2. Steps taken for the assessment

Submission date:	31 December 2012
Start of procedure:	25 January 2013
Rapporteur's preliminary assessment report circulated on:	20 March 2013
Rapporteur's updated assessment report circulated on:	19 April 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	25 April 2013
MAH's responses submitted to the CHMP on:	19 June 2013
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	04 July 2013
Rapporteur's updated assessment report on the MAH's responses circulated on:	19 July 2013
2nd request for supplementary information and	25 July 2013

extension of timetable adopted by the CHMP on:	
MAH's responses submitted to the CHMP on:	23 September 2013
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	08 October 2013
Rapporteur's updated assessment report on the MAH's responses circulated on:	18 October 2013
3rd request for supplementary information and extension of timetable adopted by the CHMP on:	24 October 2013
MAH's responses submitted to the CHMP on:	30 October 2013
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	07 November 2013
Rapporteur's final assessment report on the MAH's responses circulated on:	14 November 2013
CHMP opinion:	21 November 2013

2. Scientific discussion

2.1. Introduction

The absence, or almost complete absence, of acid α-glucosidase (GAA) in Pompe disease patients leads to the accumulation of high levels of glycogen particularly in cardiac, skeletal, and respiratory muscles, which leads to generalised myopathy, cardiomyopathy and respiratory failure. The clinical presentation of Pompe disease includes a range of phenotypes featuring different ages at onset, degrees of organ involvement, and rates of progression. The most severe form of the disease is the classical infantile-onset form, which presents early in life and is mainly characterized by cardiomegaly. Late-onset Pompe disease (LOPD), on the other hand, typically manifests with absence of noticeable cardiomegaly and normally has an age onset at ≥ 2 years. The aetiology of the classical infantile- and late-onset forms is identical; however the activity of the GAA enzyme measured in the blood differs: classical infantile-onset Pompe disease presents with almost no residual enzyme activity and death occurs within the first 2 years of life. LOPD manifests in children as well as in juvenile and adult patients. The older age at onset, lack of cardiac involvement and slower and heterogeneous progression distinguish LOPD from the classical infantile-onset phenotype.

In children, juveniles, and adults with LOPD, disease severity increases with disease duration. As the disease progresses, the symptoms become more evident, with increasing proximal muscle weakness and respiratory insufficiency being the most common signs. The resulting difficulties in motor functions and respiratory distress lead to increased wheelchair dependency and requirement for ventilation support. In addition, earlier onset of disease among children leads to a more severe and more rapidly progressive disease. Life expectancy in LOPD patients varies: in patients with the juvenile phenotype, death often occurs before the end of the third decade. In adult-onset LOPD patients, the mortality rates were higher compared with the general population and the level of disability and handicap most heavily influenced mortality. In general, respiratory failure is often the main cause of death in patients with LOPD.

Myozyme is a recombinant human acid alpha-glucosidase (rhGAA), which aims to restore lysosomal GAA activity resulting in stabilisation or restoration of cardiac and skeletal muscle (including muscles of the respiratory system). On 29 March 2006 the European Commission granted a Marketing Authorisation for Myozyme (alglucosidase alfa, EU/1/06/333/001-003) for patients of all ages with a confirmed diagnosis of Pompe disease (acid α-glucosidase deficiency). The indication section of the SmPC also stated that the benefits of Myozyme in patients with late-onset Pompe disease have not been established. Subsequently, in 2009, this statement was amended via variation to the MA to inform the prescriber that in patients with late-onset Pompe disease the evidence of efficacy is limited.

In the current variation, the MAH proposed to update section 5.1 of the SmPC with the efficacy and safety information in late-onset Pompe patients. Consequently, a deletion of the above discussed sentence from section 4.1 that the evidence of efficacy is limited in patients with late-onset Pompe disease was proposed.

The application is based on the results of:

Two observational studies about evolution of severe late-onset disease patients treated by Myozyme:
- Clinical Study Report (Pompe Phys 01 and 02) based on the analysis of interim data collected in the ongoing follow-up studies "Effects and Health Economic Aspects of Enzyme Therapy in Children and Adults with Pompe Disease" (Phys 02) and "Natural course, disease severity and supportive care in non-classic Pompe's disease (Phys 01)"
- Clinical study Report AGLU 4107: Observational study about the evolution of severe late-onset disease patients with pulmonary dysfunction and Myozyme.

A post-hoc analysis on ventilation data from study AGLU02704: A Randomized, Double-Blind, Multicenter, Multinational, Placebo-Controlled Study of The Safety, Efficacy, And Pharmacokinetics of Myozyme, Recombinant Human Acid Alpha-Glucosidase (rhGAA), Treatment in Patients With Late-Onset Pompe Disease.

Supportive data consisted of:

- a manuscript for publication by D. Güngör (2012): Impact of enzyme replacement therapy on survival in adults with Pompe's disease: results from a prospective international observational study;

- a publication by Regnery (2012): 36 months observational clinical study of 38 adult Pompe disease patients under alglucosidase alfa enzyme replacement therapy (Regnery et al, J Inherit Metab Dis 2012);

- a publication by Angelini (2011): Observational clinical study in juvenile-adult glycogenosis type 2 patients undergoing enzyme replacement therapy for up to 4 years (Angelini et al J Neurol 2011);

- a systematic review of clinical outcomes of alglucosidase alfa in the treatment of late-onset Pompe Disease.

