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ASSESSMENT REPORT
FOR
Myozyme®

International Nonproprietary Name:
alglucosidase alfa

Procedure No. EMEA/H/C/000636/II/0007

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

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III. SCIENTIFIC DISCUSSION

On 29 March 2006 the European Commission granted a Marketing Authorisation for Myozyme (alglucosidase alfa, EU/1/06/333/001-003). In support of the Marketing Authorisation (including data provided during the procedure), data were provided from two ongoing pivotal clinical studies, conducted in patients with infantile-onset Pompe disease. Data were included on a limited number of patients with late-onset Pompe disease, the majority of which were treated with Myozyme under various expanded access and compassionate use schemes.

Following the MAA, Myozyme was approved for patients of all ages with a confirmed diagnosis of Pompe disease (acid α-glucosidase deficiency). The indication section of the SPC contains additional information stating that the benefits of Myozyme in patients with late-onset Pompe disease have not been established. Genzyme conducted study AGLU02704 and committed to report the results to CHMP in order to demonstrate the benefits of Myozyme in patients with late-onset Pompe disease. The double-blind, placebo-controlled study AGLU02704 provides information on the safety, efficacy and pharmacokinetics of the treatment of patients with late-onset Pompe disease with Myozyme.

The scope of this type II variation is to update the SPC and PL, based on the final clinical study report of study AGLU02704. The MAH proposes to remove the sentence from section 4.1 stating that the benefits in patients with late-onset Pompe disease have not been established. The MAH proposes also to update the SPC with the efficacy, pharmacokinetic and safety information in late-onset Pompe disease patients.

Introduction

The absence, or almost complete absence, of GAA in Pompe disease leads to the accumulation of high levels of glycogen in various tissues, particularly cardiac and skeletal muscle, as well as respiratory muscles, leading to generalised myopathy, cardiomyopathy and respiratory failure. Pompe disease can be considered as a spectrum of disease as the clinical presentation of GAA deficiency ranges from a rapidly fatal, usually in infants (the infantile-onset form) characterised by profound muscle weakness and flaccidity (often referred to as floppy baby) and by a progressive cardiomyopathy, to a slowly progressive late-onset myopathy in juveniles and adults where involvement of skeletal muscles dominates the clinical picture and respiratory insufficiency is frequent. In general, there is an inverse correlation between the amount of residual GAA activity and the severity of the disease.

It is postulated that Myozyme, a recombinant human acid alpha-glucosidase (rhGAA), will restore lysosomal GAA activity resulting in stabilisation or restoration of cardiac and skeletal muscle (including muscles of the respiratory system). Infused Myozyme is only biologically active after lysosomal uptake. The recommended dosage regimen of Myozyme is 20 mg/kg of body weight administered once every 2 weeks as an intravenous infusion.

III.1 Clinical aspects

The early clinical development program for recombinant human acid α-glucosidase focused primarily on demonstration of safety and survival in patients with the rapidly progressive infantile-onset form of Pompe disease in uncontrolled and historical-controlled studies. An addendum to the Summary of Clinical Pharmacology and Clinical Efficacy has been prepared to support a change in the product labelling for Myozyme to include data from patients with late-onset Pompe disease treated in the placebo-controlled study AGLU02704.

The following studies have been submitted:
- **AGLU02704**: A 78-weeks randomised, double-blind, placebo-controlled, adaptive, multicentre, multinational study of the safety, efficacy and pharmacokinetics (PK) of Myozyme treatment in 90 patients with late-onset Pompe disease.
- **AGLU03206**: An Open-label extension study of Study AGLU02704 (extension interim results).

- **AGLU02303**: A 52-weeks observational study in 61 patients with late-onset disease measuring progression of disease symptoms over the course of the study.

II.1.1 Clinical pharmacology

The pharmacokinetic profile of recombinant human acid α-glucosidase (rhGAA) in patients with late-onset Pompe disease was evaluated as part of the clinical programme in AGLU02704.

Pharmacokinetics were characterised by compartmental methods under a nonlinear mixed effects model paradigm; 1-, 2-, and 3-compartment models were examined and the 2-compartment model was chosen to be the superior model on the basis of the Likelihood Ratio Test, goodness of fit, and precision of the parameter estimates. Non-compartmental models were not used because they cannot adequately account for the variable-step nature of the Myozyme infusion and lead to biased pharmacokinetic parameter estimates.

Assessment of pharmacokinetics was performed on a subgroup of patients based on those study sites that could accommodate pharmacokinetic sampling needs. A total of 1153 quantifiable pharmacokinetic observations were available from a subset of 34 patients (15 female, 19 male) from 4 primary sites that participated in serum collection for this purpose. Data from 2 patients who were randomized to the Placebo group with detectable Myozyme concentrations were removed from the dataset. At the time of first infusion, the median age of patients in the pharmacokinetic subgroup was 46.0 years (range: 20.7 to 70.0 years), weight was 77.4 kg (range: 42.5 to 118.8 kg), and the median dose of Myozyme was 1547 mg (range: 850 to 2376 mg).

The following parameters were calculated or estimated for each patient on each visit and pooled across visits: maximal concentration (C_{max}), time to maximal concentration (T_{max}), total systemic clearance (CL), inter-compartmental clearance (Q), central volume of distribution (V1), peripheral volume of distribution (V2), volume of distribution at steady-state (Vss), area under the curve from time 0 to infinity ($AUC_{[0\text{-}inf]}$), and half life.

Blood samples for the measurement of plasma rhGAA activity were collected on Day 0, Week 12, and Week 52 at each of the following time-points: 0 (before the start of the infusion), 1 and 2 hours after the start of infusion, end of the infusion, and then 0.25, 0.5, 1, 2, 3, 4, 8, 12, and 16 hours after the end of the infusion (with a 5-minute window for time-points after the start of infusion).

The following table gives a summary of the rhGAA pharmacokinetic parameters across study visits after intravenous infusion of 20 mg/kg to patients with late-onset Pompe disease.

Summary Statistics for rhGAA Pharmacokinetic Parameters by Visit in Study AGLU02704

Parameter	Week 0 (n=32)	Week 12 (n=32)	Week 52 (n=32)
Cmax (ng/mL)	385237 ± 105585	349269 ± 78620	369744 ± 88203
Tmax (h)	3.62 ± 0.33	3.62 ± 0.28	3.64 ± 0.31
AUC (µg*h/mL)	2672.47 ± 1139.85	2386.76 ± 555.09	2699.28 ± 999.97
CL (mL/h/kg) (mL/h)	 8.1 ± 1.8 632.9 ± 175.0	 8.9 ± 2.3 699.7 ± 243.9	 8.2 ± 2.4 645.0 ± 197.8
V1 (mL/kg) (mL)	 43.7 ± 9.4 3361 ± 633	 47.6 ± 12.1 3712 ± 1154	 44.5 ± 10.0 3490 ± 773
V2 (mL/kg) (mL)	 860.7 ± 1156.7 66010 ± 91395	 871.7 ± 1154.2 66655 ± 91241	 851.0 ± 1152.6 66010 ± 91395
Vss (mL/kg) (L)	 904.4 ± 1158.0 69.4 ± 91.5	 919.4 ± 1154.3 70.4 ± 91.2	 895.5 ± 1154.3 69.5 ± 91.5
Alpha Half-life (h)	2.42 ± 0.35	2.45 ± 0.33	2.47 ± 0.36
Beta Half-life (h)	219.7 ± 300.2	218.1 ± 304.2	214.8 ± 283.6

Data shown are mean ± standard deviation

According to the results for rhGAA pharmacokinetic parameters after intravenous infusion of 20 mg/kg to patients with late-onset Pompe disease, it appears that no difference in pharmacokinetics was observed across visits indicating that rhGAA pharmacokinetics were stable over time.

According to the data obtained from PK studies in the original dossier of the MAA (section 5.2 of SPC), the pharmacokinetics of Myozyme in patients with infantile-onset Pompe disease who received doses of 20 mg/kg or 40 mg/kg, Myozyme were dose proportional and did not change over time. Indeed, after the first and sixth infusion of Myozyme, mean maximum plasma concentrations (Cmax) ranged from 178.2 to 263.7 µg/mL for the 20 mg/kg and 40 mg/kg dose groups respectively. The mean area under the plasma concentration-time curve (AUC∞) ranged from 977.5 to 1872.5 µg̃hr/mL for the 20 mg/kg and 40 mg/kg dose groups. Mean plasma clearance (CL) was 21.9 mL/h/kg and mean volume of distribution at steady state (Vss) was 66.2 mL/kg for both dose groups with small between-subject variability of 15% and 11%, respectively. Mean plasma elimination half-life ($t_{1/2}$) was 2.75 hours for the two dose groups. Moreover, no difference appeared in the PK profile of Myozyme in late-onset patients compared to infantile-onset patients.

In comparison to the results obtained from these 34 late-onset patients included in AGLU02704 who received dose of 20 mg/kg Myozyme, C_{max}, AUC and Vss (respectively ranged from 349 to 385µg/mL; from 2387 to 2700 µg.hr/ml and from 69 to 70l) are higher than those already reported with 20 mg/kg or even 40mg/kg, while clearance (ranged from 8.1 to 8.9 ml/h/kg) is lower. It should also be highlighted the important between-patient variability (i.e. around 81%) observed for Vss, resulting from the contribution of V2 which was not precisely estimated.

At last, the LS mean distribution or α-half-life of rhGAA was 2.4 hours with a between-patient variability of 10.4%. A much longer terminal phase was seen in which the elimination or LS mean β-half-life was 214 hours with a between-patient variability of 134.3%; the large between-patient variability can be explained by the imprecision of the estimates related to the peripheral compartment.

According to the MAH, it seems likely that an elimination half-life of 214 hours is an overestimate of the true value.

These differences may suggest an accumulation of rhGAA in these patients and the CHMP requested the MAH to discuss this point. According to the MAH, an artefact due to quantifiable pre-dose concentrations in 2 out of 34 patients may explain the large BSV in V2 in adult-onset patients. Moreover, the observed concentrations, less than the limit of quantification of the assay, may explain the reported mean β-half-life of 214 hours in adult-onset patients. These explanations were endorsed by CHMP.

Anti-rhGAA IgG Antibody Testing

Additional analyses included the effect of antibody titres on the rhGAA pharmacokinetic parameters CL and $AUC_{(0\text{-}inf)}$ and inhibitory antibody status in patients the first time they tested positive for antibodies to rhGAA, and periodically thereafter. The titre for enzyme uptake inhibition was assessed if their inhibitory antibody status was positive.

Antibody formation in AGLU02704 was assessed in a 2-step process: an enzyme-linked immunosorbent assay (ELISA) screening assessment followed by a confirmatory radioimmuno-precipitation (RIP) assay.

All evaluable patients (n=59) in the Myozyme group in study AGLU02704 tested positive for anti-rhGAA IgG antibodies. The median time to seroconversion was 4 weeks (range of 4 to 12 weeks). Of these patients, 39 (66.1%) patients seroconverted by the Week 4 visit, 18 (30.5%) patients seroconverted by the Week 8 visit, and the remaining 2 (3.4%) patients seroconverted by the Week 12 visit.

