European Medicines Agency

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ASSESSMENT REPORT
FOR
Myozyme

International Nonproprietary Name:
alglucosidase alfa

Procedure No. EMEA/H/C/000636/II/0005

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

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SCIENTIFIC DISCUSSION

1. Introduction

Myozyme (alglucosidase alfa) is a recombinant form of human acid α-glucosidase (rhGAA)and is produced by recombinant DNA technology using Chinese Hamster Ovary (CHO) cell culture.

Myozyme is indicated for long-term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of Pompe disease (acid α-glucosidase deficiency). The benefits of Myozyme in patients with late-onset Pompe disease have not been established.

The Marketing Authorisation for Myozyme (alglucosidase alfa) was granted on 29 March 2006.

2. Clinical aspects

In support of the initial Marketing Authorisation (MA) data were provided from two ongoing pivotal clinical studies, the open-label studies AGLU01602 (interim results of 26 weeks of treatment in the first 18 patients) and AGLU01702 (results after 52 weeks of treatment in the first 15 patients). After granting of the MA these studies were completed.

The patients who completed study AGLU01602 were followed up in extension study AGLU02403 and this study has also been completed. The final clinical study reports for AGLU01602/AGLU02403 and AGLU01702 are now submitted to the CHMP as part of this type II variation.

This type II variation application aims to include additional long term, safety and efficacy treatment data in the Summary of Product Characteristics (SPC). The clinical data presented in this application consist of data from studies AGLU01602, AGLU01702 and AGLU02403.

In addition an updated Detailed Description of the Pharmacovigilance System (DDPS) has been submitted with this variation application.

2.1. Clinical Efficacy

2.1.a Clinical Studies

In order to address the lack of comparator products and the unethical use of a placebo in clinical studies evaluating patients with the fatal infantile-onset form of the disease, the MAH created matching historical reference groups for the AGLU01602/AGLU02403 and AGLU01702 studies by applying screening criteria based on the eligibility criteria for the 2 treatment studies to the 168 untreated patients with infantile-onset Pompe disease in the Natural History Study (AGLU-004-00).

The data presented in this Type II Variation are summarised in the Table 2.1.1 below.

Table 2.1.1 Clinical Studies

Study Number	Study Design	No./ Location of Enrolling Centres	Study Dates	No. of Subjects Enrolled /Treated	Planned Dose Range & Frequency	Mean Age ± SD at First Infusion
NATURAL HISTORY STUDY [1]						
AGLU-004-00	Natural History Study	33/ 9 countries	February 2002 – November 2002	168/0	NA	NA
MYOZYME INFANTILE-ONSET STUDIES						
AGLU01602	Randomized, Open-label, Multicenter Safety, Efficacy, Pharmacokinetic and Pharmacodynamic, Dose Ranging Study of Myozyme	13/ USA, Europe, Israel, Taiwan	26 May 2003 – 15 June 2005 [2]	19/18[3]	20 or 40 mg/kg qow	4.6 ± 1.7 months[4]
AGLU02403 [2] (extension of AGLU01602)	Open-label, Multicenter, Safety, Efficacy, Pharmacokinetic and Pharmacodynamic Dose-ranging, Continuation Study of Myozyme	18 [7]/ USA, Europe, Israel, Taiwan	15 June 2005 – 15 June 2006	16/16	20 or 40 mg/kg qow	4.6 ± 1.7 months[6]
AGLU01702	Open-label Multicenter Safety, Efficacy, Pharmacokinetic and Pharmacodynamic Study of Myozyme	6/ USA, Europe, Israel	19 February 2003 – 14 July 2006	22/21[5]	20 mg/kg qow	15.7 ± 10.96 months

Reference: Individual Study CSRs.
[1] AGLU-004-00 was not a Myozyme treatment study, but a retrospective chart review study of 168 untreated patients with infantile-onset Pompe disease. Historical reference groups for the AGLU01602 and AGLU01702 studies were derived from this study.
[2] After completion of AGLU01602, patients were eligible for participation in the open-label continuation treatment study AGLU02403 provided there were no safety concerns.
[3] Nineteen patients enrolled, but 1 patient required invasive ventilation prior to initiation of treatment and was therefore discontinued from the study.
[4] Age at first infusion was adjusted for gestational age.
[5] Twenty-two patients enrolled, but 1 patient died before initiating treatment.
[6] Mean age for the 18 patients who were treated in AGLU01602
[7] Number of centres increased compared to AGLU01602 as patients were transferred to local hospitals to receive their biweekly infusions

2.1.b Patient Populations

- **Natural History Study (AGLU-004-00)**

An epidemiological study that utilised retrospective chart reviews of 168 untreated patients diagnosed with infantile-onset Pompe disease to better characterise the natural course of the disease. This group of patients was also used to create historical control and reference groups for comparison with Studies AGLU01602/AGLU02403 and AGLU01702.

- **Study(ies) AGLU01602/AGLU02403**

Infantile-onset patients with the most rapidly progressive ("classic") phenotype were treated early in the course of their disease with first infusions administered by 6 months of age in open-label pivotal study AGLU01602. Patients had evidence of cardiomyopathy and endogenous GAA activity of ≤1% of mean normal values prior to their first infusion of Myozyme. They should be ≤ 6 months of age

(corrected for gestation if necessary) and ventilator-free at initiation of treatment. These patients were further followed in study AGLU02403 for up to 52 weeks to allow for up to 36 months of exposure.

Due to the commercial launch of Myozyme, Study AGLU02403 was terminated per protocol after approximately 52 weeks and AGLU02403 patients were transitioned to commercial therapy.

- **Study AGLU01702**

In AGLU01702, the patient population ranged from 3.7 to 43.1 months of age at initiation of treatment and thus included patients with advanced, rapidly progressive infantile-onset Pompe disease ("classic") as well as those who had survived untreated past 1 year of age ("non-typical"). The patients in this study were generally at a more advanced stage of disease progression compared to patients in study AGLU01602, before starting treatment with Myozyme as evidenced by extremely low Baseline motor age-equivalent scores and the requirement for ventilation in a third of the patients.

2.1.c Efficacy Endpoints in Patients with Infantile-Onset Pompe Disease

The efficacy endpoints and corresponding assessment measures consistently used in the infantile-onset studies are listed in the Table 2.1.2 below:

Table 2.1.2 Efficacy Endpoints and Assessment Measures

Infantile-onset Pompe Disease Endpoints	Measures
Survival	Status at time of Analysis
Invasive Ventilator-free survival	Status at time of Analysis
Any Ventilator-free survival	Status at time of Analysis
Ventilator Support	Type and Duration of Use
Cardiomyopathy	LVM, LVMI, EF and SF
Growth	Weight, Length, and Head Circumference
Motor Development	AIMS, PDMS-2, and Developmental Milestones
Cognitive Development	BSID-II

As primary endpoint was considered the survival of the patients free of any ventilation support and free of invasive ventilation. Secondary endpoints included cardiomyopathy, growth and motor development.

