SYNOPSIS

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

TITLE:

An Open-Label, Multicenter, Multinational, Study of the Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of Recombinant Human Acid Alpha-Glucosidase (rhGAA) Treatment in Patients > 6 and ≤ 36 Months Old with Infantile-Onset Pompe Disease (Glycogen Storage Disease Type II)

INVESTIGATORS: [redacted]

STUDY CENTERS:

Five primary investigational study centers in the United States and Europe initially participated in this clinical trial. After a minimum of 26 weeks of treatment patients could be transferred, after consultation between the Sponsor and the Investigator, to regional investigational sites for continuing treatment for the remainder of the study. Thirteen sites were added as a result of transfers to regional investigational sites during the study.

PUBLICATION (REFERENCE):

None

STUDIED PERIOD (FIRST PATIENT ENROLLED, LAST PATIENT COMPLETED):

The first patient was enrolled (parents signed informed consent) on 19 February 2003; the first patient was infused on 17 March 2003; the last patient completed infusion in the study on 12 June 2006; and the last patient completed follow-up on 14 July 2006.

PHASE OF DEVEOPMENT: Phase 1/2

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OBJECTIVES:

The overall objective of this study was to evaluate the safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of Myozyme treatment in patients with infantile-onset Pompe disease.

The primary objectives of the study were: (1) to evaluate the safety profile of Myozyme; (2) to evaluate efficacy as measured by the survival of patients over the course of treatment; (3) to determine the PK profile of Myozyme in patients with infantile-onset Pompe disease as measured by Myozyme concentration in plasma and acid alpha-glucosidase (GAA) activity in skeletal muscle tissue as measured by biochemical assessment; and (4) to determine the PD of Myozyme in patients with infantile-onset Pompe disease by evaluating the effect of treatment on glycogen depletion in skeletal muscle tissue as measured by histological and biochemical assessment. PK analyses in muscle tissue were not performed.

Secondary objectives were to determine (1) the effect on respiratory function, measured as follows: (a) for patients who were ventilator-free at the onset of the study, the proportion of patients who were alive and ventilator-free over the course of treatment, time to death or overall invasive ventilator-dependence and the ventilator-free survival time; (b) for patients who required ventilator use at the onset of the study, the overall duration of ventilator support and the number of hours of ventilator use (in the 24 hours preceding each infusion visit measured every other week [qow]); (2) the effect of treatment on cardiac status as measured by the change in left ventricular mass index (LVMI) and any presence of signs and/or symptoms of cardiac failure; and (3) the effect of treatment on motor development from Baseline as measured by Alberta Infant Motor Scale (AIMS) and/or Peabody Developmental Motor Scale-2 (PDMS-2) scores, and the patient's ability to achieve and maintain clinically relevant motor development milestones.

Other objectives included evaluation of the effect of treatment on (1) cognitive development from Baseline as measured by the Mental Development Index (MDI) of the Bayley Scales of Infant Development II (BSID-II) and/or the Brief Intelligence Quotient (IQ) score from the Leiter International Performance Scale – Revised (Leiter-R); (2) physical growth as measured by body length, weight, and head circumference; (3) change in functional status from Baseline as measured by the Pediatric Evaluation of Disability Inventory (PEDI); and (4) change in functional status from Baseline as measured by the Pompe PEDI.

For research purposes only, the objectives included exploration of (5) the potential effect of cross-reacting immunologic material (CRIM) status on primary efficacy outcomes; and (6) the potential effect of gene expression, angiotensin-converting enzyme (ACE) marker allele status, and GAA gene mutation on primary efficacy outcomes.

METHODOLOGY:

This was an open-label, multicenter, multinational, study of patients with infantile-onset Pompe disease. The initial protocol was amended 6 times, and the first patient was enrolled under protocol Amendment 1.

