SYNOPSIS

NAME OF COMPANY **Genzyme Corporation** **500 Kendall Street** **Cambridge, MA 02142** NAME OF FINISHED PRODUCT **Myozyme®** NAME OF ACTIVE INGREDIENT **alglucosidase alfa**	SUMMARY TABLE Referring to Part …… of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:

TITLE OF STUDY:

A Long-term Continuation Study of Patients With Infantile-Onset Pompe Disease Who Were Previously Enrolled in Protocol AGLU01602

INVESTIGATORS: [redacted]

STUDY CENTER(S):

18 investigational sites participated in AGLU01602 and AGLU02403 (7 in the USA, 7 in Europe, 1 in Israel, 3 in Taiwan)

PUBLICATION (REFERENCE):

Kishnani, Neurology, 2007

STUDIED PERIOD:

The treatment period for continuation study AGLU02403 was from 20 Jun 2005 to 15 Jun 2006. This final clinical study report also includes data collected under the initial study, Study AGLU01602, which began on 26 May 2003.

PHASE OF DEVELOPMENT:

Phase 2/3

OBJECTIVES:

The overall objective was to evaluate the long-term safety and efficacy of Myozyme treatment in patients with infantile-onset Pompe disease.

METHODOLOGY:

This was an open-label, multicenter, multinational, dose-ranging, continuation study of patients with infantile-onset Pompe disease who were previously enrolled in Protocol AGLU01602. The patient's legal guardian(s) provided informed consent prior to performing any protocol-related procedures.

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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). Dose reductions could be made at any time for safety reasons.

Safety and efficacy evaluations were performed at scheduled visits throughout the study treatment period. Adverse events (AEs) and concomitant medications/therapies were monitored continuously throughout the study. For patients who discontinued early from the study, the Investigator or designee contacted the patients' parent or legal guardian within 4-7 days after withdrawal to assess any AEs. Patients were treated in repeating 52-week Maintenance Phase Modules until the study was terminated.

An independent Data Safety Monitoring Board (DSMB) reviewed safety information periodically and on an ad hoc basis as outlined in the DSMB Charter, which was maintained separately from the study protocol. An independent Allergic Reaction Review Board (ARRB) was consulted on an ad hoc basis as outlined in the ARRB Charter, which was also maintained separately from this protocol.

NUMBER OF PATIENTS (PLANNED AND ANALYZED):

A minimum of 16 patients were planned in AGLU01602, and 18 patients were treated.

A maximum of 17 patients were planned in AGLU02403, and 16 patients were treated.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION:

This study was open to patients who had completed Study AGLU01602 and had not experienced any unmanageable AE in Study AGLU01602 (as determined and agreed upon by the Principal Investigator and Genzyme Corporation) due to Myozyme that would have precluded continuing recombinant human acid α-glucosidase (rhGAA) therapy.

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION; BATCH NUMBER:

Patients continued to receive the same dose of Myozyme, either 20 mg/kg or 40 mg/kg of body weight every other week (qow), that they received under Protocol AGLU01602. The patient's dose of Myozyme could be reduced at any time in a stepwise manner if he/she met pre-specified criteria. No dose reductions due to safety concerns occurred during the study. The total amount of Myozyme administered was adjusted monthly to account for changes in body weight.

Lot numbers, 160L scale: [redacted]

Lot numbers, 2000L scale: [redacted]

DURATION OF TREATMENT:

Patients were treated in 52-week Maintenance Phase Modules until the study was terminated on 14 Jun 2006, shortly after Myozyme approval by the US FDA. The last study infusion was given on 15 Jun 2006.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION; BATCH NUMBER:

There was no comparator treatment or placebo in this study given the universal fatality of untreated patients and the absence of alternative treatments.

