ADVISORY COMMITTEE OPEN SESSION

INFORMATION FOR PUBLIC RELEASE

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# 1 ABBREVIATIONS AND TERMS

| | |
|---|---|
| 2D | 2 dimensional |
| 4-MUG | 4-methyl-umbelliferyl-$\alpha$-D-glucopyranoside |
| 6MWT | Six Minute Walk Test |
| °C | degrees Celsius |
| °F | degrees Fahrenheit |
| $\alpha$-half-life | Effective half-life |
| $\beta$-half-life | Terminal half-life |
| AE | Adverse event |
| AIMS | Alberta Infant Motor Scale |
| ANCOVA | Analysis of covariance |
| ANOVA | Analysis of variance |
| ATS | American Thoracic Society |
| AUC | Area under the curve |
| $\beta$-half-life | Terminal half-life |
| BiPAP | Bi-level positive airway pressure |
| BLA | Biologics License Application |
| BMI | Body mass index |
| bpm | Beats per minute |
| CFR | Code of Federal Regulations |
| CHO | Chinese hamster ovary |
| CI | Confidence interval |
| CIC | Circulating immune complex |
| cIEF | Capillary isoelectric focusing |
| CIM6Pr | Cation-independent mannose 6-phosphate receptor |
| CL | Clearance |
| Cmax | Maximal concentration |
| COPD | Chronic obstructive pulmonary disease |
| CPAP | Continuous positive airway pressure |
| CRIM | Cross-reacting immunologic material |
| CS | Clinically significant |
| CSL | Clinical Specialty Laboratory |
| CSR | Clinical Study Report |
| dL | deciliter |
| DNA | Deoxyribonucleic acid |
| DSMB | Data Safety Monitoring Board |
| ECG | Electrocardiogram |

| | |
|---|---|
| ELISA | Enzyme-linked immunosorbent assay |
| EMEA | European Medicines Agency |
| ERS | European Respiratory Society |
| ERT | Enzyme replacement therapy |
| ES | Effect size |
| EU | European Union |
| FDA | Food and Drug Administration |
| FVC | Forced Vital Capacity |
| GAA | Acid $\alpha$-glucosidase |
| GCP | Good Clinical Practice |
| GEE | Generalized estimating of equation |
| HPLC-UV | High performance liquid chromatography with ultraviolet detection |
| Hr | Hour |
| IAR | Infusion-associated reaction |
| IBD | International Birthdate |
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethics Committee |
| IgE | Immunoglobulin E |
| IgG | Immunoglobulin G |
| IND | Investigational New Drug Application |
| IRB | Institutional Review Board |
| ISC | Independent Statistical Center |
| IV | Intravenous |
| kg | Kilogram |
| L | Liter |
| LC/MS | Liquid chromatography – mass spectrometry |
| LME | Linear mixed effects |
| LOPOS | Late-Onset Patient Observational Study |
| LOQ | Limit of quantification |
| LOTS | Late-Onset Treatment Study (AGLU02704) |
| LS | Least squares |
| LSD | Lysosomal storage disorder |
| LVM | Left ventricular mass |
| M6P | Mannose 6-phosphate |
| MCID | Minimally clinical important difference |
| MCS | Mental component summary (of SF-36) |
| MedDRA | Medical Dictionary for Regulatory Activities |

| | |
|---|---|
| MEP | Maximal Expiratory Pressure |
| mEq | Milliequivalent |
| mg | Milligram |
| MIP | Maximal Inspiratory Pressure |
| mL | Milliliter |
| mM | Millimole |
| mmHg | Millimeters of mercury |
| MOS | Medical Outcomes Study |
| MPS | Mucopolysaccharidosis |
| MRI | Magnetic resonance imaging |
| MSE | Mean square error |
| MTAP | Myozyme Temporary Access Program (AGLU03907) |
| MVV | Maximal voluntary ventilation |
| NA | Not applicable |
| NCS | Not clinically significant |
| ng | Nanogram |
| NIMS | National Isometric Muscle Strength |
| nmol | nanomole |
| NTUH | National Taiwan University Hospital |
| PAS | Periodic acid-Schiff |
| pmol | picomole |
| PCS | Physical Component Summary (of SF-36) |
| PF | Physical functioning |
| PFT | Pulmonary function test |
| PK | Pharmacokinetics |
| PSUR | Periodic Safety Update Report |
| Q | Intercompartmental clearance |
| QMT | Quantitative Muscle Testing |
| qow | Every other week |
| rhGAA | Recombinant human acid $\alpha$-glucosidase |
| REMS | Risk Evaluation and Mitigation Strategy |
| RIP | Radioimmunoprecipitation assay |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| sBLA | Supplemental Biologics License Application |
| SD | Standard deviation |
| SE | Standard error |
| SEM | Standard error of the mean |

| SF-36 | Medical Outcomes Study (MOS) 36-Item Short Form |
|---|---|
| SMQ | Standardized MedDRA Query |
| SOC | System organ class |
| Tmax | Time to maximal concentration |
| U | Unit |
| US | United States |
| V1 | Central volume of distribution |
| V2 | Peripheral volume of distribution |
| Vss | Volume of distribution at steady-state |
| WCB | Working cell bank |
| WMW | Wilcoxon-Mann-Whitney |

## 2            EXECUTIVE SUMMARY

Alglucosidase alfa, a form of recombinant human acid alpha-glucosidase (rhGAA) developed by Genzyme Corporation, is currently the only approved therapy for the treatment of Pompe disease, a rare and life threatening neuromuscular disorder with an estimated global incidence of 1:40,000.  Clinical manifestations of Pompe disease can develop during infancy (referred to as 'infantile-onset' disease) or anytime after infancy through late adulthood (referred to as 'late-onset' disease).  All patients with Pompe disease share an underlying deficiency in acid alpha-glucosidase (GAA) that causes progressive proximal and respiratory muscle deterioration secondary to glycogen accumulation in these muscle tissues; however, there is significant heterogeneity in the clinical presentation and progression of the disease, particularly among late-onset patients.  The clinical hypothesis for enzyme replacement therapy (ERT), in all Pompe patients, is that increasing GAA activity (through the administration of exogenous enzyme that is taken up into target tissue lysosomes) will lead to a reduction in lysosomal glycogen accumulation in muscle tissue and a resultant improvement in contractile function.

United States (US) commercial supplies of alglucosidase alfa are currently manufactured by Genzyme using a "160 L scale" mammalian cell culture process (where scale refers to bioreactor volume).  The 160 L process scale for alglucosidase alfa, which was described in Biologics License Application (BLA) 125141, submitted July 2005, was licensed by the US Food and Drug Administration (FDA) on 28 April 2006 under the trade name Myozyme®.  Alglucosidase alfa produced at the 160 L scale is indicated for the treatment of all phenotypes of Pompe disease based on improved invasive ventilator-free survival in a pivotal study of patients with infantile-onset Pompe disease.

Genzyme recognized early on that demand for alglucosidase alfa was going to increase substantially due to the expanding number of patients receiving treatment and the high therapeutic dose (20 mg/kg every other week [qow]) relative to other ERTs (e.g., Fabrazyme® (agalsidase beta) = 1 mg/kg qow; Aldurazyme® (laronidase) = 0.58 mg/kg once weekly [qw]).  In anticipation of this projected (and now realized) increase in global demand for alglucosidase alfa, Genzyme developed a scaled-up 2000 L manufacturing process for alglucosidase alfa.  An overview of the 2000 L manufacturing process is provided in **Section** 4 of this briefing package.  Alglucosidase alfa produced using the

2000 L process scale is now approved for the treatment of Pompe disease in all global markets outside of the US that are served by Genzyme (over 40 countries), beginning with approval by the European Medicines Agency (EMEA) in March 2006.

In the US, Genzyme provided data supporting the 2000 L process (as well as the 160 L process) in BLA 125141, which was submitted in July 2005. Genzyme subsequently withdrew the 2000 L process from the application due to FDA concerns about the limited comparability data available for the 2000 L process, and to avoid delays in the review of the application while generating additional data requested by FDA. In October 2007, Genzyme submitted a supplement to BLA 125141 for the 2000 L process with additional biochemical and nonclinical data and a retrospective review of clinical data for infantile-onset patients receiving both 160 L and 2000 L product, including analyses specifically requested by FDA. Given that alglucosidase alfa is a highly complex glycoprotein, extensive analyses were conducted for a substantial number of alglucosidase alfa product lots at each scale. As summarized in **Section 4**, the primary comparability concerns were focused on glycan structures that may influence the biodistribution, targeting and/or uptake of the enzyme. While analytical differences were observed between lots manufactured at the different scales with respect to the relative amounts (though not the predominant type) of specific glycans, the nonclinical evaluation of 160 L and 2000 L product did not reveal meaningful differences in glycogen clearance (the intended biological effect) in a GAA knockout mouse model of Pompe disease. However, the FDA ultimately concluded that the comparability of alglucosidase alfa derived from the 160 L and 2000 L manufacturing processes could not be established. The agency therefore advised Genzyme on 15 April 2008 that alglucosidase alfa produced at the 2000 L process scale should be licensed as a distinct drug product with approval based upon safety and efficacy data from the pivotal AGLU02704 late-onset treatment study (hereafter referred to as "LOTS"). The LOTS study, which was fully enrolled at the time of US approval of 160 L alglucosidase alfa in April 2006, became part of Genzyme's post-marketing commitments to the BLA and was completed in September 2007. In accordance with the recommendation of FDA, Genzyme has submitted the 2000 L process for approval under a new application, BLA 125291, which includes efficacy, safety, and pharmacokinetic data from LOTS and was filed on 30 May 2008.

Approval of the 2000 L process in the US has become critical to providing treatment to US patients, and to assuring a continued supply of commercial alglucosidase alfa for all patients worldwide. There are over 950 patients receiving treatment with alglucosidase alfa worldwide as of 28 August 2008. Approximately 80 of these patients, all of whom are in the US, are currently receiving commercial treatment with 160 L alglucosidase alfa. The remaining patients (approximately 870) are receiving alglucosidase alfa produced at the 2000 L scale. During 2007, US patient demand for alglucosidase alfa exceeded the maximum production capacity of the approved 160 L process. Genzyme has endeavored to maintain uninterrupted access to alglucosidase alfa for US patients, including supplying a majority of US adult patients (i.e., those patients $\geq$ 18 years of age) with 2000 L alglucosidase alfa at no cost to the patient under a treatment protocol known as the Myozyme Temporary Access Program (MTAP), which is conducted under the US investigational new drug application (IND). As of 28 August 2008, MTAP is supplying 2000 L alglucosidase alfa to 157 adult patients, representing an estimated 55% of the US Pompe population. However, US demand for alglucosidase alfa has now increased to the extent that it is no longer feasible for Genzyme to supply additional adult patients with 2000 L alglucosidase alfa under MTAP, due in part to the challenges that the program presents to patients and physicians, including travel to participating clinical sites and the often lengthy institutional review procedures that must be completed in order to initiate therapy through this program. Therefore, MTAP has been closed to new patients as of April 2008, although patients in the LOTS Extension will continue to transition into MTAP. While the commercial supply of 160 L alglucosidase alfa is, at present, adequate to supply treatment to the small number of US Pompe patients who are < 18 years of age, these supplies are inadequate to provide treatment to the adult population. Consequently, as of 28 August 2008, Genzyme is aware of 53 newly diagnosed adult patients in the US (almost 20% of all US patients known to Genzyme) who are waiting for access to treatment with alglucosidase alfa.

In this briefing package, Genzyme has provided the Advisory Committee with a summary of the data supporting licensure of 2000 L alglucosidase alfa, including the pivotal efficacy (**Section 5.2.1**), safety (**Section 5.2.2**), and pharmacokinetic (PK) (**Section 5.2.3**) data from LOTS, a randomized, double-blind, placebo-controlled trial in 90 patients with late-onset Pompe disease. Genzyme believes the results from the LOTS

trial and supplemental clinical safety data for 2000 L alglucosidase alfa support the following proposed indication:

> TRADE NAME (alglucosidase alfa) is indicated for long-term use in patients with late-onset Pompe disease (GAA deficiency). TRADE NAME has been shown to improve distance walked and stabilize pulmonary function in patients with late-onset Pompe disease.

The co-primary efficacy endpoints for LOTS were the Six-Minute Walk Test (6MWT) distance walked and Forced Vital Capacity (FVC) % of predicted normal values based on age, gender, race, and height. Both co-primary endpoints were met in the LOTS study.

Plots of mean change from Baseline over time in 6MWT distance walked and FVC % predicted are presented in **Figure 2-1** and **Figure 2-2**, respectively.

**Figure 2-1: Mean (+/- Standard Error of the Mean [SEM]) Change From Baseline Over Time in Six-Minute Walk Test Total Distance Walked**
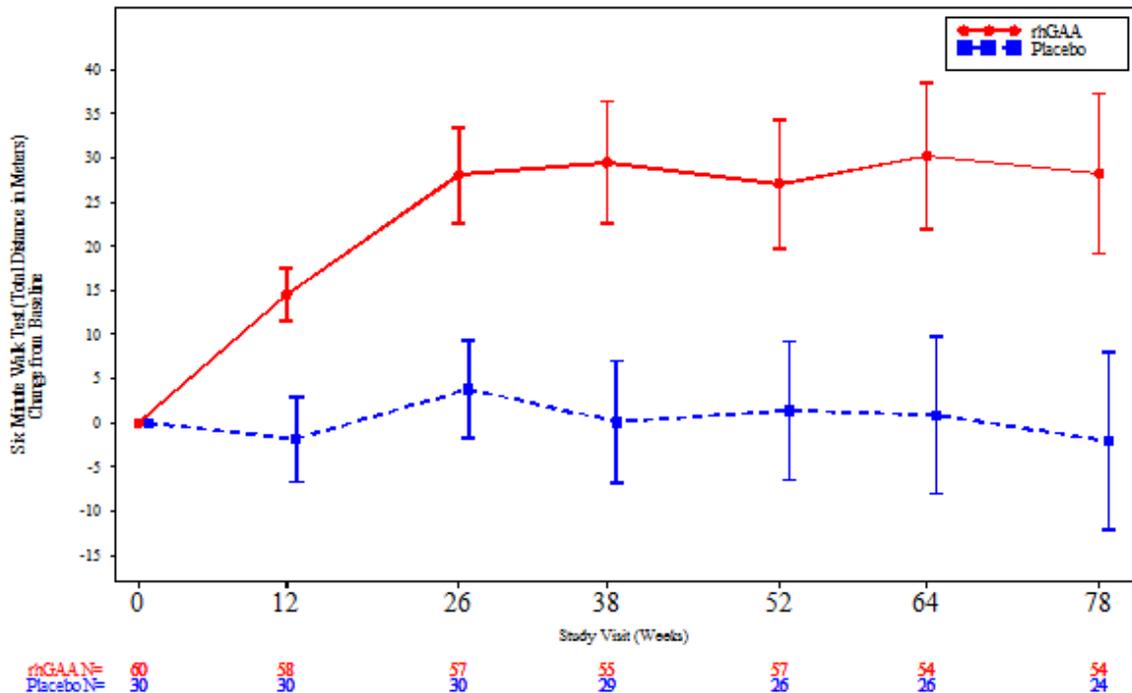
**Figure 2-2: Mean (+/- SEM) Change from Baseline Over Time in FVC % Predicted (Upright)**
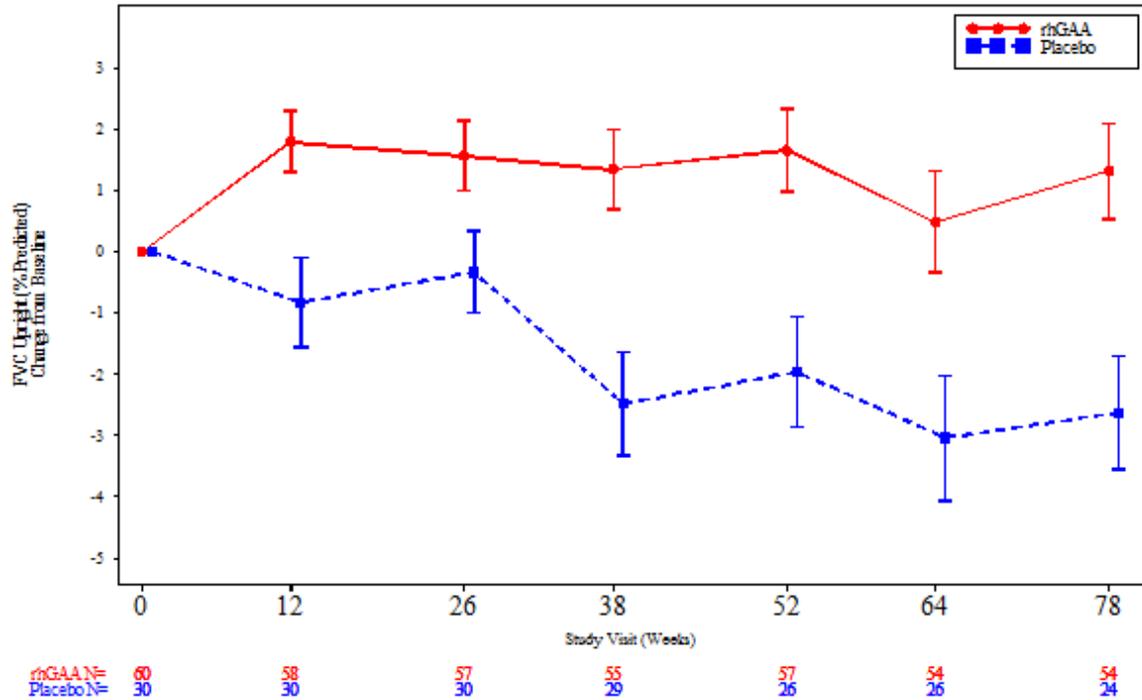


Statistically significant treatment differences were observed for 2000 L alglucosidase alfa relative to placebo for the primary analysis of the overall rate of change, as well as the supportive analysis of the change from Baseline to Week 78 (or last observation). The estimated mean treatment difference in rate of change was 1.24 meters/month for 6MWT distance walked (p=0.0464) and 0.18%/month for FVC % predicted (p=0.0041) using the linear mixed effect (LME) model with robust variance estimation. The estimated mean treatment difference from Baseline to Week 78 was 28.12 meters (p=0.0347) for 6MWT distance walked and 3.40% (p=0.0055) for FVC % predicted using analysis of covariance (ANCOVA). Of note, significant treatment differences were evident in 6MWT and FVC despite the substantial variability in proximal limb and respiratory muscle involvement observed in LOTS patients at Baseline. Moreover, a positive treatment effect of alglucosidase alfa over placebo was consistently observed for 6MWT and FVC, regardless of patient Baseline characteristics such as age, gender, disease duration, walking ability (6MWT) or pulmonary function (FVC), suggesting that 2000 L

alglucosidase alfa therapy may benefit a broad spectrum of patients in this clinically heterogeneous population.

Results of secondary and tertiary efficacy endpoints that measure the strength of proximal muscles in the lower and upper limbs (quantitative muscle testing [QMT] leg and arm scores, respectively) and the strength of diaphragm and other respiratory muscles (maximal inspiratory pressure [MIP] % predicted and maximal expiratory pressure [MEP] % predicted, respectively) demonstrate a consistent pattern of response in favor of 2000 L alglucosidase alfa treatment over placebo, and further support the statistically significant findings for the co-primary endpoints.

The statistically significant treatment effect of 2000 L alglucosidase alfa relative to placebo on walking ability and pulmonary function in late-onset patients over the 18 months of treatment in LOTS signals an important therapeutic advancement and can be expected to positively impact the lives of patients with this progressive neuromuscular disease. Importantly, the treatment effect sizes of alglucosidase alfa on 6MWT (0.48) and FVC (0.65) were consistent with effect sizes for these endpoints in the pivotal trials for other recombinant protein products that are now approved in the US for the treatment of orphan diseases involving progressive neuromuscular decline: mucopolysaccharidosis [MPS] type I (Aldurazyme) and MPS type II (Elaprase[®] (idursulfase)).

The LOTS safety data demonstrate that alglucosidase alfa produced at the 2000 L scale has an acceptable safety profile in late-onset patients. While a very small percentage of patients experienced serious IgE-mediated anaphylactic reactions (2 of 60 patients; 3.3%), the majority of all reported adverse events (AEs) were non-serious, mild or moderate in severity, and consistent with the clinical manifestations and complications of underlying Pompe disease and assessed as not related to the study drug. One patient in the alglucosidase alfa group died of causes not related to treatment. The most-frequently reported treatment related AEs were infusion-associated reactions (IARs), defined as those events occurring during infusion or in the post-infusion observation period. The majority of IARs were assessed as mild to moderate in severity, and these events were primarily managed with infusion rate reduction and/or interruption of infusion. Infusion-associated reactions occurring in $\geq 5\%$ of patients treated with alglucosidase alfa included headache, nausea, urticaria, dizziness, chest discomfort, hyperhidrosis, flushing, blood pressure increased, and vomiting. Adverse events, serious adverse events (SAEs),

treatment-related AEs, and IARs were observed in similar proportions of alglucosidase alfa- and placebo-treated patients.

All patients with post-Baseline assessments (n=59) in LOTS had detectable antibodies on or before Week 12. Titers generally remained low or decreased over time. Importantly, anti-rhGAA immunoglobulin G (IgG) antibody titers had no impact on the efficacy or safety of treatment with 2000 L alglucosidase alfa in the LOTS trial.

Additional safety data (**Section 5.3**) with 2000 L alglucosidase alfa were obtained for patients in the LOTS extension study and 4 additional completed or ongoing trials in late-onset patients, as well as international post-marketing experience for infantile-onset and late-onset patients receiving exclusively 2000 L product. These data were generally supportive of the safety observations from LOTS. As observed in LOTS, a small percentage (1%) of patients in the post-marketing setting experienced anaphylactic reactions; some of which were life threatening and/or immunoglobulin E (IgE)-mediated. In addition, approximately 2% of patients treated with alglucosidase alfa experienced serious allergic reactions. Patients presented with a constellation of signs and symptoms primarily respiratory, cutaneous and/or cardiovascular in nature. The majority of patients recovered and continued to receive treatment with alglucosidase alfa under close clinical supervision.

In addition to the clinical data supporting the safety and efficacy of 2000 L alglucosidase alfa in late-onset patients, Genzyme has also provided the Advisory Committee with a summary of retrospective clinical analyses that evaluated the efficacy of alglucosidase alfa in infantile-onset patients who received both 2000 L and 160 L product (**Section 6**). Cox proportional hazards analysis did not indicate a difference in the risk of death or becoming invasively ventilated between patients receiving 160 L and 2000 L alglucosidase alfa (p=0.866, Hazard Ratio=1.18 comparing 2000 L to 160 L, 95% confidence interval [CI]: 0.18 - 7.85), nor was there any evidence of a meaningful difference in cardiac or motor response for alglucosidase alfa produced at the 2000 L and 160 L scales.

Although Genzyme is only seeking approval of 2000 L alglucosidase alfa for a late-onset indication, Genzyme has provided the Advisory Committee with a summary of the efficacy and safety data for all 11 infantile-onset patients treated with 2000 L

alglucosidase alfa in a single-center, investigator-sponsored study in Taiwan in which assessments were prospectively defined based on the pivotal study AGLU01602 (**Section** 7).  The clinical outcomes in 11 Taiwanese infantile-onset patients treated with 2000 L alglucosidase alfa (**Figure 2-3**) were consistent with those in infantile-onset patients treated with 160 L alglucosidase alfa in AGLU01602 (also shown in **Figure 2-3**). Alglucosidase alfa produced at both process scales markedly prolonged survival and invasive ventilator-free survival, mitigated the cardiac hypertrophy and cardiomegaly associated with Pompe disease, and enabled progressive motor development.  These results are in marked contrast to the natural history of disease progression that has been seen in virtually all untreated patients with infantile-onset Pompe disease (**Figure 2-3**).

**Figure 2-3: Kaplan-Meier Estimate of Percentage of Patients Alive and Free of Ventilator Support in the Taiwan Study**
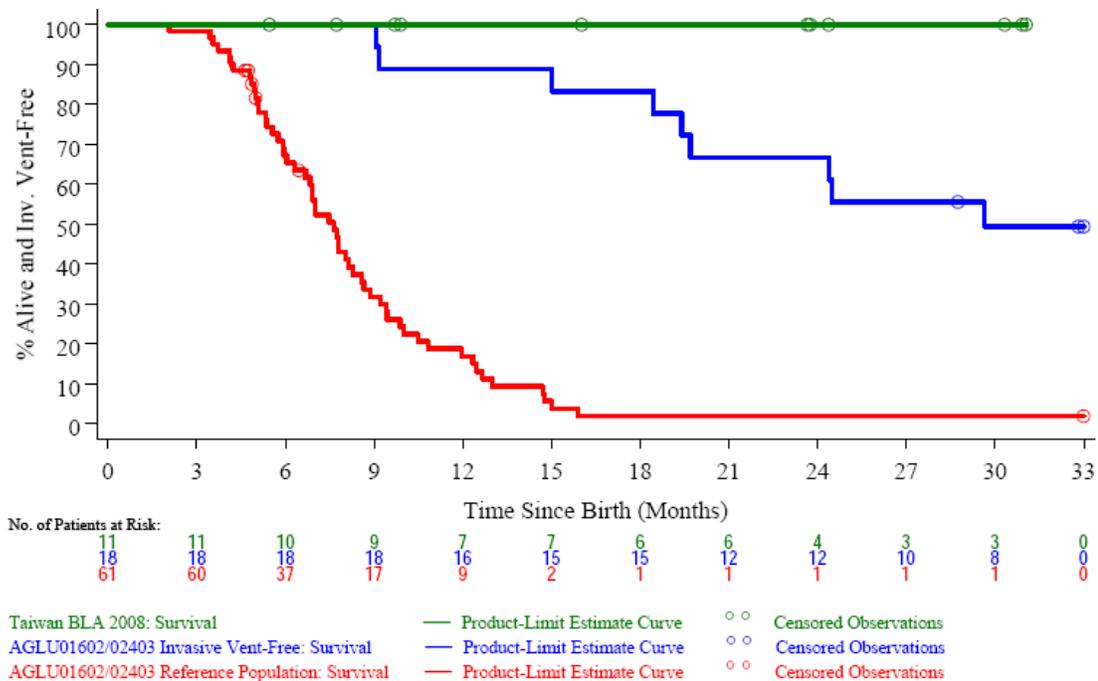


Together, the retrospective clinical analyses and the clinical data for patients treated in an investigator-sponsored study in Taiwan demonstrate the efficacy and safety of 2000 L alglucosidase alfa in patients with the rapidly progressive infantile-onset form of Pompe disease, and provide further support for the approval of 2000 L alglucosidase alfa for the treatment of patients with late-onset Pompe disease.

In summary, Genzyme believes that the LOTS safety and efficacy data, in combination with the additional clinical and post-marketing safety data, support the approval of the alglucosidase alfa manufactured using the 2000 L process. Genzyme looks forward to a discussion of these data with FDA and Advisory Committee on 21 October 2008 to facilitate a successful first-cycle approval for the 2000 L product and thereby assure a continued supply of alglucosidase alfa, the only treatment for patients with Pompe disease.

# 3      INTRODUCTION

Alglucosidase alfa, a form of rhGAA, was developed by Genzyme Corporation as an ERT for the treatment of Pompe disease, a rare and life threatening neuromuscular disorder, which can present in infancy (referred to as 'infantile-onset' disease) or anytime after infancy through late adulthood (referred to as 'late-onset' disease), and for which there is currently no other approved treatment. Alglucosidase alfa is produced by recombinant DNA technology in a Chinese hamster ovary cell line and is identical to a commonly occurring form of human GAA in amino acid sequence. Alglucosidase alfa is a hydrolase that degrades lysosomal glycogen to glucose. In the lysosome, GAA is proteolytically processed, resulting in the formation of an enzymatically active multi-subunit complex. Alglucosidase alfa is provided as a lyophilized powder in 20 mL (50 mg active substance) vials containing, upon reconstitution, 5 mg/mL alglucosidase alfa, 2% mannitol, 0.005% polysorbate 80 in 25 mM sodium phosphate, pH 6.2. Alglucosidase alfa is reconstituted in Water for Injection and further diluted with 0.9% sodium chloride prior to intravenous administration.

Alglucosidase alfa for commercial use is currently produced at 2 manufacturing scales (where scale is defined by the volume of the cell culture in the production bioreactor): 160 L and 2000 L. The scale-up to a 2000 L process was initiated by Genzyme in 2003 in anticipation of the need for greater production capacity to continue to meet the expanding global demand for alglucosidase alfa, and in recognition of the fact that such capacity could not be feasibly attained using only the 160 L process.

Alglucosidase alfa produced at the 160 L manufacturing scale has been approved in the US (28 April 2006) for the treatment of all patients with Pompe disease. Alglucosidase alfa produced at the 2000 L scale is currently approved for the treatment of all patients with Pompe disease in over 40 global markets outside of the US that are served by Genzyme, including the European Union (EU), Canada, and Japan.

Genzyme initially pursued US licensure of the 2000 L process under the original application (BLA 125141) and submitted additional biochemical and nonclinical data and a retrospective analysis of clinical data to support approval of the 2000 L process in a supplement to the application in October 2007. However, FDA ultimately concluded that the comparability of alglucosidase alfa derived from the 160 L and 2000 L manufacturing

processes could not be established, and advised Genzyme to pursue licensure of 2000 L alglucosidase alfa as a distinct drug product under a separate BLA. Accordingly, Genzyme is currently seeking US licensure of alglucosidase alfa produced at the 2000 L scale under BLA 125291, which was filed on 30 May 2008. To support the approval of the 2000 L process, 18 months of safety and efficacy data from AGLU02704, a Phase 3, randomized, double-blind, placebo-controlled study of 90 patients with late-onset Pompe disease (hereafter referred to as "LOTS" [late-onset treatment study]) were submitted to BLA 125291. Genzyme believes the data from the LOTS trial support the following proposed indication:

> TRADE NAME (alglucosidase alfa) is indicated for long-term use in patients with late-onset Pompe disease (GAA deficiency). TRADE NAME has been shown to improve distance walked and stabilize pulmonary function in patients with late-onset Pompe disease.

The intent of this briefing package is to provide the Advisory Committee with a summary of the clinical data to support licensure of 2000 L alglucosidase alfa. Accordingly, this briefing package provides a comprehensive summary of the key efficacy data (**Section 5.2.1**) and safety data (**Section 5.2.2)** from LOTS.

Safety data from the LOTS extension study and an additional 4 completed or ongoing trials in late-onset patients, as well as international post-marketing experience in both infantile-onset and late-onset patients receiving exclusively 2000 L product, were also submitted to BLA 125291 in support of the approval of the 2000 L process; these data have been summarized in this briefing package for the Advisory Committee (**Section 5.3**).

Finally, although Genzyme is only seeking approval of 2000 L alglucosidase alfa for a late-onset indication, Genzyme has also provided the Advisory Committee with a summary of retrospective clinical analyses that evaluated the efficacy of alglucosidase alfa in infantile-onset patients who received both 2000 L and 160 L product (**Section 6**), as well as a summary of the comprehensive efficacy and safety data for 11 infantile-onset patients treated with 2000 L alglucosidase alfa in a single-center, investigator-sponsored study in Taiwan in which assessments were prospectively defined based on AGLU01602, the pivotal study for approval of 160 L product (**Section 7**).

### 3.1 Pompe Disease

Pompe disease is a rare, autosomal recessive genetic disease caused by the deficiency of lysosomal GAA, an enzyme that degrades glycogen. The resulting accumulation of glycogen in body tissues, especially in cardiac, respiratory, and skeletal muscle, disrupts the architecture and function of affected cells, leading to progressive multi-systemic signs and symptoms that include skeletal muscle weakness, respiratory insufficiency, and, in infants, cardiac failure. While falling under the broader category of a lysosomal storage disorder (LSD), Pompe disease is also classified as a neuromuscular disease, a metabolic myopathy, and a glycogen storage disorder. The estimated global incidence of Pompe disease is 1:40,000, with variations in incidence reported between different ethnic groups (Martiniuk, 1998, *Am J Med Genet*; Ausems, 1999, *Eur J Hum Genet*; Poorthuis, 1999, *Hum Genet*; Hirschhorn, 2001, *The Metabolic and Molecular Bases of Inherited Disease*).

All presentations of Pompe disease are caused by the same underlying deficiency of lysosomal GAA. However, there is significant heterogeneity in the clinical presentation of Pompe disease, and the disease manifests as a broad clinical spectrum with a continuum of clinical signs and symptoms (Chen, 2000, *Mol Med Today*; Hirschhorn, 2001, *The Metabolic and Molecular Bases of Inherited Disease*; Van den Hout, 2003, *Pediatrics*; Kishnani, 2004, *J Pediatr*). Pompe disease has been classified into different phenotypes based on age at onset of symptoms, extent of organ involvement, and rate of progression to death. These phenotypes range from a rapidly progressive infantile-onset form of the disease and a more slowly progressive late-onset form (with symptom onset anytime after infancy through adulthood), although there is considerable variability and overlap between these 2 extremes. Genetic mutation analyses in patients with Pompe disease have revealed a number of different allelic mutations in GAA, including missense, nonsense, frame-shift, and other mutations, with resulting phenotypes that range from a low level of GAA gene expression and sub-normal endogenous GAA activity (generally <1% to 40% of normal levels) to expression of nonfunctional enzyme or complete loss of GAA protein expression. A validated Western blot assay of cross-reacting immunologic material (CRIM) in skin fibroblasts may be utilized to discern whether residual, detectable levels of GAA protein are present ('CRIM-positive') or absent ('CRIM-negative'), while endogenous GAA activity may be measured using validated blood, muscle, or skin-fibroblast enzyme assays. While the level of residual

GAA activity tends to show a positive correlation with age at symptom onset and an inverse correlation with disease severity in many patients, there are frequent exceptions to this rule, suggesting that residual GAA activity level is not the sole determinant of clinical phenotype.

Patients with the infantile-onset form of Pompe disease typically present with clinical signs and symptoms within the first 12 months of life. 'Classic' infantile-onset Pompe disease involves a massive accumulation of glycogen in the heart and skeletal muscle resulting in rapidly progressive cardiomyopathy and generalized muscle weakness with hypotonia. Motor development is often completely arrested, or if motor milestones are achieved, they are subsequently lost. Death from cardiac and/or respiratory failure occurs before most patients reach 1 year of age (Hirschhorn, 2001, *The Metabolic and Molecular Bases of Inherited Disease*). A subset of patients with 'nontypical' infantile-onset Pompe disease have a slightly later age at onset (although still before 12 months of age), slower progression of cardiomyopathy, and may survive beyond 1 year of age, although respiratory failure (leading to death) typically occurs between 1 and 2 years of age (Slonim, 2000, *J Pediatr*). Overall, the mortality rate in patients with infantile-onset Pompe disease approaches 90% at 18 months of age (Kishnani, 2006, *J Pediatr*).

Patients with the late-onset form of Pompe disease exhibit more variability in disease onset and progression of signs and symptoms, and generally progress less rapidly than those with the infantile-onset form. Clinical manifestations appear after infancy, and may occur anytime from early childhood through late adulthood (e.g., the 6th decade of life). Patients typically present with slowly progressive myopathy (predominantly in the proximal muscles of the trunk and pelvic and shoulder girdles), and a variable degree of respiratory involvement. In most patients, the proximal muscle weakness is greater in the lower than the upper limbs. These patients rarely develop cardiomyopathy (Chen, 2000, *Mol Med Today*; Laforêt, 2000, *Neurology*; Hirschhorn, 2001, *The Metabolic and Molecular Bases of Inherited Disease*).