Protocol AGLU01702 was designed to enroll up to 20 patients with infantile-onset Pompe disease to receive intravenous (IV) infusions of Myozyme at doses of 20 mg/kg qow. Protocol Amendment 4 allowed patients to receive an increased dose of 40 mg/kg qow with Genzyme approval. This study was designed to continue for 52 weeks and included the option of continuation in repeating 52-week maintenance modules if there were no patient safety concerns.

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After the first 4 enrolled patients completed their first 2 infusions of 20 mg/kg qow Myozyme, and before any additional patients received treatment, available safety data were reviewed by Genzyme Pharmacovigilance and an independent Data Safety Monitoring Board (DSMB) for any safety-related issues. A review of available safety data was also performed after the eighth patient had received a total of 2 infusions. As neither review revealed any significant safety concerns, an additional 13 patients were enrolled and treated with 20 mg/kg qow Myozyme for 26 weeks. Following 26 weeks of treatment, written dose augmentation requests were reviewed by the Genzyme Medical Monitor to determine whether criteria for dose augmentation were met. Any emergent safety issues related to patients undergoing dose augmentation would be reviewed by Genzyme Pharmacovigilance and forwarded to the DSMB, if deemed necessary by the Medical Affairs (Pharmacovigilance) Officer, or designee.

Safety, PK, and PD assessments and efficacy evaluations were performed at scheduled visits throughout the study, while adverse events (AEs) and concomitant medications/therapies were monitored continuously. In addition, throughout the conduct of this study, an independent DSMB reviewed safety information as outlined in the DSMB Charter. Moreover, an independent Allergic Reaction Review Board (ARRB) was consulted as needed for evaluation of moderate or severe infusion-associated reactions (IARs) as outlined in the ARRB Charter.

Interim analyses were performed after the 15th patient completed 26 and 52 weeks of treatment. Maintenance modules were repeated until the study was terminated shortly after market approval.

NUMBER OF PATIENTS IN OVERALL STUDY (PLANNED AND ANALYZED):

Planned: Up to 20 patients with infantile-onset Pompe disease would be treated with Myozyme. Actual: A total of 22 patients were enrolled. The first patient enrolled in the study died prior to administration of study drug and was, therefore, replaced. With only 1 slot remaining for enrollment in the study, 2 patients presented over a very short period of time. Due to the severity of infantile-onset Pompe disease, and because the timing was so close, the decision was made to expand the enrollment to include both patients. This brought the total number of patients enrolled to 22 and the number of patients treated to 21.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION:

Inclusion Criteria: Patients who met all of the following inclusion criteria were eligible to participate in this study:

Patient's legal guardian(s) provided written informed consent prior to any study-related procedures being performed;

Patient had a clinical diagnosis of infantile Pompe disease as defined by both:

- documented (in a medical record) onset of symptoms compatible with Pompe disease by 12 months-of-age adjusted for gestation, if necessary (gestational age of <40 weeks was adjusted to a full term gestational age of 40 weeks); AND
- documented GAA deficiency as illustrated by an endogenous GAA activity ≤2 % of the mean of the normal range as assessed in cultured skin fibroblasts using 4-methylumbelliferyl-alpha-D-glucoside (4-MUG) as substrate (assay performed by the Glycogen Storage Disease [GSD] Laboratory at Duke University Medical Center; GAA activity results obtained from Genzyme screening protocol AGLU01802 could be used);

Patient was >6 and ≤36 months-of-age, adjusted for gestation (gestational age of <40 weeks was

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adjusted to a full term gestational age of 40 weeks) at the time of the first dose of Myozyme;

Patients ≤12 months-of-age had LVMI ≥65 g/m^2; patients >12 months-of-age had LVMI >79 g/m^2. LVMI was determined by a study site cardiologist using 2D echocardiography. Age-specific LVMIs were equivalent to mean LVMI plus 2 standard deviations (SDs) as published by Vogel.

Patient and his/her legal guardian(s) must have had the ability to comply with the clinical protocol.