The median peak anti-rhGAA IgG antibody titre was 6,400 (range 200 to 819,200); 39 (66.1%) of the patients who seroconverted had a peak titre of 6,400 or less. The geometric mean titre increased to a maximum of 2,925 at Week 44 and thereafter declined. The median titre remained steady at 1,600 throughout most of the study, i.e., from Week 8 to Week 64. The median last titre was 1,600 (range 100 to 819,200); 35 (59.3%) of the patients who seroconverted had a last titre of 1,600 or less.

IgG Inhibitory Antibody Testing

After Week 78, archived serum samples of all IgG seropositive patients were tested, as appropriate, for the presence of IgG inhibitory antibodies to rhGAA.

In vitro inhibitory antibody assays were performed to evaluate inhibition of enzyme activity or cellular uptake into fibroblasts for all seroconverted patients at the point of seroconversion and approximately quarterly thereafter. Based on the samples tested, none of the 59 (0%) evaluable patients tested positive for *in vitro* inhibition of enzyme activity.

The inhibition of uptake assay detects the presence of antibodies that can interfere with the incorporation of fluorescently labelled rhGAA into human fibroblasts *in vitro*.

Serum samples were considered positive or borderline positive for inhibition based on the above mentioned definitions. However, due to the complexities of the inhibition uptake assay, and the inconsistency of some of the inhibition of uptake results over time, it was also necessary to delineate clear criteria that would determine whether patients were considered truly positive for uptake inhibition. For the purposes of this analysis, patients were therefore classified as positive for uptake inhibition if they demonstrated an end point titre of 40 (i.e., a serum sample positive for inhibition at dilution 1:10, 1:20 and 1:40) or greater at 2 or more consecutive time points. Patients who demonstrated an end point titre of 40 or greater at only 1 time point or at non-consecutive time points, and patients who showed inhibition below the 1/40 dilution only, were classified as borderline positive for uptake inhibition.

Of the 59 patients tested, 10 (16.9%) were classified as positive, 8 (13.6%) were classified as borderline positive, and 41 were classified as negative for *in vitro* inhibition of enzyme uptake. Patients who tested positive for uptake inhibition had a mean time to first detection of inhibitory antibodies of 36 weeks after first infusion, or 30 weeks after first positive IgG titre. Patients who tested borderline positive for uptake inhibition had a mean time to first detection of inhibitory antibodies of 37 weeks after first infusion, or 32 weeks after first positive IgG titre.

Patients classified with positive uptake inhibition assay results generally had higher median peak IgG titres (102,400) and higher median last IgG titres (72,408) than patients who remained negative for uptake inhibition (median peak IgG titre 3,200; median last IgG titre 400). Median IgG titres for the borderline positive inhibition group were between the values for the negative and positive groups (median peak IgG titre 12,800; median last IgG titre 3,200). This pattern of data supports the concept of a difference between the classification as positive and borderline positive for uptake inhibition. The clinical significance of high IgG titres or positive uptake inhibition assay results is unclear, as some patients with high IgG titres responded well while others did not.

A small number of patients (N=5) who tested positive for uptake inhibition and who had pharmacokinetic samples available for analysis showed a statistically significant lower AUC and Cmax and higher CL compared to patients who tested negative for uptake inhibition. In patients positive for inhibitory antibodies, the LS mean AUC was 1951 µg*h/mL compared to 2547 µg*h/mL in patients negative for inhibitory antibodies (F=8.73, p = 0.0042). LS mean C_{max} was 300 µg/mL in positive patients compared to 363 µg/mL in negative patients (F=4.55, p=0.0361), and LS mean CL was 813 mL/h in patients positive for inhibitory antibodies compared to 608 mL/h in patients negative for inhibitory antibodies (F=11.04, p=0.0014). This data needs to be interpreted with caution in light of the small number of patients included in the analysis.

Plasma and urine oligosaccharide (Hex4) levels were also measured in study AGLU02704 as a pharmacodynamic assessment. An analysis of the oligosaccharide data and, specifically, the correlation between oligosaccharides and efficacy endpoints was performed and is described in the efficacy part.

III.1.2 Clinical efficacy

III.1.2.1 Main study

Study AGLU02704 is a Randomised, 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

Methods

This was a randomised, double-blind, placebo-controlled, adaptive, multicenter, multinational study of the safety, efficacy and PK of Myozyme treatment in 90 patients with late-onset Pompe disease.

Study Participants

Patients were initially enrolled at 8 primary investigational study centres (5 in the United States and 3 in Europe). Twenty-two local, transfer investigational sites were set up to allow patients to have infusion visits closer to home after 6 months of treatment. Patients continued to return to the primary investigational site every 3 months for assessment.

Main inclusion criteria

- The patient had a diagnosis of Pompe disease based on deficient endogenous GAA activity in cultured skin fibroblasts of ≤ 40% of the normal mean of the testing laboratory and 2 GAA gene mutations;
- The patient was ≥ 8 years of age at the time of enrolment;

- The patient was able to ambulate 40 meters (approximately 130 feet) in 6 minutes on each test performed on 2 consecutive days (use of assistive devices such as a walker, cane, or crutches, was permitted);
- The patient had a Forced Vital Capacity (FVC) of ≥30% and < 80% predicted in the upright position
- The patient had a postural drop in FVC (litres [L]) of at least 10% from the upright to the supine position
- The patient had proximal muscle weakness in the lower limbs defined as unilateral Quantitative Muscle Testing (QMT) of the knee extensors < 80% of the predicted value based on age, gender and body sise
- The patient was able to tolerate pulmonary function testing (PFT) and muscle testing in the supine position. (See exclusion criteria [1] and [2].);
- The patient had testable muscle in bilateral knee flexors and knee extensors, and testable muscle in bilateral elbow flexors and elbow extensors. (Using QMT, a muscle was defined as "not testable" if the patient: 1) had a contracture > 90 degrees that prevented being able to assume the standard testing position, 2) was unable to follow directions, 3) had significant pain with resistance to the motion, or 4) was so weak that force could not be generated against the testing strap);
- The patient was able to provide reproducible muscle and pulmonary function test results (bilateral QMT measurements [% predicted] in knee extensors within 10% of the highest test value obtained from the same side of the body on 2 consecutive days and FVC measurements [in litres] within 10% of the highest test value obtained in the upright position on 2 consecutive days);

Main exclusion criteria
- The patient required the use of invasive ventilatory support. (Invasive ventilation was defined as any form of ventilatory support applied with the use of an endotracheal tube.);
- The patient required the use of non-invasive ventilatory support while awake and in an upright position. (Non-invasive ventilation was defined as any form of ventilatory support applied without the use of an endotracheal tube. For example, patients receiving positive-pressure ventilation support through a facemask or nose piece were considered as ventilated through non-invasive methods.);
- The patient had received ERT with GAA from any source, had used an investigational product within 30 days prior to study enrolment, or was currently enrolled in another study which involved clinical evaluations, unless prior approval was given by the MAH;

Treatments

The approved commercial dose of 20 mg/kg/qow was selected for use in this study. Patients received IV infusions of either Myozyme (at a dose of 20 mg/kg qow) or placebo for 78 weeks (52 weeks in the original protocol). On the basis of a planned interim analysis, based on an adaptive design, which was pre-specified in the protocol to determine the recommended date of trial termination (blinded to Genzyme), the duration of the study was extended from 52 weeks to 78 weeks.
The total amount of Myozyme or placebo administered could be adjusted approximately every 12 weeks to account for changes in body weight.

The choice of posology and the step-wise administration for infusions comply with the posology and the method of administration recommended in the approved SPC.

Outcomes/endpoints

The following efficacy assessments were performed at scheduled visits during the study:
- 6MWT (distance walked);
- Pulmonary function testing (FVC and forced inspiratory vital capacity [FIVC] in the upright and supine positions, and MIP and MEP in the upright position);
- Bilateral QMT assessments (shoulder adductors [pectoralis], elbow flexors [biceps], elbow extensors [triceps], hip adductors [adductor muscles], knee flexors [hamstrings], knee extensors [quadriceps], and grip strength);
- MMT for 34 muscle groups;

- Functional activities assessment (time to walk 10 meters, time to climb 4 standard stairs, time to stand up from the supine position; functional arm score, and functional leg score);
- MOS SF-36 Health Survey, FSS, and the RIHS-9 in patients 14 years of age;
- Ventilator use time, non-invasive and invasive (using a patient diary).

Mean monthly increase in 6MWT distance and FVC upright (% predicted) were selected as co-primary efficacy endpoints for the study. The study was to be considered to have met its primary efficacy objective if a statistically significant treatment effect of Myozyme over placebo was demonstrated in the 6MWT. FVC testing was to be performed if statistical significance was achieved upon analysis of 6MWT results.

The following table summarises all efficacy endpoints from this study.

Efficacy Endpoints
Co-Primary Endpoints Six Minute Walk Test (6MWT) Forced Vital Capacity, Upright (FVC)
Muscle Strength Testing Quantitative Muscle Testing (QMT) Lower limbs (knee flexors and extensors)[1] Upper limbs (biceps and triceps)[2] Pectorals, hip adductors, grip strength[3] Manual Muscle Testing (MMT)[3]
Additional Pulmonary Function Testing Forced Inspiratory Vital Capacity(FIVC) Maximal Inspiratory Pressure (MIP)[2] Maximal Expiratory Pressure (MEP)[2] Hours on Ventilation (invasive and non-invasive)[3]
Functional Ability Functional Activities Assessment (FAA)[3] Timed Performance Tests[3]
Surveys of General Health and Limitations SF-36 Health Survey (SF-36)[1] Fatigue Severity Scale (FSS)[3] Rotterdam 9-Item Handicap Scale[3] Late-Onset Pompe Disease Questionnaire[3]
Pharmacodynamics Oligosaccharide levels[3]

1 Secondary endpoint
2 Tertiary endpoint
3 Exploratory endpoint

The assessment of efficacy is measured by the co-primary endpoints 6MWT and FVC. This choice is endorsed by the CHMP as it allows to assess both aspects of the disease expression (disability and respiratory failure,) is non-invasive and quite reproducible through the different centres.

Randomisation

Eligible patients were randomised in a 2:1 ratio to receive an IV infusion of 20 mg/kg Myozyme or placebo matched for 20 mg/kg dose volume, qow. To reduce the likelihood of treatment imbalance across factors that might influence results on the primary efficacy variables, patients were randomised using a minimisation algorithm with the goal of achieving the proposed treatment allocation across sites, Baseline 6MWT, and Baseline FVC upright. Random treatment assignment was accomplished using an Interactive Voice Response System (IVRS).

Blinding (masking)

The study was conducted in a double-blind manner. The Investigator, other study site personnel, the patient and representatives of the MAH, with the exception of Genzyme CPRS, remained blinded to treatment assignment for the duration of the study. If a patient required invasive ventilation at any time during the study, the patient could be placed on open-label active treatment (rescue therapy) at the discretion of the Investigator and in consultation with MAH's Medical Monitor. No efficacy assessments would have been performed after rescue procedures. Prior treatment assignment (active or placebo) was to remain blinded for patients who required rescue therapy.