2.1.d. Dosing in Clinical Studies

The safety and efficacy of 20 and 40 mg/kg Myozyme administered every other week (qow) was examined in pivotal study AGLU01602 and the extension study AGLU02403. The 18 patients continued to receive the same dose of Myozyme that they were randomly assigned to receive under Protocol AGLU01602 (either 20 mg/kg or 40 mg/kg of body weight).

In the table 2.1.3 the effect of the two different doses on efficacy endpoints is summarised:

Table 2.1.3 Effect of 20 and 40 mg/kg qow Myozyme on Key Efficacy Endpoints in AGLU01602/AGLU02403

Parameter Evaluated	20 mg/kg dose (N=9)	40 mg/kg dose (N=9)
Proportion alive at 36 months of age[1]	88.9% (1 died)	60.0% (3 died)
Proportion alive and free of invasive ventilation at 36 months of age[1]	55.6% (4 with invasive ventilator support)	41.7% (5 with invasive ventilator support)
Proportion alive and free of any ventilation at 36 months of age[1]	55.6% (4 with any ventilator support)	41.7% (5 with any ventilator support)
Patients with decrease in LVMI from Baseline[2]	9 of 9	8 of 9
Patients with Normal Weight at last assessment[3]	9 of 9	8 of 9
Patients with Motor Gains at last assessment as Assessed by AIMS Age-Equivalent Scores[4]	6 of 9	5 of 9
Patients with Motor Gains at last assessment as Assessed by Developmental Motor Milestones[5]	6 of 9	5 of 9

Reference: Final CSR of AGLU01602/AGLU02403.

1 Proportions are from Kaplan-Meier analysis of time to events. One patient died 1 year after study completion after database lock and was not included in the survival analysis.

2 Includes those patients with Baseline and subsequent echocardiography assessments.

3 Patients who maintained normal weight are those with values above the third percentile at last assessment.

4 Based on AIMS age-equivalent scores.

5 Based on the total number of developmental Motor Milestones.

As concluded by the CHMP during the assessment, the initial data provided by the MAH appeared not comprehensive, as no information regarding the duration of treatment at the "last assessment" was available in order to display an integrative overview of Myozyme efficacy in a long-term setting. Furthermore, the figures regarding the number of patients appeared discrepant since several patients died during the studies AGLU01602/AGLU02403. Therefore the MAH was asked by the CHMP in a Request for Supplementary Information adopted in the May 2008 CHMP meeting to provide explanation on this topic as well as comprehensive results.

The MAH responded that in AGLU01602/AGLU02403, the mean duration of Myozyme treatment received by patients at the last assessment was 836 days (119.4 weeks). The minimum duration of treatment received by patients was 418 days (59.7 weeks) and the maximum was 1050 days (150 weeks). The majority of the patients (16/18) received at least 2 years of treatment. The proportion of patients alive and free of any ventilation and invasive ventilation was based on a measurement at the patient's age of 36 months, as defined in the protocol. The secondary endpoints of left ventricular mass index (LVMI), weight and motor gains (AIMS and Developmental Motor Milestones) were based on last assessment. The MAH provided also an updated Cox Regression Model Analysis (as had been requested by CHMP during the initial marketing authorisation application). Data from the Cox Regression Model Analysis were also proposed for inclusion in the SPC section 5.1 "Pharmacodynamic Properties".

The CHMP accepted the explanations provided by the MAH.

The dose remains unchanged as 20 mg/kg of body weight once every 2 weeks.

2.1.e Efficacy Results

For the critical endpoints of survival, invasive ventilator-free survival (survival free of invasive ventilation), and any ventilator-free survival (survival free of invasive and non-invasive ventilation), results for Myozyme-treated patients in AGLU01602/AGLU02403 were compared to overall survival in an appropriate historical control group. Similarly, 52- and 104-week survival in AGLU01702 patients was compared with estimated survival in an appropriate historical reference group.

Efficacy Results of Study AGLU01602/AGLU02403

The primary efficacy endpoint was the proportion of AGLU01602 patients alive and free of invasive ventilator support at 18 months of age in comparison to overall survival rates at 18 months of age for the AGLU01602 Historical Control Subgroup. Overall survival rates calculated using the Kaplan Meier method were used for this comparison because ventilator dependence could not be conclusively determined for the AGLU01602 Historical Control Subgroup due to a lack of ventilator data in the patient medical records.

Seventeen of the 18 enrolled patients completed AGLU01602, as one patient died during study. Sixteen patients were subsequently enrolled in extension Study AGLU02403 to continue treatment with Myozyme. The remaining patient, who continued to receive Myozyme under the International EAP, died after completion of AGLU01602. Of the 16 patients who were enrolled in AGLU02403, 13 completed the study. Two patients died during AGLU02403 study participation, one patient withdrew from the study and died after withdrawal, and one additional patient died after study completion.

Results on the Primary endpoint

Table 2.1.4 Proportion of patients alive and free of invasive ventilator support in AGLU02403

Age (months)	Dose group	N	Patients alive and invasive-ventilator-free	Patients censored	Pat-ients failed	Proportion estimate and 95% CI
12	Overall	18	16	0	2	88.9 (74.4, 100.0)
	20 mg/kg	9	8	0	1	88.9 (68.4, 100.0)
	40 mg/kg	9	8	0	1	88.9 (68.4, 100.0)
18	Overall	18	15	0	3	83.3 (66.1, 100.0)
	20 mg/kg	9	8	0	1	88.9 (68.4, 100.0)
	40 mg/kg	9	7	0	2	77.8 (50.6, 100.0)
24	Overall	18	12	0	6	66.7 (44.9, 88.4)
	20 mg/kg	9	6	0	3	66.7 (35.9, 97.5)
	40 mg/kg	9	6	0	3	66.7 (35.9, 97.5)
36	Overall	18	5	4	9	49.4 (26.0, 72.8)
	20 mg/kg	9	3	2	4	55.6 (23.1, 88.0)
	40 mg/kg	9	2	2	5	41.7 (7.8, 75.6)

[a] Proportions are from Kaplan-Meier analysis of time to invasive ventilation dependence or death
[b] Censored indicated the number of patients who were event-free, yet were not followed up to the time point analysed
[c] failed indicates the number of patients who either died or became invasive ventilation dependent before the time point analysed.

At month 36, nine (9) of the 18 patients were receiving invasive ventilatory support yielding an invasive ventilator-free survival rate of approximately 26 times the overall survival rate for untreated patients at 36 months of age. Compared to untreated patients, the primary efficacy endpoint for this pivotal study was achieved. However, it should be noted that this difference was reduced, as it reached approximately 43 times at 18 months of age.

Furthermore, as shown in the above Table 2.1.4, four patients at 36 months of age were censored i.e. patients who were event-free, yet were not followed up to the time point analysed, as mentioned by the MAH. The MAH was requested by the CHMP in the Request for Supplementary Information adopted in May 2008 to explain how it could be feasible to hypothesise that patients, whose outcome was not known, could be considered at benefit of treatment.