Exclusion Criteria: Patients were excluded from this study if they did not meet the specific inclusion criteria, or if the patient met any of the following criteria:

signs and symptoms of cardiac failure *and* an ejection fraction <40 % as determined by a study site cardiologist;

major congenital abnormality;

clinically significant (CS) organic disease (with the exception of symptoms relating to Pompe disease), including CS cardiovascular, hepatic, pulmonary, neurologic, or renal disease, or other medical condition, serious intercurrent illness, or extenuating circumstance that, in the opinion of the Investigator, precluded participation in the trial or potentially decreased survival;

use of any investigational product within 30 days prior to study enrollment;

received enzyme replacement therapy (ERT) with GAA from any source.

DOSE/ROUTE/REGIMEN:

Patients initially received IV infusions of Myozyme at a dose of 20 mg/kg qow; dose was adjusted monthly to account for changes in body weight. After at least 26 weeks of treatment with Myozyme, patients could be evaluated to determine whether they met at least 1 of the criteria for augmentation to a maximum dose of 40 mg/kg qow. Eight patients qualified for dose augmentation and received the augmented dose (from a minimum of 20 doses to a maximum of 52 doses).

Prior to each infusion, the patient was assessed by the Investigator or appropriate designee to determine if the patient was free of acute illness symptoms and was stable enough to receive the infusion. Infusions were administered incrementally. Patients received infusions of the 20 or 40 mg/kg dose at an initial rate of approximately 1 mg/kg/hr; this was gradually increased by approximately 2 mg/kg/hr every 30 minutes if there were no signs of IARs, until a maximum rate of approximately 7 mg/kg/hr was reached.

Dose reduction: The patient's dose of Myozyme could be reduced at any time in the study if he/she experienced severe or intolerable reactions defined as: (1) liver (or other) toxicity attributed to Myozyme: (2) symptoms suggestive of immune complex disease attributable to Myozyme; or (3) an unmanageable IAR, defined as an IAR that did not respond to pretreatment, rate reduction or treatment during the reaction. The final decision to reduce the dose was to be made by the Sponsor in consultation with the Investigator, and upon recommendation by the DSMB/ARRB. Dose reductions were to be performed in a step-wise manner. No patients required downward adjustment of dosing for safety reasons**.**

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

Myozyme was administered by IV infusion at 20 mg/kg or 40 mg/kg qow.

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DURATION OF TREATMENT: (PLANNED AND ACTUAL)

Planned: 52 weeks with repeating 52-week modules. Actual: 17 March 2003 to 12 June 2006. Patients received a minimum of 1 infusion and a maximum of 85 infusions (168 weeks of treatment) of Myozyme.

REFERENCE TREATMENT:

There was no comparator treatment or placebo in this study given the universal fatality of untreated infantile-onset patients and the lack of any approved treatment.

CRITERIA FOR EVALUATION:

EFFICACY:

The primary efficacy endpoint was survival of patients over the course of treatment.

Secondary efficacy was evaluated by (1) the effect on respiratory function, measured as follows: (a) for patients who were ventilator-free at the onset of the study, the proportion of patients who were alive and ventilator-free over the course of treatment and the ventilator-free survival time; (b) for patients who required ventilator use at the onset of the study, the overall duration of ventilator support and the number of hours of ventilator use (in the 24 hours preceding each infusion visit, measured qow); (2) the effect of treatment on cardiac status as measured by LVMI and LVM Z-score, and presence of any signs and/or symptoms of cardiac failure; (3) the effect of treatment on motor development as measured by the AIMS and/or PDMS-2, and the patient's ability to achieve and maintain clinically relevant motor milestones.

Additional efficacy outcomes included the effect of treatment on: (1) cognitive development from Baseline as measured by the MDI of the BSID-II and/or the Brief Scale IQ score of the Leiter-R; (2) physical growth by body length, weight, and head circumference; (3) change in functional status from Baseline as measured by the PEDI; and (4) change in functional status from Baseline as measured by the Pompe PEDI.

