SYNOPSIS

NAME OF COMPANY **Genzyme Corporation** **500 Kendall Street** **Cambridge, MA 02142** NAME OF FINISHED PRODUCT **Myozyme™** NAME OF ACTIVE INGREDIENT **Recombinant Human Acid Alpha-Glucosidase**	SUMMARY TABLE Referring to Part …… of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:

TITLE OF STUDY:

A Single Center, Open-Label, Bridging Study of the Safety, Pharmacokinetics and Efficacy of Recombinant Human Acid Alpha-Glucosidase (rhGAA) Treatment in Patients with Late-Onset Pompe Disease (Glycogen Storage Disease Type II)

INVESTIGATOR(S):

[redacted]

STUDY CENTER(S):

[redacted]

PUBLICATION (REFERENCE):

Not applicable

STUDIED PERIOD:

This report describes findings from a 74-week Myozyme treatment period (38 infusions). The first patient received the first infusion on 02 February 2005 and the last patient completed the Week 74 visit on 13 July 2006.

PHASE OF DEVELOPMENT:

Phase 2

OBJECTIVES:

The objectives of this study in late-onset Pompe patients were: (1) To evaluate the safety profile of rhGAA; (2) To determine the pharmacokinetic (PK) profile of rhGAA; (3) To determine the effect of treatment on pulmonary function as measured by Forced Vital Capacity (FVC) in the upright (sitting) and supine positions; (4) To determine the effect of treatment on muscle strength as measured by Manual Muscle Testing (MMT) and hand-held dynamometry (HHD); (5) To determine the effect of treatment on muscle function as measured by the distance walked in either the 6-minute walk test (6MWT) or the 3-minute walk test (3MWT), the time to perform a 10-meter walk test, and the time to stand up from a supine position; (6) To determine the effect of treatment on cardiovascular endurance as measured by the energy expenditure index (EEI) during the 6MWT or 3MWT.

METHODOLOGY:

This was a single center, open-label study of rhGAA in patients with late-onset Pompe disease. Eligible patients received an IV infusion of 20 mg/kg of rhGAA qow for an initial period of 26 weeks. Thereafter, as there were no safety concerns and in accordance with Protocol Amendment 1, a 24-week Maintenance phase module was to be repeated successively until the study was terminated or until reimbursement of rhGAA, whichever occurred first. Two Maintenance phase modules were completed giving a total treatment period in the clinical study of 74 weeks. All patients were subsequently transferred to treatment with commercial product and the study is now closed. Interim analyses were conducted after all patients had completed the Week 12, Week 26 and Week 50

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assessments. Although originally designed as a single center study, after the initial 26 weeks of treatment patients could be transferred to a local site to receive treatment, but were still required to return to the primary investigational site every 12 weeks to complete the safety and efficacy assessments.

Safety, PK and efficacy assessments were performed at scheduled visits throughout the study. Adverse events (AEs), infusion-associated reactions (IARs), concomitant medications and therapies including use of assistive devices were monitored continuously throughout the study.

Safety was evaluated in consultation with an independent Data Safety Monitoring Board (DSMB) which assembled periodically to review safety information. The DSMB was to also convene on an ad hoc basis to review AEs that may have necessitated temporary or permanent discontinuation of rhGAA treatment.

An independent Allergic Reaction Review Board was also to be consulted on an ad hoc basis for evaluation of moderate or severe IARs and to provide guidance on IAR management.

NUMBER OF PATIENTS (PLANNED AND ANALYZED):

Five patients ≥5 and <18 years old with late-onset Pompe disease were planned, enrolled, and analyzed.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION:

INCLUSION:

Subjects who met all of the following inclusion criteria were eligible to participate in this study: (1) The patient's legally authorized guardian(s) provided written informed consent prior to performing any study-related procedures. If the patient understood the written informed consent form, signature was required from both the patient and the legally authorized guardian(s); (2) The patient had a confirmation of diagnosis of Pompe disease by documentation of either acid α-glucosidase (GAA) gene mutation analysis or deficient endogenous GAA activity as determined by the assaying laboratory; (3) The patient had demonstrable muscle weakness as measured by MMT; (4) The patient was ≥5 and <18 years of age; (5) The patient was able to provide 3 reproducible FVC measurements (values within 5% of each other) in the upright (sitting) position; (6) The patient was able to perform pulmonary and muscle function testing in the supine position; (7) The patient was able to ambulate 10 meters (use of assistive devices such as a walker, cane, crutches, was permitted); (8) The patient (and legal guardian) had the ability to comply with the clinical protocol.