In late-onset Pompe disease, initial myopathic symptoms can be very subtle, but typically include difficulty rising from a chair, climbing stairs, or rising from a squatting position. Over time there is increasing involvement of truncal and upper body muscles, which can manifest as difficulty sitting up and a compromised ability to perform overhead tasks

such as combing one's hair (Hirschhorn, 2001, *The Metabolic and Molecular Bases of Inherited Disease*). Many patients ultimately become wheelchair-dependent. Although only a minority of late-onset patients present with respiratory symptoms prior to the onset of clinically significant proximal muscle weakness, respiratory involvement typically becomes an inevitable consequence of disease progression (Hirschhorn, 2001, *The Metabolic and Molecular Bases of Inherited Disease*; Mellies, 2001, *Neurology*). Initial respiratory symptoms may include manifestations of sleep-disturbed breathing (daytime somnolence and morning headache), orthopnea, and/or exertional dyspnea. Over time, patients may require noninvasive ventilation, first at night and then during the day as well. Many patients ultimately require invasive ventilation, and respiratory failure is the leading cause of death in these patients (Chen, 2000, *Mol Med Today*; Hirschhorn, 2001, *The Metabolic and Molecular Bases of Inherited Disease*; Kishnani, 2004, *J Pediatr*). While the heart is typically spared in these patients, cardiomyopathy has been reported to occur in up to 4% of patients with late-onset Pompe disease (Hirschhorn, 2001, *The Metabolic and Molecular Bases of Inherited Disease*), and other cardiac manifestations have been observed secondary to chronic respiratory failure (Felice, 1995, *Medicine*; Kurz, 1998, *Respiration*).

Overall, the presentation and course of late-onset Pompe disease is much less predictable than the classic infantile-onset form. Some late-onset patients experience a rapid deterioration in both proximal limb strength and respiratory muscle function, leading to loss of ambulation and respiratory failure, while others progress less rapidly or exhibit a divergent rate of progression of proximal limb and respiratory muscle involvement (Laforet, 2000, *Neurology*). The marked variability in the clinical presentation of late-onset Pompe disease presents a challenge to any attempt to further classify patients and underscores the extent to which Pompe disease encompasses a continuum of disease severity (Hagemans, 2005, *Neurology)*.

Genzyme has sponsored 2 observational studies to further investigate the clinical presentation and natural course of infantile-onset Pompe disease (AGLU-004-00) and late-onset Pompe disease (AGLU02303; hereafter referred to as "LOPOS" [late-onset patient observational study]), respectively (Kishnani, 2006, *J Pediatr*, Wokke, *Muscle & Nerve*, in press). These studies support and extend the findings in the medical literature, which suggest that while the rate of progression of pathology differs between infants and

adults, the ultimate disease outcome is the same: deteriorating skeletal and respiratory muscle function, leading to invasive ventilation, and eventually to death.

Study AGLU-004-00 was a multi-center, multinational, natural history study of 168 patients diagnosed with infantile-onset Pompe disease (independent of any assigned disease phenotype, i.e., classic vs. nontypical), who had symptom onset within their first year of life and received only palliative and supportive care. These patients generally exhibited significant cardiomyopathy, respiratory impairment and severe muscle weakness with hypotonia, as well as the lack of acquisition and/or loss of motor skills. Median patient age was 2.0 months at symptom onset, 5.9 months at first ventilator support, and 8.7 months at death. Only 25.8% survived to 1 year of age, 14.4% survived to 18 months of age, 8.6% survived to 2 years of age, and 7.1% survived to 3 years of age. These survival findings are generally consistent with those reported by others, including a study by Van den Hout et al. (Van den Hout, 2003, *Pediatrics*), who found that the median age of death in a group of 20 Dutch patients with classic infantile-onset Pompe disease was 7.7 months, while the median age of death in 133 cases reported in the literature was 6.0 months.

In LOPOS, a prospective 12-month observational study in 58 patients with late-onset Pompe disease who were not receiving alglucosidase alfa treatment, marked variability in clinical presentation was observed across all patients. In this group of patients, which ranged from 24.3 to 68.5 years of age at Baseline, age at symptom onset ranged from 7.5 to 58.7 years, while age at diagnosis ranged from 12.3 to 63.7 years. Quantifiable lower and upper extremity muscle weakness and impaired pulmonary function was observed in these patients relative to normal controls, as evidenced by the results of muscle strength (QMT) and pulmonary function (FVC) assessments. Baseline QMT scores for the lower limbs ranged from 8.9 to 97.0% of predicted normal values, while FVC ranged from 19 to 104% of predicted levels. The diminished proximal muscle strength and respiratory function in these patients translated into clear functional impairment, as indicated by compromised performance on the 6MWT and functional activities testing. Consistent with these findings, results for the Medical Outcomes Study (MOS) 36-Item Short Form (SF-36) indicated that patients perceived themselves as having diminished physical health status relative to the US general population. Over the course of the 12-month observational period, statistically significant declines in mean

percent predicted values were observed from Baseline to Month 12 in QMT arm and leg scores, FVC, maximal voluntary ventilation (MVV), MIP, and MEP, indicating the progression of proximal limb and respiratory muscle weakness.  Clinical decline in walking ability was not assessed in LOPOS, as the 6MWT was administered only at the final assessment at Month 12 (this test was added as a study assessment after prospective agreement with FDA that this would be a co-primary efficacy endpoint for LOTS). However, at Month 12 the mean distance walked during the 2 administrations of the test, 326.0 and 336.0 meters (or 51.% and 53.1% predicted), suggested a diminished walking ability within this cohort of late-onset patients relative to healthy controls.

As previously stated, the multi-systemic manifestations observed in patients with Pompe disease are due to the accumulation of glycogen in muscle (e.g., proximal limb, respiratory, cardiac) and the subsequent disruption of cellular architecture and function. In infantile-onset patients, virtually all muscle fibers are affected, and the deposition of glycogen and resulting muscle pathology is evident on analysis of skeletal muscle biopsy tissue, regardless of the biopsy site (Thurberg, 2006, *Lab Invest*).  In late-onset patients, however, muscle fiber involvement is much more variable, and glycogen levels and pathomorphological findings on muscle biopsy vary widely by biopsy site (Hirschhorn, 2001, *The Metabolic and Molecular Bases of Inherited Disease*; Schoser, 2007, *Neuropath App Neurobiol*).  This variability in muscle biopsy findings presents a challenge when attempting to use biopsies to assess Pompe disease severity and may in fact lead to initial incorrect diagnoses in up to 26% of late-onset patients (Müller-Felber, 2007, *Neuromuscular Disorders*).  Consequently, muscle biopsies are not a reliable tool for monitoring the response to ERT in late-onset Pompe disease.  No urine or blood markers have been identified that can consistently predict disease severity and progression in late-onset Pompe patients and could therefore be utilized as surrogate markers of clinical response to treatment.

In late-onset Pompe disease, the variable nature of muscle fiber involvement may influence treatment outcomes.  The clinical hypothesis for ERT is that enhancement of GAA activity (through administration of exogenous enzyme that is taken up into target tissue lysosomes) will lead to a reduction in glycogen accumulation in muscle tissue and consequent recovery of muscle function.  However, the capacity for regeneration may be limited in muscle tissue that has degenerated and has been replaced by fat.  The

replacement of muscle by fat in advanced disease has been observed on magnetic resonance imaging (MRI) examination of adult Pompe muscle (Katirji, *Neurology.* 2008), and similar changes have been observed in the later stages of Duchenne's muscular dystrophy and polymyositis (Silverberg, 1997, *Principles and Practice of Surgical Pathology and Cytopathology*). This destruction of the myofibrils (the contractile cells in muscle fibers) and of normal cyto-architecture may irreparably damage muscle fibers such that functional recovery of those fibers is no longer possible.

### 3.2  History of the Development of Alglucosidase Alfa for Pompe Disease

Prior to 2006, palliative and supportive care was the mainstay of patient management for Pompe disease, and was (and continues to be) used by patients and physicians to manage disease manifestations and minimize complications, whenever possible. It is not, however, effective at preventing the progression of the disease. Examples of supportive care therapies that are commonly used by late-onset patients, and that offer some benefit to the patient, are the use of devices to assist mobility (e.g., walking aids, wheelchairs) and the use of ventilator support to prevent nocturnal hypoventilation and sleep disordered breathing. Dietary, occupational, and physical therapy regimens have also been utilized by late-onset patients, although the benefit of these regimens has not been established in controlled studies.

In the 1960s and 1970s, ERT was first attempted in Pompe disease patients using GAA purified from human placenta and *Aspergillus niger* (yeast), but the clinical significance of these treatments was limited by the quantity and quality of enzyme preparations and the immunogenicity of non-human forms of the enzyme. A study in the early 1990s in normal mice concluded that GAA (purified from bovine testes) that contained mannose-6-phosphate (M6P) was taken up by the heart and skeletal muscle, while GAA that lacked M6P was not (Van der Ploeg, 1991, *J Clin Invest*). Taken together, these studies demonstrated the feasibility of using GAA with appropriate glycosylation to exploit receptor-mediated uptake of enzyme to target tissues. It should be noted, however, that recent studies by Genzyme indicate that appropriate targeting of GAA may be mediated by mechanisms in addition to M6P-mediated receptor uptake, particularly in the heart (Bali, 2004, *Amer J Hum Gen*).

Beginning in 1998, recombinant human GAA was produced from the milk of transgenic animals, initially mice (*Bijvoet, 1998, Human Mol Gen*) and then also rabbits, and later from conditioned medium from genetically altered Chinese hamster ovary (CHO) cells. Enzyme produced using these methods confirmed the ability of alglucosidase alfa to remove glycogen from cultured fibroblasts and skeletal muscle cells of patients with Pompe disease.  Beginning in 2003, Genzyme sponsored clinical studies in Pompe disease using alglucosidase alfa produced from a CHO cell-based process.  These studies demonstrated improvement in survival and invasive ventilator-free survival in patients with infantile-onset Pompe disease compared with untreated historical control patients. In the pivotal trial (AGLU01602), 160 L alglucosidase alfa dramatically prolonged life, with 15 of 18 (83%) patients still alive and free from invasive ventilation at 18 months of age compared to a survival rate of 1.9% in an untreated historical subgroup (Kishnani, 2007, *Neurology*).  This historical cohort consisted of 61 patients from the AGLU-004-00 natural history study who met the AGLU01602 study eligibility criteria.  On the basis of these results in infants, alglucosidase alfa has been approved globally (in over 40 countries) for the treatment of all patients with Pompe disease (GAA deficiency), and remains the only currently approved treatment for this disease.

As shown in **Figure 3-1**, alglucosidase alfa was first approved in the EU by the EMEA on 29 March 2006, and received marketing approval and orphan exclusivity in the US on 28 April 2006.  In the original marketing applications to the US (BLA 125141, submitted 29 July 2005) and EU (submitted December 2004), Genzyme described 3 manufacturing scales for alglucosidase alfa, each of which is defined by the bioreactor working volume: an initial clinical development scale (30 L/ 60 L), a 160 L scale, and a 2000 L scale.  The progressive scale up of the manufacturing process was undertaken to ensure a supply of alglucosidase alfa sufficient to meet expected global demand, in consideration of the growing number of patients on treatment and the high protein dose administered to individual patients.  Alglucosidase alfa from all 3 scales has been used in clinical trials. The 160 L process was used to generate the drug product used in the pivotal clinical study in infantile-onset patients (AGLU01602) described in the original 160 L application, and is currently approved in the US for the treatment of all patients with Pompe disease.  The 160 L process is also approved in Canada, although it has yet to be distributed in this market.  The 2000 L process has been approved in all global markets outside the US that are served by Genzyme, including the EU, Canada, and Japan.

In the US, the validated 160 L scale and 2000 L scale manufacturing processes were both fully described in BLA 125141; however, only the 160 L process was approved at the time of US licensure on 28 April 2006. Genzyme withdrew the 2000 L process from consideration for licensure under BLA 125141 on 30 December 2005 due to FDA concerns about the limited comparability data available for this process, and to avoid delays in the review of the application while generating additional data requested by FDA. Genzyme submitted a supplement to BLA 125141 for the 2000 L process on 15 June 2007. This supplement included additional biochemical and nonclinical data, as well as a retrospective review of clinical data in infantile-onset patients receiving 2000 L and 160 L product. This supplement was withdrawn by Genzyme on 13 July 2007 following a request by FDA for further clinical analyses of motor response. On 30 October 2007, Genzyme re-submitted a supplement to BLA 125141 for the 2000 L process, including the additional analyses requested by FDA. While biochemical characterization showed measurable differences in some product quality attributes, nonclinical evaluation of product from both scales did not detect a difference in glycogen clearance (the intended biological effect) between 160 L and 2000 L alglucosidase alfa. Consistent with these nonclinical findings, retrospective analyses of clinical data showed that alglucosidase alfa produced at both scales dramatically prolonged survival in infantile-onset patients when compared with a historical cohort of untreated patients. However, FDA ultimately determined that these clinical data, taken together with existing biochemical and non-clinical data, were inadequate to confirm the comparability of the 160 L and 2000 L product, and advised Genzyme on 15 April 2008 that alglucosidase alfa produced at the 2000 L process scale should be licensed as a distinct drug product with approval based upon safety and efficacy data from the pivotal LOTS trial. In accordance with this FDA advice, BLA 125291 for the 2000 L process was filed on 30 May 2008.

**Figure 3-1: Chronology of Key Alglucosidase Alfa Regulatory Activities**
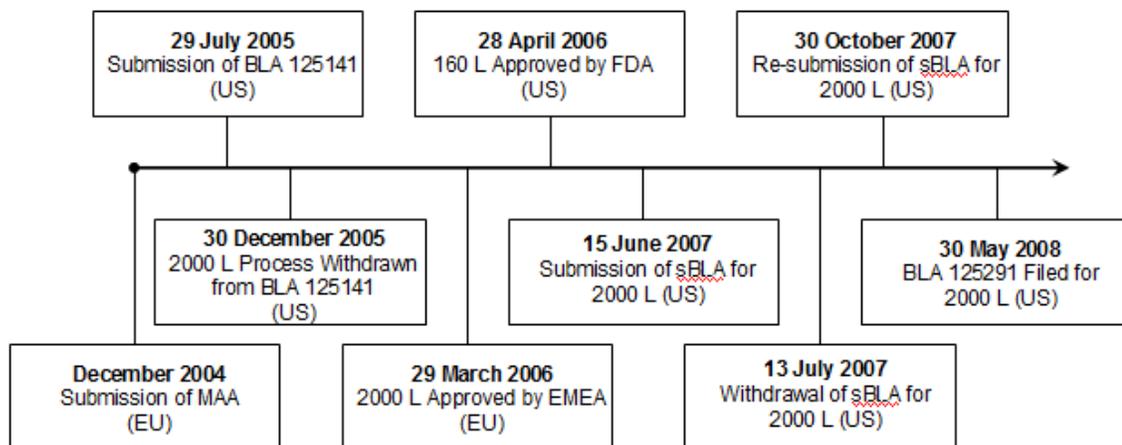


sBLA= Supplemental Biologics License Application

## 3.3 Current Status and Future Plans for the Global Supply of Alglucosidase Alfa

The supply issues for alglucosidase alfa are somewhat unique among those for currently approved ERTs due to the nature of Pompe disease and the consequent high doses required to achieve efficacy. Delivering therapeutic doses of recombinant enzyme to skeletal muscle, a key target tissue in the treatment of Pompe disease, presents a challenge given the low uptake from systemic circulation into muscle tissue and the large proportion of overall organ mass that must be targeted. Consequently, the recommended dose for alglucosidase alfa (20 mg/kg every other week [qow]) is approximately 20 times higher than recommended doses for other ERTs such as Fabrazyme® (agalsidase beta) and Aldurazyme, which are 1 mg/kg qow, and 0.58 mg/kg qw, respectively.

During 2007, US patient demand for alglucosidase alfa exceeded the maximum production capacity of the approved 160 L process. To address this need, Genzyme has been supplying the majority of US adult patients with 2000 L product via a treatment protocol (as per 21 Code of Federal Regulations [CFR] 312.34) known as MTAP, which is being conducted under the US IND. This program was initiated in May 2007, and has allowed Genzyme to offer therapy to adult patients (i.e., patients who are 18 years of age or older), while maintaining uninterrupted access to commercial treatment (with 160 L alglucosidase alfa) for all infants and children in the US. Adult patients in the US are being supplied with 2000 L alglucosidase alfa under MTAP at no cost to the patient.

Limited clinical data are being collected for these patients to evaluate safety and efficacy outcomes over time; safety data collected through 15 April 2008 are presented in this briefing package.

MTAP was specifically created to bridge alglucosidase alfa availability until the anticipated FDA approval of the 2000 L process. Genzyme has been able to make alglucosidase alfa available through MTAP to all patients who had previously been on commercial therapy, and a limited number of newly diagnosed patients who met specific MTAP enrollment criteria, while pursuing approval of the 2000 L product.

As of 28 August 2008, MTAP is supplying alglucosidase alfa to 157 adult patients, representing an estimated 55% of the US Pompe population. However, US demand for alglucosidase alfa has now increased to the extent that it is no longer feasible for Genzyme to supply additional adult patients with 2000 L alglucosidase alfa under MTAP, due in part to the challenges that the program presents to patients and physicians, including travel to participating clinical sites and the often lengthy institutional review procedures that must be completed in order to initiate therapy through this program. Therefore, MTAP has been closed to new patients as of April 2008, although patients in the LOTS Extension continue to transition into MTAP. Genzyme remains committed to continuing to provide current MTAP patients with 2000 L alglucosidase alfa, and ensuring that treatment continues to be accessible to the most severely affected patients. For the present time, the commercial supply of 160 L alglucosidase alfa remains adequate to supply treatment to the small number of US infantile-onset and late-onset Pompe patients who are < 18 years of age (approximately 80 patients as of 28 August 2008). However, supplies of 160 L alglucosidase alfa are inadequate to provide treatment to the adult population. Genzyme is currently aware of 53 newly diagnosed adult patients in the US (almost 20% of all US patients known to Genzyme) who are waiting for access to treatment with alglucosidase alfa. Approval of the 2000 L process in the US has become critical to keeping pace with the rising supply demands for alglucosidase alfa to treat this serious and life threatening disease.

**4      MANUFACTURING DEVELOPMENT PROGRAM FOR ALGLUCOSIDASE ALFA**

Genzyme developed a cell culture process for alglucosidase alfa using the same manufacturing technology employed for its other marketed enzyme replacement therapy products (e.g. Cerezyme®(imiglucerase for injection) and Fabrazyme).   In this process, alglucosidase alfa is produced using a recombinant DNA construct expressed in a CHO cell line, and subsequently purified by multiple filtration and column chromatography operations.

The Genzyme process was originally developed at a clinical manufacturing scale using 30 L and 60 L bioreactors (30 L/60 L scale).  However, Genzyme recognized early on that demand for alglucosidase alfa was going to increase substantially due to the expanding number of patients receiving treatment and the high therapeutic dose (20 mg/kg qow) administered to individual patients relative to other ERTs.  Genzyme began scale up activities in 2002 and has twice scaled up its manufacturing process, first to the 160 L scale and subsequently to the 2000 L scale, to address the need for increasing amounts of alglucosidase alfa to supply the global market.  In addition, Genzyme is currently validating a new manufacturing facility in which it anticipates future production of alglucosidase alfa at a 4000 L scale.

The 30 L/60 L scale was used only to produce material for initial nonclinical and early clinical studies.  The 160 L and 2000 L scales have both been used to supply material for clinical trials (including pivotal trials) as well as US and global commercial supply. Detailed descriptions of the alglucosidase alfa cell culture and purification operations for the 160 L and 2000 L process scales were provided in the original application for alglucosidase alfa (BLA 125141).  The original application also included process development and validation, comparability, and stability data for both manufacturing processes.

During scale-up of the process from the 160 L to 2000 L scale, efforts were made to minimize the number of process changes implemented during scale up, due to the potential for such changes to alter the biochemical attributes of the macromolecule. Changes were made to the seed train (bioreactor inoculum preparation) and bioreactor operations to improve process productivity and to facilitate bioreactor operations at the larger scale.  The purification train was also scaled up in accordance with the capacity

required for the increased conditioned medium feedstream at each scale. Purification process changes were minimized, and chromatography scale-ups were linear, such that column heights, linear flow rates, column volumes of buffer applied and column loading remained constant. All changes were implemented only after process development data indicated that they would have the desirable outcomes with no adverse impact on product quality.

Genzyme completed a comprehensive comparability exercise with alglucosidase alfa derived from the 160 L and 2000 L manufacturing scales to support licensure of the 2000 L process. This comparability effort was performed in accordance with International Conference on Harmonisation (ICH) Q5E: *Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process*, and also took into account specific guidance provided to Genzyme during extensive discussions with FDA.

Alglucosidase alfa is a complex glycoprotein with a calculated polypeptide chain mass of 99,377 daltons and a total mass (including carbohydrates) of approximately 109,000 daltons. Genzyme employed 38 distinct analytical tools to comprehensively evaluate the biochemical characteristics of a large number of lots manufactured at both the 160 L scale (22 drug substance lots) and 2000 L scale (24 drug substance lots). Biochemical comparability was confirmed for the vast majority of quality attributes tested. However, there were measurable differences in some attributes, including the relative amounts (though not the predominant type) of specific glycans. Comparability concerns were focused on differences in phosphorylated glycans (i.e., M6P and bis-M6P) and sialylated glycans. While the range of sialylation levels in 2000 L alglucosidase alfa has been largely controlled through the implementation of stringent process controls, concerns remain about differences in bis-M6P levels. Phosphorylated glycans have been shown to play a role in M6P-receptor-mediated cellular targeting based on published work by Genzyme (McVie-Wylie, 2008, *Molecular Genetics and Metabolism*). The biochemical comparability data have indicated that these phosphorylated glycans are present within a narrow range of values in alglucosidase alfa produced at each manufacturing scale, although there is some overlap of the ranges for each glycan species between 160 L and 2000 L product. Given the difficulty in assessing the potential clinical impact of observed differences in phosphorylated glycan levels on the basis of

biochemical characterization alone, Genzyme proactively engaged in nonclinical and retrospective clinical analyses of alglucosidase alfa produced at the 160 L and 2000 L scales.

The nonclinical evaluation of 160 L and 2000 L product did not reveal differences in glycogen clearance (the intended biological effect) in GAA knockout mice, an animal model of Pompe disease, despite an apparent inconsistent demonstration of pharmacokinetic equivalence.

Additional retrospective comparative analyses of clinical data available from infantile-onset patients treated with alglucosidase alfa from both manufacturing scales did not support any meaningful difference in efficacy or safety, as discussed in **Section 6**.

**5          CLINICAL STUDIES SUPPORTING APPROVAL OF 2000 L
            PRODUCT FOR LATE-ONSET PATIENTS**

**5.1        Overview of 2000 L Clinical Experience In Patients With Late-Onset
            Pompe Disease**

A summary of the clinical studies conducted with 2000 L alglucosidase alfa that were
submitted to BLA 125291 and provide the basis for approval of the 2000 L process is
provided in **Table 5-1**.  This application includes a large, pivotal, randomized, double-
blind, placebo-controlled study in 90 patients with late-onset Pompe disease (60 of whom
received 2000 L alglucosidase alfa) that provides both safety and efficacy data, and forms
the basis for approval of the 2000 L product.  Additional safety data are provided from
3 other completed studies in 19 late-onset patients (all of whom received 2000 L
alglucosidase alfa), from 2 ongoing alglucosidase alfa treatment studies that provide
supportive safety data for a total of 216 late-onset patients, and from worldwide
post-marketing experience with 2000 L alglucosidase alfa.  In all studies and in the
post-marketing setting, 2000 L alglucosidase alfa was administered intravenously at a
dose of 20 mg/kg qow.

**Table 5-1: Summary of Clinical Studies In Patients With Late-Onset Pompe Disease Receiving 2000 L alglucosidase alfa (Submitted To BLA 125291)**

| Study ID | Location / # Study Centers | Completion Status and Study Dates[2] | Study Design & Control Type | Study Objective(s) | Drug, Dose, Route, and Regimen | Patients Enrolled/ Treated | Gender (%) and Median Age (Range) at First Infusion | Planned Treatment Duration/ Data Analysis Cutoff Date |
|---|---|---|---|---|---|---|---|---|
| Randomized, Double-blind, Placebo Controlled Studies | | | | | | | | |
| AGLU02704 (LOTS) | US/20 EU/7 Canada/2 Australia/1 | Completed 06 September 2005 to 28 September 2007 | Phase 3, randomized, double-blind, placebo-controlled, adaptive, multi-center, multinational study | Evaluate safety, efficacy and pharmacokinetics. | alglucosidase alfa, 20 mg/kg, IV, qow OR placebo, IV, qow | 90/ 60 alglucosidase alfa 30 placebo | Male 45 (50.0%) Female 45 (50.0%) 44 Years (10.1-70.0) | 78 Weeks |
| Uncontrolled Studies | | | | | | | | |
| AGLU02603 (US Expanded Access Study) | US/7 | Completed 23 November 2004 to 13 August 2006 | Open-label, uncontrolled, expanded access study | Provide alglucosidase alfa to severely affected patients with late-onset Pompe disease for whom there was no alternative treatment or study option available. | alglucosidase alfa, 20 mg/kg, IV, qow[1] | 9/ 9 | Male 4 (44.4%) Female 5 (55.6%) 43.6 Years (17.6-71.1) | 52-Week Modules |
| AGLU02804 | The Netherlands/ 1 | Completed 02 February 2005 to 13 July 2006 | Open-label, uncontrolled study | Evaluate safety, efficacy and pharmacokinetics in 5 juvenile patients with late-onset Pompe disease | alglucosidase alfa, 20 mg/kg, IV, qow | 5/5 | Male 3 (60.0%) Female 2 (40.0%) 12.7 Years (5.9-15.2) | 74 Weeks |

**Table 5-1: Summary of Clinical Studies In Patients With Late-Onset Pompe Disease Receiving 2000 L alglucosidase alfa (Submitted To BLA 125291)**

| Study ID | Location / # Study Centers | Completion Status and Study Dates[2] | Study Design & Control Type | Study Objective(s) | Drug, Dose, Route, and Regimen | Patients Enrolled/ Treated | Gender (%) and Median Age (Range) at First Infusion | Planned Treatment Duration/ Data Analysis Cutoff Date |
|---|---|---|---|---|---|---|---|---|
| AGLU03105 | France/1 | Completed 12 December 2005 to 30 March 2007 | Open-label, uncontrolled study | Evaluate safety and efficacy in patients with advanced late-onset Pompe disease | alglucosidase alfa, 20 mg/kg, IV, qow | 5/5 | Male 2 (40.0%) Female 3 (60.0%) 49.1 Years (29.0-62.5) | 52 Weeks |
| AGLU03206 (LOTS extension) | US/20 EU/6 Canada/2 Australia/1 | Ongoing from 23 March 2007 | Open-label, uncontrolled, extension study of LOTS | Assess the long-term safety and efficacy of alglucosidase alfa treatment in patients with late-onset Pompe disease who were previously treated under LOTS | alglucosidase alfa, 20 mg/kg, IV, qow | 81/ 81 | Male 43 (53.1%) Female 38 (46.9%) 46.5 Years (15.9-70.0 | Up to 52 Weeks/ 15 April 2008 |
| AGLU03907 (MTAP) | US/70 | Ongoing from 24 May 2007 Closed to new patients as of April 2008[4] | Open-label, uncontrolled treatment protocol | Provide adult patients with Pompe disease in the US access to 2000 L product | alglucosidase alfa, 20 mg/kg, IV, qow | 138/135 | Male 61 (45.2%) Female 73 (54.1%) Unknown 1 (0.7%) 52.0 Years[3] (21.6-79.5) | Indefinite – until commercial approval of the 2000 L product/ 15 April 2008 |

1. One patient received 6 infusions of 160 L alglucosidase alfa in study AGLU02603 prior to beginning treatment with 2000 L alglucosidase alfa in this study.

2. Study dates represent the date that the first patient screened for the study and the date that the last patient completed the study.

3. Age at first infusion is only calculated for naïve patients. Date of first infusion was not collected for patients who were already receiving alglucosidase alfa prior to entering this program

4. Patients in the LOTS Extension continue to transition into MTAP.

The 4 completed studies include the pivotal, randomized, double-blind, placebo-controlled trial (AGLU02704; LOTS) and 3 open-label trials (AGLU02603, AGLU02804, and AGLU03105). While the 3 open-label trials included efficacy assessments, the differences in the clinical status of patients at the time of enrollment and the fact that various muscle strength and pulmonary outcome measures were administered in each study prevent the integration of this open-label data with the LOTS data. For example, all patients in AGLU02603 and AGLU03105 were wheelchair-dependent and required continuous invasive ventilation (AGLU02603) or at least 12 hours of noninvasive ventilation (AGLU03105) per day, making assessment of walking distance and pulmonary function testing difficult or impossible. In these 4 completed studies, all patients were treated exclusively with 2000 L alglucosidase alfa, with the exception of 1 patient who had limited exposure to alglucosidase alfa produced at the 160 L scale (6 infusions) in study AGLU02603 prior to beginning treatment with 2000 L alglucosidase alfa in that study. The small number of infusions of 160 L alglucosidase alfa received by this 1 patient are not expected to confound the interpretation of the safety of 2000 L alglucosidase alfa based on data from these studies.

The 2 ongoing studies include the extension study for the pivotal LOTS trial (AGLU03206; "LOTS extension") and the US-based Myozyme Temporary Access Program (AGLU03907; "MTAP"). Interim safety data from both studies, in which 2000 L alglucosidase alfa is being administered, have been submitted to BLA 125291 as further evidence of the acceptable safety profile for treatment with alglucosidase alfa produced at the 2000 L scale. While a majority of patients enrolled in MTAP had previously been on treatment with 160 L product in the commercial setting, given the large number of late-onset patients receiving therapy under this program, Genzyme feels that this study provides relevant supportive data on the safety of 2000 L product. Although efficacy assessments are also being performed in these studies (albeit of very limited scope), these data are not presently available due to the ongoing nature of these trials; therefore these efficacy data are not part of BLA 125291.

The total duration exposure to 2000 L alglucosidase alfa among patients in all completed and ongoing studies is 203.7 patient years (**Table 5-2**).

**Table 5-2: Patient Exposure to 2000 L Alglucosidase Alfa in Clinical Studies**

| Study | Number of Patients in Study | Number of Unique Patients Studied[1] | Total Exposure in Patient Years[2] |
|---|---|---|---|
| LOTS (AGLU02704) | 90 (60 alglucosidase alfa and 30 placebo) | 90 | 137.3 |
| LOTS Extension (AGLU03206) - data cut off 15 April 2008 | 81 | 0 | |
| AGLU02603 | 9 | 9 | 7.4 |
| AGLU02804 | 5 | 5 | 7.1 |
| AGLU03105 | 5 | 5 | 5.0 |
| MTAP (AGLU03907) - data cut off 15 April 2008 | 138[3] | 119 | 50.6 |
| TOTAL | | 228[4] | 203.7 |

[1] Unique patients represent those who were not previously treated with alglucosidase alfa in a prior study.
[2] Patient years was calculated for each patient as (date of study discontinuation) – (date of first infusion of alglucosidase alfa +1) / 365.25.
[3] As of the data cut off, 138 patients had enrolled and 135 had received treatment, including 5 who participated in AGLU02704, 4 who participated in AGLU02603, 7 who participated in AGLU02704 and AGLU03206, 27 naïve patients, and 92 patients from commercial therapy.
[4] Of the 228 unique patients studied, 226 received treatment with 2000 L alglucosidase alfa in one or more of the above studies.

## 5.2        AGLU02704 (LOTS)

The LOTS trial provides the most relevant clinical data demonstrating the safety and efficacy of 2000 L alglucosidase alfa relative to placebo in patients with late-onset Pompe disease, as well as providing a complete pharmacokinetic profile for alglucosidase alfa produced at the 2000 L scale. It is the first randomized, double-blind, placebo-controlled treatment study ever conducted in Pompe disease, and the first large scale study of alglucosidase alfa in adults.

In this multi-center, multinational study, 90 patients were enrolled at a total of 8 primary centers in the US and EU, and received biweekly IV infusions of 20 mg/kg alglucosidase alfa (60 patients) or placebo (30 patients). After a minimum of 6 months of treatment, patients could receive infusions at one of the 22 local transfer sites in the US, EU, Canada, and Australia; however, all patients continued to return to the primary center every 3 months for the administration of efficacy assessments. The study was conducted as planned with few major protocol deviations, and a majority (90%) of patients

completed the 18-month (78-week) treatment.  For both treatment groups, median patient exposure was 39.0 infusions, with individual patient exposure ranging from 2 to 40 infusions in the alglucosidase alfa group and 9 to 41 infusions in the placebo group.  Alglucosidase alfa produced at the 2000 L scale was used exclusively in this study.

Patients who met all study inclusion and exclusion criteria were eligible to participate in the LOTS trial.  Among these study entrance criteria, patients were required to be $\geq$ 8 years of age at the time of enrollment and have a confirmed diagnosis of Pompe disease based on the presence of 2 GAA gene mutations and GAA activity (in cultured skin fibroblasts) $\leq$ 40% of the normal mean.  Patients had to exhibit proximal lower limb weakness (defined as unilateral QMT knee extensors values < 80% of predicted normal), but be able to walk at least 40 meters in the 6MWT.  All patients were required to have evidence of respiratory insufficiency, with an FVC of $\geq$ 30% and < 80% predicted in the upright position and a postural drop (from the upright to the supine position) in FVC (liters) of at least 10%.  Patients who required invasive ventilator support at any time, or who required noninvasive ventilator support while awake and in the upright position, were excluded from participation in LOTS.

While all 90 patients enrolled in LOTS exhibited significant proximal limb and respiratory muscle weakness at Baseline relative to normal, healthy individuals, significant heterogeneity existed within the study population, as shown in **Table 5-3**.  On average, patients were only able to walk a distance approximately 50% that of their healthy peers in the 6MWT, but performance on this test ranged from 41 meters to 626 meters across all patients (6-99% predicted), so some patients were significantly impaired while other patients' walk distances were that of normal, healthy individuals.  Similarly, mean FVC was also approximately 50% that of healthy individuals, indicating that, on average, pulmonary impairment was in the "moderately severe" range (50-59% predicted) based on Amercian Thoracic Society (ATS) criteria for the assessment of restrictive respiratory disease (ATS, 1991, *Am Rev Respir Disease*); however, FVC results indicated a broad spectrum of respiratory involvement with values from 30-78% of predicted.  This diversity in the clinical presentation of Pompe disease (as measured by 6MWT and FVC) among LOTS patients was not unexpected, and is consistent with the broad spectrum of clinical symptoms and variable rate of progression previously observed in patients with late-onset Pompe disease (Hirschhorn, 2001, *The*

*Metabolic and Molecular Bases of Inherited Disease*). Disease-related characteristics were similar between the two treatment groups at Baseline due to implementation of a randomization scheme that stratified patients based on 4 predefined strata (6MWT < 300 m, 6MWT ≥ 300m, FVC % predicted < 55%, FVC % predicted ≥ 55%).

Patient demographic data indicated that a majority (93.3%) of patients participating in the study were Caucasian, which may be due to the prevalence among Caucasians of a common GAA mutation (c.-32-13T > G) associated with late-onset Pompe disease. There were more males in the alglucosidase alfa group (56.7%) compared to the placebo group (36.7%). A higher percentage of patients utilized walking devices in the placebo group (53.3%) compared with the alglucosidase alfa group (38.3%). Similar proportions of patients required respiratory support at Baseline in the alglucosidase alfa group (33.3%) and the placebo group (36.7%). Mean age at first infusion was comparable between the alglucosidase alfa group (45.3 years) and placebo group (42.6 years).