- a literature analysis on the clinical relevance of the outcome measures used in Pompe Disease. (Lachmann-Schoser, 2013, Orphannet J Rare Dis)

- international observational survey" Enzyme replacement therapy and fatigue in adults with Pompe disease (Güngör, 2013, Mol Genet Metab)

- the Rasch-built Pompe-specific Activity (R-PAct) scale (van der Beek, 2013, Neuromuscul Disord)

2.2. Clinical Efficacy aspects

2.2.1. Methods – analysis of data submitted

Evaluation criteria for Pompe Disease

- Muscle strength

Medical Research Council Score (MRC)
Muscle strength was determined by Manual Muscle Testing using the MRC grading scale. Muscle strength was graded from 0 to 5 by physical examination, in which grade 5 represents normal muscle strength and grade 0 paralysis of the muscle group tested. Twenty-six muscle groups were tested (neck extensors, neck flexors, bilateral shoulder abductors, shoulder adductors, elbow flexors, elbow extensors, hip flexors, hip abductors, hip extensors, and hip adductors, knee flexors, and knee extensors, exorotators and endorotators). An MRC sum score was derived by adding the grades for all the 26 muscle groups and expressing the sum as a percentage of the maximum possible score. If values for three or more muscle groups were missing, no sums cores were calculated.

Hand-held Dynamometry (HHD)

A quantitative muscle testing was also used to determine muscle strength. Sixteen muscle groups were tested (neck extensors, neck flexors, bilateral shoulder abductors, elbow flexors, elbow extensors, hip flexors, hip abductors, knee flexors, and knee extensors). The individual HHD values of each muscle group were first expressed as a percentage of normal strength using as a cut-off the median strength of healthy adults individuals based on gender. The HHD sum score is calculated as the average percentage of all the 16 muscle groups.

Manual muscle testing (MMT)
The MMT is an evaluation of muscle strength to determine the ability of a muscle or group of muscles, to perform a movement and to ensure stability and strength.

Quantitative Muscle Testing (QMT)
QMT is designed to measure muscle strength developed during isometric contraction and assesses muscle weakness in patients with neuromuscular disorders.

- Muscle function

Quick Motor Function Test [QMFT]
To evaluate the function of the muscle groups that are specifically affected in patients with Pompe disease, a 16-item functional test has been developed (QMFT). The patient is asked to perform several activities related to daily activities in supine, sitting and standing position. These activities require the use of muscles of the shoulder girdle, trunk, pelvic girdle and/or proximal lower limbs. Each item was scored on a 5-point ordinal scale, with 0 representing 'cannot per-form task' and 4 'can perform task with no effort'. Adding all items gives a total score between 0 and 64. The actual sum score is expressed as a percentage of the maximum score.

Walton & Gardner-Medwin (WGM) scale
The Walton scale is a generic clinical evaluation tool used to evaluate a change in functional state and was adapted to produce an 11-point ordinal scale. The scale essentially evaluates weakness.

Brooke and Vignos test
Arm function evaluation test (Brooke): Patients were to hold their arms out straight, the palms of the hands facing one another. One of the arm function scores featuring is awarded according to the maximum activity they were capable of accomplishing.

Leg function evaluation test (Vignos): The Vignos test evaluates leg function. Patients should be able to perform actions and a score is allocated according to maximum activity they were able to accomplish.

Motor function measurement (MFM) scale
This clinical tool is used to measure the motor possibilities of patients with neuromuscular diseases such as Pompe disease. Three dimensions are explored, regrouping the items in sub-groups during measurements carried out in the standing, sitting and supine positions.

10-metre walking test
For this test, the patient has to prepare to walk a distance of 10 metres (30 feet) in a corridor or on a walkway. The distance is timed from the moment the patient began to walk until the 10- metre walk was complete.

Climbing stairs
The evaluation covered climbing of four standard steps. For this test, the patient is to stand at the foot of the central part of the first step, then climb four stairs without holding onto the handrail; they were then to stop and stand with their arms by their side.

Six-Minute Walk Test (6 MWT)
This test measures the distance patients can walk at their own pace along a flat, hard surface in a period of 6 minutes.

- Pulmonary function

Forced vital capacity (FVC)
This was a measure of respiratory muscle weakness and the strength of the diaphragm according to ATS/ERS standards. Patients were tested in upright seated and supine position.

Three repeated flow volume curves are made and the maximum value of the three reproducible tests was used for analysis. Results were expressed as a percentage of the predicted normal value.

Dyspnoea Borg scale
The Borg scale is the combination of a scale of verbal categories and a numeric scale. This scale is used to measure the effort during an exercise by a scale easily understood by the subjects and enabling comparison between individuals.

Dyspnoea VAS
Dyspnoea is measured by the patient themselves using an analogue scale. The subject is to evaluate the intensity of their dyspnoea by indicating a point on the line, from 0- 10, after 20 minutes without ventilation.

Maximum static pressure: Pimax and Pemax
Maximal inspiratory static pressure (Pimax) and expiratory (Pemax) pressure produced by a subject are clues to evaluating the inspiratory and expiratory strength of the respiratory muscles.

Transdiaphragmatic pressure (Pdi)
Transdiaphragmatic pressure (Pdi) is defined as the difference between pleural pressure (Ppl) and abdominal pressure (Pab) and, in practice, is generally measured as the difference between gastric pressure (Pga) and oesophageal pressure (Poes). It makes it possible to assess the quality of the mechanical coupling between the diaphragm and the passive respiratory system and to titer inspiratory assistance.

Transdiaphragmatic pressure (Pdi) with cervical magnetic stimulation
Magnetic stimulation of the cervical spine produces bilateral contraction of the diaphragm. The reel is centred above the spine of vertebra of the 7th cervical vertebra. Cervical magnetic stimulation stimulates nerve elements, leading to the contraction of various neck muscles and of the upper chest, and this in a concomitant manner to contraction of the diaphragm.

- Quality of life

Fatigue severity scale (FSS)
The FSS is a self-administered questionnaire and comprises 9 answers for evaluating the severity of fatigue felt when carrying out daily activities. The FSS is based on a score from 1-7; 1 means that the subject totally disagrees with the proposal and 7 which means they totally agree with the proposal. Clinical improvement in fatigue is shown by a reduction in the total FSS score.

SF-36 quality of life scale
The SF-36 (Short Form Health Survey) is a self-questionnaire for evaluating the quality of life relating to the state of health of healthy or sick adult subjects. It contains 36 items organised into 8 areas evaluating physical activity, limitations due to physical condition, physical pain, and mental health, limitations due to mental condition, social activity, vitality and general state of health. The SF-36 also contains two summary measures of physical health and a mental health component derived from scale aggregates.