The MAH explained that the censored patients had no impact on the results of the analysis. Furthermore, the MAH confirmed that all four censored patients were alive and not on ventilation at the age of 36 months. The most recent survival and ventilation status information for these patients was also given. In addition data of two of these four patients are available in the Pompe Registry and safety and efficacy data were submitted as part of the Annual Pompe Registry Report . The CHMP agreed with the explanation. Data from the Cox Regression Model Analysis were proposed for inclusion in the SPC (section 5.1)

Other Clinical Endpoints

Regarding the other clinical endpoints, main results are reported below.

Cardiomyopathy

Progression of cardiomyopathy was evaluated through echocardiographic assessment of left ventricular mass index (LVMI). In addition, gross measurements of left ventricular function were obtained non-invasively through echocardiographic measurements of ejection fraction (EF) and shortening fraction (SF).

Marked improvements in echocardiographic parameters that measure progression in cardiomyopathy were observed in AGLU01602/AGLU02403. LVM Z-scores and LVMI were highly elevated in all patients' first measurements as compared to values in normal pediatric subjects (mean baseline LVMI 193.4 ± 62.18, mean baseline LVM Z-score 7.1 ± 1.64). Seventeen of 18 patients (94.4%) showed LVM decreases of at least one Z-score from first assessment to last assessment. At study end, mean LVMI had decreased 40%, corresponding to a mean reduction of 3.9 in the LVM Z-score. In total, 7 (38.9%) patients had LVMs that had returned to within normal limits at their last evaluation. Treatment effects, i.e., changes from Baseline in mean LVMI and LVM Z-scores > 2, were evident from Week 26 onward.

Physical Growth: Changes in Length and Weight

Physical growth was measured at regular intervals throughout the study. Patients were considered to maintain normal growth if the respective percentiles remained within normal limits throughout the study (i.e., above the 3rd percentile).
At the last available assessment:
- All patients (100%) were above the 3rd percentile for length,
- 17 of 18 patients (94.4%) had maintained or improved weight for age percentiles,
- Sixteen of 18 patients (88.9%) were above the 3rd percentile for head circumference.

Motor development

The Alberta Infant Motor Scale (AIMS) was used for assessment of all 18 patients:
- Seven of the 18 patients made motor development gains during the study and were walking independently by the last study assessment.

- An additional 4 patients made motor development gains during the study and were sitting independently by the last study assessment, although they did not have functional use of the legs.
- The remaining 7 patients made no clinically significant motor gains or were unable to sustain the motor gains made and had very limited motor movement by the last study assessment.

Regarding the above clinical endpoints, the efficacy of Myozyme seems globally maintained, as shown by the sustained decrease of LVMI, the maintenance of normal growth percentiles and acquisition of new gross motor skills in some patients.

Nevertheless, as shown in the LVMI scores, only 8 patients at 104 weeks (some receiving 20mg/kg and some receiving 40mg/kg) have been studied for cardiomyopathy. Although both dose groups showed an overall decrease in LVMI from baseline, differences were noted between the 20 mg/kg and 40 mg/kg groups at Week 104, at which time the 40 mg/kg groups demonstrated a more modest reduction than the 20 mg/kg group. This difference may be attributed to the small sample size, as the 40 mg/kg group contained only 3 patients.

The CHMP further noted that at Month 36, five (5) patients died leading to a diminution of the survival rate from 100% (at 18 months of age) to 72%. Two further patients died after study completion or withdrawal. According to the safety part, a total of 3 treatment-emergent deaths have been reported in these studies and were due to cardio-respiratory causes, consistent with complications of the underlying Pompe disease. It should be noted that if cardio-respiratory complications occurred, it implied that efficacy was not achieved.

In addition it appeared that treatment with Myozyme was effective on invasive ventilator-free survival and survival when compared to overall survival in untreated patients. Nevertheless, this efficacy could be interpreted as a prolongation of invasive ventilator-free survival and survival rather than as a persistent and long-term efficacy (as shown by the consistent rates diminutions from 18 to 36 months of age).

In view of the above the MAH was requested in May 2008 to analyse the results in light of the last data and to comment on the potential loss of efficacy over time. The MAH was also requested to follow and provide efficacy data of patients over 36 months of age.

In their reply the MAH argued that in studies AGLU01602/02403 it was observed that a lower survival rate at the age of 36 months appeared not to be caused by Myozyme over time losing some of it's efficacy, but related to a sub-optimal response in certain patients who have a poor prognosis (for reasons not yet fully understood) and who ultimately die. Of the 18 patients enrolled in study AGLU01602, of whom 16 patients were enrolled in its extension study AGLU02403, 6 patients died during or shortly after the end of study AGLU02403. Of those 6 patients, all but one never showed a motor improvement with Myozyme treatment; they were never able to sit independently, walk or climb stairs. Conversely, the 7 patients who learned to walk and climb stairs and three of the 4 patients who did not learn to walk, but did show a motor response (ability to sit independently), all survived to the age of 36 months. None of these 10 patients have shown a decline of their clinical response, and therefore in none of these patients there appeared to be a loss of efficacy of Myozyme over time.

The CHMP considered that regarding studies AGLU01602/02403, the MAH's interpretation on a potential loss of efficacy over time focuses on a potential correlation between improvement of motor response in surviving patients, and conversely no improvement in patients who died. The Committee agrees that these data would be further assessed through the analysis of the annual Pompe Registry report, provided that the follow-up (every 6 months) of patients is assured.

Relationships between Oligosaccharide Levels, Age at First Infusion, and Functional Outcome

Hex-4 was measured in both plasma and urine in Study AGLU01602 and Study AGLU02403. The upper limit of normal (defined as the mean +2 SD) for urine Hex-4 is 18.8 mmol/mol creatinine (Cr) for infants from 0-0.5 years old; 14.0 mmol/mol Cr, for infants 0.5-1 year old, and 5.0 mmol/mol Cr, for children 1 to 5 years old (Duke University Medical Center normal reference values).

Urinary Hex-4 levels were elevated (above the upper limit of normal) in all 16 patients who had Baseline measurements. Mean urinary Hex-4 remained stable (20 mg/kg dose group) or decreased (40 mg/kg dose group) from baseline to Week 52 but increased at later time points in both dose groups.
At Week 104 the mean urinary Hex-4 had increased in both dose groups (mean increase in urinary Hex-4 was 63% in the 20 mg/kg dose group and 47% in the 40 mg/kg dose group).

Median baseline urinary Hex-4 levels in patients above and below the median age at first infusion (5.6 months, not corrected for gestational age) were comparable between the 2 age categories. Similar trends in the development over time of Hex-4 levels were observed in the 2 age groups, with a reduction in Hex-4 levels at the beginning of the study and increases later in the study (typically after Week 52).