SAFETY:

Safety was evaluated in terms of AEs, vital sign parameters, physical examination findings, hearing testing, electrocardiogram (ECG) parameters, and routine laboratory measurements (hematology, chemistry, and urinalysis) including anti-rhGAA immunoglobulin G (IgG) antibody monitoring.

Additional exploratory safety studies conducted for research purposes only included the evaluation of: (1) circulating immune complex detection, when clinically indicated by symptoms suggestive of immune complex disease; (2) inhibitory antibody formation in patients testing positive for IgG; (3) anti-rhGAA immunoglobulin E (IgE), serum tryptase, and complement activation, when clinically indicated following moderate or severe 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.

PK AND PD:

PK and PD evaluations were conducted in all patients. PK in plasma was evaluated by measuring GAA activity in plasma at time points before and after Myozyme infusions at Day 0 and Week 12. PD in tissue was evaluated in muscle biopsy samples taken at least 24 hours prior to the first infusion at Baseline and 48 hours after the infusions at Weeks 12 and 52; biochemical assessment of GAA activity, and biochemical and histological assessment of glycogen in quadriceps muscles was performed.

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RESEARCH PURPOSES ONLY:

The potential effect of ACE marker allele status on the primary efficacy outcome was analyzed. CRIM status and GAA gene mutations are reported but no further analyses were peformed.

STATISTICAL METHODS:

Patient disposition and accountability, demography, background and Baseline characteristics, and efficacy and safety results were listed and summarized where appropriate. Categorical variables were summarized by frequency tables, while continuous variables were summarized using descriptive statistics including the sample size (n), median, mean, SD, minimum, and maximum. All analyses were carried out using SAS® Software, Version 8.

The following analyses were prospectively defined in the Statistical Analysis Plan for the overall study and have been conducted on all patients through Week 104 and, as appropriate, beyond Week 104.

EFFICACY:

Primary Efficacy: The survival over the course of treatment was summarized by the Kaplan-Meier estimates of the probability of survival (with 95% confidence limits) at Week 26, Week 52, Week 78, Week 104, and Week 130) The proportion of patients alive at their final visit was also calculated. Kaplan-Meier plots of the survival time from birth, survival time from first symptoms, survival time from confirmed diagnosis, and survival time from treatment initiation have been prepared.

Secondary Efficacy: The effect of treatment on respiratory function was evaluated by:

For patients who were ventilator-free at the onset of the study,

- the proportion of patients alive and ventilator-free for at least 14 consecutive days bracketing the target time points – Week 26, Week 52, Week 78, Week 104, Week 130, and End of Study. If the Investigator determined the patient was on ventilator due to secondary causes only (e.g., aspiration, pneumonia) at the target time points, the patient was followed for up to an additional 30 days. If the patient became ventilator-free for at least 14 consecutive days during this additional 30-day period, he/she was considered as ventilator free;
- time to death or overall invasive ventilator-dependence, defined as the date when the patient was first placed on invasive ventilator support and afterward remained ventilated without a 14-day invasive ventilator-free period;
- time to death or first ventilator use;
- the ventilator-free survival time from birth to Week 26, Week 52, Week 78, Week 104, Week 130, and End of Study (Final Visit) was analyzed by evaluating the time to ventilator use or death as well as the overall time and the proportion of time that a patient was alive and not on ventilatory support throughout the study treatment;
- Cox regression analysis was also used to evaluate survival and ventilator-free survival.

The overall duration of any ventilator support and the number of hours of ventilator use in the 24 hours preceding each infusion visit were summarized; the number of hours was collected from the time of first ventilator use and qow thereafter (if applicable) until (a) ventilator support was no longer needed; (b) patient died; or (c) the target endpoint, i.e., Week 52, Week 104, and End of Study (Final Visit), whichever came first. The reason for ventilator use was provided through listings and summaries.