2.2.2. Results

Main results
The two main outcome measures used in patients with late-onset Pompe disease are the 6-minutes walking test (6 MWT) and the percentage of predicted forced vital capacity (% predicted FVC) as they reflect altered muscle function and pulmonary capacity. The MAH made a literature analysis to determine the clinical relevance of 6MWT and FVC in patients with compromised physical functional capacity, and apply these findings to patients with late-onset Pompe disease. Overall, 19 publications discussed the clinical relevance of absolute changes and percentage change from baseline in 6 MWT results. In the different studies, a change of 25 to 50 m (representing 10 to 15% change from baseline) represented a clinically relevant effect for the patient. In patients with chronic lung disease, a 10% improvement or decline from absolute FVC values at baseline has been identified as the level of change required to indicate valid variation in disease severity as opposed to measurement fluctuation for lung disease (ATS/ERS guidelines 2002).
The CHMP noted that due to the lack of published data in Pompe disease, this estimation was made using data in other diseases (e.g. chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis).

These extrapolations may be flawed considering that comparator diseases used in this analysis are characterized by respiratory components only, while Pompe disease has both respiratory/diaphragm and skeletal muscle components of pathophysiology.

6 MWT
The 6MWT has been assessed in two published observational studies: Angelini 2011 and Regnery 2012.
In Angelini 2011, the 6 MWT was assessed in 58 patients: it increased in average 63 m (19 % from the baseline). In Regnery 2012, the 6 MWT was assessed in 21 patients: it increased in average 32 m (10 % from the baseline) at M12, was stable at M24 and decreased between M24 and M36 in average 39 m (8%).

FVC %
The FVC was assessed in the PHYS 01-02 and AGLU 04107 studies and in Regnery 2012 and Angelini 2011 publications. In the PHYS 01-02 study, FVC in upright position evaluated in 46 patients remained stable (+ 0.1% per year; p=0.92) and the FCV in decline position evaluated in 42 patients declined (-1.1% per year ; p=0.03).

In the AGLU 04107 study, due to the low initial Vital Capacity values in the 8 studied patients, FVC was not measured, only Slow Vital Capacity was measured. The SVC (as percentage of the theoretical values) in upright position between D0 and M24 decreased in average -4.63$\pm$10.58 and the SVC (as percentage of the theoretical values) in supine position between D0 and M24 increased in average 1.13$\pm$4.16.

In Angelini 2011, the mean FVC% was performed for 69 patients and remained stable (65.2$\pm$26.5 to 66.5$\pm$26.6 p=0.22) during treatment. In Regnery 2012, the mean FVC% was performed for 28 patients. After 36 months, the result was a mean decrease of 3.08% of FVC% (p=ns)

Supportive results

Muscle strength
MRC
In PHYS 01-02, MRC increased in average 1.4% (95%CI 0.8 to 2.1) per year during ERT (N=69); p < 0.001 in the overall population. In patients with pre-ERT and ERT data (N=49), MRC rose by an average of 2.1% (95%CI 1.2 to 3.0) per year during ERT while declined by 1.2 % (95%CI -2.1 to 0.4) per year before ERT. In Regnery 2012, the mean MRC sum score remained stable from 42.29±8.49 at baseline, 41.92± 8.62 at M12, 43.89±5.16 at M24, and 41.19±7.61 after M 36 of ERT (all p = n.s.)

HHD
In PHYS 01-02, HHD increased in average 4.0% (95%CI 2.5 to 5.6) per year during ERT (N=64); p < 0.001 in the overall population and rose by an average of 5.1% (95%CI 2.5 to 5.6) per year during ERT in patients with pre-ET and ERT data (N=42) while declined by 4.8 % (95%CI -4.2 to -1.3) per year before ERT.

Quick Motor Function Test [QMFT]
In PHYS 01-02, QMFT increase in average 0.7% per year during ERT (N=69 - NS); p=0.14. No comparison with pre-treatment data was performed.

Walton & Gardner-Medwin (WGM) Brooke and Vignos scale
In AGLU 04107 (N=7) a one point improvement was observed in 2 patients and remained unchanged in 5 patients. In Angelini 2011 (N=68) the score remained unchanged during treatment. In Regnery 2012 (N= 38) the mean WGMS at base line was 4.45 $\pm$2.1 and remained stable.

Motor function measurement (MFM) scale
In AGLU 04107 (N=7) the scale increased from 4 to 8% in 5 patients, remained stable in 1 patient and decreased by 2% in 1 patient.

10-metre walking test
In AGLU 04107 (N=5) at 24 months, 2 patients improved their performance (3 and 1 seconds) and 2 reduced their performance (2 and 6 seconds). Another patient improved his performance (4 seconds) between D0 and M12.

Climbing stairs (4 steps)

In AGLU 04107 (N=4), 24 months, 2 patients improved their performance (1 and 4 seconds) and 2 reduced their performance (1 and 6 seconds).

Fatigue severity scale (FSS)
In AGLU 04107 (N=7), at M 24 fatigue had reduced in 5 patients (from -4% to -20%).

SF-36 quality of life scale
In AGLU 04107 (N=8) at M12 (3 patients) or M24 (5 patients), the overall physical component score improved by 0.9 to 11.9 points, mildly decreased for 2 patients (0.5 and 2.1 points respectively) and significantly reduced for 1 patient by 18.9. In Regnery 2012, SF-36 did not change on a group or individual basis from baseline to month 36 of ERT (all p = n.s.).

Dyspnoea Borg scale
In AGLU 04107, the mean score remained stable in the sitting position (N=7), but gained 2 points in the supine position (N=6), improving from a "severe" degree of dyspnoea (Borg score 5) at D0 to a "moderate" degree of dyspnoea (Borg score 3) at M24.