EXCLUSION:

Subjects who met any of the following exclusion criteria were not eligible for participation in this study: (1) The patient required the use of invasive ventilatory support (invasive ventilation was defined as any form of ventilatory support applied with the use of an endotracheal tube); (2) The patient required the use of non-invasive ventilatory support whilst awake and in an upright position. (Non-invasive ventilation was defined as any form of ventilatory support applied without the use of an endotracheal tube.); (3) The patient had received enzyme replacement therapy with GAA from any source; (4) The patient had received an investigational drug or device within 30 days prior to study enrolment, or was currently participating in another clinical or observational study; (5) The patient had a medical condition, serious intercurrent illness, or other extenuating circumstance that, in the opinion of the Investigator, may significantly interfere with study compliance, including all prescribed evaluations and follow-up activities; (6) For female patients of child bearing potential only, the patient was pregnant or lactating, or was unwilling to practice birth control methods during the course of the study, such as abstinence, barrier methods, hormonal methods (oral contraceptives or injectable), or use of intrauterine devices; (7) For male patients only, the patient was unwilling to use barrier contraceptives during the

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course of the study.

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

Investigational drug: Recombinant human acid alpha-glucosidase (rhGAA) produced in Chinese hamster ovary cells (2000L scale bioreactors).

Dose: 20 mg/kg qow
Route: IV infusion
Regimen: The total amount of rhGAA was adjusted every 4 weeks to account for changes in body weight. Prior to each infusion, the patient was assessed by the Investigator or appropriate designee to determine if the patient was free from acute illness symptoms and sufficiently stable to receive the infusion. The therapy was administered at an initial rate of 0.2 mg/kg/hr and could be gradually increased incrementally every 30 minutes (if there were no signs of IARs) until a maximum rate of 10 mg/kg/hr was reached. The total duration of infusion was approximately 3.5 hours. No shortening of the infusion duration was permitted during the first 26-week treatment period. Thereafter, a faster infusion scheme could be used to decrease infusion duration with prior approval from Genzyme.

Batch numbers: [redacted]

DURATION OF TREATMENT:

The duration of the initial treatment period was 26 weeks. Thereafter, patients completed two consecutive 24-week Maintenance phase modules giving a total study treatment period with Myozyme of 74 weeks. All patients in the study subsequently transferred to treatment with commercial product following the approval of Myozyme by the European Commission for use in patients with Pompe disease.

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

No reference treatment was used in this open-label study.

CRITERIA FOR EVALUATION:

SAFETY:

Safety assessments consisted of AEs, serious AEs (SAEs), laboratory tests (serum chemistry, hematology, and urinalysis), 12-lead electrocardiogram (ECG), hearing tests, anti-rhGAA antibody (immunoglobulin G [IgG]), vital signs, concomitant medications and therapies, physical examination, and for females of childbearing potential, urine pregnancy tests. In addition, exploratory safety evaluations were to be performed to assist in the clinical management of patients and /or for research purposes only. These include testing for serum immunoglobulin E (IgE) antibodies, serum tryptase activity, and complement activation as well as skin testing when clinically indicated following moderate or severe IARs; testing of all seropositive patients for the presence of inhibitory antibodies to rhGAA; and circulating immune complex detection when clinically indicated by symptoms suggestive of immune complex disease.

PHARMACOKINETICS:

Blood samples were drawn at selected time points to assess GAA activity in plasma. Pharmacokinetic parameters for rhGAA were calculated using standard non-compartmental methods. The following PK parameters were estimated from the plasma rhGAA concentration-time data at Day 0, Week 12, and Week 26: C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$, CL, V_z, V_{ss}, t_v, and $t_{1/2}$.

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EFFICACY:

The following efficacy assessments were performed at Baseline, Week 12, Week 26 and every 12 weeks during the Maintenance phases of the study:

- Pulmonary function testing (FVC measured in upright [sitting] and supine positions);
- MMT – 34 muscle groups assessed;
- HHD;
- Functional activities assessment (6MWT or 3MWT, time to walk 10 meters, time to stand up from the supine position);
- Cardiovascular endurance as measured by EEI.

OTHER:

Height, weight, and echocardiogram

STATISTICAL METHODS:

Interim analyses of the safety data, PK data, and efficacy endpoints were performed after the last patient had completed the Week 12 and Week 26 assessments. In addition, an interim analysis of safety and efficacy data was performed after the last patient had completed the Week 50 assessments. An analysis of all efficacy and safety data was performed after the last patient had completed the Week 74 visit and is described in this report.

All efficacy measurements and safety data were compared to Baseline and were summarized descriptively. All patient data are presented in patient listings.

SUMMARY – CONCLUSIONS

Five patients (3 males, 2 females) with late-onset Pompe disease were enrolled and treated with Myozyme 20 mg/kg qow under Protocol AGLU02804. All 5 patients received 38 infusions (i.e., a total of 190 Myozyme infusions were administered) and completed the 74-week treatment period of the study, i.e., initial 26-week treatment period plus two consecutive 24-week Maintenance phases. Three patients transferred to a local site for treatment during the study: Patients 103 and 104 both transferred to the same local site in Leuven, Belgium during Weeks 32 and 44 of their respective treatment periods; Patient 105 transferred to a site in London during Week 52 of treatment. Patients 101 and 102 remained at the primary site in Rotterdam for the entire study.