As mentioned in the study report, almost half of the patients (42 patients) completed a 52-week Late-Onset Pompe Observational Study (AGLU02303) prior to participating in the AGLU02704 study. By recognising the effects, positive as well as negative, blinding of these patients could be broken; therefore CHMP believed that an accurate double-blind is debatable. As a result the CHMP requested that the distribution of these patients by groups (Myozyme or placebo) should be provided and the potential impact on the double-blind maintenance during the study. The MAH responded that everything had been done to preserve the blinding of people (investigator and patient) involved in this AGLU02704 study. Moreover, the distribution of patients from the AGLU02303 study was balanced between groups in the AGLU02704 study. The MAHs responses were deemed satisfactory and the issues have been resolved.

Statistical methods

The 6MWT (meters walked) and FVC upright (% predicted) were considered as co-primary efficacy endpoints. The primary efficacy analysis of the co-primary endpoints was performed using a fixed sequence testing procedure with the test for treatment effect on 6MWT performed first. The fixed sequence test procedure preserved an overall 5% level of significance by linking the test of the FVC upright endpoint to the results of the test for the 6MWT endpoint. The treatment effect on 6MWT was tested with a two-sided test at a 5% significance level. As the test for 6MWT was significant, a formal test for treatment effect on FVC upright at the 5% significance level was performed. To assess whether treatment with Myozyme had a beneficial effect on functional endurance (as measured by performance on the 6MWT) in late-onset Pompe patients, the mean monthly increase in 6MWT distance in the group of patients randomised to Myozyme was compared to that of the group randomised to placebo. The effect of Myozyme versus placebo on change in meters walked for the 6MWT was analysed using a linear mixed effects model (LME).

The observed 6MWT data (including baseline) was modelled with an LME model that included terms for the baseline strata used in the minimisation algorithm for treatment randomisation (baseline 6MWT and FVC stratification levels and their interaction), time and treatment-by-time interaction where time is the number of months between date of 6MWT assessment and date of first study drug infusion. There were random effects for the intercept and for the linear effect of time. The estimate of the treatment-by-time interaction which quantifies the linear slope differential was used for the hypothesis testing and represents the average monthly increase in 6MWT distance walked if treated with Myozyme compared to placebo.
An analogous model was used for the analysis of the FVC Upright (% Predicted) endpoint.
To support the results of the LME, a sensitivity analysis was performed with Wilcoxon-Mann-Whitney test and with analysis of covariance on change from Baseline to the last observed assessment time.

The analysis of covariance model (ANCOVA) was used to model the change from baseline and, separately, relative change from baseline to the last observed assessment time. The model included the randomisation strata, the baseline observation and treatment indicator. The Wilcoxon-Mann-Whitney test was applied to the change from baseline to the last observed assessment time. The test was performed stratified by randomisation strata.

Since the data did not fit the model assumptions of the LME model, the supportive analyses described below that were planned as modifications and extensions of the LME model were replaced with the analogous extensions of the revised LME with robust variance estimation as well as with the analogous extensions of the generalised estimating equations (GEE) model.

Missing Data Sensitivity Analysis

A sensitivity analysis was performed to assess the robustness of the primary efficacy analysis to the missing data due to early study withdrawal. The sensitivity analysis included the following strategies for handling missing data:

1. Last observation carried forward (LOCF): The missing values after dropout were set to the last observed value prior to dropout.
2. Multiple imputation (regression method): A monotonic missing data pattern is imputed via Markov Chain Monte Carlo (MCMC) and the regression method for monotone missing data was applied to the monotonic missing data to impute the remaining missing observations.
3. Multiple imputation (propensity score method): A monotonic missing data pattern was to be imputed via MCMC and the propensity score method for monotone missing data was to be applied to the monotonic missing data to impute the remaining missing observations.

Re-randomisation Inference

A re-randomisation analysis was performed in addition to the analysis of the co-primary endpoints described above. The re-randomisation analysis consisted of running the minimisation algorithm used for the treatment assignments 10000 times. The algorithm was applied to the observed sequence of enrolled patients with their respective clinical site/baseline covariate strata. After re-randomisation, the LME model for the 6MWT and the FVC upright were applied and the p-values for the Myozyme treatment effect recorded. The resulting empirical distribution of the p-values for testing the 6MWT and, separately, for testing the FVC upright Myozyme treatment effect was compared with the observed p-value obtained from the model used to perform the primary efficacy analysis.

The CHMP noted that the GEE approach highlighted by the firm was not planned in the statistical analysis plan. But ANCOVA model and the Wilcoxon-Mann-Whitney (WMW) were planned as supportive analyses. So, if assumptions underlying the planned LME model do not hold, other planned models should be used instead. At this stage, the ANCOVA model cannot be considered as valid since the analysis of the residuals distribution is lacking. To be complete, the clinical study report should contain this information otherwise one does not know if these results can be taken into account. However, the results of the WMW test can be assessed since its validity is less questionable. The Type I error was 0.04999 after taking into account the adaptive design analysis. Furthermore, FVC testing was to be performed if statistical significance was achieved upon analysis of 6 MWT results.

Eligible patients were randomised in a 2:1 ratio to receive Myozyme or placebo. To reduce the likelihood of treatment imbalance across factors that might influence results on the primary efficacy variables, patients were randomised using a minimisation algorithm with the goal of achieving the proposed allocation across sites, baseline 6MWT and baseline FVC upright. Therefore a re-randomisation was performed to assess the sensitivity of the primary efficacy results to the randomisation procedure used in treatment allocation. As previously mentioned, attention should be paid to the planned models, Wilcoxon-Mann-Whitney as well as ANCOVA and the sensitivity of their results to the randomisation procedure should be assessed.

The re-randomisation p-value for the planned models, both Wilcoxon-Mann-Whitney and ANCOVA (for the clarity of the clinical study report and assuming that this model is shown to be valid) the CHMP requested more information. Following assessment of the MAH answers to the questions of the CHMP related to the ANCOVA model validity, it was concluded that the ANCOVA model cannot be considered as valid, therefore the focus should be on the WMW test results. The MAH performed two re-randomization tests and their results are concordant with p-values of 0.038 and 0.033 for an initial p-value of 0.028. The CHMP agreed with the justifications and the point is considered as resolved.

Patients Demographic

Almost half of the patients (42 patients) completed a 52-Week Late-Onset Pompe Observational Study (AGLU02303) prior to participating in the AGLU02704 study.

One hundred and eight patients with late-onset Pompe disease were eligible for screening for participation in the AGLU02704 study. 18 patients were not enrolled (10 patients failed to meet the enrolment criteria upon screening, 5 patients did not proceed to screening based on their pre-screening results; 2 patients were not screened as the site was already fully enrolled and 1 patient decided not to participate prior to screening). A total of 90 patients were successfully randomised into the study and received treatment, 60 patients in the Myozyme treatment group and 30 patients in the Placebo treatment group.

During the study, 33 (55.0%) of the 60 patients in the Myozyme treatment group and 13 (43.3%) of the 30 patients in the Placebo treatment group transferred from a primary investigational site to local treatment sites.

Nine patients discontinued without completing the study, including 5 (8.3%) patients in the Myozyme treatment group (1 chose to pursue treatment with commercial Myozyme therapy, 2 experienced serious hypersensitivity reactions, 1 died at 74.0 weeks for reasons unrelated to the treatment and 1 chose to discontinue for personal reasons) and 4 (13.3%) patients in the Placebo treatment group (3 chose to pursue treatment with commercial Myozyme therapy, 1 experienced ongoing head discomfort).
Eighty-one (90.0%) of the 90 patients enrolled successfully completed the study, i.e., 55 (91.7%) of the 60 patients in the Myozyme treatment group and 26 (86.7%) of the 30 patients in the Placebo treatment group. The proportion of patients completing the study was comparable across regions, with 51 (87.9%) of the 58 patients in the U.S. and 30 (93.8%) of the 32 non-U.S. patients completing the study.

Patients who completed treatment under this protocol could be eligible for participation in an open-label extension study (AGLU03206, LOTS).

It should be noted that some patients who did not meet the reliability criteria on the FVC or QMT assessments on first screening could be re-screened for inclusion. As a result, 14 of the 90 patients were randomised after a second screening, of whom 10 patients were randomised to the Myozyme treatment group and 4 patients were randomised to the Placebo treatment group.

It should also be noted that half of patients transferred from a primary investigational site to local treatment sites during the study.

The full analysis population includes all 90 patients randomised and treated, 60 patients in the Myozyme treatment group and 30 patients in the Placebo treatment group.

The per protocol population (n = 78) as defined in the SAP included 52 patients in the Myozyme treatment group and 26 patients in the Placebo treatment group who received at least 80% of the scheduled infusions, did not miss 3 or more consecutive infusions, remained in the study for the full 78 weeks, and met all inclusion/exclusion criteria for the study.

Patient Demographics and Baseline data

Patient Demographics and Baseline Characteristics

The great majority of patients were Caucasian. The Myozyme treatment group was 57% male while the Placebo treatment group was only 37% male.
The randomisation scheme resulted in both treatment groups having similar proportions of patients from each of the 4 predefined strata (a combination of 6MWT and percent predicted FVC), with higher proportion of patients able to ambulate ≥300m. Overall, 23 patients in the Myozyme treatment

group (38%) used a walking device at Baseline, compared to 16 patients in the Placebo treatment group (53%) This proportion of patients using a walking device at baseline appears larger in the placebo group. This could impact on 6MWT changes observed when comparing the two groups. The MAH should comment. The mean (± SD) distance walked at Baseline was similar among both groups (332.20 ± 126.69 m in the Myozyme treatment group and 317.93 ± 132.29 m in the Placebo treatment group) The use of a walking device by some patients must be pointed out. Use of a walking device may have changed in some patients throughout the study period and across repeated assessments of 6MWT. During the procedure the MAH provided further details on the use (and type) of walking devices by patients in the study and on the relationship between walking devices and response. CHMP considered this issue to be resolved.
The mean (± SD) percent predicted FVC upright at Baseline was similar among both groups (55.43 ± 14.44% in the Myozyme treatment group and 53.00 ± 15.66% in the Placebo treatment group). Similar proportions of patients in both groups used respiratory support at Baseline (33% Myozyme treatment group, 37% placebo treatment group).