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The effect of treatment on cardiac status was evaluated by changes (Changes, % Changes, and Z-scores) in LVMI, LVM, LV Posterior Wall Thickness, LV Septal Wall Thickness, Ejection Fraction, and Shortening Fraction from Baseline at Week 26, Week 38, Week 52, Week 78, Week 90, Week 104, Week 130, and Final Visit. Measurements were also compared to values from normal peers.
The presence of signs and/or symptoms of cardiac failure was also tallied. The proportion of patients who had an onset of cardiac failure signs and/or symptoms was summarized.

The effect of treatment on motor development was evaluated by AIMS scores (for patients ≤18 months-of-age and for those patients who had not reached the ceiling of the AIMS if they were >18 months-of-age) or PDMS-2 (for patients >18 months-of-age), and achievement and maintenance of clinically relevant motor development milestones. Changes from Baseline to Week 26, Week 52, Week 78, Week 104, Week 130, and Final Visit in AIMS and PDMS-2 scores were summarized through tables, listings, and figures. In addition, changes in age-equivalent for AIMS and/or PDMS-2 were summarized descriptively. The total number of clinically relevant motor development milestones achieved and/or maintained was summarized descriptively.

Other Efficacy: Other efficacy outcomes analyzed include the effect of treatment on cognitive development indices (BSID-II raw score and MDI and/or the Brief IQ score of the Leiter-R). Standardized age- and gender-adjusted measurements (i.e., length, weight, and head circumference), with reference to the Centers for Disease Control and Prevention growth curves, were analyzed and summarized descriptively. Changes from Baseline in functional status domain scores of the PEDI and the Pompe PEDI were evaluated. All of these endpoints were evaluated at Baseline, Week 12, Week 26, Week 38, Week 52, Week 64, Week 78, Week 90, Week 104, Week 130, and Final Visit.

SAFETY:

The incidence of AEs was summarized by severity, treatment relationship, and outcome. AEs, serious AEs (SAEs), IARs, vital signs, physical examination findings, hearing testing, and ECG assessments were summarized through tables and listings. Analyses of AEs, SAEs, and IARs were stratified by gender, by maximum anti-rhGAA antibody titer, and for the subgroup that underwent dose augmentation. The analysis of clinical laboratory measurements was based on the frequencies of abnormal values and frequencies of CS abnormal values. Changes in other safety variables, including anti-rhGAA IgG antibody development, IgE antibody, serum tryptase activity, complement activation, and circulating immune complex detection (if applicable), were summarized using descriptive statistics.

PK AND PD:

The following PK parameters were estimated from the plasma Myozyme concentration-time data at Day 0 and Week 12, whenever possible: observed peak drug concentration (C_{max}); observed time to reach peak drug concentration (T_{max}); area under the concentration versus time curve from time=0 to time of last quantifiable concentration ($AUC_{(0-t)}$); area under the plasma concentration-time curve from 0 to infinity (AUC_{∞}); clearance (CL); volume of distribution during terminal phase after IV administration (V_z); volume of distribution at steady-state (V_{ss}); and terminal half-life ($t_{1/2}$). All pharmacokinetic calculations were done using SAS® for Windows® Version 9.1. The primary PD parameter evaluation was the difference in skeletal muscle glycogen content after Baseline, 12 weeks of treatment, and 52 weeks of treatment. Results were summarized descriptively. Changes (absolute and percent change) in glycogen content and GAA activity in muscle biopsy samples from Baseline were summarized. The number and proportion of patients with a decrease in glycogen content and those patients with increased tissue GAA activity over time was summarized.

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SUMMARY – CONCLUSIONS

All enrolled patients had a confirmed diagnosis of infantile-onset Pompe disease. None of the 21 treated patients were diagnosed prenatally. The majority of patients in this international population (N=21) were Caucasian. Neither gender predominated, and the majority of patients were between 6 and 24 months-of-age when they began Myozyme treatment. The median age at first symptoms was 3.0 months, and the median age at diagnosis was 6.8 months. One-third (n=7) of the patients were ventilated (invasively or noninvasively) at treatment initiation, and 2 patients were CRIM (-). At Baseline, mean GAA activity in skin fibroblasts in all patients was <1%.