All 5 patients had confirmed diagnosis of late-onset Pompe disease (GAA deficiency and/or genotyping) between the ages of 13 months and 11.6 years. The patients in this study exhibited clinical features typical of patients with late-onset Pompe disease, including scoliosis, lordosis, joint contractures, abnormal gait and difficulties with climbing and running. The median age at first Myozyme infusion was 12.7 years (range 5.9 to 15.2 years).

EFFICACY:

At Baseline, 3 of the 5 patients showed evidence of significant pulmonary involvement (i.e., FVC < 80% predicted). All 3 of these patients showed improvement in % predicted FVC (increase ranged from 6.8% to 21.8%) in the upright position at Week 74 with one patient (Patient 105) showing a clinically meaningful improvement based on American Thoracic Society / European Respiratory Society guidelines which suggest that a change in FVC of at least 15% over the course of a year represents a clinically significant change

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in pulmonary function.

Muscle function testing using MMT indicated all patients had barely detectable or mild muscle weakness at Baseline with greater involvement of proximal muscles relative to distal muscles, and lower extremities relative to upper extremities. At Week 74, total MMT scores had increased from Baseline for 4 of the 5 patients (increase in these 4 patients ranged from +21 to +79 points) indicating a clinically detectable improvement in overall body muscle strength after 74 weeks of Myozyme treatment. Similarly, HHD data showed that 4 patients achieved a meaningful increase in muscle strength in at least 3 muscle groups at Week 74 compared to Baseline, although there was no consistent pattern of improvement across patients.

For the 6MWT at fast speed, all 4 patients with Week 74 data achieved increased walk test distances ranging from +67 to +158 meters compared to Baseline, which were considered to represent clinically meaningful improvements in walking distance. For the 6MWT at the comfortable speed, only Patient 105 demonstrated an increased walk test distance (+64 meters) at Week 74 compared to Baseline; the 3 other patients with Week 74 data showed a decrease from Baseline ranging from 5 to 61 meters. Patient 102 was unable to complete the Week 74 6MWT as the patient was recovering from surgery for Achilles tendon release. The results of the fast speed walk test suggest that this may be a more appropriate and physically challenging test than the comfortable speed test.

Cardiovascular endurance was assessed using the EEI from the 6MWT administered at two different speeds. Interpretation of the changes from Baseline in EEI data at comfortable speed is difficult due to the decrease in distance walked at the Week 74 test. EEI values at fast speed did not show any discernible trend.

The 10-meter walk test and stand from the supine position test were performed at Week 74 either faster or in the same time as at Baseline for 4 of the 5 patients. The exception was Patient 102 who performed both tests in a longer time at Week 74 than at Baseline, but these findings need to be considered in light of the patient's ongoing rehabilitation from Achilles tendon release surgery.

PHARMACOKINETICS:
Although assessed in only a small number of patients, the PK data from this study indicate there was no obvious change in the PK profile of Myozyme (prepared at the 2000L scale) over the course of the initial 26-week study period during which PK assessments were performed.

SAFETY:

Treatment with Myozyme at a dose of 20 mg/kg qow was well tolerated and no new safety concerns were identified. No patients died or withdrew from treatment during the 74 weeks of this study. A total of 137 treatment-emergent AEs were experienced by the 5 patients in this study. The most frequently reported AEs by preferred term were pharyngolaryngeal pain, abdominal pain upper, headache, malaise, nasopharyngitis, and epistaxis. No patients experienced an AE of severe intensity and no patients had an AE that was considered by the Investigator to be possibly, probably or definitely related to study treatment. No patients experienced an IAR. Three SAEs were reported in 3 patients. Two of the SAEs (joint contracture and road traffic accident) were considered to be of mild intensity and one SAE (talipes) was considered to be of moderate intensity. None of the SAEs was assessed by the Investigator as related to study treatment.

None of the abnormal laboratory values reported in the study were considered by the Investigator to be clinically significant. All patients exhibited elevated levels of CK, CK-MB, AST, and ALT at almost all assessments including Baseline, consistent with late-onset Pompe disease. All 5 patients seroconverted, i.e., developed anti-rhGAA IgG antibodies with antibody titers of 800 to 6400; seroconversion was observed between Week 8 and Week 38. No patient developed inhibitory antibody activity (defined as inhibitory antibody activity of > 10%).

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One patient (Patient 103) had non-specific ECG abnormalities at Baseline and Week 74. Echocardiogram data indicated that no patient had cardiomyopathy at Baseline or at Week 74 in those patients with repeat assessments. Two patients (Patients 101 and 104) had an abnormal hearing test at Baseline. At Week 74, hearing assessment was normal in Patient 104 whereas Patient 101 still had a mild hearing abnormality. Small improvements (e.g., reduced headlag and Gower's sign) were observed in the physical examination status of 3 patients at Week 74 compared with Baseline.

CONCLUSION: [redacted]