Results

Co-primary endpoints

Six-Minute Walk Test

Table Change in Distance Walked in Six-Minute Walk Test

	Myozyme N = 60	**Placebo N = 30**	**Difference**	**P value**
Estimates/Tests of Monthly Change in Distance Walked (Repeated Measures Analysis)				
GEE, meters/month (95% CI)	1.37 (0.42, 2.33)	-0.13 (-1.12, 0.85)	1.51 (0.12, 2.89)	0.0326
LME with model-based variance estimation, meters/month (95% CI)	1.18 (0.34, 2.03)	-0.06 (-1.26, 1.14)	1.24 (-0.21, 2.70)	0.0931
LME with robust variance estimation, meters/month (95% CI)	1.18 (0.26, 2.11)	-0.06 (-0.90, 0.78)	1.24 (0.02, 2.47)	0.0464
Wei-Lachin test	--	--	--	0.0133
Estimates/Tests of Change in Distance Walked From Baseline to Last Observation				
ANCOVA, meters (95% CI)	25.13 (10.07, 40.19)	-2.99 (-24.16, 18.18)	28.12 (2.07, 54.17)	0.0347
Wilcoxon-Mann-Whitney test				0.0283

P-values of change of six minute walk test (total distance) from baseline- full analysis population
(p-values are from the Wilcoxon-Mann-Whitney statistic stratified by randomisation strata)

Weeks	N	**Change (p-values) – Myozyme v. Placebo**
Week 12	88	0.0079
Week 26	87	0.0059
Week 38	84	0.0039
Week 52	83	0.0926
Week 64	80	0.0749
Week 78	78	0.0992
Last Observed Value	89	0.0283

Mean Absolute and % Predicted 6MWT Distance Walked at Baseline and Last Observation

	Myozyme N = 60	**Placebo N = 30**
Mean (SD) Distance Walked at Baseline, meters	332.20 (126.69)	317.93 (132.29)
Mean (SD) Distance Walked at Last Available Observation, meters	357.85 (141.32)	313.07 (144.69)
Mean (SD) % Predicted Distance Walked at Baseline, % Predicted	50.74 (18.74)	48.72 (20.44)
Mean (SD) % Predicted Distance Walked at Last Observation, % Predicted	56.66 (21.46)	49.12 (22.62)

As mentioned already in the statistical methods, the GEE approach was not planned in the statistical analysis plan. As assumptions underlying the planned LME model do not hold, other planned models, i.e. ANCOVA model and the Wilcoxon-Mann-Whitney planned as supportive analyses, should be used instead. Since the ANCOVA model cannot be considered as valid, the results of the WMW test can be assessed since its validity is less questionable. The analysis of the 6 MWT change from baseline to last observed visit performed with the non-parametric WMW test stratified by randomisation strata is statistically significant (p-value of the difference between groups = 0.0283).

The CHMP requested that sensitivity analysis to missing data of the results of the planned models, Wilcoxon-Mann-Whitney and ANCOVA (for the clarity of the clinical study report and assuming that this model is shown to be valid), should be performed by the MAH. The MAH submitted the results and they were statistically significant with $p<0.05$.

Forced Vital Capacity (FVC)

Table FVC Upright (% Predicted)

	Myozyme N = 60	Placebo N = 30	Difference	P value
Estimates/Tests of Monthly Change in % Predicted FVC (Repeated Measures Analyses)				
LME, % predicted (95% CI)	0.03 (-0.05, 0.10)	-0.16 (-0.27, -0.05)	0.18 (0.05, 0.31)	0.0084
LME, with robust variance estimation % predicted (95% CI)	0.03 (-0.05, 0.10)	-0.16 (-0.25, -0.06)	0.18 (0.06, 0.30)	0.0041
GEE, % predicted (95% CI)	0.03 (-0.05, 0.11)	-0.17 (-0.26, -0.07)	0.20 (0.07, 0.32)	0.0019
Wei-Lachin test				0.0009
Estimates/Tests of Change in % Predicted FVC From Baseline to Last Observation				
ANCOVA—Mean Change, % Predicted (95% CI)	1.20 (-0.16, 2.57)	-2.20 (-4.12, -0.28)	3.40 (1.03, 5.77)	0.0055
Nonparametric Inference—Median Change, % Predicted (95% CI)	0.00 (-1.00, 3.00)	-3.00 (-5.00, 0.00)		
Wilcox-Mann-Whitney test				0.0026
ANCOVA—Mean Relative Change, % of % predicted (95% CI)	1.94 (-0.62, 4.50)	-3.79 (-7.40, -0.19)		

Estimated Mean % Predicted FVC at Baseline and Last Observation

	Myozyme N = 60	Placebo N = 30
Mean (SD) % Predicted FVC at Baseline, % Predicted	55.43 (14.44)	53.00 (15.66)
Mean (SD) % Predicted FVC at Last Observation, % Predicted	56.71 (16.30)	50.70 (14.88)

Subgroup Analyses

In order to evaluate the consistency of the observed treatment effect on 6MWT and on % predicted upright FVC results, the treatment effect was estimated in prospectively defined subgroups defined by the following Baseline characteristics: gender, age, duration of disease symptoms, use of walking device, noninvasive ventilator use, 6MWT results and % predicted upright FVC, randomisation strata and GAA activity.

The study was not powered to detect a statistically significant treatment difference in these subgroups. Most subgroup analyses of the 6 MWT, as well as for FVC upright, change from baseline to last observed visit are not statistically significant, even if the results are in favour to the Myozyme group. Thus there is a trend toward improvement in distance walked and in FVC outcomes in Myozyme patients and in particular in the subset "6MWT≥300m" and/or "FVC≥55%", suggesting that Myozyme could have more of a benefit in late-onset patients at a time in the disease course when they are mildly to moderately affected.

The MAH was requested by the CHMP to discuss the possibility of excluding the severely affected late-onset patients from the indication.

In their responses the MAH have replied that as part of the inclusion criteria in the LOTS study, subjects had to demonstrate quantifiable evidence of lower extremity muscle weakness (as measured

by QMT) and respiratory muscle weakness (as measured by pulmonary function testing) at Baseline. While all 90 patients enrolled in LOTS exhibited significant proximal limb and respiratory muscle weakness at Baseline relative to normal, healthy individuals, significant heterogeneity existed within the study population.

On average, patients were only able to walk a distance approximately 50% that of their healthy peers in the 6MWT, but performance on this test ranged from 41 meters to 626 meters across all patients (6-99% predicted). Thus, some patients were significantly impaired while other patients' walk distances were comparable to normal, healthy individuals. Similarly, mean FVC was also approximately 50% that of healthy individuals, indicating that, on average, pulmonary impairment was in the "moderately severe" range (50-59% predicted) based on American Thoracic Society (ATS) criteria for the assessment of restrictive respiratory disease. However, FVC results indicated a broad spectrum of respiratory involvement with values from 30-78% of predicted. This diversity in the clinical presentation of Pompe disease (as measured by 6MWT and FVC) among LOTS patients was not unexpected, and is consistent with the broad spectrum of clinical symptoms and variable rate of progression previously observed in patients with late-onset Pompe disease.

A positive treatment effect was observed in the cohort of 90 patients and neither Baseline 6MWT nor % predicted FVC were found to be significant, independent predictors of treatment response. The interaction between 6MWT and treatment (p=0.596) and % FVC and treatment (p=0.290) were both tested to be non-significant, which indicates that a difference between subgroups is unlikely.

It should be noted that the study was not designed and planned to perform subgroup analyses for detecting significant differences between Myozyme and placebo within subgroups.

Apart from the broad spectrum of severity of disease as evaluated in study AGLU02704, Genzyme has also investigated treatment in a separate, even more severely affected population of late-onset patients, in study AGLU03105. This study was a Follow Up Measure, for which the final CSR was submitted to CHMP in December 2007. In the assessment report for this study, the Rapporteur indicated that the results in patients with severe late-onset Pompe disease in this study could be assessed in light of the results of study AGLU02704.

According to the inclusion criteria for study AGLU03105 patients enrolled were dependent on a wheelchair for mobility (unable to move without aids such as walking frame, stick, crutches), presented with diaphragmatic dysfunction (defined by at least 2 out of 3 of the following criteria: orthopnea, vital capacity below 50%, paradoxical respiration detected on measurement of Pdi), and required invasive ventilation from 5 to 23 years (defined as the fitting of a tracheotomy tube). One patient needed non-invasive ventilation (defined as any form of ventilatory support assisted by a facemask or nose piece) day and night (≥12 h/24 h). Four patients completed the 52-week treatment period of the study, and one patient died one day after the infusion at Week 50 due to tracheal haemorrhage assessed as not related to Myozyme.

Results of study AGLU03105 showed that after 12 months of treatment no significant deterioration was observed in 4 of 5 patients, and some patients experienced minor improvements in pulmonary function, muscle strength and quality of life: 2 patients moderately increased their sitting Slow Vital Capacity (SVC) at week 52, 3 patients improved sitting and proximal motor function and 2 patients improved standing and transfer.

Patients with late-onset Pompe disease typically show progressive clinical decline if untreated, including a significant increase in the number of hours of respiratory daily support and a significant decrease in muscle function activity.

Finally, the MAH stressed out the importance of the stabilization of disease progression in patients with more progressed disease will have a life-changing effect for these chronically affected patients, even if they would improve less on 6MWT or % predicted FVC. This is particularly true for severely affected patients. In view of the above, Genzyme is of the opinion that severely affected late-onset

Pompe disease patients should not be excluded from the treatment indication, thereby denying the option of stabilization of disease for this group of patients.

The CHMP commented that even if the study was not designed and planned to perform subgroup analyses for detecting significant differences between Myozyme and placebo within subgroups, the results following that analysis indicate a more marked effect of Myozyme on 6MWT distance walked and on % predicted FVC (see corresponding 95%CI) in subgroups of patients less affected (i.e. baseline 6MWT ≥ 300m or baseline FVC≥55%).

Regarding the comments on the responder analysis according to different thresholds, CHMP felt the justification of the MAH was limited.

The MAH reminded the results of the study AGLU03105 in severely affected patients with late-onset form, which could be assessed in light of the results of study AGLU02704. Nevertheless, it should be highlighted that the very limited number of patients (5) and the lack of comparative data precluded drawing any conclusions and therefore the results of the study AGLU03105 cannot be considered as corroborative data.

Responder Analysis Based on 6MWT and FVC

In order to fully evaluate the meaningfulness of the results of the co-primary endpoint, a "responder" analysis was conducted that addressed both improvement and prevention of decline based on 6MWT and FVC outcomes. Based on previously published work by Redelmeier (Redelmeier, 1997, *Am J Respir Crit Care*), 3 responder thresholds were used for 6MWT: 1) 54 metres (the estimated threshold), 2) 37 metres (the lower bound of the 95% confidence interval [CI] of the estimated threshold), and 3) 30 metres (the difference in 6MWT that result in patients feeling 'a little bit better'). Although the clinical significance of changes in FVC for subjects with restrictive pulmonary disease have not been established in the literature, the American Thoracic Society (ATS) has defined the clinically significant proportional changes in FVC % predicted in healthy subjects as a within-day change of 5%, between-weeks change of 11-12%, and yearly change of 15% above or below the patient's baseline value. These change thresholds for 6MWT and FVC were used to conduct the responder analysis.
The proportions of patients improving or declining using various thresholds for absolute change in 6MWT and for proportional change (from Baseline) in % predicted FVC are given in table below.

Patients Improving or Deteriorating Beyond Various Thresholds for 6MWT and % Predicted FVC

Change Threshold	Patients Improving		Patients Declining		Myozyme versus Placebo Treatment Effect[1]
	Myozyme N = 60	Placebo N = 30	Myozyme N = 60	Placebo N = 30	
6MWT					
54m	23.7%	13.3%	5.1%	13.3%	16.2%
37m	28.8%	16.7%	8.5%	20.0%	19.3%
30m	30.5%	20.0%	11.9%	20.0%	14.9%
FVC					
15%	11.9%	0.0%	6.8%	6.7%	11.0%
10%	20.3%	6.7%	8.5%	26.7%	27.0%
5%	40.7%	20.0%	20.3%	46.7%	32.1%

[1] Calculated using the methods of Guyatt et al (1998).