CRITERIA FOR EVALUATION:

Efficacy was assessed by invasive ventilator-free survival; any ventilator-free survival; survival; cardiac

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status (measured by changes in left ventricular mass index [LVMI] and LVM Z-scores), physical growth (measured by changes in length and weight); motor development (measured by changes in Alberta Infant Motor Scale [AIMS] and Peabody Developmental Motor Scale-2 [PDMS-2] scores and the number of motor development milestones achieved); cognitive function (measured by changes in modified Bayley Scale of Infant Development II [BSID-II] and modified Leiter International Performance Scale – Revised [Leiter-R] scores); functional status (measured by changes in Pompe Pediatric Evaluation of Disability Inventory [PEDI] scores); and plasma and urine oligosaccharide levels.

SAFETY:

Safety was assessed by the incidence of AEs, results of laboratory tests (clinical chemistry, hematology, and urinalysis), presence of anti-rhGAA antibodies (immunoglobulin G [IgG]), vital signs (blood pressure, heart rate, respiratory rate, and temperature), physical examinations, electrocardiograms (ECGs), magnetic resonance imaging (MRI), and hearing testing. Additional exploratory safety evaluations included the assessment of: (1) circulating immune complex detection, when clinically indicated; (2) inhibitory antibody formation in patients testing positive for IgG; (3) immunoglobulin E (IgE), serum tryptase, and complement activation, when clinically indicated following moderate or severe infusion-associated reactions (IARs); and (4) skin testing, if clinically indicated following moderate or severe IARs. These tests were performed to gain additional research information as to individuals' responses to Myozyme, and not solely for the active clinical management of patients.

PHARMACOKINETICS:

Under AGLU02403, to evaluate the impact of the change of Myozyme manufacturing scale (160 L versus 2000 L), blood samples for the measurement of plasma concentrations of rhGAA were collected at specified time points on 3 days: on the day of last infusion of Myozyme manufactured at 160 L scale, on the day of first or second infusion of Myozyme manufactured at 2000 L scale, and 12 weeks later.

STATISTICAL METHODS:

The statistical analysis methods were designed to allow for an evaluation of the long-term safety and efficacy of Myozyme treatment with the cumulative data from studies AGLU01602 and AGLU02403.

The Genzyme BioMedical Operations Department performed the statistical analysis and used the SAS® statistical software system Version 8. In general, all analyses performed in the final analyses of Study AGLU01602 were reproduced using the same statistical and analytical methods employed previously.

EFFICACY:

Primary Efficacy: The proportion of patients treated with Myozyme (20 mg/kg dose group, 40 mg/kg dose group, and both dose groups combined) who were alive and free of invasive ventilator support were estimated using the Kaplan-Meier methodology. These estimated proportions were compared with estimated probabilities of survival in an untreated historical control group selected on the basis of the inclusion and exclusion criteria employed for AGL01602.

Various sensitivity analyses were conducted to address possible sources of bias in the comparison of treated patients against the historical control group. In particular, the Kaplan-Meier distributions of time from first infusion to event in the treated patients were compared to the Kaplan-Meier distribution of time to death in those historical control group patients who survived up to the age equal to the median age at which the treated group had their first infusion (5.6 months).

Time to invasive ventilator dependence or death was defined as the date when patient became invasive

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ventilator dependent or died. The Kaplan-Meier and Cox regression analyses were based on time to event derived in this manner.

Secondary Efficacy: The proportion of patients treated with Myozyme (20 mg/kg dose group, 40 mg/kg dose group, and both dose groups combined) who were alive and free of any ventilator dependence (invasive or non-invasive) were estimated using the Kaplan-Meier methodology. The same criteria for defining invasive ventilator dependence were applied to define any ventilator dependence.

Changes from Baseline in LVMI and physical growth (length and weight) were summarized. The standardized age- and gender-adjusted length and weight with reference to the Centers for Disease Control and Prevention Growth charts were summarized descriptively.

Tertiary Efficacy: The proportion of patients treated with Myozyme (20 mg/kg dose group, 40 mg/kg dose group, and both dose groups combined) who were alive were estimated using the Kaplan-Meier methodology.