**Table 5-3: Patient Baseline Disease Characteristics**

|  | Alglucosidase Alfa (N=60) | Placebo (N=30) |
|---|---|---|
| Age at Pompe symptom onset (years)[1] | 30.3 ± 12.29 (5.3, 58.6) | 23.9 ± 10.96 (2.7, 42.6) |
| Duration of disease at Baseline (years)[1] | 9.0 ± 6.31 (0.3, 24.8) | 10.1 ± 8.44 (0.5, 31.3) |
| % normal GAA activity at Baseline[1] | 10.4 ± 6.67[1] (< 1, 26.3) | 10.1 ± 9.5 (< 1, 32.2) |
| Distance walked on 6MWT at Baseline (meters)[1] | 332.20 ± 126.69 (77, 626) | 317.93 ± 132.29 (41, 608) |
| 6MWT distance walked (% predicted) at Baseline | 52.49 ± 18.97 (9.8, 82.2) | 50.26 ± 20.53 (6.2, 99.0) |
| FVC upright (% predicted) at Baseline[1] | 55.43 ± 14.44 (31.0, 78.0) | 53.00 ± 15.66 (30.0, 78.0) |
| Use of walking device at Baseline[2] | 23 (38) | 16 (53) |
| Use of respiratory support at Baseline[2, 3] | 20 (33) | 11 (37) |
|    Ventilator | 4 (6.7) | 3 (10.0) |
|    CPAP | 0 | 1 (3.3) |
|    BiPAP | 14 (23.3) | 7 (23.3) |
|    Supplemental Oxygen | 0 | 2 (6.7) |
|    Other | 1 (1.7) | 0 |

[1] Data are presented as the mean ± SD (range).

[2] Data are presented as the number (percentage) of patients

[3] Patients could indicate more than one type of respiratory support or may not have specified the type of respiratory support used.

### 5.2.1 Summary of Efficacy in AGLU02704 (LOTS)

Two clinically relevant co-primary endpoints were analyzed in the LOTS trial: the 6MWT distance (a measure of functional endurance, which in this study was used to measure walking ability) and FVC % predicted in the upright position (a measure of pulmonary function). Results for these co-primary endpoints are presented in **Section 5.2.1.2**.

Secondary and tertiary efficacy endpoints consisted of measures of proximal limb strength (QMT leg and arm scores), respiratory muscle strength (MIP and MEP % predicted), and of health-related quality of life (physical component summary [PCS]

score of the MOS SF-36).  Results for these secondary and tertiary efficacy endpoints are presented in **Section 5.2.1.3**.

A discussion of the clinical significance of the efficacy outcomes data from LOTS and the benefit that alglucosidase alfa therapy affords patients with late-onset Pompe disease relative to the natural course of the disease are presented in **Section 5.2.1.5**.

### 5.2.1.1 Efficacy: Study Design and Analysis Considerations

Because the primary clinical manifestations of Pompe disease are musculoskeletal and respiratory in nature, most of the efficacy assessments were designed to evaluate the strength and function of proximal limb and/or respiratory muscles.  Two co-primary endpoints, which were prospectively agreed upon with FDA, were evaluated in this study: distance walked in meters on the 6MWT and FVC % predicted measured in the upright (sitting) position.  The 6MWT and % predicted FVC were considered the most clinically relevant measures of walking ability and pulmonary function, respectively, for patients with late-onset Pompe disease.  For each co-primary endpoint, the rate of change from Baseline to Week 78 was pre-specified as the primary summary efficacy parameter. The study was to be considered to have met its primary efficacy objective if a statistically significant treatment effect of 2000 L alglucosidase alfa over placebo was demonstrated for the 6MWT.

The 6MWT is a submaximal exercise test that is widely regarded as an objective measure that is easy to administer, well tolerated by most patients, and more reflective of the performance of daily physical activities (which are typically performed at submaximal exertion levels) than other functional endurance tests.  The reliability, validity, and responsiveness to change of the 6MWT have been established in several interventional studies involving chronic disease populations, including chronic obstructive pulmonary disease (COPD), cystic fibrosis, heart failure, and pulmonary hypertension.  However, the 6MWT had not been used previously to evaluate treatment response in placebo-controlled studies for a neuromuscular disease.  Preliminary evaluation of the 6MWT in an open-label treatment study of 5 pediatric patients with late-onset Pompe disease (AGLU02804) and an observational study of 58 adults with late-onset Pompe disease (LOPOS; AGLU02303) were conducted by Genzyme to assess the feasibility of using the 6MWT as an efficacy endpoint in LOTS.  The test-retest correlation for the

6MWT (0.98) in LOPOS indicated that this assessment can be reliably performed in ambulatory late-onset patients with varying degrees of respiratory impairment; however, the sensitivity of the 6MWT to the natural progression of proximal lower extremity and respiratory muscle weakness could not be determined because the 6MWT was conducted only during the final LOPOS assessment at Month 12. Therefore, the LOTS trial is the first large, randomized trial to employ the 6MWT as a primary efficacy endpoint with the purpose of demonstrating the effect of treatment in a progressive neuromuscular disease. For patients with late-onset Pompe disease, performance on the 6MWT is likely to be compromised by weakness in various leg and hip muscle groups involved in ambulation (e.g., quadriceps, hamstrings, and hip flexors, extensors, abductors, and adductors), as well as respiratory dysfunction due to weakness of the respiratory muscles.

Reductions in FVC are the most commonly reported abnormality in patients with respiratory muscle weakness, and the ATS and the European Respiratory Society (ERS) both recommend the use of FVC to monitor respiratory status in neuromuscular diseases (ATS/ERS, 2002, *Am J Respir Crit Care Med*). Furthermore, changes in FVC have been shown to be associated with changes in multiple functional domains, including use of ventilator support, fatigue, dyspnea, exercise performance, and respiratory failure. In patients with neuromuscular disease with associated diaphragmatic weakness, FVC is markedly reduced in the supine relative to the sitting (upright) position (ATS/ERS, 2002, *Am J Respir Crit Care Med;* Fromageot, 2001, *Arch Phys Med Rehabil*) due to the effect of gravitational force on the contents of the abdomen when in the supine position, which pushes the diaphragm in the cranial direction, reducing the lung volume. In LOTS, FVC eligibility criteria were defined so as to ensure enrollment of late-onset Pompe patients with quantifiable pulmonary impairment (based on ATS guidelines) due to weakness in both the diaphragm and other respiratory muscles.

In LOTS, all tests of proximal limb and respiratory muscle strength and function were administered by licensed physical therapists, who participated in study-mandated reliability training sessions conducted by experts with extensive experience in neuromuscular research testing. All testing was performed in accordance with ATS/ERS guidelines to ensure the standardized administration of the tests and to establish inter-rater reliability.

Because Baseline 6MWT and FVC values have the potential to influence outcomes for these efficacy endpoints, patients were stratified according to Baseline 6MWT and Baseline FVC upright values using a minimization algorithm specified in the Statistical Analysis Plan (SAP), with the goal of achieving a balance between treatment groups with respect to disease severity at treatment initiation.

To ensure adequate power to allow for a robust and conclusive analysis for the 6MWT, an adaptive design was implemented (under a protocol amendment) in which the initial 52-week treatment duration could be extended by 3 or 6 months based on an interim estimate of the accrual of statistical information for 6MWT and the duration of patient follow-up required to achieve a pre-specified level of statistical information relevant to the primary efficacy analysis. The interim analysis of the 6MWT data was performed by an external Independent Statistical Center (ISC) after all patients who were continuing on treatment had completed Week 38. The precise rules for extending the treatment duration were defined in the ISC charter. Upon completing its review of the interim data, the ISC recommended that the study duration be extended to 78 weeks. This recommendation was supported by the Data Safety Monitoring Board (DSMB) on the basis of their review of available safety and efficacy data that demonstrated a continued acceptable risk/benefit profile for 2000 L alglucosidase alfa, and was implemented by Genzyme. It is important to note that the interim analysis did not include any conditional power calculations or any other procedures based on the estimated treatment differences. Therefore, one can use conventional methods of statistical inference to analyze the data.

As described in further detail in **Section 5.2.1.2.1**, the primary efficacy analysis method for 6MWT and FVC used a linear mixed effects (LME) model with random intercepts and slopes. Linear mixed effects models with random linear slopes have been widely used in studies of lung function in asthma, muscular dystrophy and other clinical conditions (Alfonso, 2004, *Thorax*; Djikstra, 2006, *Thorax*; Covar, 2004, *Am J Resp Crit Care Med*). Further details of the LME model and other statistical analyses are provided in Appendix 1 (**Section 11.1**).

A fixed sequence testing procedure was utilized to preserve an overall 5% level of significance for both co-primary endpoints. Thus, formal testing for treatment effect on FVC upright at the 5% significance level was performed only after the significance of 6MWT results had been demonstrated at a 5% significance level using a two-sided test.

**5.2.1.2        Primary Efficacy Endpoints**

**5.2.1.2.1        Six-Minute Walk Test**

As stated in **Section 5.2**, patients in both treatment groups were similarly and substantially impaired at Baseline in their ability to walk; on average, patients were only able to walk a distance approximately 50% that of a normal, healthy individual of similar age, gender, and body mass index (BMI) (mean values: $52.49 \pm 18.97\%$ for alglucosidase alfa and $50.26 \pm 20.53\%$ for placebo).

The primary efficacy analysis for 6MWT distance walked was based on the average monthly rate of change over the 18-month treatment period.  As specified in the SAP, an LME model with model-based variance estimation was used to make statistical inferences about the difference in linear slopes (i.e., rate of change) between 2000 L alglucosidase alfa and placebo on 6MWT distance walked.

The validity of the statistical inference about the treatment effect based on using the LME with model-based variance estimation for the primary analysis was dependent on 3 critical assumptions regarding this model:

(i)     Linearity of the time trend of the responses (prospectively specified in the SAP)

(ii)    Correct specification of the variance-covariance structure of the responses

(iii)   Normal distribution of the responses and random effects (prospectively specified in the SAP)

Therefore, it was important to assess whether these assumptions were met for the 6MWT data, as failure to meet these assumptions would compromise the statistical inference. As seen in **Figure 5-1**, the plot of mean change from Baseline over time in 6MWT distance walked shows marked departures from linearity, especially for the alglucosidase alfa group.  Formal statistical testing rejected linearity, as well as the other 2 model assumptions ($p<0.0001$ for all assumptions).

**Figure 5-1:  Mean (+/- SEM) Change From Baseline Over Time in Six-Minute Walk Test Total Distance Walked**
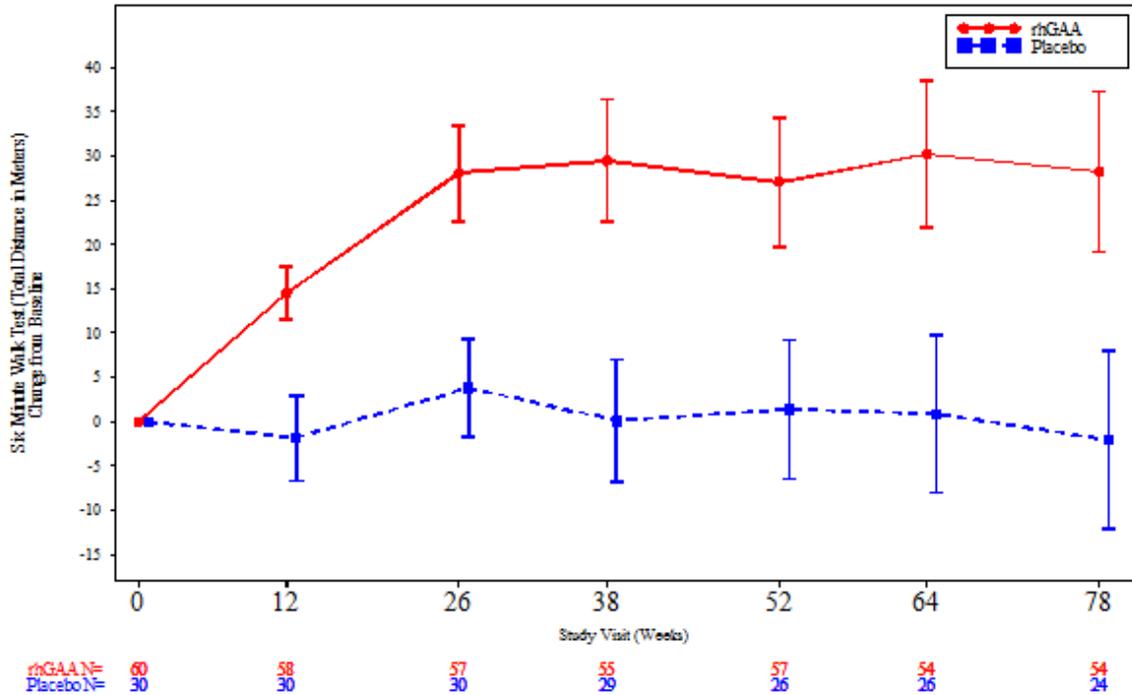


Given the failure of these 3 model assumptions, the LME with model-based variance estimation yields invalid standard errors, confidence intervals, and p-values, and therefore misleading inferences concerning the treatment difference.  Therefore, Genzyme used a robust repeated measures analysis method, which used the same underlying LME model, but which included a standard and commonly-used robust variance estimate that is often referred to as the "sandwich" variance estimate (Fitzmaurice, 2004, *Applied Longitudinal Analysis*).  This method, the LME with robust variance estimation, uses the pre-specified LME model and thus yields an identical point estimate for the difference in slopes (i.e., treatment difference).  However, it provides valid statistical inference about the treatment difference even when model assumptions are violated.

As shown in **Table 5-4**, the primary analysis using the LME with robust variance estimation resulted in a statistically significant estimated treatment difference of 1.24 meters/month (p=0.0464).  Over the course of 18 months of treatment, this average monthly treatment difference corresponds to a positive treatment effect of 2000 L

alglucosidase alfa of over 22 meters (as calculated by multiplying 1.24 meters/month by 18 months).

**Table 5-4: Primary Repeated Measures Analysis of Monthly Change in Distance Walked in Six-Minute Walk Test**

| Statistical Method | 2000 L alglucosidase alfa (N = 60) | Placebo (N = 30) | Difference | P value |
|---|---|---|---|---|
| LME with robust variance estimation, meters/month (95% CI) [SE] | 1.18 (0.26, 2.11) [0.47] | -0.06 (-0.90, 0.78) [0.43] | 1.24 (0.02, 2.47) [0.62] | 0.0464[1] |

[1] Robust variance estimation provides a more appropriate basis for inference than model-based variance estimation, given the failure of the model assumption. The p-value based on the invalid model-based variance estimate is 0.0931.

Additional complementary repeated measures analyses that provide valid inferences were also applied to assess the robustness of the treatment difference in slopes for 6MWT distance walked. Specifically, an analysis using generalized estimating equations (GEE) and a profile analysis method with unconstrained covariance structure both provided estimates of the treatment difference in slopes but with robust standard errors that corrected for the model misspecification mentioned above. These methods are arguably even less dependent on the assumption of correct specification of the variance-covariance structure, linearity, and/or normality than the LME with robust variance estimation.

The GEE and profile analysis methods both provided confirmation of the statistically significant treatment difference in the average monthly rate of change in 6MWT distance walked (**Table 5-5**). Importantly, there was very good agreement in the estimated average monthly treatment difference between the GEE method (1.51 meters/month) and the profile analysis method (1.51 meters/month). Over the course of 18 months of treatment, these average monthly treatment differences correspond to a positive treatment effect of 2000 L alglucosidase alfa of 27.18 meters.

A third repeated measures analysis method, the Wei-Lachin test, was used to test for treatment group differences in patterns of change in 6MWT distance walked. The Wei-Lachin test is a purely nonparametric method that utilizes all data and does not rely on assumptions regarding linearity, variance-covariance structure, and normality. The

Wei-Lachin test can be considered a multivariate generalization of the Wilcoxon-Mann-Whitney (WMW) test to the repeated measures setting. This test also resulted in a statistically significant treatment difference on 6MWT distance walked (**Table 5-5**).

**Table 5-5: Confirmatory Repeated Measures Analyses of Monthly Change in Distance Walked in Six-Minute Walk Test**

| Statistical Method | 2000 L alglucosidase alfa (N = 60) | Placebo (N = 30) | Difference | P value |
|---|---|---|---|---|
| GEE, meters/month (95% CI) [SE] | 1.37 (0.42, 2.33) [0.49] | -0.13 (-1.12, 0.85) [0.50] | 1.51 (0.12, 2.89) [0.71] | 0.0326 |
| Profile analysis model with unconstrained covariance structure[1], meters/month (95% CI) [SE] | 1.24 (0.38, 2.10) [0.43] | -0.28 (-1.49, 0.94) [0.61] | 1.51 (0.02, 3.00) [0.75] | 0.0468 |
| Wei-Lachin test | | | | 0.0133 |

1. A linear contrast (-3 -2 -1 0 1 2 3 3 2 1 0 -1 -2 -3) was used to estimate and test the difference in linear trends (slope difference) between treatment groups.

In addition to the primary analysis of the difference in the monthly rate of change between 2000 L alglucosidase alfa and placebo, as described above, supportive analyses of the 6MWT specified in the SAP were also conducted to estimate the change from Baseline to Week 78 (or last observation) in 6MWT distance walked for 2000 L alglucosidase alfa compared with placebo (**Table 5-6**).

The first 2 supportive analyses methods, an ANCOVA adjusting for Baseline stratification variables and the nonparametric WMW, are not dependent on assumptions of linearity and correct specification of the variance-covariance structure, and the WMW is also less sensitive to non-normality of the data. Therefore, these supportive analyses provide valid estimates of and statistical inferences about the treatment difference from Baseline to Week 78 on 6MWT distance walked. Using ANCOVA, the estimated mean distance walked increased by 25.13 meters for alglucosidase alfa-treated patients and decreased by 2.99 meters for placebo-treated patients, for a statistically significant positive treatment effect of 28.12 meters (p=0.0347). This treatment effect is numerically consistent with the estimate of the change in 6MWT distance walked over 18 months

obtained using the GEE and profile analysis methods (1.51 meters/month corresponding to 27.18 meters), and only marginally different from the estimated treatment difference obtained from the pre-specified LME model (1.24 meters/month corresponding to 22.32 meters). The WMW also yielded a statistically significant treatment difference in favor of alglucosidase alfa (p=0.0283).

**Table 5-6: Supportive Analyses of Change From Baseline to Week 78 in Distance Walked in Six-Minute Walk Test**

| Statistical Method | 2000 L alglucosidase alfa (N = 60) | Placebo (N = 30) | Difference | P value |
|---|---|---|---|---|
| ANCOVA—Mean Change, meters<br>　　(95% CI)<br>　　[SE] | 25.13<br>(10.07, 40.19)<br>[7.57] | -2.99<br>(-24.16, 18.18)<br>[10.64] | 28.12<br>(2.07, 54.17)<br>[13.10] | 0.0347 |
| Wilcoxon-Mann-Whitney test | | | | 0.0283 |
| LME with robust variance estimation and quadratic effects of time, meters (95%CI)<br>[SE] | 20.15<br>(3.64, 36.66)<br>[8.39] | -3.61<br>(-19.09, 11.87)<br>[7.87] | 23.76<br>(1.42, 46.10)<br>[11.36] | 0.0372[1] |

1.  Robust variance estimation provides a more appropriate basis for inference than model-based variance estimation, given the failure of the model assumption. The p-value based on the invalid model-based variance estimate is 0.0702.

A third supportive analysis specified in the SAP was based on an LME model with quadratic effects of time. This method addresses the non-linearity of the 6MWT data by allowing for a more complex (quadratic) pattern of change over time. Unlike the ANCOVA and WMW, it uses all observed 6MWT repeated measurements to estimate the treatment effect at Week 78 relative to Baseline. The LME with quadratic time effects analysis yielded a statistically significant positive treatment effect of 23.76 meters (p=0.0372) using a robust variance estimator. The rejection of the assumptions of variance-covariance structure in the 6MWT data in the context of the quadratic model (p=0.0001) make the robust variance estimator the appropriate choice for making statistical inferences with the LME model, as discussed above.

In summary, the totality of the evidence supports a statistically significant treatment effect of 2000 L alglucosidase alfa over placebo on 6MWT distance walked. The pre-specified LME with model-based variance estimation was dependent upon failed

model assumptions of linearity, variance-covariance structure, and normality, and therefore valid inferences about the treatment effect could not be obtained using this method. However, comprehensive statistical analysis, including the same pre-specified LME model with a more robust method for estimation of variance structure, as well as other repeated measures analysis approaches that reduced the dependency of the inference on model assumptions, consistently demonstrated a statistically significant treatment difference in the average monthly rate of change in 6MWT distance walked. Furthermore, pre-specified supportive analyses consistently demonstrated a statistically significant treatment difference in the estimated change from Baseline to Week 78.

Further details of the statistical analyses are presented in Appendix 1 (**Section 11.1**).

### 5.2.1.2.2    Forced Vital Capacity

As stated in **Section 5.2**, patients in both treatment groups had, on average, moderately severe respiratory impairment at Baseline, as measured by % predicted FVC (mean values: 55.43 ±14.44% for alglucosidase alfa and 53.00 ± 15.66% for placebo). Of note, 11 (12%) of the 90 patients in LOTS had very severe (< 34% predicted) respiratory impairment at Baseline, which is associated with increased risk of respiratory infection, respiratory distress, and invasive ventilation (Visser, 2007, *Neurology*; Thieben, 2005, *Muscle Nerve*; Sharshar, 2003, *Crit Care Med*; Schmidt, 2006, *Muscle Nerve*; Mayhew 2007, *Muscle Nerve*), and a further 27 (30%) patients had severe respiratory impairment (34-49% predicted) at Baseline.

As for 6MWT, the primary efficacy analysis for FVC % predicted (upright) was based on the average monthly rate of change over the 18-month treatment period, and the LME with model-based variance estimation was the repeated measures analysis method specified in the SAP for estimation of difference in linear slopes (i.e., rate of change) between 2000 L alglucosidase alfa and placebo.

For FVC % predicted, the data were in better agreement with the LME model assumptions than were the data for 6MWT. As seen in **Figure 5-2**, the plot of mean change from Baseline over time in FVC % predicted does not suggest discernible departures from linearity, and linearity was not rejected (p=0.1227) when using the same statistical method that was used to test linearity of 6MWT. However, the specification of the variance-covariance structure was rejected (p=0.0007). With misspecification of the

variance-covariance structure, the use of the robust variance estimator described for 6MWT is warranted.

**Figure 5-2: Mean (+/- SEM) Change from Baseline Over Time in FVC % Predicted (Upright)**
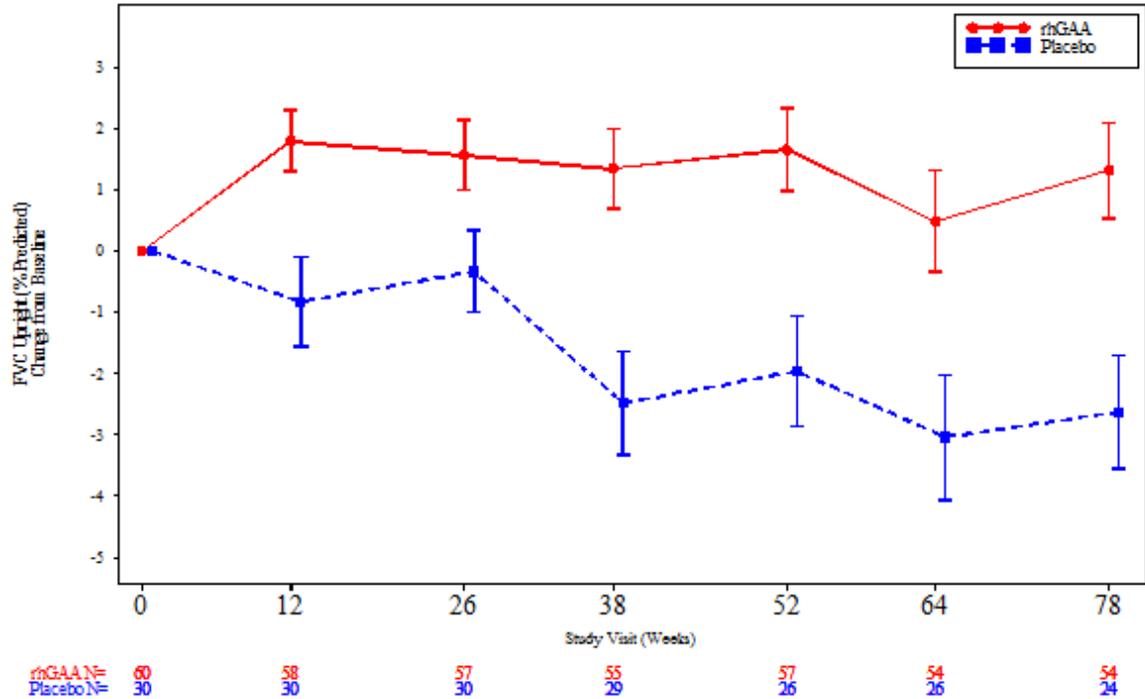


As shown in **Table 5-7**, the primary analysis using the LME with robust variance estimation resulted in a statistically significant estimated treatment difference of 0.18%/month (p=0.0041). Over the course of 18 months of treatment, this average monthly treatment difference corresponds to a positive treatment effect of 2000 L alglucosidase alfa of 3.24%.

**Table 5-7: Primary Repeated Measures Analysis of Monthly Change in FVC Upright % Predicted**

| Statistical Method | 2000 L alglucosidase alfa N = 60 | Placebo N = 30 | Difference | P value |
|---|---|---|---|---|
| LME, with robust variance estimation % predicted     (95% CI)     [SE] | 0.03 (-0.05, 0.10) [0.04] | -0.16 (-0.25, -0.06) [0.05] | 0.18 (0.06, 0.30) [0.06] | 0.0041[1] |

1. Robust variance estimation provides a more appropriate basis for inference than model-based variance estimation, given the failure of the model assumption of correct specification of variance-covariance. The p-value based on the model-based variance estimation is 0.0084.

Additional complementary repeated measures analyses were also performed to illustrate the treatment difference in slopes for FVC % predicted, consistent with the approach taken for 6MWT. Results of these repeated measures analyses confirmed the statistically significant results obtained in the primary analysis using the LME with robust variance estimation.

The GEE and profile analysis provided confirmation of the statistically significant treatment difference in the average monthly rate of change in FVC % predicted. There was very good agreement in the estimated average monthly treatment difference between the GEE method (0.20%/month), the profile analysis method (0.18%/month) and the pre-specified LME model with linear time effects (0.18%/month). Over the course of 18 months of treatment, these average monthly treatment differences correspond to a positive treatment effect of 2000 L alglucosidase alfa of between 3.2% and 3.6% (**Table 5-8**). A third repeated measures analysis method, the nonparametric Wei-Lachin test, was used to test for treatment group differences in patterns of change in FVC % predicted. This test also resulted in a statistically significant treatment difference on FVC % predicted (**Table 5-8**).

**Table 5-8: Confirmatory Repeated Measures Analyses of Monthly Change in FVC Upright % Predicted**

| | 2000 L alglucosidase alfa N = 60 | Placebo N = 30 | Difference | P value |
|---|---|---|---|---|
| GEE, % predicted<br>(95% CI)<br>[SE] | 0.03<br>(-0.05, 0.11)<br>[0.04] | -0.17<br>(-0.26, -0.07)<br>[0.05] | 0.20<br>(0.07, 0.32)<br>[0.06] | 0.0019 |
| Profile analysis model with unconstrained covariance structure[1], meters/month<br>(95% CI)<br>[SE] | 0.02<br>(-0.05, 0.10)<br>[0.04] | -0.15<br>(-0.26, -0.04)<br>[0.06] | 0.18<br>(0.04, 0.31)<br>[0.07] | 0.0110 |
| Wei-Lachin test | | | | 0.0009 |

1. A linear contrast (-3 -2 -1 0 1 2 3 3 2 1 0 -1 -2 -3) was used to estimate and test the difference in linear trends (slope difference) between treatment groups.

In addition to the primary analysis described above, supportive analyses of FVC specified in the SAP were also conducted to estimate the change from Baseline to Week 78 (or last observation) in FVC % predicted for 2000 L alglucosidase alfa compared with placebo.

Analyses using ANCOVA and Wilcoxon-Mann-Whitney (WMW) were conducted to estimate the change from Baseline to last observation (Week 78) in FVC % predicted for alglucosidase alfa compared with placebo (**Table 5-9**). Using ANCOVA, the estimated mean % predicted FVC increased by 1.20% for alglucosidase alfa-treated patients and decreased by 2.20% for placebo-treated patients, for a statistically significant positive treatment effect of 3.40% (p=0.0055). This treatment effect is numerically consistent with the estimate of the change in FVC % predicted over 18 months obtained using the pre-specified LME model and the confirmatory GEE and profile analysis methods (range: 3.2-3.6%). The WMW also yielded a statistically significant treatment difference in favor of alglucosidase alfa (p=0.0026).

**Table 5-9: Supportive Analyses of Change From Baseline to Week 78 in FVC Upright % Predicted**

|  | 2000 L alglucosidase alfa N = 60 | Placebo N = 30 | Difference | P value |
|---|---|---|---|---|
| ANCOVA—Mean Change, % Predicted (95% CI) [SE] | 1.20 (-0.16, 2.57) [0.69] | -2.20 (-4.12, -0.28) [0.97] | 3.40 (1.03, 5.77) [1.19] | 0.0055 |
| Wilcoxon-Mann-Whitney test |  |  |  | 0.0026 |
| LME with robust variance estimation and quadratic effects of time, meters (95%CI) [SE] | 0.34 (-1.08, 1.77) [0.72] | -2.75 (-4.38, -1.12) [0.83] | 3.09 (0.93, 5.26) [1.10] | 0.0053[1] |

1. Robust variance estimation provides a more appropriate basis for inference than model-based variance estimation, given the failure of the model assumption of correct specification of variance-covariance. The p-value based on the invalid model-based variance estimation is 0.0103.

The third supportive analysis was a goodness-of-fit assessment of the LME model with respect to the linearity assumption. Although the assumption of linearity was not rejected for FVC, for consistency and comparative purposes with 6MWT, a repeated measures analysis using an LME with quadratic effects of time was also performed. This method provided confirmation of the statistically significant treatment difference for the change from Baseline to Week 78 on FVC % predicted (**Table 5-9**).

In summary, the totality of the evidence supports a statistically significant treatment effect of 2000 L alglucosidase alfa over placebo on FVC % predicted. The pre-specified LME model and other repeated measures analyses consistently demonstrated a statistically significant treatment difference in the average monthly rate of change in FVC % predicted, and these findings were supported by the statistically significant treatment difference in the estimated change from Baseline to Week 78.

### 5.2.1.2.3 Subgroup Analyses of Primary Efficacy Endpoints

In order to evaluate the consistency of the observed treatment effect on the co-primary endpoints, the treatment effect was estimated in prospectively defined patient subgroups defined by the following Baseline characteristics: gender, age, time since symptom onset, use of walking devices, use of nighttime noninvasive ventilator use, 6MWT distance, FVC % predicted in the upright position, randomization strata, and GAA activity. The

results are summarized in **Table 5-10**.  The outcome shows a favorable trend for patients receiving 2000 L alglucosidase alfa compared with placebo within each subgroup.  These results suggest that the alglucosidase alfa treatment effect is robust and not limited to any particular subpopulation among those examined.

While the study was not powered to detect statistically significant treatment differences in these subgroups, it was noted that a larger treatment effect was observed for both co-primary endpoints among patients who had less advanced disease at treatment initiation (i.e. patients with Baseline 6MWT $\geq$ 300 meters, Baseline FVC $\geq$ 55% predicted, or not using a respiratory support device at Baseline) compared with patients with more advanced disease at treatment initiation (i.e. patients with baseline 6MWT < 300 meters, Baseline FVC<55% predicted, and using a respiratory support device at Baseline). Correspondingly, only in the less advanced disease subgroups is the treatment effect statistically significant (95% CIs exclude zero).  The larger treatment effects on 6MWT and FVC among patients with less advanced disease supports Genzyme's hypothesis that early initiation of treatment, prior to terminal muscle damage, is critical to maximizing the potential therapeutic benefit of ERT (see **Section 5.2.1.4** for further discussion of this hypothesis).

Disease duration (i.e., duration < 15 years versus $\geq$ 15 years) did not appear to influence treatment effect on 6MWT and FVC.  This observation is likely due in part to the highly variable rate of disease progression in patients with late-onset Pompe disease (Hirschhorn, 2001, *The Metabolic and Molecular Bases of Inherited Disease*; Winkel, 2005, *J Neurol*), which results in a broad spectrum of disease severity among patients with similar disease duration.  As indicated above, more objective measures of disease progression, i.e., 6MWT distance walked, FVC % predicted, and use of respiratory devices at Baseline, are better predictors of alglucosidase alfa treatment effect.

**Table 5-10: Estimates of Mean Change from Baseline to Last Available Observation for Six-Minute Walk Test and Forced Vital Capacity Upright (% Predicted) by Subgroup**

| | Number of Patients | | Estimated Treatment Difference (95% CI)[1] | |
|---|---|---|---|---|
| | **2000 L alglucosidase alfa** | **Placebo** | **6MWT Distance Walked (meters)** | **FVC (% predicted)** |
| Walking device used at Baseline | 23 | 16 | 32.47 (-6.67, 71.62) | 3.04 (-0.40, 6.47) |
| No walking device used at Baseline | 37 | 14 | 27.58 (-9.67, 64.82) | 3.84 (0.54, 7.14) |
| Baseline 6MWT ≥ 300 m | 36 | 18 | 34.01 (0.58, 67.44) | 3.67 (0.61, 6.73) |
| Baseline 6MWT < 300 m | 24 | 12 | 19.96 (-20.68, 60.59) | 3.34 (-0.36, 7.04) |
| Baseline FVC ≥ 55% | 28 | 14 | 40.65 (1.96, 79.34) | 4.74 (1.35, 8.14) |
| Baseline FVC < 55% | 32 | 16 | 22.28 (-14.07, 58.64) | 2.25 (-0.98, 5.47) |
| Respiratory support device use at Baseline | 20 | 11 | 22.61 (-21.91, 67.14) | 1.16 (-2.75, 5.06) |
| No respiratory support device use at Baseline | 40 | 19 | 35.49 (2.26, 68.73) | 4.85 (1.96, 7.74) |
| Disease duration ≥ 15 years | 14 | 7 | 50.35 (-4.05, 104.75) | 3.56 (-1.28, 8.41) |
| Disease duration < 15 years | 46 | 23 | 24.39 (-5.82, 54.60) | 3.54 (0.85, 6.22) |
| Male | 34 | 11 | 15.61 (-24.13, 55.34) | 1.48 (-2.09, 5.05) |
| Female | 26 | 19 | 31.46 (-3.44, 66.35) | 4.58 (1.44, 7.72) |
| Age ≥ 45 | 30 | 12 | 40.50 (0.46, 80.54) | 3.77 (0.19, 7.34) |
| Age < 45 | 30 | 18 | 18.61 (-16.33, 53.55) | 3.46 (0.31, 6.62) |
| GAA activity < 9.82% Normal | 29 | 15 | 33.20 (-4.97, 71.37) | 1.84 (-1.47, 5.16) |
| GAA activity ≥ 9.82% Normal | 30 | 15 | 28.65 (-9.18, 66.49) | 5.38 (2.08, 8.67) |
| Baseline 6MWT ≥ 300 m and FVC upright ≥ 55% Predicted | 19 | 9 | 39.0 (-8.4, 86.4) | 6.2 (1.9, 10.4) |
| Baseline 6MWT ≥ 300 m and FVC upright < 55% Predicted | 17 | 9 | 28.0 (-20.9, 76.9) | 0.2 (-4.3, 4.7) |
| Baseline 6MWT < 300 m and FVC upright ≥ 55% Predicted | 9 | 5 | 39.5 (-25.7, 104.8) | 2.0 (-3.8, 7.9) |
| Baseline 6MWT < 300 m and FVC upright < 55% Predicted | 15 | 7 | 6.6 (-47.0, 60.2) | 4.3 (-0.5, 9.1) |

CI=confidence interval
1. Estimates using ANCOVA model

**5.2.1.3        Secondary and Tertiary Efficacy Endpoints: MIP, MEP, QMT, SF-36**

A number of secondary and tertiary efficacy endpoints were assessed in LOTS, including measures of respiratory muscle strength (MIP, MEP; **Section 5.2.1.3.1**) and proximal muscle strength in the lower and upper extremities (QMT; **Section 5.2.1.3.2**).