Regarding a possible analysis including different thresholds, for 6MWT, the numerically smallest benefit of Myozyme versus Placebo is actually associated with the lowest threshold, although the differences between 14.9, 19.3 and 16.2% are fairly minor. And for FVC, there is basically no major difference between the 5% and 10% thresholds. Therefore, there is little indication that the benefit of Myozyme depends on the threshold used.

Quantitative Muscle Testing (QMT)

The mean (± SD) QMT Leg Score at Baseline was 37.69 ± 18.88% predicted in the Myozyme treatment group and 32.49 ± 18.24% predicted in the Placebo treatment group indicating significantly diminished leg strength compared to a normative sample of healthy individuals of similar age, gender, and BMI. At the last available observation, the mean QMT Leg Score had increased to 39.05 ± 21.83% predicted in the Myozyme treatment group and decreased to 30.40 ± 20.54% predicted in the Placebo treatment group. The ANCOVA estimated mean QMT Leg Score increased by 1.18 ± 1.13% predicted in the Myozyme treatment group and decreased by 2.00 ± 1.59% predicted in the Placebo treatment group, for a treatment effect of 3.18% predicted and a treatment difference in relative change from Baseline of 12.44% The estimated treatment effect is not statistically significant using the LME with the model-based variance estimator (P = 0.2615), and similar results are reached using the robust variance estimator and GEE (P = 0.1387 and 0.1293, respectively). The ANCOVA estimated Myozyme treatment effect is 3.18% (P = 0.1093), with the WMW test yielding P = 0.0224. In addition, the treatment difference in relative change from baseline is 12.44% (P = 0.0051) using ANCOVA.

The mean (± SD) QMT Arm Score at Baseline was 55.89 ± 20.38% predicted in the Myozyme treatment group and 56.88 ± 18.17% predicted in the Placebo treatment group indicating significantly diminished arm strength compared to a normative sample of healthy individuals of similar age, gender, and BMI. At the last available observation, the mean QMT Arm Score had increased to 60.88 ± 21.74% predicted in the Myozyme treatment group and increased to 58.30 ± 20.85% predicted in the Placebo treatment group. The ANCOVA estimated mean QMT Arm Score increased by 5.05 ± 1.57% predicted in the Myozyme treatment group and increased by 1.47 ± 2.21% predicted in the Placebo treatment group, for a treatment effect of 3.57 ± 2.71% predicted and a treatment difference in relative change from Baseline of 9.35%. The estimated treatment effect is not statistically significant using the LME with the model-based variance estimator (P = 0.1812), and similar results are reached using the robust variance estimator and GEE (P = 0.1699 and 0.1859, respectively). The ANCOVA estimated Myozyme treatment effect of 3.57% is not significant (P = 0.1917), with the WMW test yielding P = 0.0712. In addition, the treatment difference in relative change from baseline of 9.35% is not significant using either the ANCOVA or WMW test (P = 0.1094 and P = 0.0948, respectively).

Additional Pulmonary Function Testing

i) Maximal Inspiratory Pressure (MIP) and Maximal Expiratory Pressure (MEP)

The mean MIP score at Baseline was 40.04% of predicted in the Myozyme treatment group and 42.57% of predicted in the Placebo treatment group indicating significant inspiratory muscle weakness compared to age/gender-matched healthy individuals. The ANCOVA estimated mean MIP % predicted score increased by 3.48% predicted in the Myozyme treatment group and decreased by 0.35% predicted in the Placebo treatment group, for a treatment effect of 3.83% predicted (P = 0.0895). The estimated treatment effect is statistically significant using the LME with the model-based variance estimator (estimated difference in monthly change in MIP = 0.28 % predicted; P = 0.0344).
The mean MEP score at Baseline also showed significant expiratory muscle weakness and was approximately 30% of predicted in the Myozyme and Placebo treatment groups. The ANCOVA estimated mean MEP % predicted score increased by 3.24% predicted in the Myozyme treatment group and decreased by 0.56% predicted in the Placebo treatment group, for a statistically significant treatment effect of 3.80% predicted (P = 0.0352).

ii) Forced Vital Capacity-Supine

At screening, patients were required to demonstrate a drop in vital capacity of at least 10% from the upright to the supine position, which suggested the presence of diaphragmatic weakness or paralysis. The mean FVC supine score at Baseline was 37.32% of predicted in the Myozyme treatment group and 35.50% of predicted in the Placebo treatment group, indicating significant respiratory muscle weakness. Over time the FVC supine % predicted of patients in the Myozyme treatment group remained stable, while the FVC supine % predicted of patients in the Placebo treatment group progressively declined, for a Myozyme treatment effect of 2.50% predicted and a treatment difference in relative change from Baseline of 6.0%.

iii) Ventilatory Support Use

An exploratory objective of this study was to evaluate the effect of Myozyme treatment on respiratory function as measured by ventilation use. At Baseline, 20 (33.3%) of the 60 patients in the Myozyme treatment group and 11 (36.7%) of the 30 patients in the Placebo treatment group were using nocturnal non-invasive ventilatory support, primarily bi-level positive airway pressure (BiPAP) or continuous positive airway pressure (CPAP) support. Patients who utilised any form of ventilatory support during the study completed a bi-weekly ventilator diary during the study.

Based on these diary data, at the last observation 21 (35.0%) patients in the Myozyme treatment group and 15 (50.0%) patients in the Placebo treatment group had used ventilatory support, of whom 3 (5.0%) patients in the Myozyme treatment group and 4 (13.3%) patients in the Placebo treatment group initiated non-invasive ventilator use during the study. No patients in either treatment group became invasively ventilated during the study, the condition specified for consideration to be placed on rescue therapy with open-label Myozyme.

Additional Endpoints

i) Manual Muscle Testing

In addition to QMT, muscle strength in 34 muscle groups throughout the body was evaluated by a trained clinician at the Screening/Baseline visit and subsequent evaluations using manual muscle testing (MMT). The grading system of 0 (no palpable muscle activity) to 5 (normal strength) was converted to MMT scores ranging from 0 to 10, which were summed to generate a total MMT score of upper and lower body strength. A total of 34 muscle groups (16 upper body,18 lower body) were assessed, with a maximum total MMT score of 340 (160 upper body; 180 lower body). The mean MMT Total Score at Baseline was 256.72 in the Myozyme treatment group and 244.27 in the Placebo treatment group, indicating significantly diminished overall body strength. At the last available observation, the mean MMT Total Score had decreased slightly to 254.93 ± 35.90 in the Myozyme treatment group and remained consistent in the Placebo treatment group at 244.00 ± 30.26 indicating no clinically meaningful change in total body strength as measured by MMT for either treatment group.

ii) Timed Performance Tests

Timed performance tests were performed by a subset of patients who (at baseline) were able to safely complete the tests in the judgment of the Investigator (33 [55.0%] Myozyme patients, 12 [40.0%] Placebo). Although the number of patients tested decreased over time, the time to achieve a standing position from supine decreased by approximately 2 seconds in the Myozyme treatment group and increased by between 2 and 3 seconds in the Placebo treatment group, with an apparent separation between the two. No change was observed for the assessment of the timed 10 metre walk test or the time required to climb 4 standard stairs.

iii) Questionnaires of General Health and Physical Limitation

Self-administered questionnaires assessed changes in health-related quality of life (SF-36), level of fatigue (Fatigue Severity Scale), and functional ability and handicap level (Rotterdam 9-Item Handicap Scale).

The mean Physical Component Summary scores (PCS) of the SF-36 at baseline (Myozyme 34.33, Placebo 34.91) were well below that of the general U.S. population (mean PCS of 50.00), indicating significantly diminished physical health status in the study population. There was minimal change from Baseline to last available visit for the PCS score, as well as all 8 subscales of the PCS score, in both treatment groups. No statistically significant or clinically meaningful treatment differences were found between the two treatment groups.

Mean changes from baseline in Fatigue Severity Scale score and Rotterdam 9-Item Handicap Scale score were minimal and not clinically meaningful. The high Rotterdam Handicap score at baseline relative to the maximum total score suggested that this patient cohort was not significantly impaired in the areas assessed by this instrument, thereby leaving little room to observe treatment-related change.

iv) Efficacy Outcomes by Oligosaccharide Levels

Mean urine oligosaccharide levels (Hex4) were characteristically elevated at Baseline in both treatment groups (Myozyme 11.94 mmol/molecule of creatinine [mol Cr]; Placebo 14.61 mmol/mol Cr). Mean change from Baseline in urine Hex4 levels showed a decrease in absolute value at Week 78 by -4.02 mmol/mol Cr in the Myozyme treatment group, while there was little change in the Placebo treatment group (+0.66 mmol/mol Cr).
To explore the correlation between Hex4 and respiratory and proximal muscle strength, analyses of change from baseline in 6MWT, FVC upright, and QMT leg score were performed with patients stratified by Baseline urine Hex4 level above and below the Baseline median urine Hex4 level for the full population (9.85 mmol/mol Cr).

Summary of 6MWT, FVC, and QMT-Leg Score Results by Baseline Urine Hex4 Level in Study AGLU02704

Parameter	Myozyme Patients		Placebo Patients	
	Baseline Hex4 < Median[1]	Baseline Hex4 ≥ Median[1]	Baseline Hex4 < Median[1]	Baseline Hex4 ≥ Median[1]
Number (%) of Patients[2]	34 (57.6)	25 (42.4)	11 (36.7)	19 (63.3)
Mean Change from Baseline to Last Observation in:				
6MWT, metres	38.56 ± 63.62	-1.33 ± 35.51	8.64 ± 45.25	-12.68 ± 44.54
FVC% Predicted	1.26 ± 5.50	1.04 ± 5.77	-1.73 ± 4.65	-2.63 ± 4.23
QMT Leg Score, % predicted	1.88 ± 12.13	0.32 ± 5.77	-1.48 ± 7.26	-2.44 ± 3.53

[1] Median urine Hex4 level for the full population was 9.85 mmol/mol Cr (n = 89).
[2] Percentages are based on the total number of patients with a Baseline urine Hex4 value.

Regarding the secondary and tertiary endpoints, if change in QMT leg score % predicted from baseline to last observation can be considered as better in the Myozyme treatment group than in the Placebo treatment group (MWM p-value = 0.0224), neither the other secondary endpoint result (change in SF-36 PCS from baseline to last observation) nor the tertiary endpoints results (change in MIP % predicted from baseline to last observation, change in MEP % predicted from baseline to last observation and change in QMT arm score % predicted from baseline to last observation) were statistically significant.

Regarding the urinary Hex4 levels there appeared to be a more favourable outcome among patients with lower urinary Hex4 levels at Baseline in both treated and untreated patients. This correlation was discussed before and considering the similar observations reported throughout the studies. The prognostic value of urinary Hex4 levels for motor and respiratory outcome was further dicussed by the MAH.

In their responses the MAH suggested that late-onset patients with a lower (below the median; 9.85 mmol/molCr) urinary Hex-4 level at Baseline, appear to show a trend for a better response to Myozyme on the 6MWT than patients with a urinary Hex-4 level at Baseline above the median (6MWT change from Baseline to last observed value of +38,56 m and -1.33m, respectively). Similarly, placebo patients with a urinary Hex-4 above the median also showed a decline of the 6MWT distance walked over the course of the study while placebo patients with a urinary Hex-4 below the median showed an improvement of the 6MWT distance walked (-12.68m and +8.64m, respectively). This apparent predictive value for response to treatment, however, is limited to the 6MWT, as the same trend was not seen in other outcome measures.