Table 2.1.5 Hex-4 Levels Over Time by Age Group

	Baseline		Week 26		Week 52		Week 78		Week 104	
Age group	**N**	**Mean, µmol/L (SD)**	**N**	**Mean, µmol/L (SD)**	**N**	**Mean, µmol/L (SD)**	**N**	**Mean, µmol/L (SD)**	**N**	**Mean, µmol/L (SD)**
< 5.6 months at first infusion	7	39.25 (12.785)	9	12.48 (6.178)	9	35.75 (32.717)	9	35.76 (21.681)	8	54.87 (39.903)
≥ 5.6 months at first infusion	9	37.21 (11.002)	8	21.32 (11.349)	8	27.83 (15.934)	7	47.39 (43.151)	5	63.87 (30.599)

Likewise, no differences in motor functional status distribution at the end of the study were noted between the 2 age groups.

The relationship between baseline urinary Hex-4 levels and motor functional status at the end of the study shows a trend towards a higher proportion of patients having better motor response (walkers or functional sitters) among those with baseline urinary Hex-4 below the median. Seven of 8 patients (87.5%) who had baseline urinary Hex-4 levels below median showed some motor gains at the end of the study, while only 3 of 8 patients (37.5%) with urinary Hex-4 levels at Baseline above the median showed motor gains, although this difference did not reach statistical significance in this study.

Table 2.1.6 Functional Status at End of Study by Baseline Hex-4 Level

	Motor functional category at end of study			
Hex4 level at Baseline	**Walker n (%)**	**Sitter n (%)**	**Non-responder n (%)**	**p-value**
Low (< median) n = 8	4 (50.0)	3 (37.5)	1 (12.5)	0.2308
High (≥ median) n = 8	2 (25.0)	1 (12.5)	5 (62.5)	

Similarly, baseline absolute urinary Hex-4 levels were lower in the patients who achieved motor gains during the study (walkers and functional sitters) than in those who did not achieve motor gains during the study (non-motor responders). While on Myozyme, the group of walkers had the lowest mean levels at Week 104, followed by functional sitters, compared to non-motor responders who had the highest mean Week 104 levels of the 3 functional groups.

Urinary Hex-4 levels do not seem to have a strong prognostic value for motor functional outcome and with the current knowledge can not be used to identify infantile onset patients that may not benefit from Myozyme. In view of the severity of Pompe disease and the uniformly fatal outcome of infantile onset Pompe disease when untreated, the decision on initiation or continuation of treatment can not be based on Baseline Hex-4 level alone, but should always be based on the clinical disease course and response to treatment.

Although determination of urinary Hex-4 levels may represent a potential non-invasive biomarker to monitor therapeutic responses in Pompe disease, it is considered unlikely, based on the available data, that urinary Hex-4 levels can ever be predictive of long term clinical outcome.

The CHMP agreed with the MAH in the conclusion that no notable differences between the age categories were observed in Baseline urinary Hex-4 levels in this study. It is possible that the ages of all patients in this study were too similar (age range at first infusion 1.2 to 7.3 months), and the patient population too small, for broader age-based differences to be observed. However, urinary Hex-4 levels do seem to have a prognostic value for motor functional outcome, which may be worth further investigating, for example throughout the other pivotal study AGLU01702.

The MAH clarified that study AGLU01702 was completed on 14 July 2006 and no extension of this study was conducted. In the AGLU01702 study, urinary Hex-4 measurements were not performed as they were not part of the protocol. Study AGLU01702 could not be used to further investigate this issue.

In addition the MAH argued that studies in such infantile-onset patients will, however, always include a very limited number of patients in view of the low incidence of infantile-onset Pompe disease, and in view of the fact that early treatment is recommended. Even if a cut-off value of urinary Hex-4 measurement in these patients could be found, the number of patients above the cut-off not responding to treatment would per definition be even lower. The numbers needed to base such a decision on are very unlikely to be reached by additional clinical studies.

Additional information that will not lead to a hypothetical cut-off as mentioned above is very unlikely to lead to changes in clinical decision making: in all cases, treatment with Myozyme will have to be initiated and the individual patient's treatment response must be assessed.

Although the MAH generally believe that further studies aimed at elucidating the predictive value of urinary Hex-4 levels will not lead to differences in the use of Myozyme, they agree that further investigating urinary Hex-4 is scientifically interesting and necessary. The MAH is currently funding investigator sponsored studies aimed at further elucidating the prognostic value of urinary and plasma Hex-4.

The CHMP agreed with the above comments by the MAH, and is awaiting further data in due course.

Gene expression analyses

RNA from muscle biopsy specimens at Baseline was analysed by hybridisation to commercial microchips (Affimetrix) to identify transcriptional differences between patients in an effort to characterize genes that may influence severity and disease progression as well as response to therapeutic intervention with Myozyme. Comparison of Baseline microchip data between patients based on clinical outcome data at various time points, including degree of glycogen clearance, motor function (based on AIMS score and motor functional assessment), and ventilator status, yielded a list of differentially expressed genes that span a wide range of cellular processes including apoptosis, lipid

and amino acid metabolism, inflammation, homeostasis, cellular transport, and cell structure that may have relevance to the disease phenotype. These initial data provided some insight into the transcriptional differences present between patients which may contribute to differences observed in patient severity and outcome to therapeutic intervention with Myozyme. However it is considered too early to draw a conclusion on these candidate genes based on gene expression data alone.

Efficacy Results of Study AGLU01702

The primary efficacy endpoint for this pivotal study was the proportion of patients alive after 52 weeks of treatment. Sixteen patients completed 52 weeks of treatment. Five patients died by Week 52 and one additional patient died after Week 52.

Considering that patients with infantile-onset Pompe disease have a higher risk of death during the first 12 months of life than afterwards, survival of AGLU01702 patients was analysed separately for those patients who were (1) ≤12months-of-age at first infusion (n=10) and (2) those patients who were >12 months-of-age at first infusion (n=11), and (3) all patients (N=21).

The Table 2.1.7 below presents estimates of 12-month (Week 52) and 24-month (Week 104) survival from treatment initiation for patients in AGLU01702, stratified by age at first infusion, side by side with estimated conditional survival (from the reference age) for the corresponding reference groups derived from the AGLU01702 Historical Reference Subgroup.

Table 2.1.7 52- and 104-Week Survival Rates in AGLU01702 and the AGLU01702 Historical Reference Subgroup Categorised by Age at First Infusion

AGLU01702 Patients				AGLU01702 Historical Reference Subgroup	
Age Category at 1st Infusion (months)	**Median Age at 1st Infusion**	**52-Week Survival Estimate[1]**	**104-Week Survival Estimate[1]**	**Conditional 52-Week Survival Estimate[1,2]**	**Conditional 104-Week Survival Estimate[1,2]**
≤ 12	8.2 months[3]	60.0% (29.6%, 90.4%) n=10	50.0% (19.0%, 81.0%) n=10	16.5% (6.7%, 26.3%) n=59	9.2% (1.5%, 16.8%) n=59
>12	17.8 months[4]	90.9% (73.9%, 100.0%) n=11	90.9% (73.9%, 100.0%) n=11	45.5% (16.0%, 74.9%) n=11	45.5% (16.0%, 74.9%) n=11
All patients	13.0 months[5]	76.2% (58.0%, 94.4%) N=21	71.1% (51.6%, 90.6%) N=21	31.6% (10.7%, 52.5%) N=19	26.3% (6.5%, 46.1%) N=19

1 Kaplan-Meier method was used to compute nonparametric estimates of the survival distribution.
2 Conditional survival estimates were based on reference ages for the corresponding subpopulation of AGLU01702 (e.g., 52-Week conditional survival rate corresponded to survival rate at 8.2 + 12 = 20.2 months of age for the ≤ 12-month category).
3 Median age at first infusion in AGLU01702 patients first infused at ≤ 12 months.
4 Median age at first infusion in AGLU01702 patients first infused at >12 months.
5 Median age at first infusion in all AGLU01702 Patients.