Changes from Baseline to study time points in (1) AIMS / PDMS-2 scores and the number of motor development milestones achieved; (2) modified BSID-II / modified Leiter-R scores; (3) Pompe PEDI scores; and (4) plasma and urine oligosaccharide levels were summarized.

The overall days of ventilator support for each patient were summarized descriptively.

Other Analysis: Effects of Myozyme treatment on invasive ventilator-free survival, any ventilator-free survival, and overall survival were evaluated using Cox regression modeling. The treated patients together with the historical control group were analyzed using Cox regression models of time from disease diagnosis to event. These analyses adjusted for age at symptom onset and age at diagnosis, and estimated the effect of Myozyme by coding Treatment versus No Treatment as a time-varying covariate. The analysis was repeated using only the 42 historical control patients born after 1993 as a comparator.

PHARMACOKINETICS:

The following PK parameters were estimated from the plasma rhGAA concentration-time data: maximum concentration of drug, Tmax, area under the curve (AUC0-t), clearance, volume of distribution, volume of distribution at steady state, and half-life (t1/2). Results were summarized descriptively (number, mean, median, standard deviation, minimum and maximum) for each infusion. Graphical displays were presented as appropriate.

SAFETY:

AEs were coded using the Medical Dictionary of Regulatory Affairs (MedDRA version 6.1) and summarized by system organ class (SOC) and preferred term. The incidence of AEs was summarized by severity and relationship to treatment. The analyses of clinical laboratory measurements were based on the frequencies of abnormal values and frequencies of clinically significant abnormal values. For selected laboratory assessments (e.g., SGOT, SGPT, CK, and CK-MB), changes from Baseline over time were summarized. Changes from Baseline to study time points in other safety variables such as anti-rhGAA antibody development (IgG), vital signs, hearing testing, MRIs, and physical examination and ECG parameters were summarized using descriptive statistics. IgE antibody, inhibitory antibody, serum tryptase activity, complement activation, skin testing (if applicable), and circulating immune complex detection (if applicable) were presented in patient data listings. Graphical displays of antibody titers over time were presented. Other graphical displays were presented as appropriate.

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SUMMARY – CONCLUSIONS

Nineteen patients were enrolled in Protocol AGLU01602 and 18 patients were treated with Myozyme. Sixteen of these received treatment in the extension study AGLU02403. The patients in this study exhibited clinical symptoms of infantile-onset Pompe disease at a very early age, including the presence of cardiomyopathy and a severe deficiency in GAA activity (in both skin and skeletal muscle tissues). Thus, Studies AGLU01602 and AGLU02403 enrolled very young infantile-onset patients with a very severe form of Pompe disease.

Eighteen patients (11 male and 7 female) received Myozyme treatment. The median age at first symptoms was 1.0 months, and the median age at diagnosis was 4.4 months. Patients began Myozyme treatment between the ages of 1.2 and 6.1 months of age corrected for gestational age (median age of 5.25 months corrected for gestational age; median age of 5.6 months, uncorrected). Fourteen patients were Cross-Reacting Immunologic Material (CRIM) positive and 4 were CRIM (-).

All 18 patients who received any dose of Myozyme in AGLU01602 were included in this report, and the data presented are combined data from AGLU01602 and AGLU02403. The median time on study was 121.4 weeks (range 59.7 – 150.0 weeks). No dose reductions due to safety concerns occurred during the study at either dose used in this study (20 mg/kg qow [n=9] and 40 mg/kg qow [n=9]). Thirteen patients remained on study at the time of study close.

EFFICACY RESULTS:

Kaplan-Meier estimates of survival in these patients were 100.0% at 18 months of age and 72.0% (95% CI 47.9 – 96.0%) at 36 months of age; invasive ventilator-free survival was 83.3% (95% CI 66.1 – 100.0%) at 18 months of age and 49.4% (95% CI 26.0 – 72.8%) at 36 months of age; and any ventilator-free survival was 66.7% (95% CI 44.9 – 88.4%) at 18 months of age and 49.4% (95% CI 26.0 – 72.8%) at 36 months of age. In a conservative comparison, survival in a historical control population was 1.9% at both 18 and 36 months of age (95% CI 0 – 5.5%).