EFFICACY RESULTS:

Twenty-two patients were enrolled under Protocol AGLU01702 and 21 received treatment. One patient died prior to receiving treatment. Of 21 patients who received at least 1 infusion of Myozyme, 15 patients were alive as of the time of discontinuation or end of study. None of the deaths were assessed as treatment-related. The Kaplan-Meier estimate of survival probability was 76.2% at Week 52 and 71.1% at Week 104, and the binomial estimate of survival at the end of study was 71.4%. Twelve- and 24-month survival estimates, stratified by age at first infusion were compared to estimated conditional survival rates for reference groups derived from an AGLU01702 Historical Reference Subgroup. In every category, survival rates for patients treated with Myozyme were greater than the corresponding upper limit of the 95% confidence intervals (CIs) of the untreated reference groups, which suggests that treatment with Myozyme extended survival in these patients. Cox regression analyses also showed Myozyme to reduce the risk of death by 79% (hazard ratio of 0.209, 95% CI: 0.083, 0.524; p-value 0.0009) compared to the untreated historical reference group.

Cox regression analyses also showed Myozyme to reduce the risk of death or overall invasive ventilator-dependence by 58% (hazard ratio of 0.421, 95% CI: 0.202, 0.876; p-value 0.0207) compared to the untreated historical reference group. Note that the estimate of the treatment effect for invasive-ventilator-free survival is very conservative in that, while it counts deaths in addition to ventilation for the treated patients, it only counts deaths in the untreated patient reference subgroup.

Seventeen (81%) of 21 patients demonstrated improved or maintained normal LVM from first to last study evaluation. Mean LVMI declined by 42% at Week 52 and by 63% at Week 104. Echocardiographic measurements of cardiac function (EF and SF) demonstrated a trend toward normalization over the course of treatment. Mean improvements of 39% and 30% in EF and SF, respectively, were observed after 104 weeks of treatment.

Growth parameters measured showed maintenance above the 3rd percentiles in 17 (81%) of 21 patients in weight-for-age percentiles; in 19 (90%) of 21 patients in length-for-age percentiles; and 16 (89%) of 18 patients in head circumference-for-age percentiles.

Thirteen of 21 patients (62%) had measurable gains in motor assessments (AIMS and/or PDMS-2 gross and fine motor skills), as determined by increases in raw scores and age-equivalent scores from Baseline. The remaining patients did not demonstrate measurable gains across these motor assessments. Eleven of 12 patients with BSID-II evaluations at Baseline and beyond the Week 52 study visit demonstrated consistent increases in age-equivalent scores after the first 52 weeks of Myozyme treatment, indicating the continued acquisition of cognitive, language, and personal/social development skills.

In summary, in spite of the wide range of ages at initiation of treatment and the advanced stage of the disease progression at Baseline, these results from administration of Myozyme to patients with

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infantile-onset Pompe disease indicate that Myozyme treatment tended to prolong patient survival. Marked improvement in cardiomyopathy parameters occurred, and gains in growth and cognitive parameters were observed. A subgroup of 13 patients showed improvement in motor function. Initiation of Myozyme therapy at an early age, prior to irreversible muscle tissue damage, may optimize clinical response.

SAFETY RESULTS:

Twenty-one patients were treated with Myozyme with exposures ranging between 1 and 85 infusions (median of 61 infusions), corresponding to up to 168 weeks of treatment. Six (28.6%) patients died during the study, and a seventh died during the Baseline period (prior to receiving therapy). Following review of this event by the Sponsor and the DSMB, Investigators were cautioned with regard to the significant risks associated with the use of general anesthesia in infantile-onset Pompe patients. None of the deaths were related to treatment with Myozyme.