Time without assisted ventilation
In AGLU 04107, among patients in invasive assisted ventilation, 3 decreased their ventilation time by 1 hour between D0 and M24 (24hrs to 23hrs and 12hrs to 11hrs) and 1 stayed stable (24hrs/24). Among the 5 patients in non-invasive assisted ventilation, 1 reduced his ventilation time by 1 hour, 1 stayed stable and 2 increased their ventilation time (15 minutes and 2hrs). In AGLU02704, after 78 weeks of treatment, in patients who reported the use of NIV at baseline, the mean number of hours per day of treatment, the mean number of hours on NIV per day increased in both groups; by 0.27 ± 2 hours in the Myozyme treatment group (N=20) and 1.3 ± 2 hours in the placebo group (N=11) (p=0.0474).

The above described results from the various data sources are presented in the tabulated format:

Clinical trials

Study Title	Design	Dose,regimen	Criteria	Outcome
"Effects and Health Economic Aspects of Enzyme Therapy in Children and Adults with Pompe Disease" (Phys 02) and "Natural course, disease severity and supportive care in non-classic Pompe's disease (Phys 01)"	observational investigator-driven, open-label, single-centre. 69 adults with late-onset Pompe disease (of whom 49 patients with pre-treatment and treatment data) 13 infants with classic infantile Pompe disease. 16 children with non-classic Pompe disease.	Alglucosidase alfa: 20 mg/kg IV every other week Patients treated for a minimum of 5 months Treatment duration: Median 23 months (range 0.4-3.9 years)	Medical Research Council Score (MRC) Hand-held Dynamometry (HHD) Quick Motor Function Test (QMFT) %Forced vital capacity (FVC)	**MRC** During ERT **(N=69):** ↗ Average 1.4% per year (p<0.001) Patients with pre-treatment data(N = 49) : Before ERT ↘ 1.2% per year (p=0.006) During ERT ↗ 2.1% per year (p<0.001) Before ERT vs ERT ↗ 3.3% per year (p<0.001) **HHD (N = 64):** During ERT ↗ 4.0% per year (p<0.001) Patients with pre-treatment data(N = 42): Before ERT ↘ 2.8% per year (p<0.001) During ERT ↗ 5.1% per year (p<0.001) Before ERT vs ERT ↗ 7.9% per year (p<0.001) **QMFT (N=69)** During ERT ↗ 0.7% per year (p=0.14 ns) **FVC Upright position** (N=62) During ERT annual change of 0.1% per year, p = 0.92 Patients with pre-treatment data(N = 49): Before ERT ↘ 2.0% per year (p=0.001) During ERT ↘ 0.2% per year (p=0.76)

Study Title	Design	Dose,regimen	Criteria	Outcome
				Before ERT vs ERT ↗ 1.8% per year (p=0.08) **FVC% Supine position** (N=54) During ER↘ 1.1% per year (p=0.03) Patients with pre-treatment data(N = 42): Before ERT ↘ 1.8% per year (p=0.002) During ERT ↘ 1.0% per year (p=0.12) Before ERT vs ERT ↗ 0.8% per year (p=0.38)

AGLU 04107 : Observational Study about the Evolution of severe late on-set Pompe disease Patients with pulmonary dysfunction and receiving Myozyme	observational, open-label, single-centre 8 patients included	Alglucosidase alfa: 20 mg/kg every other week Patients treated for a minimum of 6 months at initiation Treatment duration: 24 months	Manual muscle testing (MMT) Motor function measurement (MFM) scale Quantitative Muscle Testing (QMT) test Brooke, Vignos and Walton & Gardner-Medwin scale 10-metre walking test Climbing stairs (4 stairs) Slow Vital capacity (VC) Dyspnoea Borg scale Maximum static pressure: Pimax and Pemax Transdiaphragmatic pressure (Pdi) Transdiaphragmatic pressure (Pdi) with cervical magnetic stimulation Assisted ventilation time Muscle MRI scan SF-36 quality of life scale Fatigue severity scale (FSS)	**MMT** Could not be calculated **MFM (N=7)**: ↗ (4 to 8%) N=5 Stable N=1 ↘ (2%) N=1 **QMT (N=7):** Absolute delta Do/last evaluation (Mean + - SD) Upper limb/ right: ↘ 2.2± 7.7 Upper limb/ left: ↘ 1.0± 3.3 Lower limb/ right :↘ 3.9± 6.3 Lower limb/ left: 0± 0.8 **Brooke, Vignos and Walton & Gardner-Medwin scale**: ↗ (1 point) N=2 Unchanged N = 5 **10 m walking test** (N=5): ↗ N=2 Stable N = 1 ↘ N = 2 **Climbing stairs (N=4)** ↗ N=2 ↘ N = 2 **SVC** *Sitting position (N=7)* ↗ N=3 Stable N = 1 ↘ N = 3 *Supine position (N=7)* ↗ N=4 Stable N = 2 ↘ N = 1 **Inspiratory capacity** ↗ N=5 ↘ N = 2 **Expiratory capacity** ↗ N=4 ↘ N = 2 **Daily assisted ventilation time** ↘ (1 hour) N=3 Stable N = 2 ↗ (15min and 2 hours) N = 2 **Dyspnoea Borg scale** Absolute delta Do/last evaluation (Mean + - SD) Sitting position (N=7)-0.64±2.46 (stable) Supine position (N=6): -3.00±3.16 ↘ severity : N=3 ↗ severity : N=2 **Muscle imaging (N=3):** data varied little **SF-36 quality of life scale (N=8)** ↗ N=5 ↘ N = 3 **Fatigue severity scale (FSS) (N=7)** ↘ (-4 to -20%)N = 5