Although 14 patients remained in the study beyond Week 104, meaningful comparison beyond that point was not possible due to censoring of patients as they completed the study. Note that in every age category, survival estimates for patients treated with Myozyme (AGLU01702) were greater than the corresponding estimated conditional survival and upper limit of the 95% CIs of the untreated reference groups, suggesting that treatment with Myozyme extended survival in these patients.

For the category of all patients, there was no overlap between the 95% CIs of the patients treated with Myozyme (N=21) and of the untreated reference group subset (n=19).

Invasive ventilator-free survival

Sixteen patients were free of invasive ventilatory support at Baseline. Seven of these 16 patients (43.8%) survived and were free of invasive ventilator support at the End of Study, ranging from 34.7 to 80.3 months-of-age. The 9 remaining patients either died (5 patients) or became invasive-ventilator dependent (4 patients). Of the 5 patients with invasive ventilation at Baseline four remained invasively ventilated until the End of Study, one patient died.

Cardiomyopathy

Progression of cardiomyopathy was evaluated through echocardiographic assessment of LVMIs and LVM Z-scores.

At Baseline, 18 of 19 patients with available data had evidence of left ventricular hypertrophy, as indicated by abnormal LVM Z-scores (i.e., Z-score >2) calculated from the values read by the central, blinded cardiologist (mean=6.51; minimum of 1.7 and maximum of 10.4 [n=19]). Two patients did not have Baseline/Screening Data (first available LVM measurement was at Week 4 and at Week 8 and presumed as abnormal).

Fifteen (71%) of 21 patients improved in LVM from first to last study evaluation as demonstrated by a change from abnormal to normal (i.e., Z-score ≤2) and/or a decrease in Z-score by >1. Additionally, 2 patients maintained normal LVM. In total 17 (81%) of 21 patients either improved or maintained normal LVM. In total, 12 patients had LVMs within normal limits at their last evaluation. The last LVM values from 5 additional patients were lower than their pre-treatment values, although their Z-scores remained above 2.

Motor development

AIMS Score

Eleven patients had AIMS evaluations at Baseline and at least one study visit beyond Week 52:

- Six of the 11 patients continued to make motor development gains beyond Week 52 as evidenced by increases in age-equivalent scores or in the raw score if the maximum score was achieved. Among these patients, 3 patients were ambulatory by the last study visit. Three patients had functional sitting skills by the last study visit, although they were not able to use their legs.
- The remaining 5 patients showed no significant change in motor development beyond Week 52. Four patients had no significant motor skills in any of the positions evaluated by the last study visit. One patient had functional sitting skills by the last study visit, although he was not able to use his legs.

PDMS-2 Score (Peabody Developmental Motor Scales-2)

The PDMS-2 is used to assess gross and fine motor skills that develop from birth through 6 years-of-age.

- Fifteen patients had gross motor skill evaluations using the Stationary, Locomotion, and Object Manipulation subtests of the PDMS-2 beyond the Week 52 study visit:
- Three of the 15 patients demonstrated increases in Stationary, Locomotion and Object Manipulation age-equivalent scores beyond Week 52.
- The remaining 12 patients showed no additional acquisition of gross motor skills beyond Week 52.

Fifteen patients had fine motor skill evaluations using the Grasping and Visual-Motor Integration (VMI) subtests of the PDMS-2 beyond the Week 52 study visit:

- Eleven of the 15 patients demonstrated consistent increases in age-equivalent scores on both the Grasping and VMI subtests beyond Week 52 indicating the continued acquisition of fine motor skills, specifically finger and hand control and eye-hand coordination.
- Four patients demonstrated inconsistent patterns of scores across study assessments that suggest no or minimal gains in fine motor function.

Motor development Milestone

A checklist of clinically relevant motor development milestones was used to evaluate motor milestones achieved, toward the goal of independent ambulation, at each study assessment.

Fifteen patients were evaluated using the Motor Development Milestones checklist beyond the Week 52 study visit:
- Three of the 15 patients achieved meaningful increases in total checklist scores beyond Week 52 indicating the continued acquisition of new motor milestones after the first year of treatment.
- The remaining 12 patients showed no meaningful increases in checklist scores beyond Week 52.

Growth
Seventeen (81%) of 21 patients maintained weight-for-age values above the 3rd percentile at the last assessment. Nineteen (90%) of 21 patients maintained length-for-age values above the 3rd percentile at the last assessment. Sixteen (89%) of 18 patients who were <36 months-of-age at Baseline maintained head circumference above the 3rd percentile at the last assessment for which percentiles were available.

The CHMP has commented regarding these results that the primary endpoint, after 104 weeks of treatment with Myozyme, the survival rate is better in comparison to untreated patients in the AGLU01702 Historical Reference Subgroup.

Given the wide range of ages at initiation of treatment and the finding that patients with earlier onset of symptoms and diagnosis tend to have a higher risk of death, patients were stratified by age at first infusion, and survival was analysed separately for each category.
For the category of patients who were ≤12 months-of-age at first infusion, the survival rate was reduced from Week 52 to Week 104.

It should also be noted that for the category of patients who were >12 months-of-age at first infusion, there was an overlap between the 95% CIs of the patients treated with Myozyme and of the untreated reference group subset, precluding any conclusion on a significant difference. Given these results, it seemed difficult to suggest that treatment with Myozyme prolonged survival even in patients who were at a very advanced stage of disease progression at onset of treatment.

43.8% of patients who were free of invasive ventilatory support at Baseline survived and were free of invasive ventilator support at the end of study. In view of these results, the efficacy of Myozyme may be interpreted more likely as a prolongation of invasive ventilator-free survival and survival than as an improvement or a persistent and long-term efficacy.

Regarding the other secondary endpoints, Myozyme treatment resulted in LVM Z-scores normalisation in more than the half of patients at their last evaluation, and in the maintenance or improvement in growth percentiles in most of patients.