As for the co-primary efficacy endpoints, the primary efficacy analysis for each secondary and tertiary endpoint was based on the average monthly rate of change over the 18-month treatment period, and supportive analyses were specified for estimation of the change from Baseline to Week 78.  Results are presented in this briefing package for the primary analysis using the LME model with robust variance estimation, and supportive analyses using ANCOVA and WMW.  The LME model with robust variance estimation (and not the LME with model-based variance estimation) is presented because this method provided valid estimates of and inferences about the treatment difference for both co-primary efficacy endpoints.  The ANCOVA and WMW provided valid estimates of the treatment difference for both co-primary endpoints.  While p-values are presented for completeness, it should be noted that the study was not powered to assess the statistical significance of the 2000 L alglucosidase alfa treatment effect for these secondary and tertiary endpoints.  Results of the statistical analyses demonstrate a consistent pattern of response that is supportive of the statistically significant treatment effect of 2000 L alglucosidase alfa on 6MWT distance walked and FVC % predicted.

Finally, results are presented for the effect of alglucosidase alfa treatment on physical health status, as captured using the PCS score of the MOS SF-36, a self-administered questionnaire designed to assess health-related quality-of-life (**Section 5.2.1.3.3**).

**5.2.1.3.1       Respiratory Muscle Strength**

In neuromuscular diseases with pulmonary involvement, respiratory pressures are typically compromised earlier and to a greater degree than FVC, since changes in volume as measured by FVC are caused by the progressive weakening of respiratory muscles (ATS, 1991, *Am Rev Respir Disease*; Mellies, 2001, *Neurology*).  For this reason, manometry was used to measure the strength of the inspiratory (MIP) and expiratory (MEP) muscles in LOTS.

Maximal inspiratory pressure (also referred to as PImax or negative inspiratory force) is a measurement of the maximal force that can be generated by the inspiratory muscles,

including the diaphragm muscle. Maximal expiratory pressure (also referred to as PEmax or negative expiratory force) is a measurement of the maximal force that can be generated by the expiratory muscles, including the accessory muscles. Data were expressed as centimeters of water ($cmH_2O$) and percent of predicted normal values based on age and gender (Black, 1969, *Am Rev Respir Dis*).

Patients in both treatment groups had similar respiratory muscle weakness at Baseline based on MIP % predicted normal values ($40.04 \pm 19.66\%$ for alglucosidase alfa and $42.57 \pm 20.99 \%$ for placebo) and MEP % predicted normal values ($32.00 \pm 12.09\%$ for alglucosidase alfa and $30.83 \pm 11.98\%$ for placebo).

The mean change in inspiratory muscle strength over time based on MIP % predicted is presented in **Figure 5-3**. As shown in this figure, alglucosidase alfa-treated patients exhibited improvement in MIP % predicted during treatment, whereas placebo-treated patients showed a trend toward a progressive decline in inspiratory muscle strength over the course of the 18-month study. Results of the primary and supportive analyses are presented in **Table 5-11**.

**Figure 5-3: Mean (+/- SEM) Change From Baseline Over Time in MIP % Predicted**
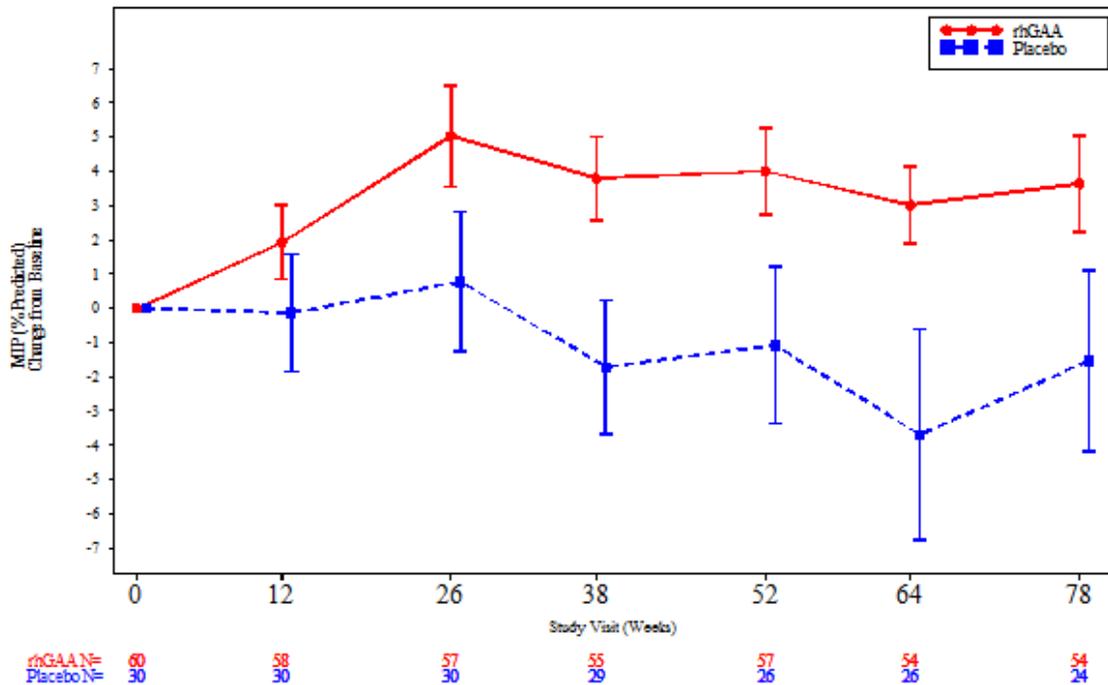
**Table 5-11:  Primary and Supportive Analyses of Change in MIP % Predicted**

| Statistical Method | 2000 L alglucosidase alfa | Placebo | Difference | P value |
|---|---|---|---|---|
| **Estimates/Tests of Monthly Change in MIP % Predicted (Repeated Measures Analysis)** | | | | |
| LME with robust variance estimation, % predicted <br> (95% CI) <br> [SE] | 0.16 <br> (0.02, 0.29) <br> [0.07] | -0.12 <br> (-0.36, 0.12) <br> [0.12] | 0.28 <br> (0.01, 0.54) <br> [0.14] | 0.0438[1] |
| **Estimates/Tests of Change in MIP % Predicted From Baseline to Week 78** | | | | |
| ANCOVA Estimated Mean Change from Baseline to Last Available Observation, % predicted <br> (95% CI) <br> [SE] | 3.48 <br> (0.91, 6.04) <br> [1.29] | -0.35 <br> (-3.95, 3.25) <br> [1.81] | 3.83 <br> (-0.60, 8.26) <br> [2.23] | 0.0895 |
| Wilcoxon-Mann-Whitney test | | | | 0.1743 |

1. Robust variance estimation is presented for consistency with the primary analysis of the co-primary efficacy endpoints.  The p-value based on the model-based variance estimation is 0.0344.

The mean change in expiratory muscle strength over time based on MEP % predicted is presented in **Figure 5-4**.  As shown in this figure, alglucosidase alfa-treated patients exhibited improvement in MEP % predicted during treatment, whereas placebo-treated patients showed a trend toward a progressive decline in expiratory muscle strength over the course of the 18-month study.  Results of the primary and supportive analyses are presented in **Table 5-12**.

**Figure 5-4:  Mean (+/- SEM) Change From Baseline Over Time in MEP % Predicted**
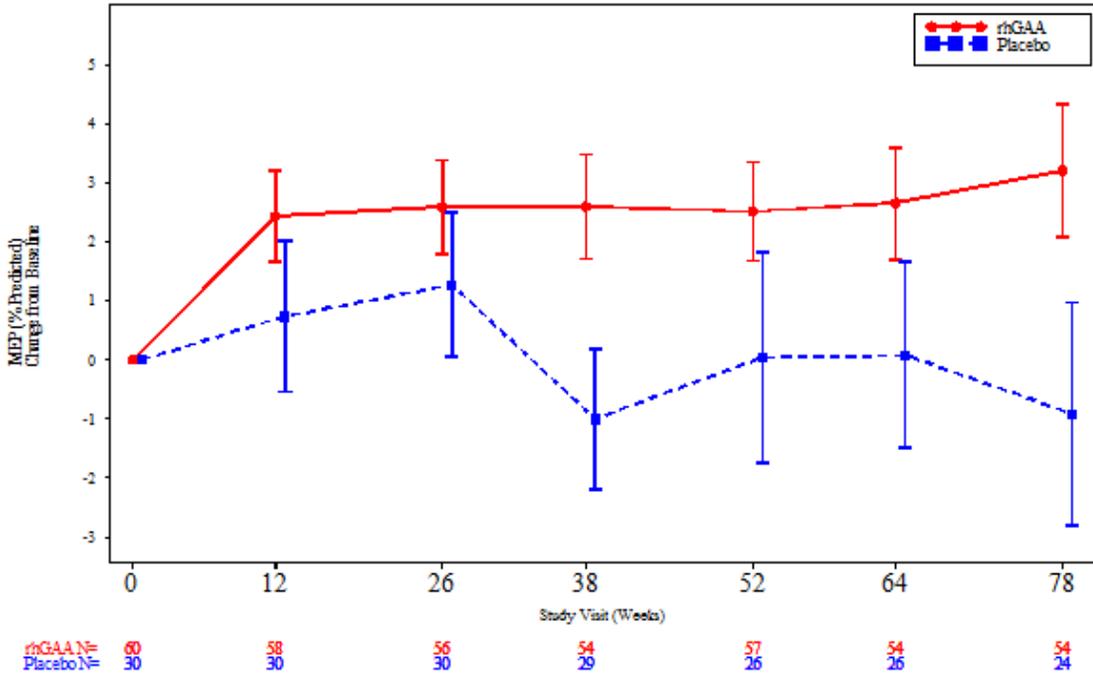


**Table 5-12:  Primary and Supportive Analyses of Change in MEP % Predicted**

| Statistical Method | 2000 L alglucosidase alfa | Placebo | Difference | P value |
|---|---|---|---|---|
| **Estimates/Tests of Monthly Change in MEP % Predicted (Repeated Measures Analysis)** | | | | |
| LME with robust variance estimation, % predicted<br>    (95% CI)<br>    [SE] | 0.13<br>(0.02, 0.24)<br>[0.06] | -0.05<br>(-0.20, 0.10)<br>[0.08] | 0.18<br>(0.00, 0.36)<br>[0.09] | 0.0544[1] |
| **Estimates/Tests of Change in MEP % Predicted From Baseline to Week 78** | | | | |
| ANCOVA Estimated Mean Change from Baseline to Last Available Observation, % predicted<br>    (95% CI)<br>    [SE] | 3.24<br>(1.19, 5.29)<br>[1.03] | -0.56<br>(-3.43, 2.31)<br>[1.44] | 3.80<br>(0.27, 7.33)<br>[1.78] | 0.0352 |
| Wilcoxon-Mann-Whitney test | | | | 0.0848 |

1. Robust variance estimation is presented for consistency with the primary analysis of the co-primary efficacy endpoints.  The p-value based on the model-based variance estimation is 0.0617.

These results for MIP and MEP % predicted support the statistically significant treatment differences on FVC % predicted by providing quantitative evidence of increased expiratory and inspiratory muscle strength in patients receiving 2000 L alglucosidase alfa and decreased strength in these muscle groups in placebo-treated patients, thus influencing the change in pulmonary function (FVC) over the course of study.

### 5.2.1.3.2       Proximal Limb Muscle Strength

Quantitative muscle function testing is a standardized system to measure muscle force production during maximal voluntary isometric contraction.  QMT has been demonstrated reliable for the assessment of 20 muscle groups (NIMS Database Consortium, 1996, *Arch Phys Med Rehabil*) and is validated for the assessment of muscle strength in adults and children with its use as an outcome measure in clinical trials of therapeutic agents for spinal muscular atrophy and Duchenne's Muscular Dystrophy (Russman, 1990, *Muscle Nerve*; Munsat, 1990, *Muscle Nerve*; Heckmatt, 1988, *Muscle Nerve*; Mendell, 1995, *NEJM*).  The system used in this study was a subset of the Tufts Quantitative Neuromuscular Evaluation, which has been used in the study of patients with amyotrophic lateral sclerosis (Shields, 1998, *Arch Phys Med Rehabil*).  The QMT Leg score is the average of the bilateral means for percent predicted values for knee flexors and extensors, and the QMT Arm score is the average of the bilateral means for percent predicted values for elbow flexors and extensors (National Isometric Muscle Strength [NIMS] Database Consortium, 1996, *Arch Phys Med Rehabil*).

Patients in both treatment groups showed similar and significantly diminished leg strength at Baseline, as measured by % predicted QMT leg score, compared to that of a healthy individual of similar age, gender, and BMI (mean values: 37.69 ± 18.88% for alglucosidase alfa and 32.49 ± 18.24% for placebo).

The mean change in lower extremity muscle strength over time based on QMT Leg Scores (expressed as % predicted) is presented in **Figure 5-5**.  As shown in this figure, alglucosidase alfa-treated patients exhibited a trend toward an overall improvement in proximal leg strength during treatment, whereas placebo-treated patients demonstrated a progressive decline in proximal leg strength throughout the study.  Results of the primary and supportive analyses are presented in **Table 5-13**.  The observed changes in the QMT Leg Score support the statistically significant treatment difference on 6MWT distance

walked by providing quantitative evidence of increased lower extremity strength in the 2000 L alglucosidase alfa group and decreased lower extremity strength in the placebo group, thus influencing the change in distance walked over the course of study.

**Figure 5-5: Mean (+/- SEM) Change From Baseline Over Time in QMT Leg Score % Predicted**
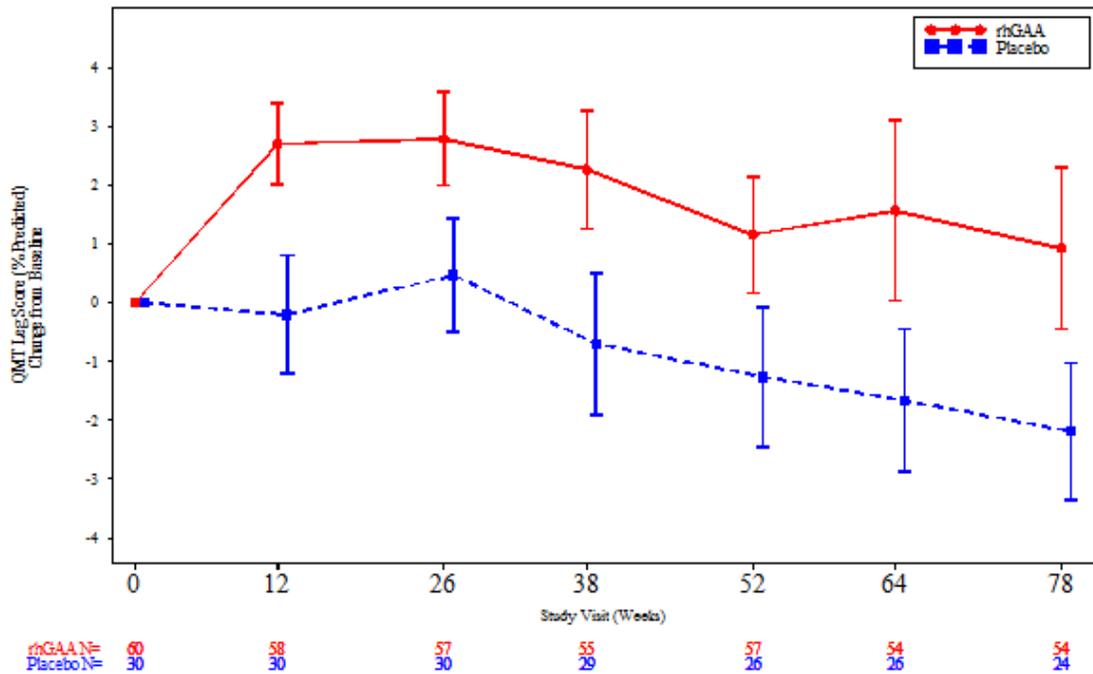
**Table 5-13:  Primary and Supportive Analyses of Change in QMT Leg Score % Predicted**

| Statistical Method | 2000 L alglucosidase alfa | Placebo | Difference | P value |
|---|---|---|---|---|
| **Estimates/Tests of Monthly Change in QMT Leg Score % Predicted (Repeated Measures Analysis)** | | | | |
| LME with robust variance estimation, % predicted (95% CI) [SE] | 0.00 (-0.15, 0.15) [0.08] | -0.13 (-0.21, -0.05) [0.04] | 0.13 (-0.04, 0.31) [0.09] | 0.1387[1] |
| **Estimates/Tests of Change in QMT Leg Score % Predicted From Baseline to Week 78** | | | | |
| ANCOVA Estimated Mean Change from Baseline to Last Available Observation, % predicted (95% CI) [SE] | 1.18 (-1.07, 3.42) [1.13] | -2.00 (-5.16, 1.17) [1.59] | 3.18 (-0.73, 7.08) [1.96] | 0.1093 |
| Wilcoxon-Mann-Whitney test | | | | 0.0224 |

1. Robust variance estimation is presented for consistency with the primary analysis of the co-primary efficacy endpoints.  The p-value based on the model-based variance estimation is 0.2615.

A similar trend toward increased proximal muscle strength with 2000 L alglucosidase alfa treatment was observed in the upper limbs based on the QMT Arm scores.  The mean change in proximal arm muscle strength over time based on QMT Arm scores (expressed as % predicted) is presented in **Figure 5-6**.  As shown in this figure, alglucosidase alfa-treated patients exhibited a clear improvement in arm strength during treatment, while placebo-treated patients showed minimal or no improvement in arm strength during the study.  Results of the primary and supportive statistical analyses are presented in **Table 5-14**.

**Figure 5-6: Mean (+/- SEM) Change From Baseline Over Time in QMT Arm Score % Predicted**
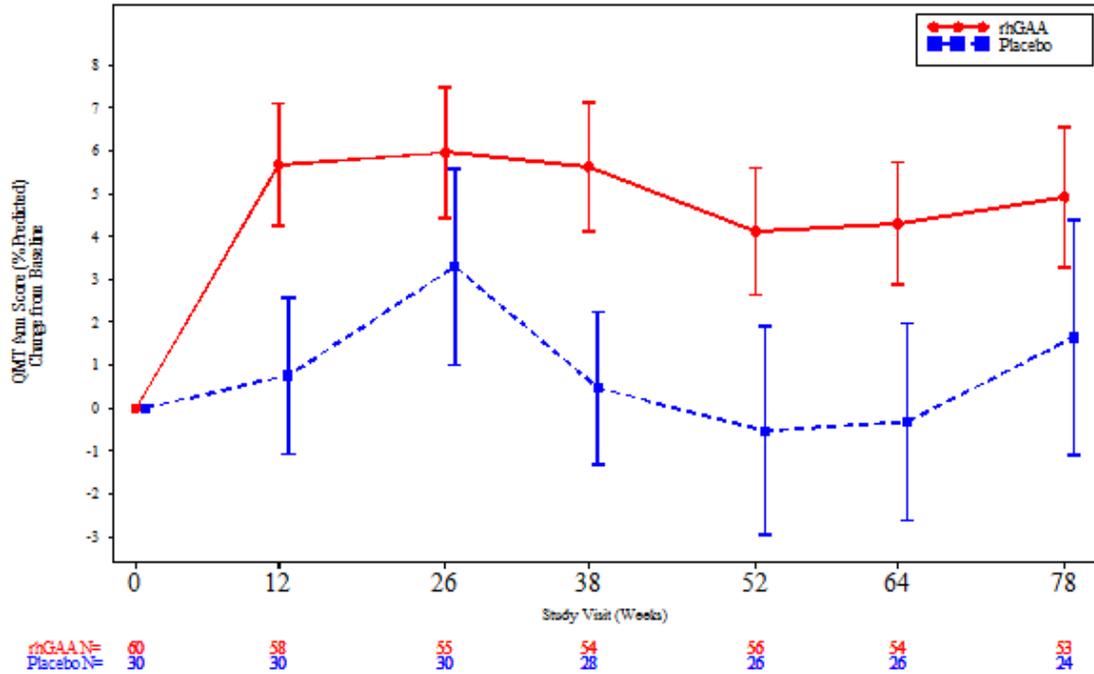


**Table 5-14: Primary and Supportive Analyses of Change in QMT Arm Score % Predicted**

| Statistical Method | 2000 L alglucosidase alfa | Placebo | Difference | P value |
|---|---|---|---|---|
| **Estimates/Tests of Monthly Change in QMT Arm Score % Predicted (Repeated Measures Analysis)** | | | | |
| LME with robust variance estimation, % predicted<br>    (95% CI)<br>    [SE] | 0.15<br>(0.01, 0.29)<br>[0.07] | -0.02<br>(-0.21, 0.17)<br>[0.10] | 0.16<br>(-0.07, 0.40)<br>[0.12] | 0.1699[1] |
| **Estimates/Tests of Change in QMT Arm Score % Predicted From Baseline to Week 78** | | | | |
| ANCOVA Estimated Mean Change from Baseline to Last Available Observation, % predicted<br>    (95% CI)<br>    [SE] | 5.05<br>(1.91, 8.18)<br>[1.57] | 1.47<br>(-2.92, 5.87)<br>[2.21] | 3.57<br>(-1.83, 8.97)<br>[2.71] | 0.1917 |
| Wilcoxon-Mann-Whitney test | | | | 0.0712 |

1. Robust variance estimation is presented for consistency with the primary analysis of the co-primary efficacy endpoints. The p-value based on the model-based variance estimation is 0.1812.

### 5.2.1.3.3    Patient-Reported Physical and Mental Health Status

In LOTS, the effect of 2000 L alglucosidase alfa treatment on physical and mental health status, based on patient self-report, was captured using the PCS score and Mental Component Summary (MCS) score, respectively, of the MOS SF-36, a self-administered questionnaire designed to assess health-related quality-of-life.

The PCS score of the SF-36 is a measure of physical health status that evaluates the ability to perform basic activities of daily living involving physical movement and exertion.  The PCS score is a summary score calculated using subscale scores that evaluate physical functioning (the ability to perform activities of daily living), role-physical (the extent to which physical limitations affect work, hobbies, etc.), bodily pain, and general health (perceived health rating relative to the previous year).  The MCS score is a summary score calculated using subscale scores that evaluate mental health, role-emotional, social functioning, and vitality.  Norm-based scores for each subscale contributing to the PCS or MCS score were calculated based on the appropriate mean and standard deviation from 1998 U.S. general population norms, and their Z-scores were used to compute the standardized PCS and MCS summary scores.  Higher scores are associated with better quality of life.

Baseline PCS scores for patients in both treatment groups were more than 1.5 SD below the US general population norms (Mean= 50, SD=10); mean PCS scores were $34.33 \pm 8.93$ for the alglucosidase alfa group and $34.91 \pm 7.26$ for the placebo group, indicating significantly diminished physical health status.  The mean change in SF-36 over time is presented in **Figure 5-7**.  Using ANCOVA, there was minimal change from Baseline to Week 78 (or last observation) for the PCS score in either the alglucosidase alfa group (+ 0.80; 95% CI:-1.22, 2.82) or the placebo group (+1.16; 95% CI:-1.64, 3.97), and no marked change in any of the 8 subscales that are factored into the calculation of the PCS score.  Given the generic nature of the SF-36, the relatively short duration of the trial, and the pattern of stabilization of function observed for patients treated with alglucosidase alfa, the inability to detect significant improvement in physical health status based on SF-36 PCS scores is not unexpected (Guyatt, 1986, *Can Med Assoc J;* Guyatt, 1993, *Ann Intern Med;* Jacobson, 1994, *Diabetes Care*).

**Figure 5-7:  Mean (+/- SEM) Change From Baseline Over Time in the Physical Component Score (PCS) of the SF-36**
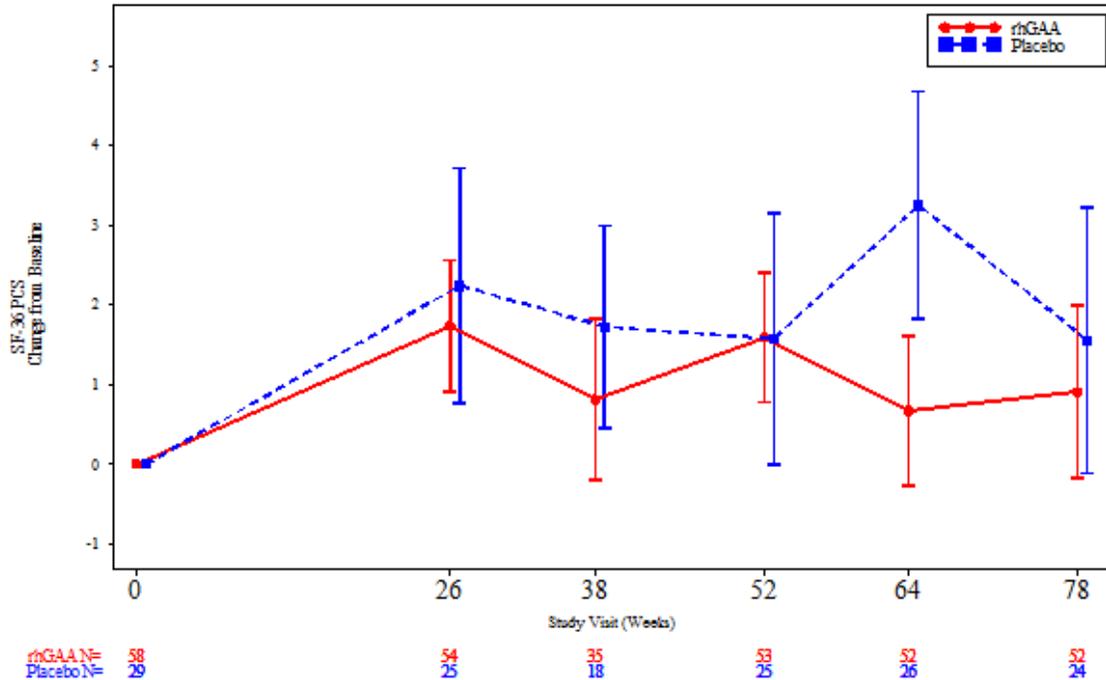


Monthly Change: LME with robust variance estimation p-value=0.5787
Change from Baseline to Week 78: ANCOVA p-value = 0.8333; WMW p-value = 0.8880

Baseline MCS scores for patients in both treatment groups were within 1 SD of the US general population norm, indicating mental health status within normal limits.  The mean change in MCS score from Baseline to Week 78 was similar in the alglucosidase alfa treatment group (1.40 ± 8.5) and the placebo group (1.60 ± 9.7).  Statistical analysis was not planned or conducted for MCS scores, because MCS scores have been found to be within 1 SD of 1998 US General Population norms in two previous studies of late-onset Pompe disease, indicating no significant impact of the disease on the mental health status of patients (Hagemans, *Neurology*, 2004; Wokke, *Muscle & Nerve*, in press).

### 5.2.1.4  Clinical Meaningfulness of LOTS Efficacy Results

The clinical significance of the efficacy outcomes observed in this study become apparent when they are compared to the natural history of the disease.  Previous studies of the natural history of late-onset Pompe disease indicate that progressive deterioration in proximal skeletal and respiratory muscle strength and function is a defining feature of the

disease, and is associated with progressive impairment of physical functioning and increased risk of morbidity and mortality. In a single-center observational study in Germany, 6 of 18 (33%) adult Pompe patients with longitudinal neurological follow-up data lost ambulation over the course of follow-up (mean follow-up 14.8 years), and 10 of 18 (55.6%) patients required initiation of mechanical ventilation during this time (Müller-Felber, 2007, *Neuromuscular Disorders*). In the Genzyme-sponsored observational study in late-onset patients (LOPOS), deterioration of proximal limb and respiratory muscle strength and function was already evident within the 12-month observational period. For the subset of LOPOS patients with Baseline pulmonary status comparable to that of LOTS patients (<80% FVC % predicted and ≥10% postural drop in FVC liters), declines were observed from Baseline to Month 12 in mean FVC % predicted (-3.31%; n=45), as well as MIP % predicted (-0.36%; n=44) and MEP % predicted (-2.54%; n=45). Similar declines in FVC, MIP, and MEP % predicted were observed for placebo-treated patients in LOTS.

Few effective treatment options exist in neuromuscular disorders, and those that are available are not disease-specific and generally have a temporary effect (e.g., corticosteroids for polymyositis and inflammatory demyelinating neuropathies) (Roper, 1997, *Adams and Victor's Principles of Neurology*). The efficacy of a drug intended to treat a progressive neuromuscular disorder such as Pompe disease may be manifested not only by facilitating improvement, but also by preventing decline in clinical status. Therefore, stabilization of function in Pompe disease represents an important advancement in the clinical management of progressive neuromuscular diseases.

To determine the clinical meaningfulness of alglucosidase alfa treatment for the individual patients, a "responder" analysis was conducted, evaluating both improvement and prevention of decline for the LOTS co-primary efficacy endpoints. In this analysis, the treatment effects for 6MWT and FVC were evaluated relative to thresholds for minimally clinical important differences (MCID), defined as the smallest changes that would be perceived as important by a patient and lead them (or their physician) to consider a change in disease management.

Due to the limited number of novel therapeutics available, the MCID has not been established for 6MWT and FVC for any neuromuscular disease. The LOTS trial is the first randomized, double-blind, placebo-controlled trial to use the 6MWT as a primary

efficacy endpoint to demonstrate the effect of an intervention in a neuromuscular disease. For late-onset Pompe patients, performance on this test is likely to be compromised by weakness in various muscle groups involved in ambulation, which can cause a limb-girdle gait and compensatory hyperlordosis, as well as respiratory muscle weakness, which can cause fatigue and dyspnea with exertion (Laforet, 2000, *Neurology*; Hirschhorn, 2001, *The Metabolic and Molecular Bases of Inherited Disease*). This was particularly true for the LOTS patients who, based on the inclusion criteria for the trial, had both proximal muscle weakness in the legs and respiratory muscle weakness. Moreover, patients in LOTS exhibited substantial variability with respect to the extent of proximal leg and respiratory muscle involvement. The inability to distinguish the relative contribution of proximal leg weakness and respiratory muscle weakness on 6MWT performance presented a challenge to identification of an MCID to evaluate the clinical significance of the alglucosidase alfa treatment effect on 6MWT.

Identification of an appropriate MCID for FVC in the LOTS study was complicated by the restrictive nature of respiratory impairment observed in late-onset Pompe disease. A reduction in FVC is the most commonly reported abnormality in patients with respiratory muscle weakness. Therefore, the ATS/ERS recommend the evaluation of FVC to monitor respiratory status in neuromuscular disease and have established criteria based on FVC % predicted values to define the severity of restrictive respiratory disease (ATS, 1991, *Am Rev Respir Disease)*. However, the ATS criteria are based on a study of bronchodilator use in patients with *obstructive* pulmonary disease. In patients with neuromuscular diseases such as late-onset Pompe disease, weakening of respiratory muscles leads to the development of progressive ventilatory *restriction*; there is no obstructive component to the pulmonary involvement. Little is known about the MCID associated with changes in FVC in patients with restrictive respiratory disease, such as those with late-onset Pompe disease.

In view of the limitations described above, several MCIDs were evaluated for each co-primary endpoint in the LOTS responder analysis. The MCIDs for both 6MWT and FVC % predicted were based on the literature for obstructive pulmonary disease and were prospectively defined in the SAP for LOTS.

For the 6MWT, 2 thresholds of clinical significance were defined for the absolute change from Baseline: 54 meters and 37 meters. These clinical responder criteria are based on

published work by Redelmeier, et al (Redelmeier, 1997, *Am J Respir Crit Care)*, who investigated the MCID in walking distance associated with the perception of differences in walking ability in a cohort of COPD patients. Redelmeier et al derived a threshold of clinical importance of 54 meters (95% CI: 37 to 71 meters) based on patient ratings. Therefore, the 2 thresholds selected for the responder analysis represent the estimated threshold (54 meters) and the lower limit of the 95% CI of the estimated threshold (37 meters). In a recent article by Puhan et al., a change in 6MWT of 35 meters (or approximately 10% from Baseline) was determined to be clinically relevant for patients with moderate-to-severe COPD (Puhan, 2008, *Eur Respir J*). Given the combined effect of both lower extremity and respiratory muscle weakness on 6MWT distance in patients with late-onset Pompe disease and the distance criteria established in the recent Puhan article, a change in distance of 37 meters (the lower limit of the 95% CI from the Redelmeier study) was determined to be the most appropriate threshold to define 6MWT "responders" in LOTS. This 37-meter threshold represents a change of approximately 10% from the mean distance walked at Baseline for both alglucosidase alfa-treated patients (332.20 meters) and placebo-treated patients (317.93 meters), and is more than twice the baseline test-retest variability of the 6MWT.

For FVC, 3 thresholds of clinical significance were defined for the relative change in % predicted compared to Baseline: 5%, 10%, and 15%. The ATS has defined the clinically significant change in % predicted FVC as a within-day change of 5%, between-weeks change of 11-12%, and annual change of 15% based on a study of bronchodilator use in patients with obstructive pulmonary disease. The thresholds increase over time because a longer treatment period is expected to yield better outcomes with this intervention in a COPD population. For consistency with the evaluation of 6MWT, a change of 10% over Baseline was also chosen as the most appropriate threshold to define FVC "responders" in LOTS; a 10% relative change over Baseline was also considered an appropriate threshold as this was the lowest of the 3 thresholds that was at least twice the baseline test-retest variability of the FVC.

Results of the responder analysis for each co-primary endpoint (analyzed separately) are presented in Table 5-15, and support an overall benefit from 2000 L alglucosidase alfa treatment in this population. For each co-primary endpoint, the proportion of patients responding was greater for alglucosidase alfa compared with placebo, regardless of the

threshold used. Additionally, Genzyme used the methodology of Guyatt et al (Guyatt, 1998, *British Medical J*), which combines the differences in proportions of patients improving versus declining to estimate a treatment effect, which represents the proportion of patients expected to have a meaningfully better outcome on alglucosidase alfa than placebo. At the threshold that was determined to be most relevant for the late-onset patients in LOTS, this treatment effect was 19.3% for 6MWT (37-meter threshold) and 27.0% for FVC (10% threshold).