Effect of treatment upon the change in the daily use in hours of NIV : Post-hoc analysis on ventilation data from study AGLU02704: A Randomized, Double-Blind, Multicenter, Multinational, Placebo-Controlled Study of The Safety, Efficacy, And Pharmacokinetics of Myozyme, Treatment in Patients With Late-Onset Pompe Disease	post-hoc analysis	Alglucosidase alfa: 20 mg/kg every other week N=60 Placebo N=30 Treatment duration: 78 weeks	Presence or absence of NIV and, if present, the number of hours of NIV Start of Non-invasive Ventilation During the Study	**Time on Non-invasive Ventilation** All population: Alglucosidase alfa (N=60) : ↗ 0.07 ± 1.7 hours Placebo (N=30): ↗ 0.88 ± 2.1h (*p=0.0474)* Patient under NIV at baseline Alglucosidase alfa (N=18): ↘ 0.27 ± 2.5 h Placebo (N=11): ↗ 1.3 ± 2.3 h *(Ns p=0.1033)* **Start of NIV** Alglucosidase alfa : 3 patients (5%) Placebo : 4 patients (13.3%)

Published data

Title	Design	Dose, regimen	Criteria	Outcome
Impact of enzyme replacement therapy on survival in adults with Pompe's disease: results from a prospective international observational study**.** D Güngör et al, (2012) *submitted for publication*	Observational study conducted between 2002 and 2011	Alglucosidase alfa: 20 mg/kg every other week N= 204 No treatment: N= 79 Follow up : median: 6 years; range, 0.04 to 9 years	Survival	**Mortality** (Intent to treat): HR of 0.51 (95% CI, 0.24 to 1.10) ERT as a time-dependent covariate HR of 0.41 (IC95% 0.19 to 0.87) after adjustment for age, sex, country of residence, and disease severity **Mortality** (excluding person-time after discontinuation of ERT) HR of 0.42 (IC95% 0.19 to 0.93) ERT as a time-dependent covariate HR of 0.33 (IC95% 0.15 to 0.73) after adjustment for age, sex, country of residence, and disease severity
Observational clinical study in juvenile-adult glycogenosis type 2 patients undergoing enzyme replacement therapy for up to 4 years. C Angelini et al, *J Neurol (2011)*	open-label observational study of Italian patients with late onset Pompe disease	Alglucosidase alfa: 20 mg/kg every other week N= 74 ERT duration Group A: 12-23 months Group B: 24-35 months Group C: over 36 months	Six minute walk test Walton and Gardner-Medwin scale Predicted forced vital capacity (FVC%) Body mass index	**Six minute walk test (N=58)** Mean ↗ 320 ± 161 m to 383 ± 178 m *(p< 0.0001)* Delta = 63 m No difference between duration groups **Predicted forced vital capacity** No difference to baseline **Walton and Gardner-Medwin scale (N= 68)** No significant changes (*p = 0.22)* Improvement N=18 Stable N = 42 Decreased N = 8 **Body mass index (N=47)** No significant changes
36 months observational clinical study of 38 adult Pompe disease patients under alglucosidase alfa enzyme replacement therapy C Regnery et al *J Inherit Metab Dis (2012)*	open-label, investigator initiate observational trial of German patients over 36 months treatment period.	Alglucosidase alfa: 20 mg/kg every other week N = 38 Treatment duration: 36 months	Walton Gardner Medwin Scale (WGMS) Arm function test (AFT) Timed function tests: 10-meter walk test,	**Walton Gardner Medwin Score** :no significant changes *p ns* **AFT:** no significant changes *p = ns* **MRC sum score:** no significant changes *p = ns* **Timed function tests :** no significant changes *p = ns*

Title	Design	Dose, regimen	Criteria	Outcome
			a 4-stair climb, 6 minute walk test Medical Research Council (MRC) grading scale Predicted forced vital capacity (FVC) SF-36	**6-minute walk test (N=21)** Mean walking distance ↗ at M12 (*p = 0.006*) Stable at M24 (*p=0.033*) ↘ at M36 (*p=0.49ns*) **Pulmonary function test:** no significant changes *p = ns* **SF-36**: no significant changes *p = ns*

Systematic overview

A systematic overview of randomised controlled trials, cohort studies, comparative studies with historical controls, single-arm studies, case series, and observational studies were also provided. Treated and untreated patient were included.

Clinical studies on natural course of untreated LOPD

Reference	Trial design	Trial location(s)	Sites (N)	Research type		Patients (N)	Follow-up duration
				Genzyme-sponsored	Academic		
Clinical trials							
Van der Ploeg, 2010	Randomized Double-blind Placebo-controlled Multicentre	Australia Canada France Germany Netherlands US	22	☑		90*	78 weeks
Observational studies							
Güngör, 2011	Observational Multicentre	NR	NR		☑†	268	Median: 3.5 years Maximum: 7 years (78% pts followed for ≥ 2 years, 62% for ≥ 3 years)
Van der Beek, 2011	Observational Prospective Single-centre	Netherlands	1		☑	92	Median: 1.6 years (range, 0.5–4.2 years)
Van der Beek, 2009	Longitudinal clinical follow-up	Netherlands	1		☑	16	Mean: 16 years (range, 4–29 years)
Wokke, 2008	Observational Multicentre Multinational	EU US	5‡	☑		58	1 year
Müller-Felber, 2007	Observational Cohort	Germany	1		☑	38§	Mean: 14.8 years (range, 3–21 years)
Hagemans, 2006	Observational	Netherlands	1		☑¶	52	2 years
Pellegrini, 2005	Observational Prospective	NR	2	NR		29	NR

Reference	Trial design	Trial location(s)	Sites (N)	Research type	Patients (N)	Follow-up duration
Hagemans, 2005a	Observational Questionnaire	NR	NR	NR†	255	NR
Hagemans, 2005b	Observational Questionnaire	Netherlands	NR	NR†	54	NR
Hagemans, 2004	Observational Questionnaire	Australia Germany Netherlands UK US	NR	NR†	210§	1 year

*Treated patients (n = 60).
†Funding for survey provided by Genzyme.
‡Sites: EU (n = 2); USA (n = 3).
§Follow-up in 18 patients.
¶1-year follow-up only for 51 Dutch patients.
NR = not reported; pts = patients.