The difference in 6MWT response between patients with a high versus a low urinary Hex-4 at Baseline may be due to chance, as it is highly improbable that urinary Hex-4 at Baseline would only

have a relationship with the efficacy of Myozyme when measured by improvement of 6MWT, but not when measured by % predicted FVC.

The CHMP agreed with the MAH that a correlation has not been fully demonstrated between level of urinary Hex-4 and outcome. Of course, the value of such a parameter will not lead to a clinical decision to treat or not, but may be considered as supportive to assess the response to treatment. The CHMP recommended that the determination of this parameter should be maintained for patients treated with Myozyme. The MAH in their responses to this question in September 2009 have committed to further explore the urinary Hex-4 parameter in the Pompe Registry and report annually to the CHMP.

III.1.2.2. Supportive data

Study AGLU02303

A Prospective, Observational Study in Patients with Late-Onset Pompe Disease. This was a multi-center, multi-national, observational study designed to collect prospective data in patients with late-onset Pompe disease. Those patients who met all of the inclusion criteria and none of the exclusion criteria went on to complete additional evaluations at 1, 3, 6 and 12 months. The duration of the observational period was 12 months.

The objective of this observational study was to collect prospective, observational data on patients with late-onset Pompe disease in order to: characterise the clinical presentation of late onset Pompe disease; determine the intra- and inter-patient variability for the planned study assessments in late-onset Pompe disease; assist in determining clinical efficacy endpoints for future clinical studies; and evaluate oligosaccharides as a biochemical marker of disease severity.

Number of patients enrolled was 61 and analysed 58.

Criteria for evaluation:

This was an observational study; therefore, no efficacy assessments were performed. The following study assessments were performed: muscle strength/function assessments including the 6 minute walk test (6MWT; performed only at the 12-month evaluation), timed functional activities tests (walk 10 meters, climb 4 stairs, rise from supine to stand), leg and arm functional testing, manual muscle testing (MMT), and quantitative muscle testing (QMT); pulmonary function testing (PFT; including spirometry for assessment of vital capacity and manometry for assessment of respiratory pressures); questionnaires including a late-onset Pompe Disease Questionnaire developed by the Sponsor as well as pain, fatigue, respiratory and quality of life questionnaires; spine x-ray; arterial blood gas (ABG); polysomnography; physical examination; vital signs; height and weight; concomitant medications and therapies; standard laboratory testing including serum chemistry, hematology and urinalysis measurements; analysis of GAA gene mutations, angiotensin-converting enzyme (ACE) marker allele status, and GAA activity in skin fibroblasts and blood; and analysis of blood and urine oligosaccharide levels. In addition, interval events (IEs; defined as any untoward signs or symptoms experienced by the patient that were not considered to be related to study procedures) were monitored from time of informed consent through study completion. Safety assessments were based on the incidence of adverse events (AEs) considered to be related to study procedures by the Investigator.

Results

Sixty-one patients were enrolled under Protocol AGLU02303; however, 3 of these patients were excluded from the study when the results of their GAA gene mutation and GAA activity analyses (performed as a part of this study) failed to confirm a diagnosis of Pompe disease. The evaluable study sample (N=58) consisted of 36 females and 22 males, and 94.8% of the patients were Caucasian. Patients ranged from 24.3 to 68.5 (mean = 43.8) years of age at the onset of the study, and all 58 completed this 12-month study.

Study assessments

Results of the 6MWT, a measure of functional capacity and endurance, indicated a diminished capacity for walking in this patient population. The mean percent predicted distance walked was

51.5% and 53.1% for the first and second administrations, respectively. Consistent with this, mean percent predicted values for the QMT Bilateral Leg Score as well as the bilateral knee extensors and flexors were well below 80% of predicted normal levels at all evaluations confirming the presence of lower limb weakness. Of note, lower limb QMT results were considerably more compromised than the upper limbs at all time points and within the upper extremities, the grip muscles, which are the most distal of those assessed, were the most well preserved. Similar results were observed with MMT.
With respect to respiratory muscle strength and function, the PFT results suggest that the majority of the patients had some degree of respiratory impairment as indicated by percent predicted FVC, maximal voluntary ventilation (MVV), maximal inspiratory pressure (MIP), and maximal expiratory pressure (MEP) values < 80% of predicted normal values. Moreover, the mean drop in FVC from the sitting to the supine position across all assessments (i.e., mean SVC) was approximately -28%, confirming the presence of marked diaphragmatic weakness in these patients. Post-hoc analysis of the QMT and PFT assessments revealed a statistically significant decline from Baseline to Month 12 in QMT Bilateral Arm and Leg Scores as well as in FVC, MVV, MIP, and MEP.

Results of the Late-onset Pompe Disease Questionnaire confirmed the presence of muscle and respiratory impairment in these patients, while the Medical Outcomes Study (MOS) 36-Item Short Form (SF-36) findings indicated a diminished health-related quality of life in these patients relative to the general population at Baseline and Month 12.
Urine and plasma glucose tetrasaccharides (Hex4) levels have been proposed as a possible non-invasive method of monitoring disease state and response to therapy in patients with Pompe disease. While no attempt was made to correlate oligosaccharide levels with any of the assessments performed, urinary Hex4 levels were well above normal limits at Baseline and throughout the 12-month study period in the majority of patients, and none of the patients had normal urine Hex4 levels at all assessments.

Results of additional assessments, including physical examinations, vital signs, clinical laboratory findings, spine x-rays, and monitoring of IEs revealed a range of complications and complaints that were not unexpected given the diagnosis of late-onset Pompe disease. For example, abnormal neurological findings including proximal muscle weakness, decreased or absent reflexes, and/or gait abnormalities were observed in the majority of patients and more than half (32/58) had abnormal spine x-ray results generally indicative of scoliosis and/or kyphosis. Similarly, analysis of the IE data revealed that 35 of 58 (60%) patients experienced 1 or more IEs in the SOC of Musculoskeletal and Connective Tissue Disorders, consistent with the muscular compromise characteristic of Pompe disease. Moreover, the most frequently occurring IE by preferred term was fall, which was likely due to lower limb muscle weakness and/or gait abnormalities secondary to Pompe disease.

Safety results
The procedures and assessments performed during the conduct of this study were generally safe and well-tolerated. Forty (69%) of the 58 patients experienced a total of 137 AEs related to performance of study procedures during the 12-month observational period; the majority of these (93%) were of mild or moderate intensity. The highest number of AEs (63 of 137 or 46%) occurred in the SOC of Musculoskeletal and Connective Tissue Disorders and tended to be associated with administration of the 6MWT, QMT, and/or MMT. This was not unexpected given the muscular compromise characteristic of Pompe disease and the challenging nature of these assessments. There were no SAEs or deaths, and all 58 patients completed the 12-month study.

Extension study AGLU03206 (LOTS extension)

During the procedure, the CHMP has requested the submission of the interim data of this extension open-label study. The final results will be provided upon completion of the clinical study report.

Study design

Study AGLU03206 was a multicenter, multinational, open-label extension study of the safety and efficacy of Myozyme treatment in patients with late-onset Pompe disease who were previously enrolled in Protocol AGLU02704. Eligible patients received an intravenous (IV) infusion of 20 mg/kg

of Myozyme every other week (qow) until their participation in both the AGLU02704 and AGLU03206 studies combined equaled a minimum of 104 weeks. Patients who provided signed written informed consent and met all the inclusion criteria and have not met the exclusion criterion were enrolled in the study. Patients retained their original identification number from the AGLU02704 Study.

Of the 90 patients enrolled in the LOTS study, 81 continued into the extension protocol, AGLU03206. The same safety and efficacy assessments performed in Protocol AGLU02704 were performed at scheduled visits throughout the study treatment period. Adverse events (AE), concomitant medications/therapies and ventilator use were monitored continuously throughout the study. The Co-primary efficacy endpoints were: (1) Change from Treatment Baseline to End of Study time point in 6MWT – meters walked, and (2) Change from Treatment Baseline to End of Study time point in % predicted FVC in the upright position. Safety endpoints included an analysis of (1) Adverse Events, Serious Adverse Events, and Infusion Associated Reactions (IARs), (2) Laboratory Assessments,3) Vital Signs (change over time in blood pressure, heart rate, respiratory rate, and temperature), (4) Physical Examinations (shift in normal/abnormal), (5) Hearing Assessment (shift in normal/abnormal), and (6) ECG (shift in normal/abnormal).

III.1.2.4. Efficacy discussion and conclusions

In conclusion, only one pivotal study was performed. The analysis of the 6 MWT change from baseline to last observed visit with Wilcoxon-Mann-Whitney test stratified by randomisation strata was planned, as well as an ANCOVA model including the randomisation strata. The provided data did not validate the ANCOVA model assumptions; therefore the focus was on the Wilcoxon-Mann-Whitney test stratified by randomisation strata, which required fewer assumptions.

CHMP believed that the robustness of the results of the first co-primary endpoint cannot be assessed, as the sensitivity analysis to the randomisation procedure used in treatment allocation and the sensitivity analysis to the missing data should be provided. In response to this question, Genzyme has provided the results of all analyses requested. These sensitivity analyses were based on the WMW test and were statistically significant. CHMP endorsed these responses. Subgroup analyses of the 6 MWT change from baseline to last observed visit show better results in the Myozyme group than in the placebo group, but due to the small number of patients these results in subgroups are not statistically significant. Results of the first co-primary endpoint are reinforced by most secondary or tertiary endpoints .

Besides, considering some entry criteria, the included patients presented a mild or moderate late-onset disease Pompe and were not late in their disease progression. Regarding the subgroup analyses there is a trend toward improvement in distance walked and in FVC outcomes in Myozyme patients and in particular in the subset “6MWT≥300m” and/or “FVC≥55%”, suggesting that Myozyme could have a benefit in late-onset patients mildly to moderately affected.

To conclude, this study suggests a positive effect of Myozyme in late-onset Pompe disease, but more probably in mild or moderate stages of the disease. The MAH has submitted the interim report data for study AGLU03206 (LOTS Extension).

Out of the 90 patients enrolled in the LOTS study, 81 continued into the extension protocol, AGLU03206. An interim analysis of the results after 26 weeks of the extension study was presented (104 weeks of total treatment). The same safety and efficacy assessments as in Protocol AGLU02704 were performed at scheduled visits throughout the study treatment period.

The patients previously treated with placebo and receiving then Myozyme showed an improvement in mean 6MWT but a decline in mean % predicted FVC at Week 104.

III.2 Clinical safety

Patients with late-onset Pompe disease may present with symptoms during infancy, childhood, adolescence or even adulthood. Late onset Pompe disease is characterised by the progressive loss of proximal skeletal and respiratory muscle strength and function. The course of late-onset Pompe disease is less predictable than the infantile form, with some patients experiencing a rapid deterioration in skeletal and respiratory muscle function leading to loss of ambulation and respiratory failure, others progressing less rapidly, and yet others presenting with a dissociation in the progression of skeletal and respiratory muscle involvement.