The potential for bias in favor of the treated patients may exist when comparing the survival of treated patients from birth to that of the historical control, because patients who are enrolled in the study have already lived to their age at enrollment while patients in the historical control could have died at any time. Four sensitivity analyses were performed to address this issue. In one sensitivity analysis, patients who died before the median age at first Myozyme infusion (5.6 months) were removed from the historical control subgroup, and Kaplan-Meier estimates for the historical control subgroup and for Myozyme-treated patients were assessed from the median age at first Myozyme infusion (5.6 months) and from the time of treatment initiation, respectively, instead of from time of birth. In the other 3 sensitivity analyses (calculating from time of birth), subsets of patients were removed from the historical control subgroup, including (1) patients who died prior to the age of 3, 4, 5, or 6 months; (2) patients who died before the median age at first Myozyme infusion (5.6 months); and (3) patients with congenital abnormalities recorded as "unknown." All sensitivity analyses showed that the proportion of Myozyme-treated patients alive and free of invasive ventilation at both 18 and 36 months of age or at all milestone time-points from the date of treatment initiation remained markedly higher than the proportion of patients who were alive in the corresponding historical control subgroup, regardless of ventilator use, with no overlap in the 95% CI. Additionally, invasive ventilator-free survival time and ventilator-free survival time were estimated from the time of diagnosis, symptom onset, and randomization. At the end of the study, 50% of Myozyme-treated patients were still alive and free of invasive ventilation or of any ventilation.

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Cox regression analyses of time from disease diagnosis to event were conducted, including the treated patients together with untreated patients from a historical control group selected based on the inclusion and exclusion criteria of Study AGLU01602. With over 3 years of data (from the beginning of AGLU01602 [26 May 2003] through the end of AGLU02403 [15 Jun 2006]), Myozyme was found to reduce the risk of death by 95% (hazard ratio of 0.05, 95% CI: 0.016, 0.141), the risk of death or invasive ventilation by 91% (hazard ratio of 0.09, 95% CI: 0.038, 0.215) and the risk of death or any type of ventilation by 87% (hazard ratio of 0.13, 95% CI: 0.059, 0.294). Similar results were obtained when a subgroup of 42 historical control patients born after 1993 was used as the comparator.

Cardiomyopathy parameters were evaluated by echocardiography over the course of the study. LVM Z-scores and LVMI were highly elevated in all patients' first measurements as compared to values in normal pediatric subjects (mean baseline LVMI 193.39 ± 62.175, mean baseline LVM Z-score 7.14 ± 1.638). Seventeen of 18 patients (94.4%) showed LVM decreases of at least one Z-score from baseline to the end of study. 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.

For the majority of patients assessed, treatment with Myozyme resulted in maintenance of growth and prevention of failure to thrive (defined as weight-for-age below the 3rd percentile). At the last available assessment, 17 of 18 patients (94.4%) had maintained or improved weight for age percentiles above the 3rd percentile, all patients (100%) were above the 3rd percentile for length, and 16 of 18 patients (88.9%) were above the 3rd percentile for head circumference. In contrast, 53% of untreated patients with infantile-onset Pompe disease in the Pompe Natural History Study (AGLU-004-00) exhibit failure to thrive.

A total of 11 patients (61%) acquired new motor skills while on treatment with Myozyme, including the achievement of independent ambulation. Based on motor responses measured using AIMS and motor milestone scores, patients can be classified at the end of study into 3 distinct groups: walkers, functional sitters, and motor non-responders. Seven of the 18 patients (39%) can be classified as "walkers" and were ambulating independently at the last assessment. An additional 4 patients (22%) can be classified as "functional sitters" and were sitting independently with trunk stability and functional use of the arms at the last assessment, although they had no functional use of the legs. The remaining 7 patients (39%) can be classified as "motor non-responders" at the end of study and had minimal or no significant gross motor function.