Clinical studies on LOPD patients treated with alglucosidase alfa

Reference	Trial design	Trial location(s)	Sites (N)	Research type		Patients (N)	Treatment duration
				Genzyme-sponsored	Academic		
Clinical trials							
van der Ploeg, 2010	Randomized Double-blind Placebo-controlled Multicentre	Netherlands France USA	1 1 6	☑		90*	1.5 years
van Capelle, 2010	Phase 2 Open-label	Belgium Netherlands UK	1 1 1	☑†	☑	5	3 years
Orlikowski, 2011	Open-label	France	NR	☑		5	1 year
Vielhaber, 2011	Open-label Single centre	Germany	1		☑	2	2 years
Observational studies							
Angelini, 2012	Non-randomized Open-label Observational Multicentre	Italy	NR	☑	☑	74	A: 12–23 months (n = 16) B: 24–35 months (n = 14) C: > 36 months (n = 44)
Strothotte, 2010	Observational Prospective Open-label Multicenter	Germany	NR		☑	44	1 year
Regnery, 2012	Observational Open-label Single centre	Germany	NR		☑	38†	3 years
Hobson-Webb, 2011	Observational Single centre	USA	NR	NR		12§	NR
Bembi, 2010	Non-randomized Observational Prospective Open-label Multicentre	Italy	NR		☑	24	3 years
Yang, 2011	Observational Single centre	Republic of China		☑		15	Median 3.5 years (range, 0.4–4.9)
Ravaglia, 2010a	Non-randomized Observational Prospective Open-label Single centre	Italy	1	NR		11	2 years
Ravaglia, 2010b	Observational Prospective	Italy	NR	NR		14	> 18 months (follow-up on 12/14 subjects)
Angelini, 2009	Observational Prospective Multicentre	Italy	NR		☑	11	3–18 months
Rossi, 2007	Observational Prospective	Italy	NR		☑	3¶	20 weeks
Case reports							
de Vries, 2011	Case report	Netherlands	NR		☑	1	17 months + pregnancy and lactation
Furusawa, 2012	Case report	Japan	NR		☑	5	2 years
Ishigaki, 2012	Case report	Japan	NR		☑	1	2 years
Papadimas, 2011	Case report	Greece	NR	NR		5	6–38 months
de Vries, 2010	Case report	Netherlands	NR	NR		1	33 months

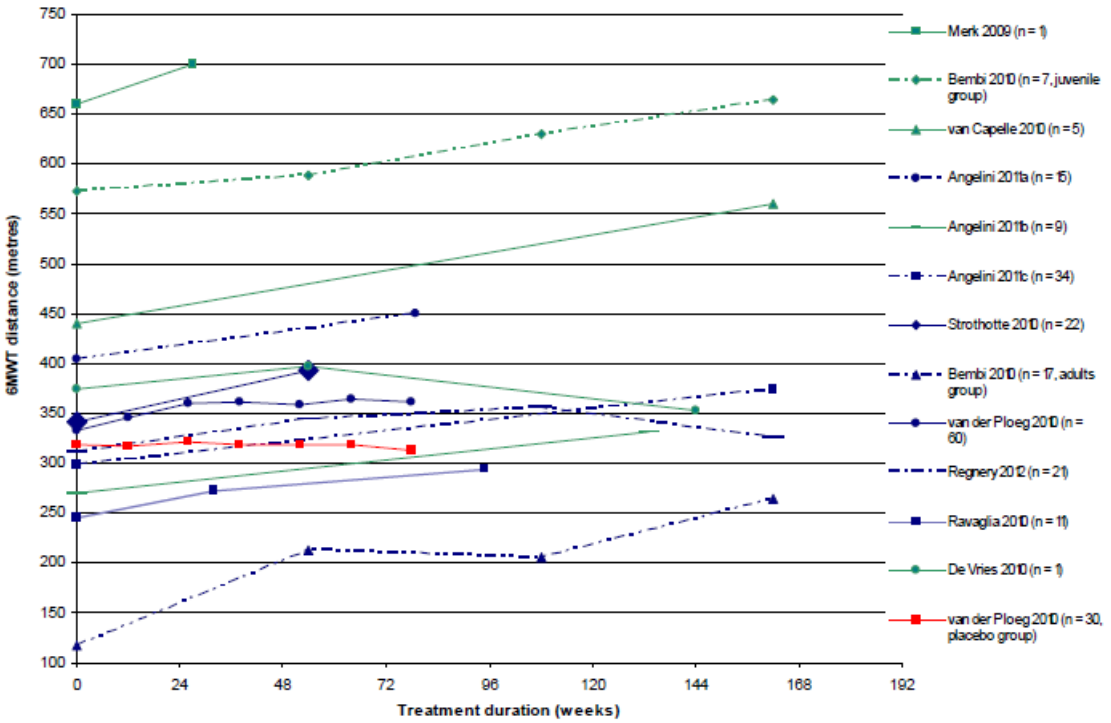
Kobayashi, 20104	Case report	Japan	NR	NR	4	≤ 21 months
Merk, 2009	Case report	Germany	NR	NR	4	6 months
Korpela, 2009	Case report	Finland	NR	NR	1	1 year
Case, 2008	Case report	USA	NR	NR	1	2 years
Laforêt, 2008	Case report	France	NR	NR	3	≤ 2 years

*30 patients in the placebo arm.
†Genzyme provided funding for first 1.5 years of study.
‡Same cohort of patients initially reported by Strothotte et al., 2010.
§9 paediatric patients.
¶2 patients with infantile-onset Pompe disease.

The publications contained data on 298 LOPD patients who were treated with alglucosidase alfa. The majority of the patients (55%) received treatment with alglucosidase alfa for a period of 12–23 months, 28% for a period > 36 months, 12% for 24–35 months, and 5% patients were treated for < 12 months.