In support of the initial Marketing Authorisation, data were included on a limited number of patients with late-onset Pompe disease, the majority of which were treated with Myozyme under various expanded access and compassionate use schemes.

The applicant has submitted in this variation the final clinical study report of the AGLU02704, a phase 3 randomised, double-blind, placebo-controlled study. The MAH proposes to update the safety section of the SPC of Myozyme to reflect the safety data from the 90 patients (Myozyme n=60; Placebo n=30) with late-onset Pompe disease treated in the study.

Patient exposure

Patients included in this study were required to be ≥ 8 years of age at the time of enrolment with a confirmed diagnosis of Pompe and naïve to enzyme replacement therapy with GAA from any source. Patients were also required to be ambulatory and free of invasive ventilation, with quantifiable respiratory and skeletal muscle weakness.

A total of 90 patients were randomised into the study. 60 patients received intravenous infusions of Myozyme at the approved commercial dose of 20 mg/kg at a frequency of every other week and 30 patients received infusion of placebo in a double-blind fashion .
For both treatment groups, the median time in the study from first to last infusion was 78 weeks and the median number of study drug infusions was 39.

The table below summarises the demographics and baseline characteristics of patients in each treatment group.

Table 2.7.4-2: Patient Demographic and Baseline Characteristics in Study AGLU02704

	Myozyme (N=60)	Placebo (N=30)
Age at first infusion (years)	45.3±12.37 (15.9, 70.0)	42.6±11.63 (10.1, 68.4)
Sex		
Male	34 (57%)	11 (37%)
Female	26 (43%)	19 (63%)
Ethnicity		
Caucasian	57 (95%)	27 (90%)
Black	0	0
Hispanic	1 (1.7%)	1 (3.3%)
Asian	1 (1.7%)	1 (3.3%)
Other	1 (1.7%)	1 (3.3%)
Height (cm)	170.6±11.04 (146.8, 196.1)	167.6±11.89 (130.8, 186.9)
Weight (kg)	73.7±17.42 (39.2, 118.8)	73.3±18.57 (20.3, 107.2)
Age at Pompe symptom onset (years)	30.3±12.29 (5.3, 58.6)	23.9±10.96 (2.7, 42.6)
Duration of disease at Baseline	9.0±6.31 (0.3, 24.8)	10.1±8.44 (0.5, 31.3)
Mean % normal GAA activity (fibroblast) at Baseline	10.4±6.67[1] (<1%, 26.3)	10.1±9.5 (<1%, 32.2)
Use of walking device at Baseline	23 (38%)	16 (53%)
Use of respiratory support at Baseline[2]	20 (33%)	11 (37%)
Ventilator	4 (6.7)	3 (10.0)
CPAP	0	1 (3.3)
BiPAP	14 (23.3)	7 (23.3)
Supplemental Oxygen	0	2 (6.7)
Other	1 (1.7)	0

Reference: AGLU02704 CSR Table 11-1
Note: Statistics are n (%) or mean±SD (min, max)
[1] Mean, SD, and Max are corrected to reflect repeat test results on which Patient 47707 was enrolled in the study, not as calculated in Table 14.1.13 in AGLU02704 CSR.
[2] Patients could indicate more than one type of respiratory support or may not have specified the type of respiratory support used.

A higher proportion of patients have been included in Myozyme group compared with the placebo group (ratio 2/1: 60 patients vs 30 patients). Mean age of patients at first infusion in both treatment groups was comparable: 45 years in Myozyme group vs 42 years in placebo group.
In Myozyme group a higher proportion of male patients have been included compared to placebo group (57% vs 37%).

Death/ Discontinuation due to treatment

55 patients (91.7%) in Myozyme treatment group and 26 patients (86.7%) completed the study. Nine patients terminated treatment early (5 in Myozyme group and 4 in Placebo group):

- 3 patients discontinued due to AEs : 2 in Myozyme group after experiencing serious hypersensitivity reactions and 1 in placebo group after experiencing recurrent episodes of headache and later discontinued due to head discomfort assessed as remote/unlikely related to treatment.

- 1 patient in the Myozyme treatment group died (at 74.0 weeks) for reasons unrelated to the treatment. Thirteen days after the Week 72 infusion this 33-year old female developed locked-in syndrome. The decision was made to withdraw life support measures 3 days later and the patient died. The cause of death was considered to be brain stem ischemia secondary to basilar artery thrombosis. At the time of death, the patient was under clinical care for 2 broad-based basilar aneurysms found on angiogram during study participation.
- 1 patient in the Myozyme treatment group chose to discontinue for personal reasons
- 4 patients (1 in the Myozyme treatment group, 3 in the Placebo treatment group) chose to discontinue pursuing treatment with commercial Myozyme therapy.

Summary of adverse events

All patients in the study experienced at least 1 treatment-emergent AE (AEs that occurred following the initiation of study treatment); a total of 2296 treatment-emergent AEs (1445 in Myozyme group vs 851 in Placebo group) were experienced by 90 patients. The total numbers of AEs reported in this study is summarised in the table below.

Table 2.5.5.1-1: Overview of Treatment-Emergent Adverse Events in Study AGLU02704

Variable	Myozyme		Placebo	
	Number of Patients (N=60) n (%)	Number of AEs n (%)	Number of Patients (N=30) n (%)	Number of AEs n (%)
Any TEAE	60 (100.0)	1445 (100.0)	30 (100.0)	851 (100.0)
Treatment-Related AEs	32 (53.3)	298 (20.6)	17 (56.7)	144 (16.9)
Infusion-Associated Reactions	17 (28.3)	236 (16.3)	7 (23.3)	73 (8.6)
SAEs	13 (21.7)	20 (1.4)	6 (20.0)	7 (0.8)
Severe AEs	14 (23.3)	29 (2.0)	10 (33.3)	18 (2.1)
Patients who Discontinued Due to AEs[1]	3 (5.0)	N/A	1 (3.3)	N/A
Patients who Died	1 (1.7)	N/A	0	N/A

Reference: Table 12-2 of the Clinical Study Report for Study AGLU02704
[1] Includes those patients experiencing events with fatal outcome
N/A = not applicable

In Myozyme treatment group, the most common AEs term were fall, nasopharyngitis, headache, hypoacusis, diarrhoea, arthralgia, and pain in extremity. The majority of AEs were assessed as mild or moderate (98.0%), unrelated to treatment (79.4%), and resolved before the end of the study (91.3%). In placebo treatment group, the most common AEs were fall, nasopharyngitis, and headache. Similar to Myozyme, the majority of AEs were assessed as mild or moderate (97.9%), unrelated to treatment (83.1%), and resolved before the end of the study (89.7%).

The majority of treatment-emergent AEs in both treatment groups were assessed as unrelated or unlikely/remotely related to treatment. In the Myozyme treatment group, 298 AEs occurring in 32 patients were considered possibly, probably, or definitely related to study treatment and in the Placebo treatment group, 144 AEs occurring in 17 patients were considered possibly, probably, or definitely related to study treatment.

In the Myozyme treatment group, the most frequent treatment-related events were nausea, headache, urticaria, hyperhidrosis, dizziness, chest discomfort. In the Placebo group, the most frequent treatment-related events were headache, fatigue, and nausea.

The majority of treatment-related AEs were non-serious. 9 related events were reported as SAEs, including 7 events (2 events of hypersensitivity and single events of angioedema, chest discomfort, non-cardiac chest pain, supraventricular tachycardia, and throat tightness) in 4 patients in the

Myozyme treatment group and 2 events (septal panniculitis and headache) in 2 patients in the Placebo treatment group. 7 of the serious related events were characterised as IARs (Infusion associated Reactions). IARs were defined as AEs that occurred during either the infusion or the observation period following the infusion which were deemed to be related (i.e., possibly, probably or definitely) to study drug.

The majority of treatment-related AEs were characterised as IARs. In the Myozyme group, 236 among the 298 related events (79.2%) were characterised as IARs and in the Placebo group 73 of the 144 related events (50.7%) were characterised as IARs. Increased frequency of IARs in the Myozyme treatment group was largely attributed to a single IgE positive patient who experienced 116 (49.2%) of the total 236 IARs in the treatment group.

The most frequent IARs (those occurring in ≥ 5% of patients) in Myozyme group were nausea, headache, urticaria, dizziness, chest discomfort, hyperhidrosis, flushing, blood pressure increased, vomiting and in the Placebo group were headache, nausea and dizziness. IARs occurring in the Myozyme group only included chest discomfort, urticaria, flushing, hyperhidrosis, blood pressure increased, and vomiting. The majority of IARs were non-serious, 7 IARs were assessed as serious, including 6 events in 3 patients in Myozyme group and 1 event in 1 patient in the Placebo group.

Most IARs occurred either at the lowest infusion rates (which were generally used early in the infusion period) or at the highest infusion rates. During infusion in the Myozyme treatment group, 112 of 169 IARs (66.3%) occurred at lower infusion rates (i.e., >0 to ≤3 mg/kg/hr) and 36 IARs (21.3%) occurred at higher infusion rates (i.e., >5 mg/kg/hr). During infusion in the Placebo treatment group, 30 of 40 IARs (75.0%) occurred at infusion rates >5 mg/kg/hr, 5 IARs (12.5%) occurred at infusion rates >3 to ≤ 5 mg/kg/hr and 5 IARs (12.5%) occurred at infusion rates >0 to ≤ 3 mg/kg/hr. Infusions rates in which IARs occurred varied between treatment groups. The majority of IARs in both treatment groups resolved spontaneously. IARs requiring intervention were managed with infusion rate reduction and / or interruption of infusion and / or administration of medications / therapies, when clinically indicated. Serious hypersensitivity reactions occurred in 3 patients of which reactions were IgE mediated in 2 patients. One Patient of the two experienced serious events of hypersensitivity, chest discomfort, and throat tightness and non-serious events of urticaria, blood pressure increased, flushing, nausea, oxygen saturation decreased, rash papular, pruritus, sinus tachycardia, wheezing, and headache. The second Patient experienced serious hypersensitivity reaction consisting of symptoms of serious non-cardiac chest pain and non-serious events of chest discomfort, urticaria, feeling hot, flushing, local swelling, pruritus, lip swelling, and rash macular. And the third patient mentioned above experienced angioedema. Two of the 3 patients were withdrawn from the study as a result of reactions. Both patients with IgE-mediated reactions were successfully re-treated with Myozyme using a desensitisation procedure under close clinical supervision and continued to receive treatment; one patient was re-treated during study participation with incrementally increasing dose from 10 mg/kg per week for 6 consecutive weeks followed by a 7th week of 15 mg/kg before resuming the protocol specified dose of 20 mg/kg qow. The second patient was re-treated in the commercial setting at lower dose of Myozyme administered at a slower rate.