A total of 11 patients (61%) made consistent gains in disability scores from Baseline to Study End (self-care, mobility and social function), as measured by the Pompe PEDI Functional Skills domain. These scores measure the patient's ability to perform independently of the care giver.

All 18 patients demonstrated gains in mental age equivalent scores (BSID-II scale) from Baseline to Study End or last assessment, including 7 patients (39%) who were developing at the same pace as normal peers. The remaining 61% patients made gains but at a pace slower than that of normal peers

Urinary Hex4 levels were elevated (above the upper limit of normal) in 16 of 18 (88.9%) patients at earliest available assessment (mean Hex4 at Baseline 38.10 ± 11.447 mmol/mol creatinine). Urinary Hex 4 decreased from Baseline to last assessment in 5 patients (28%) and increased in the remaining 13 patients (72%). Mean Hex4 at Week 104 was 58.33 ± 35.320 mmol/mol creatine. Urinary Hex4 levels at Baseline were lower in the patients who achieved motor gains during the study (walkers and functional sitters) compared to those with minimal or no motor gains. At Week 104, patients categorized

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as walkers had little change in urinary Hex4 levels from Baseline while the functional sitters had an increase, and patients categorized as having minimal or no motor gains had a greater increase. The clinical significance of urinary Hex4 levels is not yet completely understood.

In general, a similar proportion of patients assigned to the 20 mg/kg and 40 mg/kg dose groups successfully met clinical endpoints such as survival, ventilation-free survival, LVMI, growth, motor development, and disability status. Thus, differences between dose groups in efficacy parameters were not sufficiently large to conclusively demonstrate the superiority of either dose group.

PHARMACOKINETIC RESULTS:

The t1/2 ± SD for the 20 mg/kg group was calculated as 2.36 ± 0.56 hours (n=7), 2.53 ± 0.64 hours (n=5), and 2.21 ± 0.46 hours (n=6) for the 160 L, 2000 L, and 2000 L repeat samples, respectively. The t1/2 ± SD for the 40 mg/kg group was calculated as 2.08 ± 0.39 hours (n=5), 2.19 ± 0.36 hours (n=4), and 1.95 ± 0.25 hours (n=5) for the for the 160 L, 2000 L, and 2000 L repeat samples, respectively. The AUC(inf) ± SD for the 20 mg/kg group was calculated as 815,347 ± 418,759 ng x h/mL (n=7), 1,238,280 ± 619,243 ng x h/mL (n=5), and 777,156 ± 284,476 ng x h/mL (n=6) for the for the 160 L, 2000 L, and 2000 L repeat samples, respectively. The AUC(inf) ± SD for the 40 mg/kg group was calculated as 1,796,195 ± 566,697 ng x h/mL (n=5), 1,806,667 ± 200,625 ng x h/mL (n=4), and 1,678,773 ± 246453 ng x h/mL (n=5) for the for the 160 L, 2000 L, and 2000 L repeat samples, respectively.

SAFETY RESULTS:

A total of 1584 treatment-emergent AEs were reported during AGLU01602 and AGLU02403 (median time on study treatment, 121.4 weeks [range 59.7 – 150 weeks]). All 18 patients experienced at least 1 AE. Overall, the most frequently occurring events included pyrexia (119 events [7.5%], 18 patients [100.0%]), cough (53 events [3.3%], 12 patients [66.7%]), vomiting (49 events [3.1%], 13 patients [72.2%]), urticaria (48 events [3.0%], 6 patients [33.3%]), and upper respiratory tract infection (36 events [2.3%], 11 patients [61.1%]). Events occurred most commonly in the SOCs of Infections and Infestations (330 events [20.8%], 18 patients [100.0%]), and Respiratory, Thoracic, and Mediastinal Disorders (255 events [16.1%], 18 patients [100.0]). Two hundred thirty-seven events (15.0% of total events), occurring in 12 patients (66.7%) were considered possibly, probably, or definitely related to study drug. The most common of these adverse drug reactions (ADRs) were IARs (224 IARs; 94.1% of related AEs) and are discussed below. Of the 13 events considered at least possibly related to study drug by the investigator that were not IARs, 1 was reported twice: mild rash papular in 1 patient. The only one reported as a serious adverse event (SAE) was mild hyperparathyroidism; mild non-serious proteinurea was reported in the same patient as an ADR that was not an IAR.