Motor performance and ambulation status in LOPD patients treated with alglucosidase alfa

Eleven studies (104 patients) reported changes in motor performance in LOPD patients during treatment, as assessed using the 6MWT. Change in motor performance in LOPD patients during treatment with alglucosidase alfa as assessed using the 6 MWT:

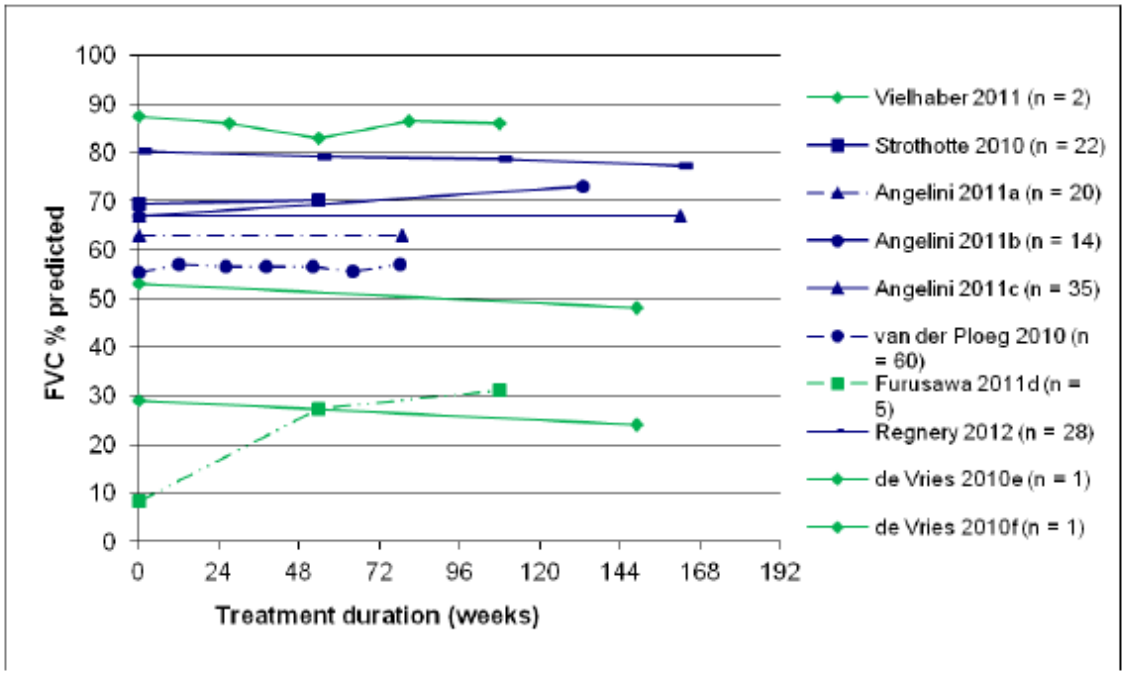


Blue and green lines represented studies in treated patients: Blue lines in studies with >10 patients, green lines in studies with <10 patients. Red line represents the placebo (untreated) population. Data from Angelini 2011 are presented in separate groups corresponding to 3 different durations of treatment. Some overlap exists between patients in the Strothotte and Regnery studies. The Regnery publication reports on data from the same cohort of patients as the Strothotte trial, but after a longer follow-up.

Respiratory status and ventilation support in late-onset Pompe disease patients treated with alglucosidase alfa

The literature search identified 18 studies reporting on the change in respiratory status and/or ventilation support in LOPD patients treated. Of these, 11 studies, including a total of 242 LOPD patients, reported on FVC outcomes. Individual changes in FVC were reported for 126 patients from 8 studies. Following treatment, 64 (51%) of these patients showed an increase in % FVC, 17 (13%) stabilized, and 45 (36%)

experienced a decrease. Change in respiratory status in LOPD patients during treatment with alglucosidase alfa as assessed using the % FVC is summarised as follows:



a:Treatment duration 12–23 months.

b:Treatment duration 24–35 months.

c:Treatment duration ≥36 months.

d:Average range of FVC (% predicted). Before treatment: 0.0–46.1; 1 year after treatment: 9.3–51.2; 2 years after treatment: 7.7–66.1.

Data on changes in requirement for ventilation support following treatment were available for 69 patients from 11 studies including 171 LOPD patients. Following treatment with alglucosidase alfa, 38/69 (55%) of these patients experienced a decrease in the number of hours of ventilation required/day, 15/69 (22%) stabilized, and 1/69 (1%) required longer duration of ventilation. A total of 4 patients (6%) required de novo ventilation.

Quality of life QoL in late-onset Pompe disease patients treated with alglucosidase alfa

QoL was evaluated in 9 studies including 182/298 patients who received alglucosidase alfa. At baseline, QoL scores were below the norms for the US general population in 144/182 (79%) patients. Following treatment, most patients (n = 104) did not report any changes in QoL. A total of 12 (8%) patients reported an overall increase in QoL scores: 4 patients showed an increase in the physical component score, 5 patients reported an increase in the mental component score, and 4 patients had decreased body pain. For some patients, improvements in outcomes following treatment had a positive, if less quantifiable, impact on their QoL: a subjective improvement in endurance and QoL was reported by 1 patient after a follow-up of 3.8 years, and in another study, patients showing increased muscle strength and function reported improved ability to participate in outdoor activities. Two patients experienced a decrease in QoL: 1 reported decreasing physical component score and the other patient showed a decrease in the mental component score and an increase in the fatigue severity scores.

2.2.3. Discussion

The data submitted by the MAH originate from observational studies with the median observational time between 78 weeks (1.5 years) and 2 years. The CHMP noted some limitations, e.g. the number of patients is limited and no comparator has been used. In the survival study, it appears that there is a difference between the two groups (treated and untreated) in terms of severity: more patients with

ventilation support or wheelchair dependency in untreated arm (66% versus 56%). The CHMP considered that the calculations of the transposition of life years were confined and thus, the results of the studies can be considered as exploratory, without a precise definition of the effect of the treatment on survival.

The 6 MWT and FVC % were the relevant evaluation criteria and were assessed in two studies showing a gain of 32 and 63 meters respectively, within 70 % of evaluated patients. The sitting FVC % was assessed in 3 studies and no difference was observed before and after treatment.