All evaluable patients in the Myozyme group tested positive for anti-rhGAA IgG antibodies. One patient who discontinued from the study due to IARs at the Week 2 infusion tested IgG-negative at the baseline test performed before the first infusion. In the 59 patients who ever tested IgG-positive, the median time to seroconversion was 4 weeks (range of 4 to 12 weeks). The median peak anti-rhGAA IgG antibody titre was 6,400 (range 200 to 819,200).
In the 16 patients in the Myozyme treatment group who were ever sero-positive and who experienced IARs, seroconversion occurred by Week 8. Six of the 16 patients experienced the first IAR with the first infusion, before seroconversion. One patient sero-converted 6 weeks after the first IAR, one patient experienced 1 IAR coincident with seroconversion at Week 4 (patient who experienced angioneurotic oedema), and 8 patients experienced the first IAR from 8 weeks to 52 weeks after seroconversion. There was no consistent effect on either co-primary efficacy endpoint (Six Minute Walk Test or Forced Vital Capacity) when patients are stratified by mean IgG titre quartiles

Patients who experienced moderate, severe, or recurrent IARs were tested for anti-rhGAA IgE antibodies, complement activation, and serum tryptase. Two of 10 patients in the Myozyme treatment group tested for anti-rhGAA IgE antibodies were positive. 6 of 9 Myozyme-treated patients who were tested were positive for complement activation. 1 of these 9 patients had a significantly elevated level of serum tryptase as well as experiencing a serious hypersensitivity reaction.

The total number of treatment-related AEs was 298 in Myozyme group vs 144 in placebo group. The majority of AEs were assessed as mild or moderate in intensity (98.0% in Myozyme group and 97.9 in placebo group) and unrelated to study drug (79.4% in Myozyme group vs 83.1% in placebo group). Most of them were consistent with the underlying Pompe disease. The rate of patients who experienced treatment related adverse events and serious adverse events are comparable between the 2 groups. The frequency of patients who experienced IARs was slightly higher in Myozyme group than in placebo group: 28% of the patients of Myozyme group experienced IARs vs 23.3% in the placebo group. Additionally, the number of AEs characterised as IARS in Myozyme group was higher than in placebo group (236 vs 73), to be noted that one patient has experienced half of the IARs in the Myozyme group. The increased should be explained by the higher number of patients included in Myozyme group (60 patients in Myozyme group vs 30 patients in placebo group), and it is due to the specificity of treatment. 9 patients discontinued from the study; among them 4 discontinued due to AEs or death. The majority of related AEs were assessed as non-serious.

13 (21.7%) patients in the Myozyme treatment group experienced 20 SAEs and 6 (20.0%) patients in the Placebo treatment group experienced 7 SAEs. A few number of serious adverse events assessed as related have been reported: 9 SAEs were assessed as related (7 events in the Myozyme treatment group and 2 in the Placebo treatment group). Serious adverse events as related in Myozyme group included: hypersensitivity, angioneurotic oedema, chest discomfort, non-cardiac chest pain, supraventricular tachycardia, and throat tightness. Except supraventricular tachycardia, all related SAEs in the Myozyme group were characterised as IARs. In Myozyme group, 3 patients experienced serious IARs. Among the 3 patients, 2 were successfully re-treated with Myozyme using desensitisation procedure (one during study participation and one in the commercial setting).

The majority of the adverse events related to Myozyme are consistent with the known safety profile of Myozyme. All evaluable patients in the Myozyme group were tested positive (59 patients) for anti-rhGAA IgG antibodies.

The CHMP agree with the MAH that there was no apparent association between IgG antibody titre and occurrence of IARs.

The MAH added that on 24 July 2008, a CHMP opinion was issued on the assessment report for Study AGLU03105 (FUM020). In that assessment report the CHMP requested the MAH to include safety information from Study AGLU03105 in the SPC. As the safety information from AGLU02704 is more comprehensive and as all safety concepts from AGLU03105 are covered by the changes proposed for this variation based on Study AGLU02704, the MAH believed that no additional type II variation is needed for AGLU03105. The CHMP is in agreement with the proposal of the MAH.

Risk Management Plan

No special risks have been identified regarding the Late-Onset Pompe disease patients. The CHMP accepted the justification not to submit a RMP.

III.2.1 Safety discussion and conclusion

Based on the safety data of the study AGLU02704 in the late onset patients, the safety profile of Myozyme appears consistent with the known safety profile of the product; no new safety concern has been raised. The majority of the adverse events was assessed as mild or moderate and was due to manifestations of Pompe disease and not related to Myozyme. Moreover, the majority of treatment related AEs were assessed as non serious. The rate of patients who experience treatment related adverse events and serious adverse events are comparable between the Myozyme group and placebo

group. Slightly more patients in Myozyme group than in placebo group experienced IARs (28% patients vs 23.3%), and the number of IARS in Myozyme group is higher than in placebo group (236 vs 73). The increased frequency of IARs in the Myozyme treatment group was largely attributed to a single IgE positive patient who experienced 116 (49.2%) of the total 236 IARs in the treatment group. The most frequently reported adverse events related to the administration of Myozyme remain IARS. Moreover, the percentage of patients treated with Myozyme who experienced IARs was lower in the late onset patients (28%) than in the infantile patients (around 50%). All evaluable patients (59 patients) treated with Myozyme developed IgG antibodies to rhGAA by Week 12, with a median time to seroconversion of 4 weeks. Immunogenicity remains a concern in patient treated by Myozyme. Serious hypersensitivity occurred in 3 patients treated with Myozyme, in 2 patients reactions were IgE mediated. Among the 3 patients, 2 were successfully re-treated with Myozyme using desensitisation procedure (one during study participation and one in the commercial setting).

Based on these data the CHMP agreed with the MAH to update the SPC and leaflet with the safety data of the AGLU02704 study however the final text for the modifications of the SPC will need to be re-discussed. The CHMP also agreed that the FUM020 is fulfilled by the submission of this variation type II and the information on safety will be inserted in the SPC accordingly.

Safety data of AGLU03206

Eighty-one patients who completed study AGLU02704 continued into the extension protocol AGLU03206. The MAH has performed an interim analysis of safety data of study AGLU03206. As of 15 April 2008, all patients have completed Week 26 assessments in the study with treatment duration of 25.1 to 53.9 weeks. No patients died or discontinued treatment due to AEs during alglucosidase alfa treatment. All patients but 2 patients experienced AEs, a total of 878 AEs were reported through 15 April 2008.

The majority of AEs were non-serious, assessed as mild to moderate in severity (98.5%), and unrelated to treatment (87.0%). 28 patients experienced 114 AEs that were assessed by the investigator as related to alglucosidase alfa, all of which were non-serious and all but 1 were assessed as mild or moderate in severity. Among the treatment related AEs, about half were characterized as IARs.

Based on the data provided by the MAH, the interim results of study AGLU03206 do not raise new safety issues compared with result of study AGLU02704 and with previous experiences in late onset and in infantile onset patients.

III.3. Overall Discussion and Benefit Risk assessment

The MAH submitted this type II variation in order to delete the reference to non established benefits for the late onset patients:

> *"The benefits of Myozyme in patients with late-onset Pompe disease have not been established."*

The main study AGLU02704 submitted was a Randomised, 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.

The analysis of the 6 MWT change from baseline to last observed visit with Wilcoxon-Mann-Whitney test stratified by randomisation strata was planned, as well as an ANCOVA model including the randomisation strata. The provided data did not validate the ANCOVA model assumptions; therefore the focus was on the Wilcoxon-Mann-Whitney test stratified by randomisation strata, which required fewer assumptions.

CHMP believed that the robustness of the results of the first co-primary endpoint cannot be assessed, as the sensibility analysis to the randomisation procedure used in treatment allocation and the sensibility analysis to the missing data should be provided. In response to this question, Genzyme has

provided the results of all analyses requested. These sensitivity analyses were based on the WMW test and were statistically significant. CHMP endorsed these responses. Subgroup analyses of the 6 MWT change from baseline to last observed visit show better results in the Myozyme group than in the placebo group, but due to the small number of patients these results in subgroups are not statistically significant. Results of the first co-primary endpoint are reinforced by most secondary or tertiary endpoints .

Considering some entry criteria, the included patients presented a mild or moderate late-onset disease Pompe and were not late in their disease progression. Regarding the subgroup analyses there is a trend toward improvement in distance walked and in FVC outcomes in Myozyme patients and in particular in the subset "6MWT≥300m" and/or "FVC≥55%", suggesting that Myozyme could have a benefit in late-onset patients mildly to moderately affected. Moreover, the responder analysis suggested an overall benefit from Myozyme treatment more marked for the lower thresholds, indicating a limited effect of Myozyme. The possibility of excluding the severely affected late-onset patients from the indication was considered.

The most frequently reported adverse events related to the administration of Myozyme remain IARS. Moreover, the percentage of patients treated with Myozyme who experienced IARs was lower in the late onset patients (28%) than in the infantile patients (around 50%).

The results of the 1-year observational study in 58 patients with a confirmed diagnosis of late-onset Pompe disease do not provide any new data.

In December 2008 the CHMP concluded that, the provided pivotal study suggests a positive effect of Myozyme in late-onset Pompe disease, but more probably in the mild or moderate stages of the disease. The efficacy and safety follow-up from patients included in the open-label extension study AGLU03206 would allow enlightening on the real benefit of Myozyme in late-onset disease. These data have now been submitted (interim report).

Following the assessment of the responses of the MAH allowed resolving some of the issues raised throughout this procedure, in particular regarding pharmacokinetic and some methodological aspects. In addition a significant effect of Myozyme has been observed in the late-onset patients on the co-primary endpoint, throughout the submitted studies. Nevertheless, no new data has been generated to fully address some of the issues, namely the supportive results of the secondary endpoints or the apparent more marked effect in the mild or moderate stages of the disease. Furthermore, interim results from the open-label extension study AGLU03206, did not clearly suggest that efficacy is strictly maintained during the extension study. In addition, the low report of change of the walking device status in treated as well as untreated patients may indicate that the benefit of Myozyme in late-onset disease, if any, will probably be observed only on a longer term, in view of the slow rate of the disease progression.

However, the real effects/benefits of Myozyme in this population, although established in some ways, remain difficult to characterise in many other aspects. In particular, when compared to the early-onset patients, the late-onset disease often progresses at a slower rate and the life threat is usually on a much longer term.

Considering the above assessment and the discussion that followed, the CHMP agreed on the following amended wording regarding the late-onset patients for section 4.1 of the SPC:

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

Following the acceptance by the MAH of the proposed amendments in the Product Information the CHMP concluded that the benefit risk balance for Myozyme remains positive.

III.4 Product Information

Summary of Product Characteristics

The section 4.1 of the Therapeutic Indication has been amended. The new full indication for Myozyme is as follows:

> *"Myozyme is indicated for long-term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of Pompe disease (acid α-glucosidase deficiency).*
>
> *In patients with late-onset Pompe disease the evidence of efficacy is limited (see section 5.1)."*

In the section 5.1 "Pharmacodynamic properties", the results of the studies related to late-onset Pompe disease are introduced. Section 5.2 "Pharmacokinetic properties" has been updated to include pharmacokinetic data from late-onset Pompe disease patients.

The sections 4.4 "Special warnings and precautions for use" and sections 4.8 "Undesirable effects" of the SPC have been reworked in order to include the information from the submitted studies as well as the distinction in the observations for infantile-onset and late-onset patients.

Package Leaflet

The Package Leaflet has been amended accordingly.

IV. CONCLUSION

On 24 September 2009 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, and Package Leaflet.