AGLU01602/AGLU02403 and AGLU01702 Cox Regression Analysis

The effect of Myozyme treatment on survival in pivotal studies AGLU01602/AGLU02403 and AGLU01702 was further assessed using the Cox model with treatment as a time-dependent covariate. As proposed by CHMP during the review of the initial marketing authorisation application, a smaller subgroup of 42 patients, born in 1993 or later, was selected from the AGLU01602 Historical Control Subgroup, and a smaller subgroup of 48 patients, born in 1995 or later, was selected from the AGLU01702 Historical Reference Group. This was proposed to be able to compare the patients from AGLU01602/AGLU02403 and AGLU01702 with a more contemporary group of patients. These subgroups were again used in the Cox model comparison of the final results from study AGLU01602/AGLU02403 and AGLU01702.

Table 2.1.8 Cox Regression Model Analysis: Comparison of Survival in Patients in AGLU01602/AGLU02403 and AGLU01702 at Study End as Compared to the Historical Reference Subgroup

Study	Number of historical control comparator patients	Endpoint	Treatment Effect Hazard Ratio	95% Confidence Interval	p-value
AGLU01602/ AGLU02403 (N=18)	N=61[1]	Survival	0.048	(0.016, 0.141)	<0.0001
	N=42 [2]	Survival	0.047	(0.015, 0.147)	<0.0001
AGLU01702 (N = 21)	N=84 [1]	Survival	0.209	(0.083, 0.524)	0.0009
	N=48 [2]	Survival	0.301	(0.112, 0.804)	0.0166

Note: Results are from a Cox proportional hazards regression analysis which includes treatment as a time-varying covariate, and also adjusts for age of diagnosis and age at symptom onset.

[1] One (1) patient in the AGLU01602/AGLU02403 Historical Reference Subgroup (62) and 2 patients in the AGLU01702 Reference Subgroup (84) were not included in the Cox regression analysis due to their missing death dates.

[2] More contemporary group of patients created upon request of the CHMP during the review of the Marketing Authorisation (42 patients born in 1993 or later for the AGLU01602/AGLU02403 Historical Control Subgroup and 48 patients born in 1995 or later for the AGLU01702 Historical Reference Subgroup)

The Cox model permited the estimation of a hazard ratio which described the risk of death for treated patients relative to untreated patients. As shown in the Table 3.2.1.8 above, the results of these analyses indicated a consistent observed survival benefit with Myozyme treatment when compared to historical data.

However, the methodological bias for AGLU01602/AGLU02403 did not allow concluding on these figures. It is worth noting that the MAH proposed no interpretation for study AGLU01702, where only 43.8% of patients who were free of invasive ventilatory support at Baseline survived and were free of invasive ventilator support at the end of study.

It should also be highlighted that, compared to AGLU02403, the hazard ratio was lower at 18 months of age (= 0.01) in AGLU01602.

Efficacy discussion and conclusions

Regarding study AGLU01602/AGLU02403 a positive effect on the primary efficacy endpoint of invasive ventilator-free survival as well as any ventilator-free survival and overall survival was noted. Treatment was also associated with improvements in cardiomyopathy, growth, and motor development in the majority of patients.

Regarding study AGLU01702 the patients were at a very advanced stage of disease progression and were disabled at the initiation of treatment. The final results obtained from this study indicate that treatment with Myozyme prolonged survival in patients affected with infantile-onset Pompe disease when compared to similar untreated historical cohorts. Some improvement in cardiomyopathy parameters also occurred.

As a similar proportion of patients in the 20 and 40 mg/kg dose groups in AGLU01602/AGLU02403 demonstrated clinical response during treatment, the recommended dose for Myozyme in infantile-onset patients with Pompe disease is still 20 mg/kg qow.

2.2. Clinical Safety

In support of the initial marketing authorisation application for Myozyme, data had been provided from two ongoing pivotal clinical studies: the studies AGLU01602 and AGLU01702. Following the granting of the Marketing Authorisation, the studies AGLU01702 and AGLU01602 and its extension AGLU02403 were finalised. The MAH submitted in this variation the final versions of these studies to include additional long term safety data in the SPC.

The current SPC contains information on treatment related adverse events (TAEs) and Infusion-Associated Reactions (IARs) based on a pooled analysis from studies AGLU01602 and AGLU01702. These two analyses were again performed on the pooled database of AGLU01602, its extension AGLU02403, and AGLU01702 to support an update of the SPC. The data from these final study reports are available for a total of 39 patients and for a treatment period up to 168 weeks.

Patient exposure

A total of 39 patients (21 males and 18 females) have received intravenous infusions of Myozyme at doses of 20 mg/kg qow and 40 mg/kg qow in studies AGLU01602/AGLU02403 and AGLU01702.

- 18 patients in the study AGLU01602,
- 16 patients in the study AGLU02403, this study is an extension of the study AGLU01602: the patients who completed study AGLU01602 were followed up in this study AGLU02403,
- 21 patients in the study AGLU01702.

Due to the similarities of the AGLU01602/AGLU02403 and AGLU01702, the safety data of these 3 studies have been pooled. All patients have infantile-onset Pompe disease and have been exposed to qow infusions of Myozyme (20 mg/kg or 40 mg/kg) for up to 168 weeks (range 1 to 168 weeks).

30 patients initially received a dose of 20 mg/kg. 9 patients enrolled in AGLU01602 were randomised to receive a dose of 40 mg/kg qow. Additionally, 8 of the 21 patients enrolled in AGLU01702 who began treatment at 20 mg/kg had dose increases to 40 mg/kg after 26 or more weeks of treatment.

33 of the 39 patients received Myozyme for at least 1 year, 30 of 39 for at least 2 years, and 7 of 39 for at least 3 years. Patients received a median of 61 (range 1 to 85) infusions. The 9 patients who received 40 mg/kg qow in AGLU01602/AGLU02403 received a median of 59 (range 41 to 76) infusions.

Baseline

At Baseline, 28 of 39 patients had abnormal neuromuscular findings, 24 had an abnormal cardiac examination, and 19 had an abnormal pulmonary examination. Moreover, at baseline, 32 patients required no ventilatory support, 2 required non-invasive ventilatory support, and 5 required invasive ventilation. 17 patients had abnormal Baseline hearing evaluations.

A total of 138 Baseline AEs (48 in AGLU01602 and 90 in AGLU01702), occurring from the time of informed consent and prior to the first infusion of Myozyme have been reported for 35 of 39 patients. The most frequently occurring Baseline AEs, by preferred term, were pyrexia (9 patients), post procedural pain (7 patients), oedema peripheral (5 patients) and cough (4 patients).

Summary of adverse events

In the infantile-onset pooled population, all patients experienced at least 1 treatment-emergent AE; a total of 2793 treatment-emergent AEs were experienced by these 39 patients. The majority of AEs was non serious, mild or moderate in intensity and not related to Myozyme treatment.

The total numbers of AEs reported in the studies AGLU01602/AGLU02403 and AGLU0102 is summarised below.