Overall, the CHMP noted that the submitted data were of observational character and unlikely to demonstrate unambiguous clinical relevance of Myozyme treatment in patient with LOPD. Therefore, the MAH was requested to provide further data to support the current variation to update the PI of Myozyme with data on patients with LOPD. These should include convincing data showing a treatment effect on survival or at least demonstrating a significant clinical improvement in respiratory and/or muscle function. In addition, the MAH was asked to submit the analysis of determination of the clinical relevance of outcomes in LOPD patients, since the size effect and its relevance were assessed from other conditions and not from LOPD patients.

In response to the CHMP's concerns, the MAH provided further justification of the scientific robustness of the Survival analysis and asked independent statistical experts to comment on the value of using the International Pompe Association/Erasmus MC (IPA/EMC) survey and the statistical analysis methods used. The IPA/EMC survey was believed to be of high quality as it was prospectively planned and specific to late-onset Pompe patients. The survival coefficients from the different models can be interpreted in the way described in the publication and included in the current variation.

The CHMP also commented on the appeared population difference. The MAH argued that the authors used epidemiological methods in order to attempt to control for potential bias. Throughout the published paper, the researchers used epidemiological methods, which are specifically designed to attempt to control for bias in observational data, to assess the impact of treatment on survival. In this progressive disease, the authors controlled for covariates that increase the risk of death (age and disease severity) or might present other confounding factors such as gender and country of residence. They also used ERT treatment as a time dependent variable in order to assess the actual time on treatment and its effect. This was considered reassuring.

The MAH agreed with the CHMP that because of the time-dependent nature of the survival analysis it is not possible to estimate the additional years of life gained under ERT as the study authors have stated. The ad hoc calculation of life years gained was exploratory in nature and based on the assumption that the adjusted hazard ratio can be interpreted as a relative risk over the 4 years median and 8 years maximum follow-up (from start of treatment). The MAH further argued that the assessment of the outcomes reflected clinical practise. In the period prior to start of therapy the number of patients in the ERT group requiring no wheelchair or ventilation decreases from 49% to 34%, while the number of patients requiring both a wheelchair and ventilation increases from 24 to 33% from study entry to the start of ERT.

The MAH also provided further review and analyses of clinical efficacy data from published literature, which also support the use of Myozyme in patients with LOPD.

The CHMP considered the above evidence of efficacy of Myozyme in the treatment of LOPD and acknowledged that the conduct of multiple double-blind, placebo controlled studies with solid endpoints would be extremely challenging, given the rarity of the disease and the heterogeneity of the patient population. It is agreed that in each study the majority of patients showed benefits, i.e. moderate improvement or status quo rather than decline, and the consistent trend across studies is reassuring. Therefore, the CHMP agreed that there is sufficient evidence of efficacy to support addition of the clinical results in section 5.1 and to consequently update section 4.1 of Myozyme SmPC, as stated below.

2.3. Changes to the Product Information

The MAH proposed the following changes to the Product Information (PI), which the CHMP reviewed and requested further modifications. The final agreed wording is as follows:

SmPC, section 4.1, Therapeutic indication:
Myozyme is indicated for long-term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of Pompe disease (acid α-glucosidase deficiency).

Myozyme is indicated in adults and paediatric patients of all ages.

~~In patients with late-onset Pompe disease the evidence of efficacy is limited (see section 5.1).~~

SmPC, section 5.1:

Late-onset Pompe disease; other clinical trials and analyses

Three independent, open-label, single arm, investigator-initiated studies with Myozyme were conducted:

- One study in Italy enrolled 74 late-onset patients with up to 48 months follow up.
- One study in Germany enrolled 38 late-onset patients with 36 months follow up.
- One study in the Netherlands enrolled 69 late-onset patients with a median follow-up of 23 months.

These three studies with Myozyme (with a follow up of at least 3 years in two studies and a median of 23 months in the other study) suggested stabilisation or improvement of motor function and stabilisation of pulmonary function.

In the above described study in 69 late-onset patients in the Netherlands, Myozyme showed an improvement in muscle strength. However, muscle function only improved in wheelchair independent patients and in those with less pronounced muscle weakness.

In two additional open-label clinical trials with Myozyme with a follow-up of 24 months, ten patients with severe late-onset Pompe disease (moderate to severe motor impairment and assisted ventilation) showed a variable response on measures of motor and respiratory functions, mostly in the form of a modest improvement (AGLU03105, AGLU04107).

PIL, section 1, What Myozyme is and what it is used for

Myozyme is used to treat adults, children and adolescents of all ages who have a confirmed diagnosis of Pompe disease.

People with Pompe disease have low levels of an enzyme called alfa-glucosidase. This enzyme helps the body control levels of glycogen (a type of carbohydrate). Glycogen provides the body with energy, but in Pompe disease the levels of glycogen can get too high.

Myozyme contains an artificial enzyme called alglucosidase alfa – this can replace the natural enzyme which is lacking in Pompe disease.

~~In patients with late-onset Pompe disease (typically a more slowly progressive form of Pompe disease with onset of symptoms after infancy) the evidence of efficacy is limited.~~

Several small linguistic corrections were proposed for product information annexes of certain languages.

Changes were also made to the PI to bring it in line with the current QRD template, which were reviewed and accepted by the CHMP.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representatives of BE, BG, DK, DE, HR, IS, FI, MT, CY, EL NO, PL and SE.

3. Overall conclusion and impact on the benefit/risk balance

Data provided by the MAH are based on five observational studies evaluating motor and respiratory functions of LOPD patients treated by ERT and one observational study evaluating the impact of ERT on survival in adult with LOPD. Overall, the new observational clinical data present a clinically relevant efficacy trend in the treatment effect of Myozyme on overall survival, motor functions and respiratory status in patients with late-onset Pompe disease. The update of section 5.1 and consequently that of section 4.1 is warranted. The benefit/risk of Myozyme remains unchanged.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Update of sections 4.1 and 5.1 of the SmPC in order to include relevant clinical data from several clinical trials and from other analyses of late-onset Pompe disease patients treated with Myozyme. The Package Leaflet was updated accordingly.

In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

Furthermore, the PI is being brought in line with the latest QRD template version 9.0.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.