**Table 5-15:  Patients Improving or Deteriorating Beyond Various Thresholds for 6MWT Distance Walked and FVC % Predicted**

| Change Threshold | Patients Improving | | Patients Declining | | 2000 L alglucosidase alfa versus Placebo Treatment Effect[1] |
|---|---|---|---|---|---|
| | 2000 L alglucosidase alfa N = 60[2] n (%) | Placebo N = 30 n (%) | 2000 L alglucosidase alfa N = 60[2] n (%) | Placebo N = 30 n (%) | |
| **6MWT only** | | | | | |
| 54m | 14 (23.7) | 4 (13.3) | 3 (5.1) | 4 (13.3) | 16.2% |
| 37m | 17 (28.8) | 5 (16.7) | 5 (8.5) | 6 (20.0) | 19.3% |
| **FVC only** | | | | | |
| 15% | 7 (11.9) | 0 | 4 (6.8) | 2 (6.7) | 11.0% |
| 10% | 12 (20.3) | 2 (6.7) | 5 (8.5) | 8 (26.7) | 27.0% |
| 5% | 24 (40.7) | 6 (20.0) | 12 (20.3) | 14 (46.7) | 32.1% |

[1] Calculated using the methods of Guyatt et al (1998).
[2] Patient 2704-16709 did not have post-Baseline data, and was excluded from the analysis.

Retrospective analyses were also performed to evaluate responders based on the outcome for both co-primary endpoints.  Based on the thresholds that were considered to be most relevant for LOTS patients, i.e., a 37-meter change in 6MWT distance walked or a 10% change in FVC % predicted, patients were classified as showing improvement, stabilization (i.e., minimal change that did not achieve the threshold), or decline.  Results of these analyses are presented in Table 5-16 and are depicted graphically in **Figure 5-8**. Of the 59 alglucosidase alfa-treated patients with post-Baseline data, 25 (42.4%) of 59 patients improved on 6MWT or FVC, including 4 patients who showed improvement on both efficacy endpoints.  In contrast, only 6 (20.0%) of 30 placebo-treated patients showed improvement on 6MWT or FVC, including 1 patient who exhibited improvement on both efficacy endpoints.  As shown in **Table 5-16** and **Figure 5-8**, the proportion of patients who declined on either endpoint during LOTS was greater for placebo than 2000 L alglucosidase alfa, while the proportion of patients who demonstrated a

stabilization of function on both endpoints was similar between treatment groups. Overall, these results represent a clinically meaningful shift in patient response with 2000 L alglucosidase alfa relative to placebo (p=0.0062 using the Mantel-Haenszel test).

**Table 5-16:  Patients Responding on 6MWT Distance Walked (37-meter Threshold) and FVC % Predicted (10% Threshold)**

|  | IMPROVED on 6MWT or FVC n (%) | STABILIZED on both 6MWT and FVC n (%) | DECLINED on 6MWT or FVC n (%) |
|---|---|---|---|
| 2000 L alglucosidase alfa (n=60)[1] | 25 (42.4) | 26 (44.1) | 8 (13.6) |
| Placebo (n=30) | 6 (20.0) | 13 (43.3) | 11 (37.7) |
| P value[2] | 0.0062 | | |

[1] Patient 2704-16709 did not have post-Baseline data, and was excluded from the analysis.
[2] Mantel-Haenszel test

**Figure 5-8: Responder Profile on 6MWT Distance Walked (37-meter Threshold) and FVC % Predicted (10% Threshold)**
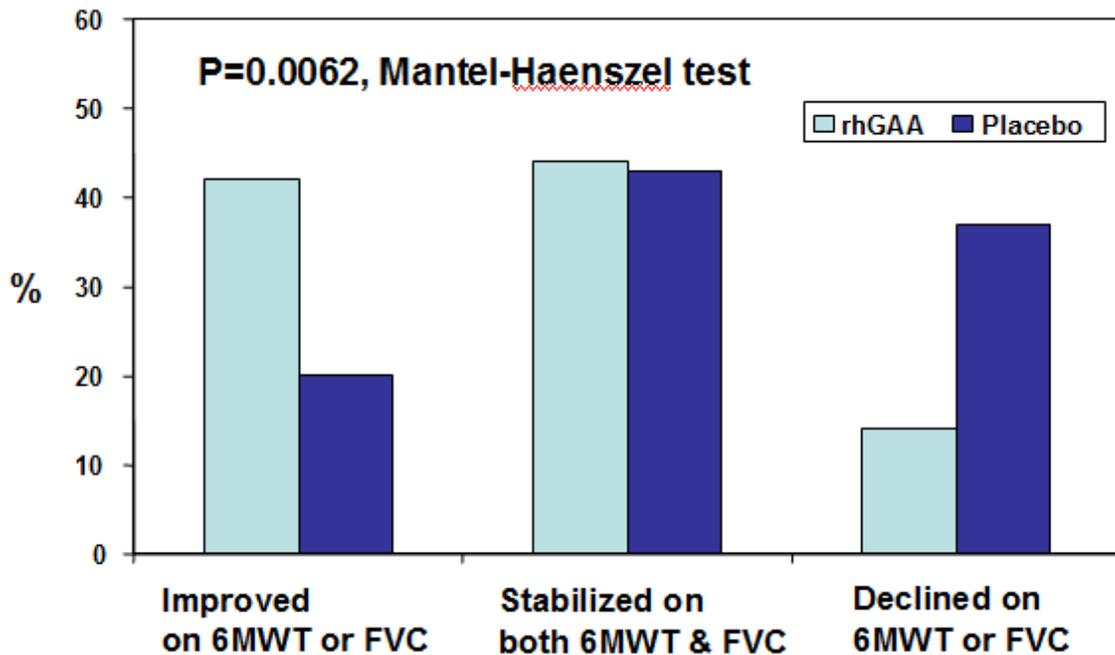


The clinical significance of the 2000 L alglucosidase alfa treatment effect in LOTS was also evaluated using effect size (ES).  Effect size, which is calculated as the difference in the mean outcome of the treatment group and the control group divided by the pooled

standard deviation, can be utilized to compare treatment outcomes relative to other clinical studies. For LOTS, ES was determined for the change from Baseline to last observation for each co-primary endpoint. The resultant effect sizes for 6MWT (0.48) and % predicted FVC (0.65) are consistent with a "medium" ES range based on work by Cohen et al to define small (0.2), medium (0.5) and large (0.8) effect sizes (Cohen, 1988, *Statistical Power Analysis for the Behavioral Sciences*; Cohen, 1992, *Psych Bull*). Effect sizes in this medium range have been posited to be clinically meaningful to patients (Sloan, 2003, *Drug Inf J*). In an international study of 210 late-onset Pompe patients, health-related quality of life scores were inversely correlated with the use of wheelchairs and artificial ventilation in (Hagemans, 2004, *Neurology*). Therefore, a therapeutic agent with a medium effect size, which prevents disease progression and dependence on invasive ventilator support and wheelchairs, is expected to have a positive impact on the lives of patients with late-onset Pompe disease.

Importantly, the effect sizes of 2000 L alglucosidase alfa on the co-primary efficacy endpoints in LOTS are consistent with effect sizes observed in pivotal trials for other recombinant protein products that have since been approved for the treatment of orphan diseases involving progressive neuromuscular decline. As shown in **Table 5-17**, effect sizes with alglucosidase alfa treatment are comparable to those observed in the pivotal, randomized, double-blind, placebo-controlled trials for recombinant enzyme products that are approved for the treatment MPS type I (Aldurazyme) and MPS type II (Elaprase). Like Pompe disease, the mucopolysaccharidoses are chronic progressive disorders caused by deficiencies of specific lysosomal enzymes (in this case, enzyme required for the catabolism of glycosaminoglycans). The effect sizes of Aldurazyme and Elaprase are considered clinically meaningful in their respective patient populations, and served as the basis for the approval of these recombinant enzyme therapies by FDA.

**Table 5-17: Mean Estimated Change in 6MWT with Enzyme Replacement Therapy for Lysosomal Storage Disorders**

|  | Aldurazyme (laronidase)[2] | Elaprase (idursulfase)[3] | 2000 L alglucosidase alfa |
|---|---|---|---|
| **Pivotal Study Design** | | | |
| Disease population | MPS-I | MPS-II | Pompe |
| Treatment duration | 6 months | 12 months | 18 months |
| Number of patients treated[1] | 45 | 64 | 90 |
| **6MWT distance walked** | | | |
| Effect size (p-value) | 0.56 (0.039) | 0.60 (0.0131) | 0.48 (0.034) |
| **FVC, % predicted** | | | |
| Effect size (p-value) | 0.61 (0.028) | 0.27 (not significant) | 0.65 (0.006) |

MPS=Mucopolysaccharidosis
1. Includes total number of patients in both active and placebo control groups
2. 6MWT ES based on Wraith, 2004, *J Pediatr;* FVC ES based on data on file at Genzyme
3. 6MWT and FVC ES based on Meunzer, 2006, *Genet Med*

As discussed in **Section 3.1**, the clinical hypothesis for ERT in Pompe disease is that enhancement of GAA activity (through administration of exogenous enzyme) will lead to a reduction in glycogen accumulation in muscle tissue and consequent recovery of muscle function. However, the capacity for regeneration may be limited in muscle tissue that has degenerated and has been replaced by fat. The replacement of muscle by fat in advanced disease has been observed on MRI examination of adult Pompe muscle (Katirji, *Neurology.* 2008). Similar changes have been observed in the later stages of Duchenne's muscular dystrophy and polymyositis (Silverberg, *Principles and Practice of Surgical Pathology and Cytopathology,* 1997). This destruction of the myofibrillar contractile elements and of normal cyto-architecture may irreparably damage muscle fibers. Thus, ERT may likely result in functional recovery within the parts of the muscle that have not yet undergone end-stage degeneration with fatty replacement, resulting in the initial observed improvement of proximal muscle strength and walking ability in LOTS. The stabilization of proximal limb strength and walking ability observed in some patients treated with 2000 L alglucosidase alfa during LOTS is hypothesized to be due to a scenario in which continued treatment with alglucosidase alfa prevents new damage to

these regenerated muscle fibers through the continued removal of glycogen, but further improvement is limited by the inability to achieve functional recovery of muscle that has undergone fatty replacement. This hypothesis is supported by the observation in LOTS that the treatment effect among patients with less advanced disease at treatment initiation appears to be larger than among patients with more advanced disease at treatment initiation (**Section 5.2.1.2.3**). This clinical hypothesis suggests that early initiation of treatment, prior to significant myofibril damage, may be critical to maximizing the potential therapeutic benefit of ERT. This is consistent with the response to ERT in other lysosomal storage disorders, such as Fabry disease (Fabrazyme), the mucopolysaccharidoses (Aldurazyme, Elaprase, Naglazyme), and Gaucher disease (Cerezyme), where the benefit from ERT does not translate into restoration of normal organ function when therapy is initiated after significant damage has occurred.

Lastly, it is important to emphasize that while 2000 L alglucosidase alfa had a medium effect size over the 18 months of treatment in LOTS, over time one would expect a widening separation between alglucosidase alfa-treated patients and untreated patients as the stabilizing effects of alglucosidase alfa therapy contrast ever more sharply with the progressive muscle degeneration, loss of mobility, and ventilator-dependence that characterize the natural course of untreated late-onset Pompe disease. In LOPOS, untreated patients experienced, on average, a 3.3% decline in FVC during the 12-month observational period, which is comparable to the approximately 2% average decline in FVC observed in placebo-treated patients in LOTS over the first 12 months of the study. Notably, in both untreated (LOPOS) and placebo-treated (LOTS) late-onset Pompe patients, decline in FVC proved to be linear over time. When extrapolated out over a 5-year period, the average decline in FVC among late-onset Pompe patients not receiving interventional therapy might therefore be expected to be between 10% to 17.5%. Given the projected decline in FVC in the absence of treatment, it is reasonable to expect that patients who already have an impaired respiratory function at Baseline (FVC <50% predicted) will have "Very Severe" restrictive respiratory disease (FVC <34% predicted), and an associated increased risk of respiratory infection, respiratory distress, and invasive ventilation (Visser, 2007, *Neurology*; Thieben, 2005, *Muscle Nerve*; Sharshar, 2003, *Crit Care Med*; Schmidt, 2006, *Muscle Nerve*; Mayhew 2007, *Muscle Nerve*), if they were to remain untreated over a 5-year period. Moreover, given the difficulties associated with weaning patients with minimal residual pulmonary

function off of ventilator support (Hill, 2002, *Semin Respir Crit Care Med),* use of invasive ventilation would often be permanent.

### 5.2.1.5 Efficacy Conclusions

The efficacy results for the LOTS trial demonstrate clearly that treatment with 2000 L alglucosidase alfa leads to improved walking ability and stabilization of pulmonary function in patients with late-onset Pompe disease.

Both co-primary efficacy endpoints in LOTS, change in 6MWT distance walked and change in % predicted FVC upright, were met, demonstrating a statistically significant treatment difference both in overall rate of change and in the change from Baseline to Week 78 (or last available observation). Results of secondary and tertiary efficacy endpoints that measure proximal limb and respiratory muscle strength demonstrated a consistent pattern of response that further supports the findings for the co-primary endpoints. The 6MWT findings are supported by results for the QMT leg score, which indicate a trend toward increased muscle strength in the lower extremities in muscle groups that are involved in ambulation (quadriceps and hamstrings). Additional support for increased muscle strength is provided by the results for the QMT arm score, which demonstrate a trend toward increased proximal muscle strength in the upper extremities (triceps and biceps). The FVC findings are supported by results for MIP and MEP % predicted, which indicate a trend toward increased muscle strength in the diaphragm muscle and other respiratory muscles. The change in each efficacy endpoint from Baseline to last observation, as analyzed using ANCOVA, is summarized in Table 5-18. When expressed as % predicted values, the magnitude of the treatment difference is similar for all primary, secondary, and tertiary endpoints.

**Table 5-18: ANCOVA Estimated Mean (95% CI) Change From Baseline to Last Observation for LOTS Efficacy Variables**

| Efficacy Variable | 2000 L alglucosidase alfa (N = 60) | Placebo (N = 30) | Difference | P value |
|---|---|---|---|---|
| **Walking Ability and Proximal Muscle Strength** | | | | |
| 6MWT distance walked, meters Mean (95% CI) | 25.13 (10.07, 40.19) | -2.99 (-24.16, 18.18) | 28.12 (2.07, 54.17)[1] | 0.0347 |
| QMT leg score, % predicted Mean (95% CI) | 1.18 (-1.07, 3.42) | -2.00 (-5.16, 1.17) | 3.18 (-0.73, 7.08) | 0.1093 |
| QMT arm score, % predicted Mean (95% CI) | 5.05 (1.91, 8.18) | 1.47 (-2.92, 5.87) | 3.57 (-1.83, 8.97) | 0.1917 |
| **Pulmonary Function and Respiratory Muscle Strength** | | | | |
| FVC, % predicted Mean (95% CI) | 1.20 (-0.16, 2.57) | -2.20 (-4.12, -0.28) | 3.40 (1.03, 5.77) | 0.0055 |
| MIP, % predicted Mean (95% CI) | 3.48 (0.91, 6.04) | -0.35 (-3.95, 3.25) | 3.83 (-0.60, 8.26) | 0.0895 |
| MEP, % predicted Mean (95% CI) | 3.24 (1.19, 5.29) | -0.56 (-3.43, 2.31) | 3.80 (0.27, 7.33) | 0.0352 |

1. The ANCOVA estimated mean treatment difference for 6MWT, when expressed as % predicted, is 4.67 (0.58, 8.76).

As discussed in **Section 5.2.1.4**, the clinical significance of the 2000 L alglucosidase alfa treatment effect in LOTS is clearly apparent when compared to the progressive muscle deterioration, loss of mobility, and ventilator-dependence that characterize the natural history of late-onset Pompe disease. Responder and effect size analyses support the clinical meaningfulness of alglucosidase alfa therapy to Pompe patients. Results of a responder analysis for each co-primary endpoint show a clinically meaningful shift in patient response with 2000 L alglucosidase alfa relative to placebo (p=0.0062 using the Mantel-Haenszel test). Treatment effect sizes of 2000 L alglucosidase alfa on 6MWT (0.48) and FVC (0.65) were consistent with effect sizes for these endpoints in the pivotal trials for other recombinant protein products that are now approved in the US for the treatment of orphan diseases involving progressive neuromuscular decline: MPS type I (Aldurazyme), and MPS type II (Elaprase).

In summary, the clinically and statistically significant treatment effect of 2000 L alglucosidase alfa over placebo observed on 6MWT and FVC in this 18-month study of patients with late-onset Pompe disease signals a meaningful therapeutic advancement and can be expected to positively impact the lives of patients with this progressive neuromuscular disease.  Moreover, alglucosidase alfa therapy has the potential to benefit a broad spectrum of patients in this clinically heterogeneous population, given the positive treatment effect of 2000 L alglucosidase alfa over placebo on both co-primary endpoints, regardless of patient age, gender, disease duration, and Baseline disease severity.

### 5.2.2       Summary of Safety in AGLU02704 (LOTS)

Comprehensive safety monitoring was performed throughout the duration of treatment in the AGLU02704 LOTS trial.

An overview of AEs reported during LOTS is provided in **Section 5.2.2.1**, and further discussion of SAEs (including deaths) and IARs (including potential anaphylactic reactions) is provided in **Section 5.2.2.2** and **Section 5.2.2.3**, respectively.

Immunogenicity testing was also performed in the LOTS trial to assess the safety of alglucosidase alfa treatment.  Information on anti-rhGAA IgG antibodies and inhibitory antibodies is provided in **Section 5.2.2.5.2** and **Section 5.2.2.5.3**, respectively. Information on additional immunologic testing that was performed where clinically indicated in patients experiencing a moderate or severe IAR is provided in **Section 5.2.2.5.4**.

The complete safety data from LOTS were submitted to BLA 125291, including the results of laboratory tests, vital signs, physical examinations, 12-lead electrocardiograms (ECGs), and hearing tests.  However, as there were no unexpected or clinically meaningful findings that would present a potential safety concern for 2000 L alglucosidase alfa, these additional safety results have not been included in this briefing package in the interest of brevity.

### 5.2.2.1       Summary of Adverse Events in LOTS

All 90 patients in LOTS experienced AEs, with a total of 2296 AEs reported across both treatment groups (**Table 5-19**).  A majority of all reported AEs were non-serious, mild or

moderate in severity, and not related to study treatment. The proportion of patients experiencing AEs, SAEs, treatment-related AEs, and IARs was similar between treatment groups. One patient in the 2000 L alglucosidase alfa group died due to causes not related to study treatment. Three additional patients discontinued treatment due to AEs and were subsequently withdrawn from the study, including 2 alglucosidase alfa-treated patients who withdrew after experiencing serious IARs that were assessed as an anaphylactic reaction and a significant IAR, respectively, and 1 placebo-treated patient who withdrew due to an AE of severe head discomfort that was assessed as not related to treatment.

**Table 5-19: Overall Summary of Treatment-Emergent Adverse Events By Treatment Group in LOTS**

| | 2000 L alglucosidase alfa | | Placebo | |
|---|---|---|---|---|
| Variable | Number of Patients (N=60) n (%) | Number of Events n (%) | Number of Patients (N=30) n (%) | Number of Events n (%) |
| Any AEs | 60 (100.0) | 1445 (100.0) | 30 (100.0) | 851 (100.0) |
| Treatment-Related AEs | 32 ( 53.3) | 298 ( 20.6) | 17 ( 56.7) | 144 ( 16.9) |
|    Infusion-Associated Reactions | 17 ( 28.3) | 236 ( 16.3) | 7 ( 23.3) | 73 ( 8.6) |
| Severe AEs | 14 ( 23.3) | 29 ( 2.0) | 10 ( 33.3) | 18 ( 2.1) |
| SAEs | 13 ( 21.7) | 20 ( 1.4) | 6 ( 20.0) | 7 ( 0.8) |
| Patients who Discontinued Due to AEs or Died During the Study | 3 (5.0)[1] | N/A[2] | 1 (3.3) | N/A[2] |

[1] One patient discontinued due to death.
[2] N/A not applicable. Only patient counts are provided as AEs resulting in discontinuation and death are not mutually exclusive.

The most frequently occurring AEs in each treatment group, including fall, nasopharyngitis, and headache, were consistent with the manifestations of underlying Pompe disease, and a majority of these events were assessed as not related to treatment. Adverse events that were assessed by the investigator as related to treatment (i.e., possibly, probably, or definitely related) and occurred in at least 5% of patients in the 2000 L alglucosidase alfa group are summarized in Table 5-20. The majority of treatment-related AEs within each treatment group (97.7% events for alglucosidase alfa; 98.6% events for placebo) were assessed as non-serious. Most treatment-related AEs (79.2% events on alglucosidase alfa; 50.7% events on placebo) were also characterized as IARs. Information on IARs and potential anaphylactic reactions in LOTS is provided in **Section 5.2.2.3**.

Further information on the one patient death in LOTS, as well as other SAEs, is provided in **Section 5.2.2.2**.

**Table 5-20:  Summary of Treatment-Related AEs that Occurred in ≥ 5% of alglucosidase alfa -Treated Patients in LOTS**

| MedDRA Preferred Term[1] | 2000 L alglucosidase alfa Patients (N=60) | | Placebo Patients (N=30) | |
|---|---|---|---|---|
| | Number of Patients[2] n (%) | Number of Events[3] n (%) | Number of Patients[2] n (%) | Number of Events[3] n (%) |
| **Any Adverse Events** | **32 ( 53.3)** | **298 (100.0)** | **17 ( 56.7)** | **144 (100.0)** |
| **SOC: General disorders and administration site conditions** | | | | |
| Chest discomfort | 4 (6.7) | 9 (3.0) | 1 (3.3) | 1 (0.7) |
| Fatigue | 3 (5.0) | 3 (1.0) | 4 (13.3) | 6 (4.2) |
| **SOC: Skin and subcutaneous tissue disorders** | | | | |
| Urticaria | 5 (8.3) | 14 (4.7) | 0 | 0 |
| Hyperhidrosis | 5 (8.3) | 8 (2.7) | 0 | 0 |
| **SOC: Nervous system disorders** | | | | |
| Headache | 5 (8.3) | 14 (4.7) | 6 (20.0) | 39 (27.1) |
| Dizziness | 4 (6.7) | 10 (3.4) | 2 (6.7) | 5 (3.5) |
| **SOC: Gastrointestinal disorders** | | | | |
| Nausea | 5 (8.3) | 24 (8.1) | 3 (10.0) | 37 (25.7) |
| Vomiting | 3 (5.0) | 3 (1.0) | 0 | 0 |
| **SOC: Musculoskeletal and connective tissue disorders** | | | | |
| Muscle twitching | 4 (6.7) | 5 (1.7) | 1 (3.3) | 1 (0.7) |
| Myalgia | 3 (5.0) | 5 (1.7) | 1 (3.3) | 1 (0.7) |
| **SOC: Eye disorders** | | | | |
| Cataract | 4 (6.7) | 4 (1.3) | 1 (3.3) | 1 (0.7) |
| **SOC: Vascular disorders** | | | | |
| Flushing | 3 (5.0) | 5 (1.7) | 0 | 0 |
| **SOC: Investigations** | | | | |
| Blood pressure increased | 3 (5.0) | 3 (1.0) | 0 | 0 |

[1] Events are presented by system organ class (SOC) and by decreasing frequency within each SOC based on alglucosidase alfa-treated patient percentages; events with the same frequency are listed by decreasing number of events.

[2] Percentages are based on the total number of patients within each treatment group.  A patient experiencing more than one AE within a preferred term is counted once for that preferred term.

[3] Percentages are based on the total number of AEs experienced by patients within each treatment group.

### 5.2.2.2        Deaths and Other Serious Adverse Events in LOTS

There were no treatment-related deaths during the LOTS trial.  However, 1 patient (2704-16708) in the 2000 L alglucosidase alfa group died of causes not related to

treatment. This patient developed locked-in syndrome at 13 days after the Week 72 infusion. Three days after the onset of the event, a decision was made to withdraw life support measures and the patient subsequently died. Cause of death was considered to be brain stem ischemia secondary to basilar artery thrombosis. The patient's medical history was significant for 2 broad-based basilar aneurysms found on an angiogram during study participation.

Table 5-21 presents the frequency of treatment-emergent SAEs by system organ class (SOC) and Medical Dictionary for Regulatory Activities (MedDRA) preferred term for each treatment group in LOTS. As shown in this table, the frequency of SAEs was similar between treatment groups: 20 SAEs (1.4% of all 1445 AEs) were reported in 13 (21.7%) patients in the 2000 L alglucosidase alfa group, and 7 SAEs (0.8% of all 851 AEs) were reported in 6 (20.0%) patients in the placebo group. Most of these events (18 of 27 events; 66.7%) were consistent with the clinical manifestations of underlying Pompe disease, and were assessed as not related to treatment. No clinically meaningful differences in SAE profiles were observed between the 2000 L alglucosidase alfa and placebo groups. The majority of SAEs were isolated events occurring in single patients. SAEs that occurred more than once in the 2000 L alglucosidase alfa group were hypersensitivity (2 events in 2 patients), coronary artery disease (2 events in 1 patient) and intervertebral disc protrusion (2 events in 1 patient). The only other SAEs occurring more than once in the overall study population were fall and humerus fracture (a total of 2 events, 1 in each treatment group). There was no consistent trend in the frequency of SAEs over time, when assessed by time intervals of 0 to 6 months, >6 to 12 months, and >12 to 18+ months, suggesting that long-term treatment with 2000 L alglucosidase alfa does not present an increased risk of serious treatment-related events.

Table 5-21: Summary of Treatment–Emergent Serious Adverse Events in LOTS

| MedDRA Preferred Term[1] | 2000 L alglucosidase alfa | | Placebo | |
| --- | --- | --- | --- | --- |
| | Number of Patients[2] n (%) | Number of Events[3] n (%) | Number of Patients[2] n (%) | Number of Events[3] n (%) |
| **Any Serious Adverse Events** | **13 (21.7)** | **20 (100.0)** | **6 (20.0)** | **7 (100.0)** |
| **SOC: Infections and infestations** | | | | |
| Diverticulitis | 0 | 0 | 1 (3.3) | 1 (14.3) |
| Gastroenteritis | 1 (1.7) | 1 (5.0) | 0 | 0 |
| Pneumonia | 1 (1.7) | 1 (5.0) | 0 | 0 |
| **SOC: Cardiac disorders** | | | | |
| Coronary artery disease | 1 (1.7) | 2 (10.0) | 0 | 0 |
| Supraventricular tachycardia | 1 (1.7) | 1 (5.0) | 0 | 0 |
| **SOC: Immune system disorders** | | | | |
| Hypersensitivity | 2. (3.3) | 2 (10.0) | 0 | 0 |
| **SOC: General disorders and administration site conditions** | | | | |
| Chest discomfort | 1 (1.7) | 1 (5.0) | 0 | 0 |
| Non-cardiac chest pain | 1 (1.7) | 1 (5.0) | 0 | 0 |
| **SOC: Respiratory, thoracic and mediastinal disorders** | | | | |
| Lung disorder | 1 (1.7) | 1 (5.0) | 0 | 0 |
| Throat tightness | 1 (1.7) | 1 (5.0) | 0 | 0 |
| **SOC: Injury, poisoning and procedural complications** | | | | |
| Fall | 1 (1.7) | 1 (5.0) | 1 (3.3) | 1 (14.3) |
| Humerus fracture | 1 (1.7) | 1 (5.0) | 1 (3.3) | 1 (14.3) |
| **SOC: Musculoskeletal and connective tissue disorders** | | | | |
| Intervertebral disc protrusion | 1 (1.7) | 2 (10.0) | 0 | 0 |
| Flank pain | 0 | 0 | 1 (3.3) | 1 (14.3) |
| **SOC: Gastrointestinal disorders** | | | | |
| Abdominal pain | 1 (1.7) | 1 (5.0) | 0 | 0 |
| Abdominal pain upper | 0 | 0 | 1 (3.3) | 1 (14.3) |
| **SOC: Nervous system disorders** | | | | |
| Brain stem ischaemia | 1 (1.7) | 1 (5.0) | 0 | 0 |
| Headache | 0 | 0 | 1 (3.3) | 1 (14.3) |
| **SOC: Skin and subcutaneous disorders** | | | | |
| Angioneurotic oedema[4] | 1 (1.7) | 1 (5.0) | 0 | 0 |
| Septal panniculitis | 0 | 0 | 1 (3.3) | 1 (14.3) |
| **SOC: Metabolism and nutrition disorders** | | | | |
| Dehydration | 1 (1.7) | 1 (5.0) | 0 | 0 |
| **SOC: Vascular disorders** | | | | |
| Aneurysm | 1 (1.7) | 1 (5.0) | 0 | 0 |

[1] Events are presented by SOC and by decreasing frequency within each SOC based on patient percentages; events with the same frequency are listed alphabetically.

[2] Percentages are based on the total number of treated patients. A patient experiencing more than one SAE within a preferred term is counted once for that preferred term.

[3] Percentages are based on the total number of SAEs experienced by patients within each treatment group

[4] Preferred term of angioedema became available with upgrade from MedDRA 9.1.

Treatment-related SAEs were reported for 6.7% of patients in each treatment group. In the 2000 L alglucosidase alfa group, 7 treatment-related SAEs were reported for 4 patients. Six of 7 events were also characterized as IARs. Only 1 event of moderate supraventricular tachycardia was not characterized as an IAR, as it did not occur on the day of infusion; this event occurred between Weeks 6 and 8 and was assessed as possibly related to study treatment, and resolved while the patient (2704-65701) continued study treatment. The remaining 6 SAEs in 3 patients were characterized as IARs; 2 of these events were suggestive of anaphylactic reactions and included preferred terms of hypersensitivity (2 events), chest discomfort, non-cardiac chest pain, and throat tightness. One patient experienced severe angioedema which was considered as a significant IAR. Refer to **Section 5.2.2.3.1** for further details on these reactions.

In the placebo group, 2 treatment-related SAEs were reported in 2 (6.7%) patients: headache and septal panniculitis. Patient 2704-29703, who had a medical history of migraines, experienced severe headache at Week 20 that was characterized as an IAR and resolved following temporary interruption of treatment. Patient 2704-47712, who had a medical history of periodic seasonal outbreaks of generalized eczema, developed moderate septal panniculitis (diagnosed by skin biopsy) between Weeks 18 and 20 that persisted for 287 days and was assessed as related to treatment with placebo, but was not characterized as an IAR.

### 5.2.2.3      Infusion-Associated Reactions in LOTS

An IAR was defined as any event that occurred during either the infusion or the observation period following the infusion that was assessed by the Investigator as related to study drug (i.e., possibly, probably, or definitely related). At the discretion of the Investigator, adverse events that occurred after completion of the post-infusion observation period that were assessed as related could also be considered IARs.

While a similar proportion of patients experienced IARs within each treatment group (28.3% of alglucosidase alfa-treated patients and 23.3% of placebo-treated patients), events were reported at a slightly higher frequency for patients in the alglucosidase alfa group, where IARs comprised 16.3% of all reported AEs (236 of 1445 events), compared with the placebo group, where IARs represented 8.6% of AEs (73 of 851 events). This difference between treatment groups was significantly influenced by 1 patient

(2704-18713) in the 2000 L alglucosidase alfa group who experienced 116 IARs, or almost half of the IARs reported for this treatment group. When excluding this patient, the frequency of events was similar for patients on alglucosidase alfa (120 IARs for 1329 AEs; 9.0%) compared with patients on placebo (8.6%).

The profile of IARs differed for the 2 treatment groups. Urticaria, hyperhidrosis, chest discomfort, flushing, blood pressure increased, and vomiting were frequent IARs observed only in the 2000 L alglucosidase alfa group, while other symptoms (e.g., headache, nausea, dizziness) occurred at a similar frequency in both treatment groups.

**Table 5-22:    Summary of Infusion-Associated Reactions Occurring in at Least 5% of Patients by Treatment Group in LOTS**

| MeDRA Preferred Term[1] | 2000 L alglucosidase alfa | | Placebo | |
|---|---|---|---|---|
| | Number of Patients[2] n (%) | Number of Events[3] n (%) | Number of Patients[2] n (%) | Number of Events[3] n (%) |
| | | | | |
| **Any Infusion-associated reaction** | **17 (28.3)** | **236 (100.0)** | **7 (23.3)** | **73 (100.0)** |
| | | | | |
| **SOC: Nervous system disorders** | | | | |
| Headache | 5 (8.3) | 14 (5.9) | 5 (16.7) | 25 (34.2) |
| Dizziness | 4 (6.7) | 10 (4.2) | 2 (6.7) | 4 (5.5) |
| **SOC: General disorders and administration site conditions** | | | | |
| Chest discomfort | 4 (6.7) | 8 (3.4) | 0 | 0 |
| **SOC: Gastrointestinal disorders** | | | | |
| Nausea | 5 (8.3) | 15 (6.4) | 3 (10.0) | 37 (50.7) |
| Vomiting | 3 (5.0) | 3 (1.3) | 0 | 0 |
| **SOC: Skin and subcutaneous tissue disorders** | | | | |
| Urticaria | 5 (8.3) | 13 (5.5) | 0 | 0 |
| Hyperhidrosis | 3 (5.0) | 6 (2.5) | 0 | 0 |
| **SOC: Vascular disorders** | | | | |
| Flushing | 3 (5.0) | 5 (2.1) | 0 | 0 |
| **SOC: Investigations** | | | | |
| Blood pressure increased | 3 (5.0) | 3 (1.3) | 0 | 0 |

[1] Events are presented by SOC and by decreasing frequency within each SOC based on patient percentages for the alglucosidase alfa treatment group; events with the same frequency are listed by decreasing number of events and alphabetically.

[2] Percentages are based on the total number of patients within each treatment group.  A patient experiencing more than one event within a preferred term is counted once for that preferred term.

[3] Percentages are based on the total number of IARs experienced by patients within each treatment group

A majority of IARs in both treatment groups were assessed as non-serious and mild or moderate in severity.  In the 2000 L alglucosidase alfa group, only 6 (2.5%) of 236 IARs in 3 (5.0%) patients were serious, and only 1 IAR (angioedema) was considered to be severe.  As discussed further in **Section 5.2.2.3.1**, 2 patients experienced serious IARs that were classified as anaphylactic reactions and a third patient experienced a significant IAR.

Further analyses showed no clear or consistent trends in the frequency of IARs over time or by infusion rate. There was no apparent relationship between anti-rhGAA IgG antibody status and the occurrence of IARs (**Section 5.2.2.5.2**).

### 5.2.2.3.1    Significant Allergic Reactions in LOTS

An immune response may be elicited upon repeated administration of any recombinant protein. Generally, IgG-specific antibodies develop upon exposure to antigen and usually function to clear antigen from blood via the formation of IgG-antigen complexes. Other classes of antibodies, such as IgE-specific antibody response, can also develop. At times, the response to these antibody-antigen complexes results in immune-mediated clinical signs and symptoms, often referred to as allergic and/or anaphylactic reactions. IgE antibodies are present on the surface of mast cells and basophils (as well as in circulation), where they may be cross-linked by exposure to antigen, triggering a process known as "degranulation" and consequently releasing pro-inflammatory chemical mediators (e.g., histamine, tryptase, proteoglycans, and cytokines), which can affect multiple organ systems. Patients who experience events suggestive of allergic and/or anaphylactic reactions may therefore present with a constellation of signs and symptoms, primarily cardiovascular, respiratory and/or cutaneous in nature. Such allergic or anaphylactic reactions have been previously observed in a small percentage of patients treated with alglucosidase alfa (160 L) and with other enzyme replacement therapies.