Table 2.2.1 Overall summary of the number of AEs in study AGLU01602 / AGLU02403 and AGLU0102

Variable	Pooled (AGLU01602/AGLU022403 AGLU01702)		AGLU01602/AGLU02403		AGLU01702	
	N of Patients (N=18) n (%)	N of AEs n (%)	N of Patients (N=18) n (%)	N of AEs n (%)	N of Patients (N=21) n (%)	N of AEs n (%)
Any AEs	**39 (100.0)**	**2793 (100.0)**	18 (100.0)	1584 (100.0)	21 (100.0)	1209(100)
Treatment-Related AEs	**26 (66.7)**	**290 (10.4)**	12 (66.7)	237 (15.0)	14 (66.7)	53 (4.4)
Infusion-Associated Reactions	**22 (56.4)**	**266 (9.5)**	11 (61.1)	224 (14.1)	11 (52.4)	42 (3.5)
Serious AEs (SAEs)	**37 (94.9)**	**448 (16.0)**	18 (100.0)	277 (17.5)	19 (90.5)	171 (14.1)

Deaths

A total of 9 treatment-emergent deaths have been reported in the Myozyme studies (3 patients in study AGLU01602/AGLU02403 and 6 patients in study AGLU01702), although none of the deaths was assessed as related to treatment with Myozyme, and no patient discontinued therapy due to an AE. All 9 deaths were due to cardiorespiratory causes consistent with complications of the underlying Pompe disease.

SAEs

Among the 39 patients, 37 patients experienced a total of 448 SAEs after initiation of treatment. The majority of the SAEs were considered to be not related to treatment with Myozyme and some also reported at baseline. SAEs predominantly involved infections, respiratory related complications, and cardiac disorders. These events were not unexpected in this patient population given the respiratory and cardiac involvement characteristic of the disease. The most frequently occurring SAEs by preferred term included pneumonia (18 patients, 43 events), respiratory failure (17 patients, 41 events), respiratory distress (11 patients, 21 events), catheter related infection (9 patients, 14 events), respiratory syncytial virus infection (7 patients, 8 events), pneumonia aspiration (7 patients, 20 events), cardio-respiratory arrest (7 patients, 8 events), and pyrexia (7 patients, 13 events).

Among the 448 SAEs, 12 SAEs were assessed as related to treatment with Myozyme and all characterised as Infusion associated Reactions (IARs) (see section IARs of this report), except one (event of mild hyperparathyroidism).

TAEs

The most frequently treatment-emergent AEs experienced by patients in these studies were related to the underlying complications and manifestations of infantile-onset Pompe disease and as such also seen at baseline.

26 patients experienced 290 AEs assessed as treatment related and the majority (266) were characterised as IARs. The most frequently reported treatment-related AEs, were pyrexia, urticaria, oxygen saturation decreased, rash, cough, tachypnoea and flushing. The most frequently SOCs were

Skin and Subcutaneous Tissue Disorders, Investigations; General Disorders and Administration Site Conditions; Gastrointestinal Disorders; Respiratory, thoracic and mediastinal disorders.

Laboratory findings

Moreover, it should be noted that the MAH has reviewed the laboratory data for 3 patients. For these patients, the increase in ALT, AST, CK and CK-MB has been reported as possibly related to the administration of Myozyme. Considering the baseline of these patients and the fact that elevated levels of CK, CK-MB, SGOT, and SGPT have been observed in untreated patients with infantile-onset Pompe disease and are consistent with the underlying disease, the MAH considered these events as related to the underlying Pompe disease rather than treatment with Myozyme. The CHMP has agreed that these events should not be included in the SPC and the event "blood creatine phosphokinase MB increased" was removed from the SPC (section 4.8 "Undesirable effects").

Infusion Associated Reactions (IARs)

IARs were defined as related AEs which occurred during and up to 2 hours after the infusion.

22 patients of 39 (56.4%) experienced a total of 266 IARs, among these IARs 255 were assessed as non-serious and 11 as serious.

IARs were mainly managed with a rate reduction and/or an interruption of the Myozyme infusion. Antihistamines, antipyretics, and/or corticosteroids were used for pre-treatment. Patients recovered without sequelae from the IARs in most instances on the same day, and there were no discontinuations due to IARs.

IARs experienced by 7 of the patients occurred during a single infusion; the other 15 patients experienced IARs on multiple occasions (up to 41 infusions for one patient). The first episode of an IAR experienced by a patient ranged from the first infusion to the infusion at week 141.

IARs occurring in more than 1 patient included pyrexia (10 patients), urticaria, oxygen desaturation (7 patients), rash (6 patients), cough, tachypnoea, flushing (5 patients), vomiting, tachycardia (4 patients), rash maculo-papular, hypertension (3 patients), rash macular, erythema, pruritus, chills, irritability, blood pressure increased, body temperature increased, heart rate increased, retching, nausea, pallor, cyanosis, agitation, and tremor (2 patients).

3 patients experienced 11 serious IARs:
- Patient 1: episodes of urticaria and 1 episode of rales
- Patient 2: tachycardia, oxygen saturation decreased, bronchospasm, tachypnoea, periorbital oedema, and urticaria
- Patient 3: oxygen saturation decreased and hypertension

Immunologic response

The majority of patients developed anti-rhGAA IgG antibodies. 38 of the 39 patients had Baseline and post-Baseline assessments for anti-rhGAA IgG antibodies. One patient had no post-Baseline assessments, as the patient died before the Week 4 time point. Two patients were seropositive at Baseline, suggesting pre-existing cross reactivity. Among the 36 patients seronegative at Baseline 33 patients seroconverted; seroconversion generally occurred between week 4 and 12 (19 by Week 4, 9 by Week 8; 3 by Week 12; 1 by Week 38, and 1 by Week 64) and 3 remained seronegative at all time points tested (it should be noted that one of these patients died prior to the Week 8). The timing of IARs did not closely coincide with the timing of seroconversion in the majority of patients.

Of the 33 patients who became seropositive post-treatment, anti-rhGAA IgG antibody peak titre ranges varied widely. Of the 35 patients who were seropositive post-treatment, peak anti-rhGAA IgG antibody titers ranged from 400 to 3,276,800 (median 6,400). 16 patients developed anti-rhGAA IgG

antibody titres > 12,800, among them 8 had titres > 102,400. There was a tendency for patients with high antibody titres to experience more IARs.

A dose response (20 mg/kg versus 40 mg/kg) to Myozyme was assessed in studies AGLU01602/AGLU02403 showing that a comparable number of patients (5 patients in the 20 mg/kg dose group and 6 patients in the 40 mg/kg dose group) treated with 20 and 40 mg/kg qow experienced IARs. However, patients assigned to 40 mg/kg dose group experienced more IARs (177 vs 47). IARs that were common to both dose groups included urticaria, rash, rash maculo-papular and vomiting. IARs that were unique to the 40 mg/kg dose group included tachycardia, cyanosis, rash macular, rash erythematous, retching, gastroesophageal reflux disease, flushing, hypertension, hypotension, agitation, irritability, restlessness, cough and rales. IARs unique to the 20 mg/kg dose group included fever and retching.