A total of 1209 treatment-emergent events were reported in 21 patients. The majority of treatment-emergent AEs were assessed as unrelated to Myozyme. Most were mild or moderate in intensity; 56 (4.6%) AEs were reported as severe. Fifty-three (4.4%) AEs were assessed as related to Myozyme treatment. Most related events occurred on the day of infusion, and 42 (79.2%) of the related AEs were considered IARs. IARs were generally well tolerated and were managed with infusion rate reduction or interruption, as well as with treatment with antihistamines and antipyretics. In a single instance (1 patient), steroid treatment was administered following an IAR. Pre-treatment with steroids was required for only 1 patient. In all instances, patients recovered without sequelae from the IARs. There were no patient discontinuations due to IARs.

A total of 171 treatment-emergent SAEs were experienced by 19 of the 21 patients, 74% of which were mild or moderate in intensity. The majority of SAEs were respiratory or infectious in nature; the most frequently occurring SAEs by MedDRA preferred term were pneumonia, respiratory failure, pyrexia, respiratory distress, tracheitis, catheter related infection, and pneumonia aspiration. Pompe disease is often associated with compromised respiratory status. Therefore, it is not unexpected that these patients are frequently hospitalized for recurrent respiratory infections and associated pulmonary complications. Additionally, indwelling central catheters were placed in the majority of patients receiving Myozyme for ease and frequency of venous access.

Eleven (52%) of 21 patients experienced IARs following at least 1 infusion. Two patients experienced IARs suggestive of a hypersensitivity reaction. Per protocol, IgE antibodies, complement activation, and serum tryptase activity were assessed in the event of a moderate or severe IAR. Four patients who experienced moderate IARs were tested and a fifth with mild IARs was tested at the Investigator's request. None of the patients tested IgE-positive; 2 patients were positive for complement activation; and serum tryptase levels were within normal limits for all patients tested.

Nineteen of 20 treated patients with post-Baseline measurements developed IgG antibodies to Myozyme. One patient was seropositive at Baseline, suggestive of pre-existing cross-reactivity. Seventeen of the patients who seroconverted did so by Week 12. An additional patient seroconverted by Week 38. As the majority of patients developed anti Myozyme antibodies, meaningful assessment of AEs based upon seroconversion status is not possible. Seven patients developed anti-rhGAA IgG antibody titers ≥12,800. Patients who developed high antibody titers appeared to be at higher risk for developing more frequent IARs. No significant inhibitory antibody activity was detected in any of the patients.

Additionally, circulating immune complexes could be assessed when evidence of immune complex

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disease was noted. No patients experienced clinical manifestations of immune disease, and the laboratory data also indicated that no patients sustained CS abnormalities suggestive of immune complex formation. No patients were assessed for circulating immune complexes.

Changes in laboratory parameters, physical examination, and 12-lead ECG findings observed during the conduct of this study were generally consistent with the evolving clinical status of the 21 treated patients. Interpretation of hearing test results was complicated by the presence of middle ear dysfunction in most patients. At Baseline, many patients were observed to have middle ear fluid, thus, it is not surprising that the majority of patients had an abnormal tympanogram at Baseline. Flat oto-acoutstic emission (OAE) and/or abnormal wave latencies in brainstem auditory evoked response suggested that, at least in some patients, there was inner ear and/or auditory nervous system involvement contributing to abnormal hearing test results. No conclusion can be drawn regarding sensorineural hearing in the majority of patients under study. A review of the literature suggests that hearing loss has been commonly observed in patients with glycogen storage disorders, including Pompe disease. A study in a knockout mouse model of Pompe disease revealed that this most likely is caused by cochlear pathology due to glycogen accumulation. These data would strongly suggest that hearing loss in patients with Pompe disease is related to the disease itself and is not a complication of therapy.

CONCLUSION: [redacted]