In order to assess the nature and severity of hypersensitivity symptoms in patients treated with alglucosidase alfa, and to then identify potential allergic/anaphylactic reactions to alglucosidase alfa, IARs were screened using a 2-step process. Initially the Standardized MedDRA Query (SMQ) for anaphylactic reactions was used to identify any IAR terms that potentially could be associated with symptoms of anaphylaxis (see Appendix 2, **Section 11.2**). In addition, the definition of anaphylactic reactions as "severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance" which was outlined by the Second National Institute of Allergy and Infectious Disease/Food Allergy Anaphylaxis Network symposium (Sampson, 2006, *J Allergy Clin Immunol*) was used by Genzyme Pharmacovigilance as a reference to identify significant anaphylactic-like reactions. That is, all individual cases not included in the SMQ were medically reviewed by Genzyme Pharmacovigilance for identification of potential allergic/anaphylactic reactions with the Sampson definition in mind. Thus, reported

allergic reactions consist of all reactions that were (1) identified by the SMQ and confirmed upon medical review; or (2) identified upon medical review of all IARs.

Two (3.3%) of 60 patients in the 2000 L alglucosidase alfa group (Patients 2704-16709 and 2704-18713) experienced IARs that were suggestive of an anaphylactic reaction. These anaphylactic reactions were identified by the MedDRA SMQ and were IgE-mediated, as both patients tested positive for anti-rhGAA IgE antibodies. Although 1 of the 2 IgE-positive patients was withdrawn from the study due to the anaphylactic reaction, both IgE-positive patients were successfully rechallenged with alglucosidase alfa via a desensitization protocol (either in LOTS or on commercial therapy). In addition, 1 patient in the 2000 L alglucosidase alfa group (Patient 2704-90701) experienced an event of angioedema that was not identified by the MedDRA SMQ but was considered a significant IAR based upon medical review. This patient was withdrawn from the study by the investigator who felt that this IAR presented an unfavorable benefit/risk ratio for continued treatment; the patient is not known to have received any subsequent commercial therapy with alglucosidase alfa based on information available to Genzyme at this time. All reactions, which occurred during or at the completion of infusion, were managed with medical treatment and interruption or discontinuation of the infusion as appropriate and all symptoms resolved. None of the events were judged by the Investigator to be life threatening as they occurred. No patients in the placebo group experienced events suggestive of an allergic and/or anaphylactic reaction or significant IAR.

**Patient 2704-16709** experienced serious IARs of chest discomfort and throat tightness, and non-serious IARs of wheezing, pruritus, sinus tachycardia, nausea, blood pressure increased, oxygen saturation decreased, headache, rash papular, and flushing at Week 2 that were suggestive of an anaphylactic reaction. The patient responded well to intervention with medications and non-drug therapy, and symptoms resolved the same day, with the exception of headache, which lasted 4 days. This patient was seronegative at Baseline, and discontinued prior to the first post-treatment assessment for anti-rhGAA IgG antibodies. Additional immunologic testing revealed that the patient was positive for anti-rhGAA IgE antibodies and complement activation and had an elevated serum tryptase (23.7 µg/L; normal range $\leq$ 14.7 µg/L) at the time of these events. The patient was discontinued from the study as a result of these events, but was later rechallenged in

the commercial setting using a desensitization procedure at lower dose of alglucosidase alfa administered at a slower rate, and subsequently transitioned to MTAP.

**Patient 2704-18713** experienced a serious IAR of non-cardiac chest pain and non-serious IARs of feeling hot, chest discomfort, pruritus, lip swelling, local swelling, urticaria, rash macular, and flushing at Week 28 that were suggestive of an anaphylactic reaction. The patient recovered following interruption of the infusion and medical treatment, and resumed alglucosidase alfa infusions. Recurrent IARs were reported for this patient during subsequent infusions, including additional events that the investigator reported as 'hypersensitivity reaction'. These recurrent IARs were generally milder in nature and all were non-serious. At Week 50, during the administration of 10 mg/kg qw as part of an ongoing desensitization procedure, the patient experienced non-serious IARs of lip swelling, swollen tongue, chest discomfort, throat tightness, and urticaria that were identified by the SMQ as suggestive of an anaphylactic reaction. Recurrent IARs occurring at other infusions were not identified by the SMQ as suggestive of an allergic and/or anaphylactic reaction. Immunological testing revealed that the patient was positive for anti-rhGAA IgE on 7 of 12 occasions (beginning Week 30), positive for complement on 1 of 9 occasions (at approximately 3 months after the first anti-rhGAA IgE-positive result), and had normal serum tryptase on all 9 occasions tested. Given that the patient was anti-rhGAA IgE-positive, the recurrent IARs may represent additional mild allergic reactions, although they were not formally identified upon clinical review due to the mild, non-serious nature of the symptoms.

**Patient 2704-90701** experienced a serious IAR of angioedema 15 minutes after completing the infusion at Week 4 that was not identified by the SMQ. Upon subsequent medical review, this event was considered a significant IAR. This patient first tested positive for anti-rhGAA IgG antibodies at Week 4, concurrent with this event. Additional immunologic testing revealed that the patient was negative for anti-rhGAA IgE antibodies and complement activation, and had a normal serum tryptase at the time of these events. After consideration of the potential benefit versus safety risks of continued therapy in a blinded study, the patient was discontinued from treatment.

### 5.2.2.4 Skin Lesions in LOTS

Two expedited safety reports detailing potential drug-induced skin lesions were submitted to BLA 125141 for the 160 L product as part of ongoing post marketing surveillance. Given the serious nature of these events and their uncertain clinical significance, FDA requested that Genzyme provide reports on other such serious and unexpected skin reactions, regardless of relationship to alglucosidase alfa.

The initial expedited safety reports were POMP-10874 and POMP 11021. Expedited report POMP-10874 detailed a case of arthus reaction in an infantile-onset patient who was initially treated with alglucosidase alfa in AGLU01602/AGLU02403 and later transitioned to commercial therapy at the 2000 L scale. The treating physician assessed the observed skin lesions as related to alglucosidase alfa. After resolution of the skin lesion, the patient was able to continue treatment without recurrence of this reaction. Expedited report POMP-10867 detailed an event of septal panniculitis in a patient receiving placebo treatment in the LOTS trial was also submitted to BLA 125141. This event was also assessed as related to administration of study drug (treatment was blinded at the time), and it was later determined that the patient was on placebo.

In the LOTS trial, MedDRA preferred terms occurring within the SOC of Skin and subcutaneous tissue disorders that were not characterized as IARs were reviewed to identify other events suggestive of serious drug-induced skin reactions. No other significant skin reactions of the nature of those described in the expedited safety reports were identified for patients in either treatment group.

### 5.2.2.5 Immunogenicity in LOTS

Immune responses may be elicited upon repeated administration of any recombinant protein, and have the potential to trigger clinical symptoms that can impact the safety, tolerability, and/or therapeutic benefit of continued treatment. To facilitate the characterization and management of any such immune-mediated reactions to alglucosidase alfa, immunologic assessments have been included as part of the safety monitoring plan for all Good Clinical Practice (GCP) clinical trials with alglucosidase alfa, including LOTS. Immunogenicity testing methodologies are briefly described in **Section 5.2.2.5.1**. Results for anti-rhGAA IgG antibodies, inhibitory antibodies, and

additional immunologic testing are presented in **Section 5.2.2.5.2**, **Section 5.2.2.5.3**, and **Section 5.2.2.5.4**, respectively.

### 5.2.2.5.1    Immunogenicity Testing Methodologies and Terminology

All patients were monitored for anti-rhGAA IgG antibodies every 4 weeks using blood samples obtained prior to the infusion of study treatment (alglucosidase alfa or placebo). Testing was performed using a tiered approach.  Serum samples were first screened for IgG antibody binding to rhGAA using an enzyme-linked immunosorbent assay (ELISA), and samples that were reactive in the screening ELISA (i.e., those assessed as being above an absorbance cut point established from a normal serum distribution study) were subsequently confirmed using a radio-immunoprecipitation (RIP) assay.  'Seropositive' refers to samples that were reactive in the screening ELISA and subsequently confirmed by a positive RIP result.  'Seronegative' refers to samples that were negative by ELISA, or reactive in the screening ELISA but negative by the confirmatory RIP assay. Seropositive and seronegative also refer to patient antibody status.  Seroconversion refers to the transition from seronegative to seropositive status.  A patient who seroconverted and subsequently had $\geq 2$ consecutive samples that were negative by RIP assay was considered to be immunologically non-responsive and classified as 'tolerized'.  Time to seroconversion was defined as the interval between the date of the patient's first infusion of alglucosidase alfa and the date of the patient's first seropositive sample, and represents an estimate of the true value, as testing was not performed on a daily basis.

Anti-rhGAA IgG antibody titers for seropositive patients were determined by analysis of serial dilutions of serum samples using ELISA, with antibody titer reported as the reciprocal of the maximum dilution that yielded a positive result.  Titering was initiated at a 1:100 dilution.  As seropositive patient titers decreased over time, samples that had an absorbance value below the ELISA cut point but remained positive in the RIP assay were given a titer of "<100".  Each patient's titer values were also evaluated using 4 summary measures: maximum titer value during treatment ('peak titer'), average titer over the course of treatment (expressed as 'geometric mean' or 'area under the curve [AUC]/time'), and titer at the end of treatment ('last titer').  Time to peak titer was defined as the interval between the date of the patient's first infusion of alglucosidase alfa and the date of the patient's peak titer during the study, and represents an estimate of the true value, as testing was not performed on a daily basis.  It should be noted that

individual titer values were $\log_{10}$-transformed for the derivation of summary statistics, and subsequently back-transformed to permit presentation of summary statistics on the original dilution scale; therefore, summary statistics for titer may not always reflect actual dilution factors used in the ELISA.

For those patients who were seropositive, additional testing was performed to determine whether patients developed inhibitory antibodies. Two in vitro assays were developed and validated by Genzyme to determine whether patient serum was able to inhibit alglucosidase alfa enzyme activity or interfere with cellular enzyme uptake by flow cytometry.

For the inhibition of enzyme activity assay, serially diluted patient sera were pre-incubated with a constant amount of rhGAA enzyme, and the amount of inhibition was quantified by measuring enzyme activity. The initial minimal sera dilution tested was 1:4. The assay limit of detection (defined as the lowest percent inhibition that could be discriminated from normal human serum background) was 20% inhibition. Patient samples with percentage inhibition greater than 20% at any sera dilution were considered positive by inhibitory antibody assay. The last dilution that was positive (> 20% inhibition) was reported as the titer.

In addition to the enzyme activity assay, as part of the US post-marketing commitment, Genzyme also developed an in vitro assay to detect the uptake inhibition. The *in vitro* inhibition of uptake assay detects the presence of antibodies in patient sera that can interfere with the uptake of labeled GAA in human fibroblast cells in culture. Patient sera were two-fold serially diluted (initial minimal dilution of 1:10) and pre-incubated with a fixed quantity of fluorescently-labeled rhGAA. The sample was added to fibroblast cells, incubated, and intracellular labeled enzyme was assessed by flow cytometry. An assay cut-point of 20% uptake inhibition was established based on a study of normal donor sera; patient samples that had enzyme uptake inhibition greater than 20% at two or more sera dilutions were considered to be positive at that time point. Titer is reported as the reciprocal of the highest dilution where the inhibition signal is greater than the cut point.

Due to the inherent complexities of a bioassay such as the uptake inhibition assay, and the difficulties in interpreting clinical significance for inconsistent patterns of uptake

inhibition observed in some patients (i.e., low endpoint titers and/or intermittent positive results), it was necessary to delineate clear criteria for classifying a positive patient. Consequently, patients who demonstrated antibody titers for uptake inhibition of $\geq 40$ at 2 *consecutive* assessments were classified as 'positive', while patients who demonstrated uptake inhibition at least once, but did not have antibody titers for uptake inhibition $\geq 40$ at any 2 *consecutive* time points, were classified as 'borderline-positive'. It is important to note that this classification system is not based on any clinical criteria for evaluation of inhibitory antibody titers, and therefore positive or borderline positive classification does not by itself denote clinical significance.

### 5.2.2.5.2 Anti-rhGAA IgG Antibodies

Of the 60 patients in the 2000 L alglucosidase alfa group, all 59 patients with at least 1 post-treatment assessment developed anti-rhGAA IgG antibodies, with a median time to seroconversion of 4.0 weeks (range 3.6 to 12.0 weeks). The remaining patient (2704-16709) was negative at Baseline and discontinued from the study after Week 2 (and prior to the first post-treatment assessment) due to IARs suggestive of an anaphylactic reaction (**Section 5.2.2.3.1**).

The development of anti-rhGAA IgG antibody titers was evaluated for all seropositive patients in the 2000 L alglucosidase alfa group. As depicted graphically in **Figure 5-9**, geometric mean anti-rhGAA IgG titer increased from Baseline through Week 44 (2,925), and declined thereafter through the last assessment at Week 78 (1,858), while median titer remained steady at 1,600 throughout most of the study, i.e., from Week 8 to Week 78. Following seroconversion, the median time to peak titer was 12.0 weeks among all 59 seropositive patients. The median peak titer was 6,400 (range 200 to 819,200), and 39 (66.1%) of the patients who seroconverted had a peak titer $\leq 6,400$. The median last titer was 1,600 (range 100 to 819,200), and 35 (59.3%) seropositive patients had a last titer $\leq 1,600$. There was a similar decrease between mean peak titer (6,475) and mean last titer (1,886), suggesting a general trend toward decreasing IgG titers over time. Consistent with this finding, approximately 61% of patients exhibited trends toward decreasing titers from peak to last titer, as defined by a decrease in titer of at least 2 dilutions.

**Figure 5-9: Geometric Mean and Median Anti-rhGAA IgG Antibody Titers Over Time in alglucosidase alfa-Treated Patients**
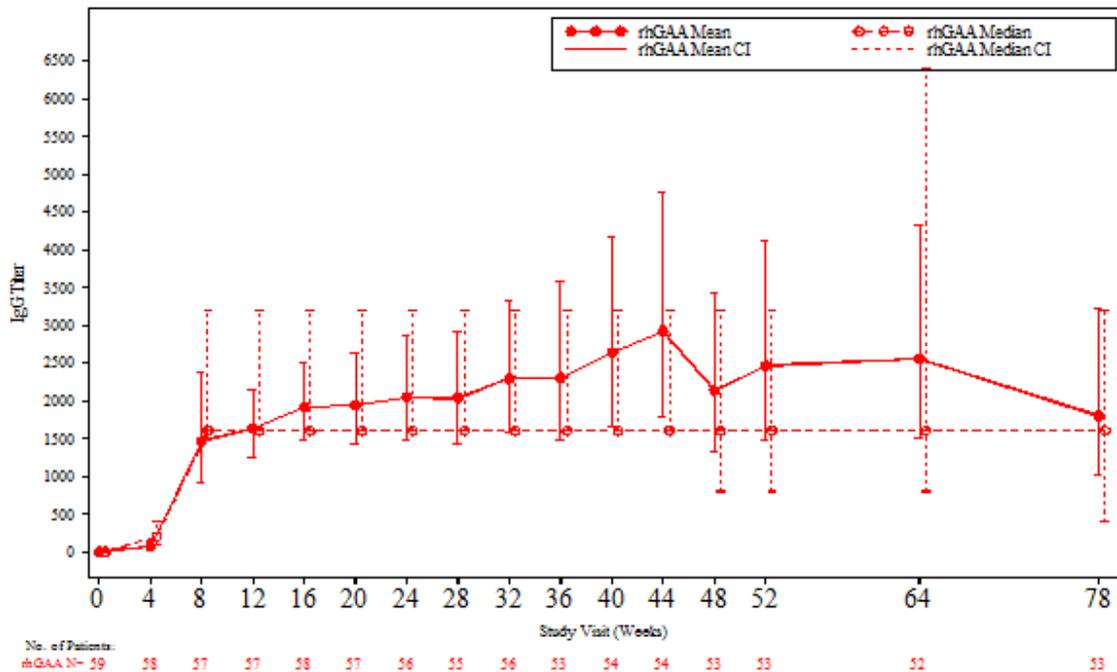


Analyses were undertaken to explore the potential relationship between the immune response to 2000 L alglucosidase alfa and safety and efficacy outcomes.

The timing of IARs and seroconversion was explored for the 2000 L alglucosidase alfa group. A total of 16 seropositive patients experienced IARs, all of whom seroconverted by Week 8. The timing of IARs in a majority of these patients did not coincide with the timing of seroconversion. Seven patients experienced 1 or more IARs prior to seroconversion, including 6 patients who experienced an IAR during the first infusion. One patient experienced 1 IAR (angioedema) coincident with seroconversion at Week 4. The remaining 8 patients experienced the first IAR between 8 and 52 weeks after seroconversion. Thus, there was no consistent relationship between time to seroconversion and onset of IARs.

Patients who experienced IARs had a median titer of 1,600 (range 0 to 409,600) at the time of IAR, and there was no association between higher IgG antibody titer and occurrence of IARs. Among the 30 patients in the placebo treatment group, all of whom tested seronegative, 7 patients experienced IARs.

Seropositive patients who experienced IARs were analyzed by IgG titers grouped by quartiles for geometric mean titer, peak titer, last titer, and area under the titer curve divided by time (AUC/time). Similar analyses were performed for seropositive patients experiencing an AE or SAE. There was no consistent relationship between the occurrence of AEs, SAEs, and IARs and anti-rhGAA IgG titer when patients were stratified by any titer quartile. Similarly, there was a lack of a relationship between anti-rhGAA IgG titer and the treatment effect of 2000 L alglucosidase alfa on the co-primary efficacy endpoints (6MWT distance walked and FVC % predicted). Results for geometric mean titer quartile and peak titer quartile, are presented in **Table 5-23** and **Table 5-24**, respectively.

**Table 5-23: Summary of Safety and Efficacy in Seropositive alglucosidase alfa-Treated Patients by Geometric Mean IgG Titer Quartiles (N=59)**

| Parameter | Quartile 1 (124-581) | Quartile 2 (729-1449) | Quartile 3 (1459-3737) | Quartile 4 (4099-135118) |
|---|---|---|---|---|
| Number of Patients n (%) | 14 (23.7) | 15 (25.4) | 15 (25.4) | 15 (25.4) |
| Number of Patients with any AE n (%) | 14 (100.0) | 15 (100.0) | 15 (100.0) | 15 (100.0) |
| Number of Patients with any SAE n (%) | 4 (28.6) | 2 (13.3) | 4 (26.7) | 2 (13.3) |
| Number of Patients with any IAR n (%) | 2 (14.3) | 7 (46.7) | 3 (20.0) | 4 (26.7) |
| 6MWT change in meters walked from Baseline to last observation, mean ± SD (median) | -6.9 ± 48.15 (-8.0) | 25.2 ± 41.61 (17.0) | 24.2 ± 46.18 (16.0) | 59.7 ± 94.17 (23.0) |
| FVC change in % predicted from Baseline to last observation, mean ± SD (median) | -0.6 ± 4.96 (-1.0) | 2.4 ± 5.72 (2.0) | 1.5 ± 5.18 (1.0) | 1.7 ± 6.33 (0.0) |

**Table 5-24: Summary of Safety and Efficacy in Seropositive alglucosidase alfa-Treated Patients by Peak IgG Titer Quartiles**

| Parameter | Quartile 1 (200-1600) | Quartile 2 (3200-3200) | Quartile 3 (6400-12800) | Quartile 4 (25600-819200) |
|---|---|---|---|---|
| Number of Patients n (%) | 17 (28.8) | 12 (20.3) | 16 (27.1) | 14 (23.7) |
| Number of Patients with any AE n (%) | 17 (100.0) | 12 (100.0) | 16 (100.0) | 14 (100.0) |
| Number of Patients with any SAE n (%) | 5 (29.4) | 2 (16.7) | 4 (25.0) | 1 (7.1) |
| Number of Patients with any IAR n (%) | 6 (35.3) | 2 (16.7) | 5 (31.3) | 3 (21.4) |
| 6MWT change in meters walked from Baseline to last observation, mean ± SD (median) | 6.1 ± 53.67 (5.0) | 16.0 ± 24.98 (9.0) | 34.8±76.60 (16.5) | 49.1 ± 79.91 (19.5) |
| FVC change in % predicted from Baseline to last observation, mean ± SD (median) | 0.8 ± 5.68 (0.0) | 1.8 ± 5.29 (3.0) | 1.5 ± 5.73 (0.5) | 1.1 ± 5.95 (0.0) |

### 5.2.2.5.3    Inhibitory Antibodies

Patients who tested positive for anti-rhGAA IgG antibodies were further evaluated to determine whether the anti-rhGAA IgG antibodies in the patients' sera inhibited alglucosidase alfa enzyme activity or interfered with cellular enzyme uptake in *in vitro* assays developed and validated by Genzyme Clinical Specialty Laboratory.  Patients were classified as 'positive', 'borderline positive', or negative, as described in **Section 5.2.2.5.1**.  This classification system was utilized to distinguish patients who consistently demonstrated inhibition versus those with intermittent inhibition and/or endpoint titers at the limit of assay detection; the system was not based on any specific clinical criteria.

*In vitro* inhibitory antibody assays were performed for all 59 seropositive patients at the point of seroconversion and approximately quarterly thereafter.  Based on the samples tested, none of the 59 (0%) evaluable patients tested positive for inhibition of enzyme activity.  However, 10 (16.9%) patients were classified as positive for inhibition of cellular enzyme uptake in an *in vitro* fibroblast assay, and an additional 8 (13.6%) were

classified as borderline-positive using the criteria defined in **Section 5.2.2.5.1**. The time to first detection of inhibitory antibodies was comparable for patients who were classified as positive and borderline-positive for uptake inhibition, with a mean of 36 weeks and 37 weeks relative to first infusion (or 30 weeks and 32 weeks relative to seroconversion) for positive and borderline-positive patients, respectively.

Patients classified as positive for uptake inhibition generally had higher median peak IgG titers (102,400) and higher median last IgG titers (72,408) than patients who were classified as borderline positive (median peak IgG titer 12,800; median last IgG titer 3,200) or patients who remained negative for uptake inhibition (median peak IgG titer 3,200; median last IgG titer 400).

There was no association between the frequency of safety events (AEs, SAEs, IARs) and inhibitory antibody status based on inhibition of cellular enzyme uptake. Treatment-emergent SAEs were reported for 10.0% (1/10) of inhibitory antibody-positive patients, 37.5% (3/8) of inhibitory antibody-borderline positive patients, and 19.5% (8/41) of inhibitory antibody-negative patients. IARs were reported in 20.0% (2/10) of inhibitory antibody-positive patients, 37.5% (3/8) of inhibitory antibody-borderline positive patients, and 26.8% (11/41) of inhibitory antibody-negative patients. All patients in the study experienced AEs.

As shown in **Table 5-25**, there was no consistent relationship between inhibitory antibody status and treatment response for the co-primary efficacy endpoints. Thus development of inhibitory antibodies does not appear to impact the efficacy of alglucosidase alfa, despite the observation of lower systemic exposure in patients who tested positive for inhibitory antibodies (n=5) compared with patients who tested negative for uptake inhibition (n=29) within the limited pharmacokinetic dataset (**Section 5.2.3**).

**Table 5-25:  Anti-rhGAA IgG Titers and Primary Efficacy Results By Patient Classification for Uptake Inhibition Status**

| | Negative Uptake Inhibition Titer (n=41) | Any Positive Uptake Inhibition Titer (n=18) | Positive for Uptake Inhibition (n=10) | Borderline Positive for Uptake Inhibition (n=8) |
|---|---|---|---|---|
| Mean IgG Peak titer | 3,042 | 36,204 | 83,175 | 12,800 |
| Median IgG Peak titer (range) | 3,200 (200, 25,600) | 25,600 (3,200, 819,200) | 102,400 (12,800, 819,200) | 12,800 (3,200, 25,600) |
| 6MWT change in meters walked from Baseline to last observation, mean ± SD (median) | 21.4±55.56 (15.0) | 36.8 ± 81.94 (13.0) | 57.5±95.89 (19.5) | 11.0 ± 55.80 (-1.0) |
| FVC change in % predicted from Baseline to last observation, mean ± SD (median) | 1.8 ± 5.48 (1.0) | -0.1 ± 5.64 (-0.5) | 0.2 ± 5.53 (-0.5) | -0.4 ± 6.14 (-0.5) |

### 5.2.2.5.4    Additional Immunologic Testing

When clinically indicated, patients experiencing a moderate or severe IAR may have had additional testing to better understand the potential immunologic mechanism involved in the reaction, including testing for serum anti-rhGAA IgE antibodies, complement activation (which occurs secondary to the formation of IgG-antigen complexes and generates biologically active products that stimulate pro-inflammatory processes designed to destroy foreign antigens), serum tryptase activity (one of the chemical mediators released from mast cells upon binding of antigen to IgE antibodies on the cell surface), and/or skin testing.

Of the 10 patients tested for anti-rhGAA IgE antibodies in the alglucosidase alfa group, 2 patients were found to be positive, both of whom experienced anaphylactic reactions (**Section 5.2.2.3.1**).

Of the 9 patients in the 2000 L alglucosidase alfa group undergoing further immunologic testing in addition to IgE testing, 6 patients tested positive for complement activation and 1 patient (2704-16709) had a significantly elevated serum tryptase.  Circulating immune complex (CIC) testing was performed retrospectively for 1 patient (2704-16705) in the treatment group due to events of haematuria and proteinuria, and samples from Day 0,

Week 52, and Week 78 were negative by both CIC-Raji Cell Replacement ELISA and CIC-C1q binding ELISA. For this patient, mild, non-serious, treatment-related haematuria was first reported in the LOTS trial and was ongoing when the patient completed the study; events of renal cyst and nephrolithiasis due to chronic haematuria were subsequently reported as SAEs in the LOTS extension study, both of which were not related to treatment.

In the placebo group, 1 patient was tested and found to be negative for anti-rhGAA IgE antibodies and complement activation, and had normal serum tryptase. Circulating immune complex testing was performed from Day 0 to Week 52 for 1 patient (2704-47712) after diagnosis of septal panniculitis by skin biopsy. Results of the Raji Cell Replacement assay for detection of aged immune complexes were all negative. Results of the CIC-C1q assay for detection of early-formed immune complexes were intermittently positive (i.e., Day 0 to Week 28 and Week 36); it should be noted that the assay is not specific for rhGAA.

### 5.2.2.6 Safety Conclusions

A majority (90%) of patients completed treatment in LOTS. Five patients discontinued treatment with 2000 L alglucosidase alfa: 3 patients discontinued treatment due to AEs (including 2 patients who discontinued due to serious IARs, and 1 patient who died due to events that were assessed as not related to treatment), 1 patient discontinued to pursue commercial therapy after the drug had received marketing approval, and 1 patient discontinued for personal reasons. Four patients discontinued treatment with placebo: 1 patient discontinued due to an AE that was assessed as remote / unlikely related to treatment, and 3 patients discontinued to pursue commercial therapy.

The proportion of patients experiencing AEs, SAEs, treatment-related AEs, and IARs in the 2000 L alglucosidase alfa group was comparable to that in the placebo group, and the most frequently occurring AEs in each group (fall, nasopharyngitis, and headache) were consistent with the manifestations of underlying Pompe disease. A majority of all reported adverse events were non-serious, mild or moderate in severity, and not related to study treatment. Of those events that were assessed as related to treatment, a majority were characterized as IARs, and were generally non-serious, mild to moderate in severity, and resolved spontaneously. There were no treatment-related deaths during

LOTS.  The most significant events reported were the occurrence of IgE-mediated anaphylactic reactions in 2 (3.3%) of the patients treated with 2000 L alglucosidase alfa. Although 1 of the 2 IgE-positive patients was withdrawn from the study due to the anaphylactic reaction, both IgE-positive patients were successfully rechallenged with alglucosidase alfa, either during LOTS or in the commercial setting after discontinuation from the study, using a slower infusion rate at lower initial doses, and both patients continue to receive treatment under close clinical supervision.  Of the small proportion of SAEs reported during LOTS (1.2% of all AEs), most events (18 of 27 events; 66.7%) were consistent with underlying Pompe disease and considered not related to treatment.

All 59 patients who had post-Baseline assessments during treatment with 2000 L alglucosidase alfa developed anti-rhGAA IgG antibodies, with seroconversion occurring within the first 3 months of exposure for all patients (median time to seroconversion was 4 weeks).   None of the 59 patients tested positive for antibodies that inhibited enzyme activity.  However, 18 patients developed antibodies that inhibited enzyme uptake, and were classified as positive (10 patients) or borderline positive (8 patients) for uptake inhibition based on the criteria provided in **Section 5.2.2.5.1**.  These results in LOTS suggest that a majority of patients receiving 2000 L alglucosidase alfa treatment are likely to develop anti-rhGAA IgG antibodies and, in some seropositive patients, these antibodies may inhibit the uptake of alglucosidase alfa in an *in vitro* fibroblast cell assay. Of note, patients who were positive for uptake inhibition tended to have higher mean peak anti-rhGAA IgG titers than patients who tested negative for uptake inhibition. Importantly, the safety and efficacy of 2000 L alglucosidase alfa was not affected by the development of anti-rhGAA antibody titers and/or inhibitory antibodies.  The timing of seroconversion did not coincide with the onset of IARs, and the occurrence of any safety events (AEs, SAEs, IARs) was not significantly influenced by anti-rhGAA IgG antibodies based on an analysis in which patients were stratified by titer quartile (based on peak, mean, AUC/time, or last titer) or by inhibitory antibody status.  There was a similar lack of a relationship between anti-rhGAA IgG titer or inhibitory antibody status and the treatment effect of 2000 L alglucosidase alfa on the co-primary efficacy endpoints.

No unexpected or clinically meaningful trends were observed for laboratory tests (clinical chemistry, hematology, and urinalysis), vital signs, physical examinations, 12-lead ECGs, and hearing tests that would present a potential safety concern for alglucosidase alfa.

### 5.2.3        Summary of Pharmacokinetics in AGLU02704 (LOTS)

Pharmacokinetic analyses were performed at study sites that could accommodate pharmacokinetic sampling, which occurred at Week 0, Week 12, and Week 52 at times just prior to, during, and following study drug infusion.  A total of 1153 quantifiable PK observations were available from 34 patients (15 female, 19 male).  The typical patient was 46.0 years old (range: 20.7 to 70.0 years) at time of first infusion, weighed 77.4 kg (range: 42.5 to 118.8 kg), and received a dose of 1547 mg (range: 850 to 2376 mg).

The pharmacokinetics of 2000 alglucosidase alfa were characterized by compartmental methods under a nonlinear mixed effects 2-compartment model.  The model examined 3 sources of variability (between-subject, inter-occasion, and residual) and 6 covariates (age, weight, sex, antibody titer, presence/absence of anti-rhGAA antibodies, and inhibitory antibody status).  Statistical analyses were performed using repeated measures analysis of variance (ANOVA).

A summary of alglucosidase alfa pharmacokinetic parameters by study visit and pooled across study visits is provided in **Table 5-26**.  Repeated measures ANOVA showed that AUC $(0-\infty)$ was not affected by weight or $Log_{10}$ IgG antibody titer nor was it different across visits.  Systemic clearance (CL) was affected by weight ($F = 9.12$, $p = 0.0046$) but not $Log_{10}$ IgG antibody titer.  Maximal concentration (Cmax) was positively affected by weight ($F = 12.76$, $p = 0.0011$).  Central volume (V1) also was positively affected by patient weight ($F=11.88$, $p=0.0014$).  In contrast, peripheral volume (V2) and volume of distribution at steady state (Vss) were not; Vss did not appear to be affected by weight because the contribution of V1 to Vss was small relative to V2.  $Log_{10}$ IgG antibody titer did not affect any volume term, and all volume terms were constant across visits. Weight, $Log_{10}$ IgG antibody titer, and visit did not affect either the effective ($\alpha$)- or terminal ($\beta$)-half-life.

**Table 5-26: Alglucosidase Alfa Pharmacokinetics at Week 0, Week 12, and Week 52**

| Parameter[1] | Week 0 | Week 12 | Week 52 | Pooled |
|---|---|---|---|---|
| Cmax (μg/mL) | 385 ± 106 | 349 ± 79 | 370 ± 88 | 368 ± 92 |
| AUC(0-∞) (μg *h/mL) | 2672 ± 1140 | 2387 ± 555 | 2699 ± 1000 | 2586 ± 933 |
| CL (mL/h) | 633 ± 175 | 700 ± 244 | 645 ± 198 | 659 ± 207 |
| Vss (L) | 69 ± 92 | 70 ± 91 | 70 ± 92 | 70 ± 90 |
| V1 (mL) | 3361 ± 633 | 3712 ± 1154 | 3490 ± 773 | 3521 ± 884 |
| V2 (L) | 66 ± 91 | 67 ± 91 | 66 ± 91 | 66 ± 90 |
| Effective (α) Half-life(h) | 2.4 ± 0.4 | 2.5 ± 0.3 | 2.5 ± 0.4 | 2.4 ± 0.3 |
| Terminal (β) Half-life (h) | 220 ± 300 | 218 ± 304 | 215 ± 284 | 218 ± 293 |
| Q (mL/h) | 333 ± 50 | 335 ± 48 | 333 ± 50 | 334 ± 49 |
| Tmax (h) | 3.6 ± 0.3 | 3.6 ± 0.3 | 3.6 ± 0.3 | 3.6 ± 0.3 |

[1] All parameters are presented as mean ± SD

Secondary PK analyses investigated the relationship between immune response and specific alglucosidase alfa PK parameters.

Anti-rhGAA IgG antibody titers had no effect on either alglucosidase alfa clearance or AUC(0-∞), when examined graphically using box plots by IgG antibody titer quartile.

Inhibitory antibody status had a significant effect on several alglucosidase alfa PK parameters, as analyzed using a repeated measures linear mixed model that included visit and inhibitory antibody status as categorical factors. For the purpose of this analysis, seronegative patients (for whom no testing was performed) were coded as inhibitory antibody-negative, and any patient who demonstrated uptake inhibition at least once (regardless of titer) was coded as inhibitory antibody-positive. After completion of the analysis, it was discovered that 1 patient in the placebo group had alglucosidase alfa concentrations at Week 12 that suggested the patient had likely received alglucosidase alfa. A sensitivity analysis indicated that removing this patient from the analysis had no impact on parameter estimates.

Scatter plots for PK parameters as a function of inhibitory antibody status are provided in **Figure 5-10**. Interpretation of results must be considered in light of the small sample size of inhibitory antibody-positive patients with available PK samples (N=5) compared inhibitory antibody-negative patients with PK samples (N=29). Patients who tested positive for uptake inhibition had a significantly lower AUC, higher CL, lower Cmax, and shorter β-half-life compared with patients who tested negative for uptake inhibition.

The least squares (LS) mean AUC was 1951 µg*hr/mL in patients positive for uptake inhibition compared with 2547 µg*hr/mL in inhibitory antibody-negative patients (F=8.73, p=0.0042) for an LS mean AUC ratio of 76.6% (90% CI: 65.9 to 89.0%).  The LS mean CL was 813 mL/hr in patients positive for uptake inhibition compared with 608 mL/hr in inhibitory antibody-negative patients (F=11.04, p=0.0014).  The LS mean Cmax was 300 µg/mL in patients positive for uptake inhibition compared with 363 µg/mL in inhibitory antibody-negative patients (F=4.55, p=0.0361).  The terminal half-life (ß-half-life) was shorter in patients positive for uptake inhibition compared with inhibitory antibody-negative patients (F=19.60, p<0.0001).  In contrast, V1 (F=2.93, p=0.0913), Vss (F=1.88, p=0.1751), and $\alpha$-half-life (F=2.90, p=0.0924) were not significantly different between the 2 patient subgroups; intercompartmental clearance (Q) and V2 could not be estimated.