CRIM (Cross Reactive Immunologic Material) status was determined in skin fibroblastes by western blot. A patient was considered to be CRIM positive if the presence of any bands corresponding to the apparent molecular weight of the major forms of GAA known to exist in the cell was detected in samples prepared from patient fibroblasts in the western blot assay.

6 of the 39 patients were CRIM negative (patients in whom no endogenous GAA protein was detected by Western blot analysis). All but 1 of the 6 CRIM negative patients developed high, sustained IgG antibodies (≥102,400). Three of the 33 CRIM positive patients developed titres higher than 102,400. Titres values ≥102,400 were more frequently found among those who died, needed ventilation, and/or had a minimal motor response.

Moreover, patients with high sustained antibody titres tended to have poor clinical response and prognosis when compared to the lower titre patients.

Among the 35 patients who developed anti-rhGAA antibodies, 3 patients exhibited enzyme activity inhibition or uptake inhibition greater than 20%. The range of peak titres in these patients was 409,600 to 3,276,800. All of these patients were CRIM negative and were treated with a dose of 40 mg/kg. None of the CRIM positive patients in both studies had antibodies that inhibited alglucosidase alfa activity and/or uptake. The time at which inhibition was initially detected ranged from 20 weeks to 84 weeks of treatment.

Even if the number of CRIM negative patients was small in these studies, the CHMP agreed with the MAH's assessment that CRIM negative patients appear to develop high and sustained antibody titres and to have a poorer prognosis than CRIM positive patients. However, it should be noted that high and sustained antibody titres also occur in some CRIM positive patients and that conclusions cannot be drawn on CRIM status alone. It should be also noted that the 3 patients who developed antibodies that inhibited enzyme activity or uptake were CRIM negative. Immunogenicity to rhGAA and the occurrence of antibodies that inhibited enzyme activity were still a concern. Moreover according to the MAH, the cause of a poor clinical response appears to be multi factorial. Therefore according to the data of these long term studies, the CHMP agreed with the MAH to add the information relating to the CRIM status in section 4.4. "Special warnings and precaution for use" of the SPC.

IgE Antibody, Serum Tryptase and Complement Activation Testing

The administration of therapeutic recombinant human proteins has been associated with antibody development. Results of anti-rhGAA IgE antibodies, complement activation, and tryptase activity assessments were evaluated in 13 patients who experienced IARs.

None of these patients were evaluated positive for IgE antibodies to Myozyme, 6 patients were positive for complement activation, and 1 patient demonstrated a slightly elevated serum tryptase level. Four patients experienced IARs suggestive of hypersensitivity reactions.

Circulating Immune Complexes

Circulating immune complexes were assessed if a patient experienced clinical symptoms consistent with immune complex disease. Testing for immune complex detection revealed that 2 patients tested positive using the CIC-C1q binding assay and negative using the Raji Cell Replacement assay.

Safety discussion and conclusions

Based on the long term data of the studies AGLU01602/AGLU02403 and AGLU01702 in the infantile-onset patients, the safety profile of Myozyme remains positive in this population.

The data were consistent with data in the original submission, the majority of AEs experienced by patients was mild to moderate in severity and assessed as not related to treatment with Myozyme.

The probability of a poor outcome and of developing high and sustained antibody titres appeared higher among CRIM-negative patients (patients in whom no endogenous GAA protein (Cross Reactive Immunologic Material) was detected by Western blot analysis) than among CRIM positive patients. The exact mechanism(s) by which anti-rhGAA antibodies could reduce the efficacy of enzyme replacement therapy are unknown. Conclusions could not be drawn on CRIM status alone, but must take other factors into consideration, such as antibody level, presence of inhibitory antibody, age and functional status at initiation of therapy, rate of disease progression, glycogen content of various muscles, receptivity or availability of muscle tissue to rhGAA and role of different genetic factors.

Most treatment related AEs were characterised as IARs.

The immunogenicity to rhGAA and the occurrence of antibodies that inhibited enzyme activity still remains a concern.

The patients in the dosing group of 20mg/kg experienced less AEs than the ones in the 40mg/kg qow.

The CHMP agreed with the MAH to update the relevant sections (4.4 and 4.8) of the SPC and Package Leaflet with the safety data of the pooled studies AGLU01602/AGLU02403 and AGLU01702. The CHMP requested a rewording of the proposed SPC by the MAH which was accepted.

3. Overall Conclusion and Benefit/Risk Assessment

The MAH has submitted in this variation application the final study reports of the studies AGLU01702 and AGLU01602 and its extension AGLU02403.

Data up to 168 weeks from patients with infantile-onset Pompe disease in studies AGLU01602/AGLU02403 and AGLU01702 demonstrate that treatment with Myozyme extends survival time, even in those patients who are severely affected prior to the initiation of treatment.

The prolongation of survival is most likely due to the effect of Myozyme on cardiomyopathy, with rapid reductions in LVMI observed in almost all of the treated patients who presented with cardiomyopathy at Baseline. The majority of patients treated with Myozyme also maintained or improved in growth parameters, in comparison of untreated patients with infantile-onset disease.

In study AGLU01602/AGLU02403, no differences between the 20 mg/kg and 40 mg/kg dosing groups were observed on survival, invasive ventilator free survival, or any ventilator-free survival, nor were there any clear differences between the 2 dose groups on any of the other main clinical efficacy parameters.

With respect to safety, treatment with Myozyme was generally well-tolerated in all patient populations, independent of age and clinical phenotype. While most patients experienced AEs, the majority were mild or moderate in intensity.

Most SAEs were also mild or moderate in intensity. The majority were respiratory, cardiac or infectious in nature given the effects of disease progression on the cardiac and respiratory system and function.

None of the deaths were considered related to Myozyme treatment.

Those AEs assessed as related to treatment were generally associated with the infusion and were managed with a change in infusion rate or, when necessary, the addition of pre-treatment such as antihistamine and/or antipyretics and/or corticosteroids.

No patients discontinued due to an IAR; however, patients with an acute underlying illness (e.g. pneumonia) at the time of Myozyme infusion appear to be at greater risk for IARs. Four patients experienced IARs suggestive of hypersensitivity reactions. Patients were negative for IgE, and were positive for complement activation on multiple occasions.

The administration of therapeutic recombinant human proteins has been associated with antibody development. The large majority of Myozyme-treated patients developed anti-rhGAA IgG antibodies during treatment. All of these patients were CRIM negative and were treated with a dose of 40 mg/kg. These studies in infantile patients treated with Myozyme suggest that patients who are CRIM negative appeared to have a poorer prognosis and appeared to have a higher probability of developing high and sustained antibody titers, than CRIM positive patients.

In conclusion, the CHMP agreed that the benefit-risk profile of Myozyme in the treatment of patients with Pompe disease remains favourable. Myozyme is generally well-tolerated, and provides clinical benefits in infantile-onset patients by prolongation of invasive ventilator-free survival, any ventilator-free survival, and overall survival, as well as the improvement of cardiomyopathy. A majority of the patients also experience a positive treatment effect on motor function and achieve major functional improvements.