Six out of the 18 patients died, including 3 patients who died while on AGLU01602 or AGLU02403, and 3 patients who died after study completion or withdrawal. Four patients died of cardio-respiratory causes (cardio-respiratory arrest in 2 patients, cardiac arrest in 1 patient, and in 1 patient desaturation and bradycardia while hospitalized for treatment of respiratory distress and pneumonia), 1 patient died of multi-organ failure secondary to septicemia, and 1 patient died of disease progression. All deaths were consistent with the underlying Pompe disease and were assessed as unrelated to study drug.

A total of 277 treatment-emergent SAEs (17.5% of total AEs) were experienced by 18 patients (100%) during the study. The most frequent SAEs were pneumonia (25 events [9.0% of SAEs] in 7 patients [38.9%]) and respiratory failure (23 events [8.3% of SAEs] in 9 patients [50%]). Respiratory complications were not unexpected, given the nature and severity of clinical manifestations and

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complications of severe infantile-onset Pompe disease. Four of the 277 SAEs (1.4%) were considered possibly, probably, or definitely related to study treatment: mild hyperparathyroidism (considered possibly related because hyperparathyroidism is considered rare in children and there was no other plausible etiology for the event), 2 events of moderate urticaria (an IAR) in the same patient on the same day, and moderate rales (an IAR).

A total of 224 AEs (14.1% of total AEs) that occurred in 11 patients (61.1%) were assessed as IARs. The most frequently reported IARs included urticaria (47 IARs [21.0%]), 5 patients [27.7%]), pyrexia (27 IARs [12.1%], 8 patients [44.4%]), oxygen saturation decreased (24 IARs [10.7%], 4 patients [22.2%]), cough (17 IARs [7.6%], 3 patients [16.7%]), vomiting (16 IARs [7.1%], 4 patients [22.2%]), rash (12 IARs [5.4%], 5 patients [27.8%]), tachypnoea (7 IARs [3.1%], 3 patients [16.7%]), tachycardia (6 IARs [2.7%], 3 patients [16.7%]), and rash maculopapular (5 IARs [2.2%], 3 patients [16.7%]). IARs were generally well tolerated, and were managed with a rate reduction and/or an interruption of the Myozyme infusion and/or administration of antipyretics, antihistamines, and/or corticosteroids. In all instances, patients recovered from the IAR(s) without sequelae and treatment with Myozyme was continued.

To further characterize IARs experienced by these patients, an expanded algorithm based on the MedDRA 9.1 Standardized MedDRA Query was used as a tool in the identification of hypersensitivity reactions. This tool identified 2 patients who experienced IARs suggestive of hypersensitivity reactions, including flushing, hypotension, rash, cough, and urticaria. Upon medical review, an additional reaction suggestive of hypersensitivity (consisting of serious rales and urticaria) was also identified in 1 of these 2 patients. Both patients had high antibody titers, were negative for IgE, and were positive for complement activation on multiple occasions, and 1 of these patients had slightly elevated serum tryptase on 3 occasions.