**Figure 5-10: Plots of Pharmacokinetic Parameters as a Function of Inhibitory Antibody Status at Week 52**
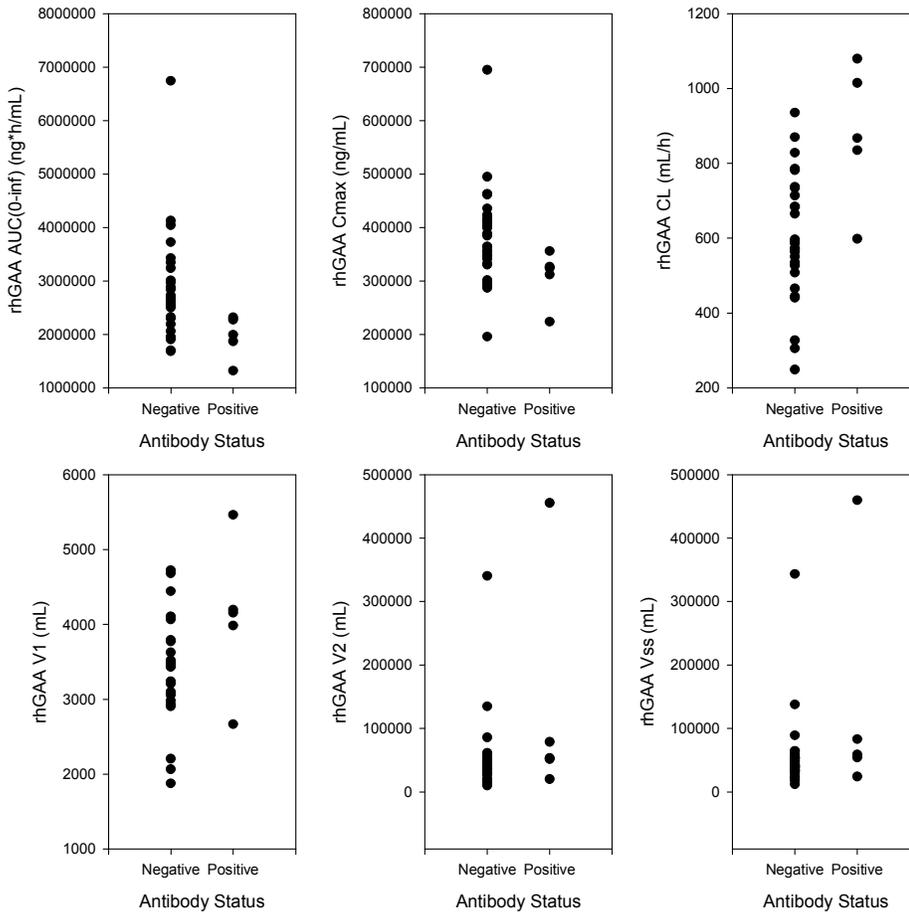


## 5.3 Safety in Other Good Clinical Practice Studies and Post-Marketing Experience

Safety data from 3 additional completed GCP studies (AGLU02603, AGLU02804, and AGLU03105), 2 ongoing GCP studies (AGLU03206 and AGLU03907), and worldwide post-marketing experience were submitted to BLA 125291 in support of approval of 2000 L alglucosidase alfa. As previously summarized in **Section 5.1**, alglucosidase alfa produced at the 2000 L scale was exclusively administered in all of these studies (with the exception of 1 patient who received 6 infusions of 160 L alglucosidase alfa in AGLU02603 prior to beginning treatment with 2000 L alglucosidase alfa). Many patients treated under MTAP (AGLU03907) had previously received 160 L product in

the commercial setting prior to enrolling in this treatment protocol; however, given the large sample size these safety data were included in the BLA.

A summary of deaths, SAEs, IARs, and immunogenicity testing results are provided for the 3 completed studies and 2 ongoing studies in **Section 5.3.1** and **Section 5.3.2**, respectively. For the ongoing studies, safety data collected through the data cutoff of 15 April 2008 are summarized in this briefing package. Additional safety assessments performed during these studies included laboratory tests (clinical chemistry, hematology, and urinalysis), vital signs, physical examinations, 12-lead ECGs, and hearing tests, as well as more detailed analyses of AEs (e.g., skin lesions). These safety data were submitted to BLA 125291. However, as there were no unexpected or clinically meaningful findings that would present a potential safety concern for 2000 L alglucosidase alfa, these safety results have not been included in this briefing package in the interest of brevity.

The post-marketing safety experience for alglucosidase alfa described in **Section 5.3.3** of this briefing package includes selected safety data captured in the Genzyme Global Pharmacovigilance database (i.e., spontaneously reported deaths and other SAEs, including allergic/anaphylactic reactions and skin lesions) or collected by Genzyme Clinical Specialty Laboratory (i.e., immunogenicity data), beginning on the International Birthdate (IBD) of the commercial product on 29 March 2006 and extending through a data cutoff of 28 March 2008, for infant and adult patients receiving exclusively 2000 L material.

Overall, the safety data from these 5 additional clinical studies and the worldwide post-marketing experience with 2000 L alglucosidase alfa are consistent with safety data from the pivotal LOTS study, and provide further support for the acceptable safety profile of 2000 L alglucosidase alfa.

## 5.3.1 Completed GCP Studies

### 5.3.1.1 AGLU02603

AGLU02603 was a US, open-label, expanded access study for severely affected patients (i.e., ventilator-dependent and wheelchair-dependent) diagnosed with late-onset Pompe

disease for whom there was no alternative treatment and who did not meet the clinical characteristics for inclusion in other Genzyme-sponsored studies.

Nine patients received alglucosidase alfa at a dose of 20 mg/kg qow for variable durations ranging from 23 to 82 weeks. One patient in this study received 6 infusions of 160 L alglucosidase alfa prior to starting treatment with 2000 L alglucosidase alfa. The remaining 8 patients were treated exclusively with alglucosidase alfa produced at the 2000 L scale. Median patient exposure was 17.0 infusions (range 5 to 42 infusions). The total duration of exposure to alglucosidase alfa among patients in this study was 7.4 patient years.

As summarized in **Table 5-27**, 8 of the 9 patients experienced a total of 47 AEs, a majority of which were non-serious, mild or moderate in severity, and not related to alglucosidase alfa. One patient died of causes not related to treatment with alglucosidase alfa (see below), and 1 patient was withdrawn by the Investigator following a significant allergic reaction (see below).

**Table 5-27: Overall Summary of Treatment-emergent Adverse Events in Study AGLU02603**

| Variable | Number of Patients (N=9) n (%) | Number of AEs n (%) |
|---|---|---|
| Any AEs | 8 (88.9) | 47 (100.0) |
| Treatment-Related AEs | 3 (33.3) | 11 ( 23.4) |
| Infusion-Associated Reactions | 2 (22.2) | 9 ( 19.1) |
| Severe AEs | 1 (11.1) | 2 ( 4.3) |
| SAEs | 3 (33.3) | 5 ( 10.6) |
| Patients who Discontinued Due to AEs or Died During the Study[1] | 2 (22.2) | N/A[2] |

[1] One patient discontinued due to death.
[2] N/A=not applicable. Patient counts only are provided as AEs resulting in discontinuation and death are not mutually exclusive.

Patient 2603-819 died of end-stage Pompe disease (mucus plugging of the patient's tracheostomy leading to respiratory failure) that was assessed as not related to treatment. This female patient was 39.9 years of age at the time of death, and had been receiving alglucosidase alfa therapy for 23 weeks. An autopsy was not performed. A second patient who completed treatment in AGLU02603 (2603-811) died approximately

2 months after transitioning to commercial therapy with 160 L alglucosidase alfa. This patient, a 19-year old male with history of profound muscle weakness and ventilator dependency, developed left-side hemiplegia; MRI and angiogram revealed multiple infarcts, as well as fusiform aneurysm of the distal vertebral artery, involving the basilar artery and right posterolateral filling defect, compatible with thrombus. A decision was made to withdraw life support measures and the patient subsequently died. The events were assessed as not related to alglucosidase alfa.

Five SAEs (10.6% of all AEs) were experienced by 3 patients, including bronchial obstruction (2 events), hypotension, dyspnoea, and respiratory failure. As described above, 1 patient died as a result of SAEs of bronchial obstruction and respiratory failure that were not related to treatment. The serious respiratory complications observed in this study were not unexpected, given the nature and severity of advanced late-onset Pompe disease and the AGLU02603 inclusion criterion that required that patients be dependent on invasive ventilation. One SAE (hypotension) was assessed as related to alglucosidase alfa treatment, and further characterized as an IAR, as well as a significant allergic reaction (see below).

Three patients experienced 11 (23.4%) treatment-related AEs, all of which occurred on the day of infusion. Two treatment-related AEs in 1 patient were not characterized as IARs (hypotension and platelet count increased). The remaining 9 events in 2 patients were characterized as IARs; these events were consistent with those previously reported for alglucosidase alfa, and all IARs were transient and mild or moderate in severity. One patient (Patient 2603-831) experienced IARs that were identified by MedDRA SMQ as suggestive of an allergic reaction. This patient experienced a non-serious IAR of flushing at approximately 5 minutes after the start of the infusion at Week 8. The infusion rate was adjusted until the flushing subsided, and was subsequently increased, at which time the patient experienced a serious IAR of hypotension, as well as non-serious IARs of nausea and rigors. The patient tested negative for anti-rhGAA IgE antibodies, positive for complement activation, and had a normal serum tryptase. The patient was subsequently discontinued from the study by the investigator, who felt that he could not safely administer alglucosidase alfa infusions without a central venous catheter line (which the patient had refused).

Of the 8 patients with post-Baseline anti-rhGAA IgG assessments, 7 patients seroconverted during treatment in AGLU02603, with a mean time to seroconversion of 8.6 weeks (range: 4 to 20 weeks). All seropositive patients had either consistently low titers throughout the study or showed trends towards decreasing titers by the end of the study. Median peak titer of 6,400 (range: 800 to 51,200). The highest peak titer occurred in the 1 patient experiencing an allergic reaction; this patient seroconverted at Week 4 and had titer levels ranging from 100 at Week 4 to 51,200 at Week 8. All 7 patients retrospectively tested for inhibition of enzyme activity were found to be negative; testing for inhibition of enzyme uptake was not performed in this study.

Additional immunologic testing (anti-rhGAA IgE antibody, serum tryptase, circulating immune complex, complement activation, and skin testing) was not clinically indicated for any patient.

### 5.3.1.2        AGLU02804

AGLU02804 was a single-center, open-label, safety, and efficacy study in juvenile patients with late-onset Pompe disease. All 5 patients received 2000 L alglucosidase alfa at a dose of 20 mg/kg qow for a period of 74 weeks (38 infusions per patient). The total duration of exposure to 2000 L alglucosidase alfa among patients in this study was 7.1 patient years.

As summarized in **Table 5-28**, all 5 patients experienced a total of 137 AEs, all of which were mild or moderate in severity and not related to treatment with alglucosidase alfa. Three events (joint contracture, road traffic accident, and talipes) were assessed as serious, all of which were not related to alglucosidase alfa treatment. No patients died or withdrew from the study.

**Table 5-28:  Overall Summary of Treatment-emergent Adverse Events in Study AGLU02804**

| Variable | Number of Patients (N=5) n (%) | Number of AEs n (%) |
|---|---|---|
| Any AEs | 5 (100.0) | 137 (100.0) |
| Treatment-Related AEs | 0 | 0 |
|    Infusion-Associated Reactions | 0 | 0 |
| Severe AEs | 0 | 0 |
| SAEs | 3 (60.0) | 3 (2.2) |
| Patients who Discontinued Due to AEs or Died During the Study | 0 | N/A[1] |

[1] N/A=not applicable.  Only patient counts are provided, as AEs resulting in discontinuation and death are not mutually exclusive.

A total of 3 SAEs (2.2% of all AEs) were experienced by 3 patients during this study: joint contracture, road traffic accident, and talipes.  All events were mild or moderate in severity. None of the SAEs was assessed by the Investigator as related to alglucosidase alfa.

All 5 patients seroconverted during treatment in AGLU02804, with the time of first detection of anti-rhGAA IgG antibodies ranging from Week 8 to Week 38.  All patients had consistently low titers throughout treatment (peak titers ranged from 800 to 6,400), and several patients showed trends towards decreasing titers by the end of the study.  All 5 patients tested negative for inhibition of enzyme activity; testing for inhibition of enzyme uptake was not performed in this study.

Additional immunologic testing (anti-rhGAA IgE antibody, serum tryptase, circulating immune complex, complement activation, and skin testing) was not clinically indicated for any patient.

### 5.3.1.3     AGLU03105

AGLU03105 was a single-center, open-label study in patients with advanced late-onset Pompe disease, defined as diaphragmatic dysfunction (orthopnoea, vital capacity below 50%, or paradoxical respiration detected on measurement of transdiaphragmatic pressure), the need of invasive or noninvasive ventilation day and night ($\geq$ 12 h/day), and the use of a wheelchair.  Five patients received 2000 L alglucosidase alfa at a dose of

20 mg/kg qow for up to 52 weeks (25 to 27 infusions per patient).  The total duration of exposure to 2000 L alglucosidase alfa among patients in this study was 5.0 patient years.

As summarized in **Table 5-29**, all 5 patients in AGLU03105 experienced a total of 59 AEs, a majority of which were non-serious, mild or moderate in severity, and not related to alglucosidase alfa treatment.  One patient died of causes not related to treatment with alglucosidase alfa (see below).  No other patients discontinued treatment due to AEs.

**Table 5-29: Overall Summary of Treatment-emergent Adverse Events in Study AGLU03105**

| Variable | Number of Patients (N=5) n (%) | Number of AEs n (%) |
|---|---|---|
| Any AEs | 5 (100.0) | 59 (100.0) |
| Treatment-Related AEs | 4 ( 80.0) | 5 ( 8.5) |
|    Infusion-Associated Reactions | 2 ( 40.0) | 3 ( 5.1) |
| Severe AEs | 1 ( 20.0) | 1 ( 1.7) |
| SAEs | 2 ( 40.0) | 9 ( 15.3) |
| Patients who Discontinued Due to AEs or Died During the Study[1] | 1 ( 20.0) | N/A[2] |

[1] One patient discontinued due to death.

[2] N/A=not applicable.  Patient counts only are provided, as AEs resulting in discontinuation and death are not mutually exclusive.

One patient (3105-196005) died during treatment under AGLU03105 of causes not related to treatment with alglucosidase alfa.  This male patient experienced an SAE of massive tracheal haemorrhage one day after the infusion at Week 50, and resuscitation attempts were unsuccessful.  The patient was 41.4 years of age at the time of death, and had been receiving 2000 L alglucosidase alfa therapy for 50.4 weeks.

Nine SAEs (15.3% of all AEs) were experienced by 2 patients, all of which were assessed as not related to treatment with alglucosidase alfa.  One patient experienced SAEs of asthenia, bronchitis, dizziness, dyspnoea exacerbated, gastroenteritis, hot flush, medical device complication, and respiratory disorder, all of which were mild to moderate in severity.  A second patient experienced an SAE of tracheal haemorrhage, which was severe and had a fatal outcome.

Four patients experienced 5 (8.5%) treatment-related AEs, all of which were non-serious, and occurred on the day of infusion.  Two treatment-related AEs (both events of infusion site erythema) in 2 patients were not characterized as IARs.  The remaining 3 (60.0%) events in 2 patients were characterized as mild IARs, including 2 events of pyrexia and 1 event of muscle cramp.  No IARs suggestive of an allergic/anaphylactic reaction were identified by MedDRA SMQ or on medical review.

All 5 patients seroconverted during treatment in AGLU03105, with the time of first detection of anti-rhGAA IgG antibodies ranging from Week 4 to Week 12.  One patient seroconverted at Week 4 (titer 200) and developed a peak titer of 102,400 (Week 38).  This patient was classified as positive for uptake inhibition with inhibitory antibodies detected during Week 20 (titer:20), Week 24 (titer:40), and Week 38 (titer:160).  The remaining 4 patients had peak titers ranging from 400 to 12,800.  One of these 4 patients was classified as borderline positive for uptake inhibition, with inhibitory antibodies detected at Week 38 (titer:20) and Week 52 (titer:40).  All 5 patients tested negative for inhibition of enzyme activity.

Additional immunologic testing (anti-rhGAA IgE antibody, serum tryptase, circulating immune complex, complement activation, and skin testing) was not clinically indicated for any patient.

### 5.3.2        Ongoing GCP Studies

### 5.3.2.1        AGLU03206 (LOTS Extension)

AGLU03206 (LOTS Extension) is an ongoing open-label extension study in patients with late-onset Pompe disease who completed 78 weeks of treatment in LOTS.  Safety data collected through the data cutoff of 15 April 2008 are summarized in this briefing package.  For the purpose of evaluating the safety data, 2 treatment groups were defined (the placebo/alglucosidase alfa group and the alglucosidase alfa/alglucosidase alfa group) based on the double-blind treatment administered in LOTS (placebo or alglucosidase alfa) and the subsequent open-label treatment with alglucosidase alfa in the LOTS Extension.

As of 15 April 2008, 81 patients have received 2000 L alglucosidase alfa at a dose of 20 mg/kg qow under this protocol.  All patients have completed Week 26 assessments in

the study, and 41 patients have completed the study, with treatment durations ranging from 25.1 to 53.9 weeks (mean ± SD of 33.1 ± 8.82 weeks). The total duration of exposure to alglucosidase alfa among patients in this study, inclusive of exposure in LOTS, was 137.3 patient years.

As summarized in Table 5-30, all but 2 patients have experienced AEs in the LOTS Extension, with a total of 878 AEs reported as of 15 April 2008. A majority of AEs were non-serious, mild or moderate in severity, and not related to treatment. No patients died or discontinued treatment due to AEs. There is no apparent increase in the proportion of AEs, SAEs, and IARs during open-label treatment with alglucosidase alfa in the LOTS Extension compared with either blinded treatment group (alglucosidase alfa or placebo) in LOTS. However, these results should be interpreted with caution as the LOTS Extension is still ongoing and, as of 15 April 2008, total patient exposure to alglucosidase alfa in the LOTS Extension was less than that in LOTS.

**Table 5-30: Overall Summary of Treatment-Emergent Adverse Events in the LOTS Extension Study (AGLU03206)**

| Variable | Number of Patients (N=81) n (%) | Number of AEs n (%) |
|---|---|---|
| Any AEs | 79 ( 97.5) | 878 (100.0) |
| Treatment-Related AEs | 28 ( 34.6) | 114 ( 13.0) |
|    Infusion-Associated Reactions | 10 ( 12.3) | 67 ( 7.6) |
| Severe AEs | 10 ( 12.3) | 13 ( 1.5) |
| SAEs | 5 ( 6.2) | 7 ( 0.8) |
| Patients who Discontinued Due to AEs or Died During the Study | 0 | N/A[1] |

[1] N/A=not applicable. Only patient counts are provided as AEs resulting in discontinuation and death are not mutually exclusive.

In the LOTS Extension, 7 SAEs (0.8% of all AEs) were experienced by 5 patients: nephrolithiasis, renal cyst, gastric ulcer, fall, spinal compression fracture, hydronephrosis, and cervix carcinoma stage II. All SAEs in the LOTS Extension were assessed as not related to treatment, representing a decrease in the frequency of treatment-related SAEs experienced by patients in the LOTS Extension compared to either blinded treatment group in LOTS.

Twenty-eight (34.6%) patients experienced 114 treatment-related AEs. Forty-seven (41.2%) treatment-related AEs were not characterized as IARs, all of which were non-serious and mild or moderate in severity; events reported by ≥ 2 patients were cataract, fatigue, hypoacusis, headache, and protein urine present. The remaining 67 (58.8%) events in 10 patients were characterized as IARs. Eight (14.5%) patients in the alglucosidase alfa/alglucosidase alfa group and 2 (7.7%) patients in the placebo/alglucosidase alfa group experienced IARs during the extension study, suggesting a decrease in the frequency of IARs compared with LOTS where IARs were reported for 28.3% of alglucosidase alfa-treated patients and 23.3% of placebo-treated patients. Of 20 patients who experienced IARs in LOTS, 6 patients (5 in the alglucosidase alfa/alglucosidase alfa group and 1 in the placebo/alglucosidase alfa group) also experienced IARs during the LOTS extension, while the remaining 14 patients (9 in the alglucosidase alfa/alglucosidase alfa group and 5 in the placebo/ alglucosidase alfa group) had no additional IARs during the extension study. One patient who was previously on placebo developed IARs for the first time after beginning open-label treatment with alglucosidase alfa in the extension study. Three patients previously treated with alglucosidase alfa during the LOTS trial experienced their first IARs in the extension study.

The most frequent IARs (those occurring in more than 1 patient) were nausea (24 events in 3 patients), urticaria (12 events in 3 patients), pruritus (5 events in 2 patients), headache (3 events in 2 patients), and rash (3 events in 2 patients). Events that occurred in single patients multiple times were ear discomfort (6 events), asthenia (2 events), fatigue (2 events), and hypersensitivity (2 events). All IARs were non-serious and all but 1 event (headache) were mild or moderate in severity. No IARs suggestive of an allergic/anaphylactic reaction were identified by MedDRA SMQ or on medical review.

LOTS and LOTS Extension seroconversion data as of 15 April 2008 were combined for the purpose of analysis of anti-rhGAA IgG antibodies. Anti-rhGAA IgG antibodies were detected in 19 (73.1%) of 26 patients in the placebo/ alglucosidase alfa group, with a mean time to seroconversion from first alglucosidase alfa infusion of 13 weeks. All 55 patients (100%) in the alglucosidase alfa / alglucosidase alfa group seroconverted during treatment in LOTS, with a mean time to seroconversion from first alglucosidsase alfa infusion of 5.7 weeks. Overall, 91% of patients in the LOTS extension have tested

positive for anti-rhGAA IgG antibodies. As the LOTS Extension is ongoing, the seroconversion rate for placebo/alglucosidase alfa patients may increase over time. In addition, the sampling schedule in the LOTS Extension was reduced to every 3 months after Week 12, which may have artificially increased the time to seroconversion in the placebo/alglucosidase alfa group. Among the patients who seroconverted, a majority of patients in each treatment group had peak titers $\leq 6,400$, i.e., 13 of 19 [68.4%] patients in the placebo/ alglucosidase alfa group and 36 of 55 [65.5%] patients in the alglucosidase alfa / alglucosidase alfa group. Although titer at seroconversion was similar in both groups, mean time to first occurrence of peak titer from first alglucosidase alfa infusion was considerably longer in the alglucosidase alfa / alglucosidase alfa group compared to the placebo/ alglucosidase alfa group, which is most likely due to the approximately 78-week longer exposure to alglucosidase alfa in the alglucosidase alfa/alglucosidase alfa group.

All 74 seropositive patients tested were negative for inhibition of enzyme activity throughout both studies. Of the 18 patients in LOTS who showed in vitro inhibition of enzyme uptake, 17 patients continued treatment in the extension study. Of these 17 patients, 7 continued to show inhibition of enzyme uptake (3 patients classified as positive and 4 patients classified as borderline positive) during the LOTS Extension and 10 (7 who had been classified as borderline positive and 3 who had been classified as positive) showed no further uptake inhibition during the LOTS Extension. None of the patients who were classified as borderline positive during LOTS changed to a positive classification during the LOTS Extension. None of the 19 placebo/alglucosidase alfa patients who seroconverted during the LOTS Extension showed in vitro inhibition of cellular uptake.

Three patients, all of whom were in the alglucosidase alfa/alglucosidase alfa group, underwent additional immunologic testing after experiencing moderate or severe IARs during the LOTS Extension. All 3 patients tested anti-rhGAA IgE-negative; 1 patient also tested negative for complement activation and had a normal serum tryptase. As discussed in **Section 5.2.2.5.4**, 1 patient (2704-16705) who experienced SAEs of renal cyst and nephrolithiasis tested negative for circulating immune complexes on retrospective testing of samples from LOTS.

### 5.3.2.2     AGLU03907 (MTAP)

During 2007, US patient demand for alglucosidase alfa exceeded the maximum production capacity of the approved 160 L process.  Therefore, the Myozyme Temporary Access Program, a treatment protocol referred to as MTAP (AGLU03907), was initiated in May 2007 to provide adult patients with Pompe disease in the US with access to 2000 L alglucosidase alfa until this process scale is approved for commercial use by FDA.

Safety data collected through the data cutoff of 15 April 2008 are included in this briefing package.  As of this date, 138 patients had enrolled and 135 patients had received treatment under MTAP for a period of 0.1 to 46.6 weeks (mean $19.4 \pm 11.23$ weeks). The 135 patients treated include 5 patients who participated in LOTS, 4 patients who participated in AGLU02603, 7 patients who participated in LOTS and the LOTS Extension, 27 naïve patients, and 92 patients from commercial therapy.  The total duration of exposure to 2000 L alglucosidase alfa among patients in MTAP was 50.6 patient years.  The dose for all patients treated in this program is 20 mg/kg qow.

As summarized in **Table 5-31**, 55 (40.7%) of 135 patients treated under MTAP experienced a total of 268 AEs as of the data cutoff of 15 April 2008.  A majority of AEs were non-serious, mild or moderate in severity, and not related to alglucosidase alfa. Two patients died of causes not related to alglucosidase alfa (see below), and 1 patient discontinued treatment due to IARs (see below).

**Table 5-31:  Overall Summary of Treatment-Emergent Adverse Events in MTAP**

| Variable | Number of Patients (N=135) n (%) | Number of AEs n (%) |
|---|---|---|
| Any AEs | 55 (40.7) | 268 (100.0) |
| Treatment-Related AEs | 17 (12.6) | 74 ( 27.6) |
|    Infusion-Associated Reactions | 12 ( 8.9) | 57 ( 21.3) |
| Severe AEs | 9 ( 6.7) | 28 ( 10.4) |
| SAEs | 15 (11.1) | 38 ( 14.2) |
| Patients who Discontinued Due to AEs or Died During the Study[1] | 3 ( 2.2) | N/A[2] |

[1] Two patients discontinued due to death.
[2] N/A=not applicable.  Patient counts only are provided as AEs resulting in discontinuation and death are not mutually exclusive

As of 15 April 2008, 2 patients had died of causes not related to treatment with alglucosidase alfa. Patient 3907-50094 died after 5.0 weeks in the study while hospitalized for respiratory failure due to mucus plug on tracheostomy; this patient was 52.0 years of age at the time of death. Patient 3907-10401 died after 17.7 weeks in the study from anoxic brain damage due to cardiac arrest; this patient was 60.0 years of age at the time of death. After the data cutoff for this ongoing study, an additional patient (Patient 3907-10272) died from respiratory failure assessed as not related to alglucosidase alfa treatment and possibly due to intracranial bleed; this patient had received treatment under MTAP for 40.7 weeks.

Thirty-eight SAEs (14.2% of all AEs) were experienced by 15 patients. The most frequent SAEs (those occurring in 2 or more patients) were pneumonia (5 events in 4 patients), respiratory failure (3 events in 3 patients), abdominal pain (2 events in 2 patients), and muscular weakness (2 events in 2 patients). All SAEs were assessed as not related to alglucosidase alfa. With respect to severity, 21 were severe, 13 were moderate, and 4 were mild.

Seventeen patients experienced 74 (27.6%) treatment-related AEs, all of which were non-serious and mild or moderate in severity. Seventeen treatment-related AEs were not characterized as IARs, including headache and hypoaesthesia facial (3 events each), hypoaesthesia, muscular weakness, nausea (2 events each), and arthralgia, dyskinesia, pain in extremities, palpitations, and rash (1 event each). The remaining 57 (77.0%) treatment-related AEs in 12 patients were characterized as IARs, all of which were mild in severity. The most frequent IARs (those occurring in more than 1 patient) were rash (5 events in 4 patients), pruritus (4 events in 3 patients), urticaria localised (11 events in 2 patients), urticaria (7 events in 2 patients), feeling jittery (3 events in 2 patients), and chills (2 events in 2 patients). Events that occurred in single patients multiple times were hypoaesthesia facial (4 events), catheter site urticaria (3 events), hypoaesthesia (3 events), infusion site urticaria (2 events), nasopharyngitis (2 events), non-cardiac chest pain (2 events), and urine abnormality (2 events). One patient (3907-50036) discontinued due to IARs; this patient experienced 3 IARs (hypotension, lightheadedness, and nausea) at the Week 6 infusion. The infusion was attempted again at Week 8, but treatment was permanently discontinued when the patient experienced a single IAR (chills). All IARs

were mild, non-serious, and resolved the same day. No IARs suggestive of an allergic/anaphylactic reaction were identified by MedDRA SMQ or on medical review.

As of 15 April 2008, anti-rhGAA IgG antibody data are available for 20 (74.1%) of 27 naïve patients and 88 (81.5%) of 108 patients with prior treatment. Among the 88 patients who had received prior treatment with alglucosidase alfa, 67 (76.1%) patients developed anti-rhGAA antibodies. As the date of first infusion for these patients was not collected, the time from first infusion to seroconversion could not be calculated. Peak titer ranged from 100 to 409,600 in these patients. Among the naïve patients who started treatment with alglucosidase alfa under MTAP, the seroconversion rate was 35.0% (7 of 20 patients) and the mean time to seroconversion from first infusion was 14.4 weeks. For these 7 patients, geometric mean values for titer at seroconversion and peak titer were both 5250; peak titer ranged from 400 to 102,400 in these patients.

Inhibition of enzyme activity or uptake was not routinely tested in MTAP and no results for ad hoc testing were received before the data cutoff of 15 April 2008.

Four patients who experienced moderate or severe IARs during treatment under MTAP underwent additional immunologic testing. Three patients were tested for anti-rhGAA IgE antibodies and all 3 patients were anti-rhGAA IgE-negative. One patient was tested and was negative for complement activation and had a normal serum tryptase.

### 5.3.3 Post-Marketing Experience

The post-marketing safety experience for alglucosidase alfa described herein includes selected safety events captured in the Genzyme Global Pharmacovigilance database (i.e., spontaneously reported deaths and other SAEs, including potential allergic/anaphylactic reactions and skin lesions) or collected by Genzyme Clinical Specialty Laboratory (i.e., immunogenicity data), beginning on the IBD of the commercial product on 29 March 2006 and extending through the data cutoff of 28 March 2008 (the 8th US Periodic Safety Update Report [PSUR] data lock point), for infant and adult patients who have exclusively received 2000 L material. For the purpose of these analyses, patients were stratified by disease phenotype (infantile-onset or late-onset) on the basis of a physician-reported diagnosis and/or age at symptom onset; patients lacking such data were categorized as 'unknown phenotype'.

The estimated total number of commercial patients treated with 2000 L alglucosidase alfa outside the US from the IBD through 28 March 2008 was calculated from sales figures to be 655 patients. At the time of the 8th US PSUR total worldwide exposure to alglucosidase alfa was estimated at 916 patients as indicated in **Table 5-32**. However, these 655 patients include some patients who were enrolled in clinical trials or treated via the International Expanded Access Program (EAP) at various product scales (i.e., 30 L/60 L development scale, 160 L scale, or both) prior to transitioning to treatment with the 2000 L scale or to commercial therapy with alglucosidase alfa. Post-marketing safety data for patients who received exclusively 2000 L alglucosidase alfa was derived by analyzing only those events reported for the subset of patients outside of the US who received their first dose of alglucosidase alfa on or after the IBD of 29 March 2006. Based on this criterion, an estimated 465 patients received exclusively 2000 L product.

**Table 5-32:  Estimated Worldwide Exposure to alglucosidase alfa per 28 March 2008 PSUR**

| Clinical Trials | |
|---|---|
| Ongoing clinical trials and Emergency IND | 193 |
| **Commercial Treatment** | |
| US[1] | 68 |
| Europe | 494 |
| Asia-Pacific | 79 |
| Americas (non-US) | 24 |
| Charitable Access Program | 58 |
| Total | 916 |
| 1. US commercial patients receive treatment with 160 L alglucosidase alfa.  Note that patients treated with commercial product may include patients who also received treatment during the PSUR reporting interval in a clinical study, as they may have transitioned from one setting to another during this time. | |

Of the estimated 465 patients who received exclusively 2000 L alglucosidase alfa, spontaneous post-marketing AE reports for serious cases were available in the Genzyme Global Pharmacovigilance database for 76 patients. As with all voluntary post-marketing surveillance, underreporting is inherent, which makes it impossible to ascertain the true frequency for a particular event and therefore all frequencies should be interpreted with caution. It is also important to emphasize that, although these events were reported to

have occurred after or during treatment with 2000 L alglucosidase alfa, they were not necessarily caused by alglucosidase alfa since relation to treatment is not always included in case reports.

### 5.3.3.1    Serious Adverse Events

A total of 214 SAEs were spontaneously reported in 76 patients, including 122 events reported in 39 infantile-onset Pompe patients, 85 events in 32 late-onset Pompe patients, and 7 events in 5 patients with Pompe disease of unknown phenotype.

In infantile-onset patients, SAEs of cardiac failure, respiratory failure, pneumonia, and disease progression were experienced by >10.0% patients with SAEs.  These events are consistent with the underlying manifestations of infantile-onset Pompe disease.  In late-onset patients, SAEs of dyspnoea and respiratory failure were reported by >10.0% of late-onset patients with SAEs.  In the patients with Pompe disease of unknown phenotype, the only SAE reported for more than 1 patient was death of unknown cause (occurring in 2 patients).  Tabular summaries of SAEs occurring in more than 1 patient in the infantile-onset and the late-onset populations are presented below in **Table 5-33** and **Table 5-34**, respectively.

**Table 5-33: Summary of Post-Marketing SAEs in More than One Patient Infantile-onset Pompe Disease**

| MedDRA Preferred Term[1] | Number of Patients[2] n (%) | Number of Events[3] n (%) |
|---|---|---|
| **Any Serious Adverse Events** | **39 (100.0)** | **122 (100.0)** |
| **SOC: Cardiac disorders** | | |
| Cardiac failure | 10 (25.6) | 12 (9.8) |
| Bradycardia | 3 (7.7) | 3 (2.5) |
| Cardiac arrest | 3 (7.7) | 3 (2.5) |
| Cardiopulmonary failure | 3 (7.7) | 3 (2.5) |
| Cyanosis | 3 (7.7) | 3 (2.5) |
| Ventricular fibrillation | 3 (7.7) | 3 (2.5) |
| Cardio-respiratory arrest | 2 (5.1) | 2 (1.6) |
| Myocardial ischaemia | 2 (5.1) | 2 (1.6) |
| Tachycardia | 2 (5.1) | 2 (1.6) |
| **SOC: Respiratory, thoracic and mediastinal disorders** | | |
| Respiratory failure | 6 (15.4) | 7 (5.7) |
| Pneumonia aspiration | 3 (7.7) | 3 (2.5) |
| Respiratory distress | 3 (7.7) | 3 (2.5) |
| Bronchospasm | 2 (5.1) | 2 (1.6) |
| **SOC: Infections and infestations** | | |
| Pneumonia | 6 (15.4) | 6 (4.9) |
| Catheter related infection | 2 (5.1) | 2 (1.6) |
| Lung infection | 2 (5.1) | 2 (1.6) |
| Respiratory tract infection | 2 (5.1) | 2 (1.6) |
| Sepsis | 2 (5.1) | 2 (1.6) |
| **SOC: General disorders and administration site conditions** | | |
| Disease progression | 4 (10.3) | 4 (3.3) |
| Pyrexia | 3 (7.7) | 4 (3.3) |
| Death[4] | 2 (5.1) | 2 (1.6) |
| General physical health deterioration | 2 (5.1) | 2 (1.6) |
| No therapeutic response | 2 (5.1) | 2 (1.6) |
| **SOC: Nervous system disorders** | | |
| Hypotonia | 3 (7.7) | 3 (2.5) |
| Convulsion | 2 (5.1) | 2 (1.6) |
| **SOC: Vascular disorders** | | |
| Hypotension | 3 (7.7) | 3 (2.5) |
| **SOC: Investigations** | | |
| Oxygen saturation decreased | 2 (5.1) | 2 (1.6) |

[1] Events are presented by SOC and by decreasing frequency within each SOC based on patient percentages; events with the same frequency are listed by decreasing number of events and alphabetically.