In this study of infantile-onset patients, the majority of IgG positive patients (10 of 16, 62.5%) tended to have consistently low titers at all time points or had titers that peaked initially and then decreased over the course of the study. The remaining 6 IgG positive patients (37.5%) had sustained higher titers (range 51,200 to 1,638,400 at last assessment). The 6 higher-titer patients had more IARs and more SAEs per patient than the other patients, although the timing of IARs did not necessarily correspond to the time of peak titer. The higher-titer patients included 5 of the 6 patients who died (83.0%) and 6 of the 9 patients who were invasively ventilated (66.7%). This group also included all 4 CRIM (-) patients and all 3 patients who developed antibodies that inhibited enzyme activity or uptake. Five of these 6 patients were in the 40 mg/kg group, and the final patient, from the low dose group, was CRIM (-). Given the numerous confounding factors in the high-titer group, the cause of a poorer clinical response in some of these patients is thought to be multi-factorial.

A retrospective analysis of all IgG positive patients detected the presence of antibodies that inhibited rhGAA enzymatic activity or uptake in 3 of 16 IgG positive patients tested during this study. All 3 patients were CRIM (-) and were treated with Myozyme at a dose of 40 mg/kg qow. One patient was seropositive at baseline, and the other patients seroconverted by Week 4 of Myozyme treatment. The range of peak IgG antibody titers by ELISA in these 3 patients was 409,600 to 3,276,800. All 3 patients had sustained IgG antibody titers $\geq$ 51,200 following the time-points when inhibition was first detected, except for 1 patient at 1 time point. Two patients tested positive for inhibition of both enzyme activity and enzyme uptake, the first testing positive for inhibition of uptake by Week 38 and inhibition of activity by Week 52, and the second for inhibition of activity and uptake by Week 84 of treatment, while the remaining patient tested positive for inhibition of enzyme uptake only by Week 20 of treatment. All

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3 patients testing positive for inhibition showed signs of clinical decline during treatment and all 3 patients became invasively ventilated. Two patients developed inhibitory antibodies before the onset of clinical decline; in the remaining patient, inhibitory antibodies developed approximately 64 weeks after the onset of clinical decline. All 3 patients have died, at ages 31.9, 34.3, and 44.4 months.

In general, patients in the 40 mg/kg dose group experienced more AEs than patients in the 20 mg/kg dose group. The number of AEs, SAEs, and IARs reported was greater in the 40 mg/kg group (919 AEs, 58.0% of AEs; 149 SAEs, 53.8% of SAEs; 177 IARs, 79% of IARs) than in the 20 mg/kg group (665 AEs, 42.0% of AEs; 128 SAEs, 46.2% of SAEs; 47 IARs, 21% of IARs). Results in the 40 mg/kg group may have been confounded by the presence of 3 CRIM (-) patients who experienced multiple AEs and SAEs. Some of the disparity in IARs between the dose groups can be accounted for by 2 patients in the high dose group who each had many IARs (43 and 102 events per patient, accounting for 65% of all IARs). In general, patients who received the 40 mg/kg dose tended to develop higher antibody titers than those who received the 20 mg/kg dose.

Changes in laboratory parameters, vital signs, physical examination, MRI, and 12-lead ECG observed during the study were generally consistent with manifestations of underlying Pompe disease.

Interpretation of hearing testing data results was complicated by the small numbers of patients with available assessments, especially after Week 52, and the number of patients with chronic middle ear effusion or other problems which complicated interpretation of test results. However, evidence of hearing loss was noted. At baseline, hearing loss was recorded in the left and right ears for 4 patients (3 with sensorineural loss and 1 with mixed conductive and sensorineural loss). At Week 104, 3 of these patients continued to exhibit hearing loss in both ears, while 3 new patients exhibited hearing loss in both ears (1 patient with conductive loss and 2 with mixed loss) and 1 new patient had mixed hearing loss in the left ear only. Abnormal tympanogram results and hearing testing results were also noted in some patients. Additionally, treatment-emergent AEs of deafness, conductive deafness, sensorineural deafness, or acoustic stimulation tests abnormal were reported for 6 patients; none of these events were considered related to study drug.

CONCLUSIONS: [redacted]