[2] Percentages are based on the total number of infantile-onset patients with an SAE. A patient experiencing more than one SAE within a preferred term is counted once for that preferred term.

[3] Percentages are based on the total number of reported spontaneous SAEs experienced by infantile-onset patients.

[4] Cause of death for these patients was not provided.

**Table 5-34:  Summary of Post-Marketing SAEs in More than One Patient
Late-onset Pompe Disease**

| MedDRA Preferred Term[1] | Number of Patients[2] n (%) | Number of Events[3] n (%) |
|---|---|---|
| **Any Serious Adverse Events** | **32 (100.0)** | **85 (100.0)** |
| **SOC: Respiratory, thoracic and mediastinal disorders** | | |
| Dyspnoea | 7 (21.9) | 7 (8.2) |
| Respiratory failure | 4 (12.5) | 4 (4.7) |
| Bronchospasm | 2 (6.3) | 2 (2.4) |
| Pneumothorax | 2 (6.3) | 2 (2.4) |
| **SOC: Vascular disorders** | | |
| Flushing | 2 (6.3) | 2 (2.4) |
| Hypertension | 2 (6.3) | 2 (2.4) |
| Hypotension | 2 (6.3) | 2 (2.4) |
| **SOC: Skin and subcutaneous tissue disorders** | | |
| Erythema | 3 (9.4) | 3 (3.5) |
| **SOC: General disorders and administration site conditions** | | |
| Chest discomfort | 3 (9.4) | 3 (3.5) |
| Chest pain | 2 (6.3) | 2 (2.4) |
| **SOC: Infections and infestations** | | |
| Lung infection | 2 (6.3) | 2 (2.4) |
| **SOC: Cardiac disorders** | | |
| Tachycardia | 2 (6.3) | 3 (3.5) |
| Cyanosis | 2 (6.3) | 2 (2.4) |
| **SOC: Immune system disorders** | | |
| Hypersensitivity | 3 (9.4) | 3 (3.5) |

[1] Events are presented by SOC and by decreasing frequency within each SOC based on patient percentages; events with the same frequency are listed by decreasing number of events and alphabetically.

[2] Percentages are based on the total number of late-onset patients with an SAE.  A patient experiencing more than one SAE within a preferred term is counted once for that preferred term.

[3] Percentages are based on the total number of reported spontaneous SAEs experienced by late-onset patients.

In infantile-onset patients, 35 (28.7%) of 122 SAEs were assessed as related (possible, probable or definite) to alglucosidase alfa, 66 (54.1%) were assessed as not related (includes those events assessed as remote/unlikely), and 21 (17.2%) were unknown (unassessable).  In late-onset patients, 50 (58.8%) of 85 SAEs were assessed as related to alglucosidase alfa, 33 (38.8%) were not related, and 2 (2.4%) were unknown (unassessable).  In patients of unknown phenotype, 1 (14.3%) of 7 SAEs was assessed as related to alglucosidase alfa, 1 (14.3%) event was not related, and 5 (71.4%) events were

unknown. SAEs reported as not related to alglucosidase alfa were consistent with the manifestation and complications of underlying Pompe disease in both infantile and late-onset patients. A majority of the related SAEs were also reported as IARs, including 24 (68.7%) of 35 SAEs in infantile-onset patients, 43 (86%) of 50 SAEs in late-onset patients, and 1 (100%) event in patients of unknown phenotype.

Related SAEs occurring in more than 1 infantile-onset patient were cyanosis (3 events in 3 patients), hypotension (3 events in 3 patients), bradycardia (2 events in 2 patients), myocardial ischaemia (2 events in 2 patients), no therapeutic response (2 events in 2 patients), oxygen saturation decreased (2 events in 2 patients), and pyrexia (2 events in 2 patients). Related SAEs occurring in more than 1 late-onset patient were dyspnoea (6 events in 6 patients), chest discomfort (3 events in 3 patients), erythema (3 events in 3 patients), hypersensitivity (3 events in 3 patients), bronchospasm (2 events in 2 patients), cyanosis (2 events in 2 patients), flushing (2 events in 2 patients), hypotension (2 events in 2 patients), and tachycardia (2 events in 1 patient).

Among events in which causality was unknown, SAEs occurring in more than 1 infantile-onset patient were disease progression (cases PV02 and PV68), death of unknown cause (cases PV34 and PV47), and cardiac failure (cases PV64 and PV74). In late-onset patients, no SAEs of unknown causality were reported in more than 1 patient. In patients of unknown disease phenotype, both reports of death (cases PV67 and PV73) were of unknown causality.

With respect to event severity, 8 (6.6%) of 122 SAEs in infantile-onset patients were assessed as mild, 9 (7.4%) were moderate, 64 (52.5%) were severe, and the severity of the remaining 41 (33.6%) SAEs was unknown (not reported). In late-onset patients, 9 (10.6%) of 85 SAEs were assessed as mild, 32 (37.6%) were moderate, 31 (36.5%) were severe, and the severity of the remaining 13 (15.3%) SAEs was unknown. In patients of unknown disease phenotype, 3 (42.9%) events were assessed as severe, and the severity of the remaining 4 (57.1%) SAEs was unknown.

### 5.3.3.1.1 Significant Allergic Reactions

Potential allergic/anaphylactic reactions to 2000 L alglucosidase alfa were detected using a 2-step process as described in **Section 5.2.2.3.1**, with the exception that the SMQ and medical review were conducted only for SAEs (not all AEs). A listing of 14 patients

with reported allergic reactions as defined by the MedDRA SMQ is provided in Appendix 3 (**Section 11.3**).  These 14 allergic reactions, 4 of which were considered anaphylactic reactions, are discussed further in **Section 5.3.3.1.1.1**.

Shortly after the data cutoff of 28 March 2008, an additional infantile-onset patient in an investigator-sponsored study in Taiwan experienced an IgE-mediated anaphylactic reaction, bringing the total number of potential allergic or anaphylactic cases in the post-marketing experience to 15.  See **Section 7.2** for further details regarding this reaction.

Three additional reactions were identified upon medical review as significant IARs, and are also discussed briefly in **Section 5.3.3.1.1.2**.

### 5.3.3.1.1.1    SMQ identified potential allergic/anaphylactic reactions

As of 28 March 2008, 14 (3.0%) of 465 patients receiving exclusively 2000 L alglucosidase alfa experienced events suggestive of significant allergic or anaphylactic reactions, as identified by the MedDRA SMQ.  Four of the 14 patients experienced reactions suggestive of anaphylaxis, including 3 patients with events that were life threatening in nature.  The remaining 10 patients experienced events suggestive of significant allergic reactions.

Among the 14 patients who experienced significant allergic or anaphylactic reactions, 5 patients had infantile-onset Pompe disease, 7 had late-onset Pompe disease, and the phenotype was not provided for 2 patients.  Infantile-onset patients (3 females and 2 males) ranged in age from 5 months to 24 months (mean age of 10.4 months) at the time of event.  Late-onset patients (6 females and 1 male) ranged in age from 28 to 59 years (mean age of 47.6 years) at the time of event.  The patients with Pompe disease of unknown phenotype were 1 female of unknown age and one male age 10 years.  Eleven of the 14 patients were on a dose of 20 mg/kg of alglucosidase alfa every 2 weeks; the remaining 3 patients were on an unknown dose of alglucosidase alfa.

In 9 of the 14 patients, reactions occurred within the first hour after the start of the infusion (range 1 minute to 45 minute).  In 2 patients it was only indicated that the reactions occurred during the infusion.  In 1 patient the reactions occurred 10 hours after completion of the infusion.  In 2 patients the reactions occurred at an unspecified time.

Thirteen (92.9%) of the 14 patients presented with a constellation of signs and symptoms, primarily cardiovascular, respiratory, and/or cutaneous in nature. The most frequently reported allergic/anaphylactic reactions included dyspnoea (6 events, 5 patients), erythema (5 events, 5 patients), cyanosis (4 events, 4 patients), tachycardia (4 events, 3 patients), hypotension (3 events, 3 patients), bronchospasm (2 events, 2 patients), hypersensitivity (3 events, 2 patients), chest discomfort (2 events, 2 patients), anaphylactic reaction (2 events, 2 patients), chest pain (2 events, 2 patients), flushing (2 events, 2 patients), rash (2 events, 2 patients) and tachypnoea (2 events, 2 patients). The majority of reactions were assessed as moderate to severe in severity.

Four of the 14 patients experienced events suggestive of anaphylactic reactions either reported as such by the treating physician [3 patients (PV37, PV41 and PV66 respectively)] or upon Genzyme medical review of cases identified by the MedDRA SMQ [1 patient (PV09)]. Three out of the 4 cases were reported as life threatening in nature. Two patients tested positive for anti-rhGAA IgE antibodies. These 4 cases included the following events by MedDRA Preferred Term: anaphylactic reactions (in 2 patients), anaphylactic shock, bronchospasm, dyspnoea, chest pain, tachycardia, hypertension, flushing, pallor, peripheral coldness, urticaria, hyperhidrosis, restlessness, dizziness, headache, back pain, and nausea (single reaction/per patient). An additional 3 patients (PV10, PV48, and PV63) who experienced significant allergic reactions that were reported by the treating physician as life threatening; these cases included events of respiratory arrest, apnoea, dyspnoea, hypotension, tachycardia, bradycardia, cyanosis, and rash. Thus, a total of 6 of the 14 patients experienced significant allergic or anaphylactic reactions that were reported by the treating physician as life threatening.

The allergic or anaphylactic reactions were generally managed with temporary interruption, rate reduction and/or discontinuation of infusion and administration of antihistamines, corticosteroids, intravenous fluids, and/or oxygen, when clinically indicated. In some cases of anaphylaxis and respiratory arrest, epinephrine or cardiopulmonary resuscitation was also administered. Of the 14 patients, 10 patients temporarily interrupted infusion with alglucosidase alfa, 2 patients had no actions taken with regard to the alglucosidase alfa infusion, 1 patient (case PV10) permanently discontinued treatment due to reactions of severe dyspnoea and rash, and the status of 1 patient (case PV02) was unknown.

Twelve (85.7%) of the 14 patients recovered from the reactions without sequelae, and the outcome of 1 patient (case PV10) was unknown. The outcome in one patient (case PV71) was fatal, although the event which caused the patient's death (cardiac arrest which did not occur on the day of infusion) was considered not related to alglucosidase alfa treatment.

Three of 4 patients who were tested for anti-rhGAA IgG antibodies were positive with titers ranging from 800 to 204,800. Two of 5 patients who were tested for anti-rhGAA IgE antibodies were positive (1 infantile-onset and 1 late-onset patient); both patients continued to receive subsequent infusions of alglucosidase alfa using desensitization protocols.

### 5.3.3.1.1.2 Other Significant Infusion Associated Reactions

As previously noted, Genzyme Pharmacovigilance performed a medical review of cases not identified by the MedDRA SMQ to identify additional cases of potential significant allergic and/or anaphylactic reactions. Based on this medical review, 3 additional cases of significant IARs were identified, each of which was limited to a single body system and thus did not meet the MedDRA SMQ criteria. Two patients (PV05, infantile-onset patient; PV69, late-onset patient) each experienced a single IAR of hypotension and 1 patient (PV31, late-onset patient) experienced IARs of stridor, hypersensitivity, and dyspnoea. All 3 patients recovered without sequelae following temporary interruption of infusion and/or administration of antihistamine, corticosteroids, intravenous fluids, and/or epinephrine.

### 5.3.3.1.2 Deaths

Death was reported for 32 patients: 24 infantile-onset patients, 5 late-onset patients, and 3 patients with Pompe disease of unknown phenotype. Although late-onset Pompe disease is more prevalent than the infantile-onset form, death occurred much more frequently in the infantile-onset patients. The higher number of fatal events reported for infantile-onset patients is consistent with the nature and severity of this form of Pompe disease, in which untreated patients have a high mortality rate and often die before the age of 1 year, while the smaller number of deaths reported for late-onset patients is consistent with the milder and more slowly progressive nature of late-onset Pompe disease. A majority of reports with fatal outcome were cardiac and/or respiratory in

nature, and were related to the underlying Pompe disease in both patient populations and consequently assessed as unlikely or not related to alglucosidase alfa. The assessment of causality by the reporter was not related for 21 deaths, remote/unlikely for 5 deaths, and not reported (unassessable) for 6 deaths. All reported deaths are summarized in **Table 5-35**.

**Table 5-35:  Listing of Post-Marketing Reports of Death**

| Patient ID | Case ID | Age at First Infusion of alglucosidase alfa | Age at Time of Death | Cause of Death | Reporter Assessment of Causality |
|---|---|---|---|---|---|
| **Infantile-onset Pompe Disease** | | | | | |
| PV01 | POMP-10940 | 24 months | 25 months | Cardiac arrest | Not related |
| PV04 | POMP-1000075 | 5 months | 15 months | Respiratory failure secondary to respiratory infection | Remote/Unlikely |
| PV08 | POMP-10991 | 0 months | 10 months | Aspiration-related pneumonia related to myotonia and muscular dysphagia | Not related |
| PV11 | POMP-1000079 | 7 months | 10 months | Cardiopulmonary failure | Unassessable |
| PV14 | POMP-10925 | 9 months | 9 months | Pulmonary infection and cardiac failure | Not related |
| PV23 | POMP-10881 | 4 months | 5 months | Cardiac arrest | Remote/Unlikely |
| PV24 | POMP-10786 | 3 months | 4 months | Ventricular fibrillation | Remote/Unlikely |
| PV29 | POMP-10853 | 9 months | 9 months | Worsening of cardiac failure triggered by the presence of a lung infection | Not related |
| PV33 | POMP-1000029 | Not reported | 8 months | Failure of cardio-vascular system because of recurrent infections (pneumonia and pyelonephritis) | Not related |
| PV34 | POMP-1000012 | 6 months | 26 months | Unknown | Unassessable |
| PV38 | POMP-10994 | 0 months | 3 months | Disease progression | Not related |
| PV39 | POMP-11099 | 5 months | 6 months | Respiratory and cardiac failure | Not related |
| PV44 | POMP-10814 | 5 months | 5 months | Disease progression | Not related |
| PV45 | POMP-11122 | Not reported | 14 months | Disease progression | Not related |
| PV47 | POMP-10758 | 0 months | 0 months | Unknown | Unassessable |
| PV52 | POMP-11130 | 5 months | 6 months | Cardiac failure | Remote/Unlikely |
| PV58 | POMP-11110 | 13 months | 14 months | Cardiopulmonary arrest due to heart failure | Not related |
| PV59 | POMP-10967 | Not reported | 12 months | Cardio-respiratory failure | Not related |
| PV63 | POMP-10966 | 5 months | 10 months | Cardiogenic shock | Not related |
| PV65 | POMP-10998 | 16 months | 28 months | Unknown | Not related |

**Table 5-35:  Listing of Post-Marketing Reports of Death**

| Patient ID | Case ID | Age at First Infusion of alglucosidase alfa | Age at Time of Death | Cause of Death | Reporter Assessment of Causality |
|---|---|---|---|---|---|
| PV71 | POMP-1000078 | Not reported | 8 months | Cardiac arrest | Not related |
| PV72 | POMP-1000072 | 5 months | 12 months | Progressive muscular weakness and respiratory insufficiency | Not related |
| PV74 | POMP-11167 | 5 months | 15 months | Cardiac failure | Unassessable |
| PV76 | POMP-11088 | 6 months | 6 months | Cardiac arrhythmia due to bronchospasm, pneumonia, and underlying Pompe disease | Not related |
| **Late-Onset Pompe Disease** | | | | | |
| PV18 | POMP-1000100 | 39 years | 39 years | Heart exhaustion | Not related |
| PV22 | POMP-11145 | 67 years | 68 years | Stroke | Not related |
| PV26 | POMP-11298 | 51 years | 51 years | Skin necrosis | Not related (Manufacturer's assessment: remote/unlikely) |
| PV51 | POMP-11218 | 67 years | 69 years | Cardio-respiratory arrest and respiratory insufficiency | Not related |
| PV70 | POMP-11228 | 61 years | 61 years | Dissection of the ascending aorta | Remote/Unlikely |
| **Pompe Disease of Unknown Phenotype** | | | | | |
| PV16 | POMP-10904 | 5 years | 5 years | Cardio-respiratory arrest | Not related |
| PV67 | POMP-1000071 | - | - | Pompe disease | Unassessable |
| PV73 | POMP-1000060 | - | - | Unknown | Unassessable |

### 5.3.3.1.3    Skin Lesions

For serious case reports (which include serious and non-serious events), MedDRA preferred terms occurring within the SOC of Skin and subcutaneous tissue disorders were reviewed for events suggestive of drug-induced skin reactions.  This review identified 7 events: erythema, drug eruption, urticaria, pruritus, rash, skin necrosis, and lichen planus.  Two preferred terms (lichen planus and skin necrosis) were identified as events potentially suggestive of drug-induced skin reactions.  An SAE of lichen planus (case POMP-11244) occurred in a patient with infantile-onset Pompe disease (PV56); this SAE was assessed by the reporter as mild in severity and remote/unlikely related to treatment with alglucosidase alfa, and resolved after an unknown duration.  An SAE of skin necrosis (case POMP-11298) characterized as necrotizing skin lesions on the back and buttocks occurred in a patient with late-onset Pompe disease (PV26); this SAE was assessed by the reporter as severe and not related to treatment with alglucosidase alfa, and was ongoing for approximately 5 months when the patient died.  Additional review of the Genzyme Global Pharmacovigilance database for non-serious skin reactions within the SOC of Skin and subcutaneous tissue disorders revealed one case of non-serious hair loss (alopecia) in a 48-year-old male late-onset Pompe patient, which occurred 3 days after the first infusion of alglucosidase alfa.  In the opinion of the reporter, the event was assessed as mild in severity and possibly related to alglucosidase alfa.

### 5.3.3.2    Immunologic Response

As of 28 March 2008, 180 patients treated exclusively with commercial 2000 L alglucosidase alfa have been tested for anti-rhGAA IgG antibodies; 110 (61.1%) patients were seropositive at $\geq 1$ time point and 70 patients were seronegative at all time points.  Time to seroconversion, which was analyzed for 80 of the seropositive patients with 2 or more samples that were collected less than 6 months apart, ranged from 14 to 481 days (mean 125 days, median 112 days).  The median peak titer for these 80 patients was 1,600 (range 100 to 204,800).  Two patients are known to have tolerized, as determined by ELISA and two consecutive negative confirmatory RIP assays.

Ten of the 110 seropositive patients were tested for the presence of inhibitory antibodies at the request of Genzyme's Pharmacovigilance department due to adverse events of decreased response to treatment, high anti-rhGAA IgG antibody titers, or at the treating

physician's request. Patients treated in commercial setting were considered positive for inhibition of cellular enzyme uptake if they demonstrate positive activity at the 1/40 dilution at one or more time points and patients were classified as borderline if they show inhibition at only 1/20 dilution. One of 10 patients tested positive for in vitro inhibition of enzyme uptake and 1 patient was borderline positive. All 10 patients tested negative for inhibition of enzyme activity. The patient who tested positive for in vitro inhibition of enzyme uptake into cells (case PV41) was a late-onset patient who experienced an anaphylactic reaction and continued to receive alglucosidase alfa following a desensitization protocol. Subsequent immunology testing revealed an elevated IgG titer of 51,200. The physician reported the patient had become stronger, walked farther, and had decreased digestive and swallowing problems since starting alglucosidase alfa treatment. After approximately 5 months of treatment, the patient experienced muscle weakness leading to frequent falls, fatigue, and abdominal distension. After approximately 11 months of treatment, the patient experienced worsening respiratory insufficiency, and was subsequently tested for inhibition of enzyme activity and enzyme uptake. The patient continued to receive treatment with alglucosidase alfa. The patient who was borderline positive for in vitro inhibition of enzyme uptake into cells (case PV64) was an infantile-onset patient who experienced myocardial ischemia and arrhythmia during the first alglucosidase alfa infusion. After approximately 11 months of treatment, the patient experienced cardiac failure exacerbation which the treating physician considered due to fluid overload during an alglucosidase alfa infusion. IgG titers increased to 204,800. The treating physician indicated there was no significant clinical response regarding the patient's cardiac function or gross motor motility since the patient started alglucosidase alfa treatment, and the patient was permanently discontinued after approximately 14 months of treatment.

In addition, shortly after the data cutoff of 28 March 2008, test results were received for a late-onset patient (case PV55), who showed no clinical decline but was tested for inhibition of enzyme activity and uptake as a result of high anti-rhGAA IgG antibody titer (204,800). The patient's sample tested negative for inhibition of enzyme activity and positive for inhibition of enzyme uptake (titer:40).

Two of 24 patients tested were positive for anti-rhGAA IgE antibodies. Both patients (cases PV09 and PV41), who were tested in the context of anaphylactic reactions,

continued treatment with alglucosidase alfa. Shortly after the data cutoff of 28 March 2008, a third patient enrolled in an investigator-sponsored study in Taiwan experienced an anaphylactic reaction and was also tested and found to be anti-rhGAA IgE-positive (see **Section 7.2**). Of 2 patients tested for complement activation, both were positive. All 6 patients tested had normal serum tryptase.

## 6 CLINICAL COMPARATIVE ANALYSES OF 2000 L AND 160 L ALGLUCOSIDASE ALFA

Alglucosidase alfa produced at the 160 L scale is currently approved in the US for the treatment of all patients with Pompe disease on the basis of safety and efficacy data in patients with infantile-onset Pompe disease. In the pivotal study in infantile-onset patients (AGLU01602), treatment with 160 L alglucosidase alfa improved survival and invasive ventilator-free survival, with 15 of 18 (83%) patients still alive and free from invasive ventilation at 18 months of age compared to a survival rate of 1.9% in an untreated historical subgroup of 61 patients (Kishnani, 2007, *Neurology*).

**Table 6-1** provides an overview of 3 clinical studies in infantile-onset patients that were submitted to BLA 125141 in the original application (July 2005) or the supplement (October 2007). Many patients enrolled in these studies received treatment with alglucosidase produced at both the 160 L and 2000 L scales either during treatment in the study or during subsequent commercial therapy. Therefore, these studies provided an opportunity to retrospectively evaluate the efficacy of alglucosidase alfa produced at both manufacturing scales. A comparative analysis was undertaken by Genzyme to investigate key efficacy outcomes, including invasive ventilator-free survival, cardiac response, and motor response, as well as the clinical pharmacokinetics of alglucosidase alfa produced at the 160 L and 2000 L scales, in these infantile-onset patients.

While the clinical studies evaluated in this retrospective comparative exercise were not designed specifically to provide a head-to-head comparison of experience with alglucosidase alfa produced at the 2 scales, and data were somewhat limited due to the small sample size available for evaluation, the results do not suggest evidence of a meaningful difference in the efficacy (**Section 6.1**) or pharmacokinetics (**Section 6.2**) of alglucosidase alfa produced at either the 160 L or 2000 L scale.

**Table 6-1: Summary of Clinical Studies In Patients With Infantile-Onset Pompe Disease Submitted to BLA 125141**

| Study ID | Study Design | Treated Patient Population | | | Alglucosidase Alfa Dose, Regimen, and Duration | Alglucosidase Alfa Scale |
|---|---|---|---|---|---|---|
| | | Total Patients Treated | Age at Treatment Initiation Chronological Mean Age (Range) | Ventilation Status at Treatment Initiation | | |
| **AGLU01602/ 02403**<br><br>**(Pivotal Study)** | Randomized Open-label Historical control | 18 patients[1] | 5.1 months (1.2 – 7.3 months) | Ventilator-free: 100% | 20 mg/kg qow<br>40 mg/kg qow<br><br>Up to 150 weeks[1] | AGLU01602: 160 L<br><br>AGLU02403: 160 L and 2000 L |
| **AGLU01702** | Non-randomized Open-label | 21 patients | 15.7 months (3.7 - 43.1 months) | Invasively ventilated: 24%<br>Non-invasively ventilated: 10%<br>Ventilator-free: 66% | 20 mg/kg qow[2]<br>AND/OR<br>40 mg/kg qow[2]<br><br>Up to 168 weeks | 30 L/60 L, 160 L, and 2000 L |
| **AGLU02203**<br><br>**(US Expanded Access Study)** | Open-label | 33 patients[3] | 44.5 months (0.5 months - 16.3 years) | Invasively ventilated: 46%<br>Non-invasively ventilated: 3%<br>Ventilator-free: 51% | 20 mg/kg qow<br><br>Up to 132 weeks | 30 L/60 L, 160 L, and 2000 L |

qow = every other week; NA=not applicable

[1] Of the 18 patients treated under AGLU01602, 16 patients continued to receive alglucosidase alfa during the extension study (AGLU02403), 1 patient transitioned to International EAP, and 1 patient died while under treatment in AGLU01602. Total duration of treatment is given for AGLU1602 and AGLU02403 combined.

[2] After a minimum of 26 weeks of treatment at the 20 mg/kg qow dose, patients could have their dose increased to 40 mg/kg qow if specific clinical criteria were met and with the approval of the Sponsor. Eight patients were approved for dose augmentation and received at least 1 infusion at 40 mg/kg qow.

[3] A subset of the 33 patients were included in the clinical comparative analyses of efficacy; refer to **Section 6.1** for further details.

**6.1      Clinical Comparative Analyses of Efficacy**

The clinical efficacy of alglucosidase alfa produced at the 160 L and 2000 L scales was retrospectively investigated by comparing survival, invasive ventilator-free survival, cardiac function, and motor development in infantile-onset patients who received treatment with alglucosidase alfa produced at the 160 L scale and the 2000 L scale.

The analyses presented in this briefing package focus on the pivotal trial that served as the basis for the approval of BLA125141 (AGLU01602/02403; hereafter referred to as the 'Pivotal Study'), in which patients received treatment with 160 L alglucosidase alfa under a randomized, open-label, dose-ranging study protocol (AGLU01602) and subsequently switched to treatment with 2000 L alglucosidase alfa during the open-label extension study protocol (AGLU02403).  Limited data are presented in this briefing document for patients who received 160 L alglucosidase alfa in the open-label study AGLU01702.  While patients in AGLU01702 subsequently switched to 2000 L alglucosidase alfa, results of the analyses of post-switch data were similar to those obtained for the Pivotal Study, and have not been included in this briefing package in the interest of brevity.  Lastly, data have also been presented in this briefing package for selected patients in the US Expanded Access Study (AGLU02203) who were comparable in age at first infusion to patients in the Pivotal Study or AGLU01702.  These patients received initial treatment with 2000 L alglucosidase alfa during the study and thereafter switched to 160 L commercial product.

A total of 49 unique patients with infantile-onset Pompe disease were included in the original clinical comparative analyses, including the following patients from each study:

  •   All 18 patients treated in the Pivotal Study.

  •   All 21 patients treated in AGLU01702.

  •   Ten of 33 patients treated in the US Expanded Access Study.  The 10 patients from the US Expanded Access Study were selected by Genzyme for inclusion in the comparative analyses on the basis of their proximity in age at first infusion to patients in the Pivotal Study or AGLU01702 (i.e., 1 month to 3.5 years at treatment initiation) and their exclusive treatment with 2000 L alglucosidase alfa during the study.

Information on the above patients was included in the original clinical comparative analyses provided to FDA in the October 2007 supplement to BLA 125141. For informational purposes, data from 2 additional patients in the US Expanded Access Study (2203-511 and 2203-521), who were slightly younger than patients in the Pivotal Study (both patients were 0.5 months of age at treatment initiation), were included in an update provided to FDA, given their proximity in age to patients in the Pivotal Study (**Figure 6-1**). Of these 12 patients, FDA identified 7 patients from the US Expanded Access Study whom they considered to be comparable to patients in the Pivotal Study on the basis of Baseline characteristics such as age and invasive ventilation status (**Figure 6-1**). While results presented in this briefing package are based primarily upon the larger cohort of patients identified by Genzyme, results for the 7-patient cohort identified by FDA (which were similar) are also discussed, where applicable.

**Figure 6-1: US Expanded Access Study (AGLU02203) Patients Identified for Comparative Analyses by Genzyme and FDA**
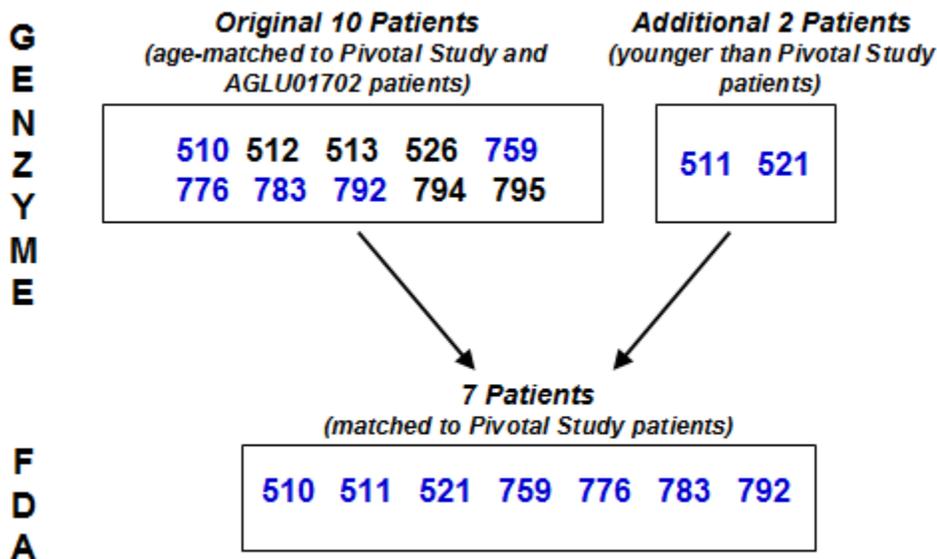


**Table 6-2** briefly summarizes the patient exposure to alglucosidase alfa produced at each scale and the clinical comparative analyses presented in this briefing document.

To evaluate the potential difference in clinical outcomes between patients treated with alglucosidase alfa derived from the 160 L and 2000 L processes, invasive ventilator-free survival was compared for the following groups of patients:

· Patients who received initial treatment with alglucosidase alfa derived from the 160 L scale, including all 18 patients in the Pivotal Study and 21 patients in AGLU01702 (statistical analyses excluded 5 patients in AGLU01702 who were invasively ventilated at Baseline);

· Ten age-matched patients in the US Expanded Access Study who received initial treatment with alglucosidase alfa derived from the 2000 L scale, (statistical analyses excluded 2 patients who were invasively ventilated at Baseline);

· Untreated patients in historical control / reference groups for the Pivotal Study (n=61) and AGLU01702 (n=84), which were derived from a larger cohort of 168 untreated patients in AGLU-004-00 (see **Section 3.1** for more details on this natural history study).

In addition, survival and invasive-ventilator-free survival were evaluated for patients in the Pivotal Study and US Expanded Access Study over their total exposure period, including the period of initial treatment with alglucosidase alfa derived from one manufacturing scale (160 L and 2000 L, respectively) and after patients had been switched to treatment with alglucosidase alfa derived from the other manufacturing scale (2000 L and 160 L, respectively) (**Section 6.1.1**).

The clinical analyses also included an evaluation of cardiac response for patients in the Pivotal Study and US Expanded Access Study for whom 2-dimensional (2D) left ventricular mass (LVM) Z-score data were available (**Section 6.1.2**), as well as an evaluation of motor response for patients who switched from 160 L to 2000 L alglucosidase alfa during the Pivotal Study (**Section 6.1.3**).

The clinical study databases were the main source for outcomes data for all patients in the Pivotal Study and AGLU01702, and for patients receiving 2000 L alglucosidase alfa in the US Expanded Access Study. Patients in the US Expanded Access Study transitioned to commercial therapy with 160 L alglucosidase alfa and, as status updates for survival

and invasive ventilation were requested by FDA, Genzyme solicited this information from each patient's treating physician.

**Table 6-2:  Summary of Clinical Comparative Analyses**

| Study ID | 'Initial' alglucosidase alfa Treatment | | | 'Switch' alglucosidase alfa Treatment | | | Number of Patients in Comparative Analyses | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | Scale | Number of Patients Treated and Analyzed | Mean Exposure for Patients Analyzed (weeks) | Scale | Number of Patients Treated and Analyzed | Mean Exposure for Patients Analyzed (weeks) | Invasive Ventilator-Free Survival Analysis | Cardiac Response | Motor Response |
| **AGLU01602/ 02403 (Pivotal Study)** | 160 L | 18 (9 patients each at 20mg/kg and 40mg/kg) | 95 | 2000 L | 16 (8 patients each at 20mg/kg and 40mg/kg) | 29 | 18 | 16 patients who switched scale | |
| **AGLU01702** | 160 L | 21 | 89 | 2000 L | 15 | 29 | 21[3] | Data on file at Genzyme; results similar to those for the Pivotal Study and thus omitted for brevity | |
| **AGLU02203 (US Expanded Access Study)** | 2000 L | 10 | 34[1] | 160 L | 10 | 82[1,] | 10 [2, 3, 4] | 18 patients (all patients with available 2D echocardiographic data) | Not evaluated |

[1] Mean exposure was summarized for 10 patients identified by Genzyme and included in the original clinical comparative analyses.  Mean exposure to 160 L alglucosidase alfa (which reflects exposure to commercial 160 L therapy after patients completed the US Expanded Access Study) was calculated as of 31 January 2008.

[2] Data for 2 additional patients who were slightly younger than patients in the Pivotal Study were included in data summaries, but excluded from all statistical analyses.

[3] Data for patients who were invasively ventilated at Baseline (2 patients in the US Expanded Access Study and 5 patients in AGLU01702) were included in data summaries, but excluded from the statistical analyses of invasive-ventilator-free survival.

[4] Similar results were obtained in the analysis of 7 age-matched patients identified by FDA.

While data were limited due to the small sample size available for evaluation, these retrospective clinical analyses do not suggest evidence of a meaningful difference in the efficacy of alglucosidase alfa produced at the 160 L versus 2000 L scale.  Summary findings for these retrospective comparative analyses are as follows:

- Alglucosidase alfa extended invasive ventilator-free survival, regardless of the manufacturing scale from which the alglucosidase alfa was derived, compared with untreated historical / reference cohorts in which less than 10% of patients survived beyond 24 months of age.

- Among patients who received treatment with alglucosidase alfa derived from both scales, there is no evidence to support a meaningful difference in the occurrence of events (death or invasive ventilation) between patients receiving initial treatment with 160 L alglucosidase alfa (Pivotal Study) versus 2000 L alglucosidase alfa (US Expanded Access Study).  The 95% CI intervals of the proportion of patients who experienced an event at each age milestone overlapped between patients in the Pivotal Study and the US Expanded Access Study.  At 18 months of age (the primary efficacy endpoint for the Pivotal Study), the proportion of patients who experienced an event was 17% (95% CI: 4 - 41%) in the Pivotal Study and 38% (95% CI: 9 - 76%) or 29% (4 – 71%) for the US Expanded Access Study patients identified by Genzyme and FDA, respectively.  Cox proportional hazards analysis did not support a difference in the risk of death or becoming invasively ventilated between patients receiving 160 L and 2000 L alglucosidase alfa (p=0.866, Hazard Ratio=1.18 comparing 2000 L to 160 L, 95% CI: 0.18 - 7.85).

- In the Pivotal Study and US Expanded Access Study, patients with CRIM-negative status and a persistent high anti-rhGAA IgG titer tended to respond more poorly to treatment, regardless of the manufacturing scale from which the alglucosidase alfa was derived.

- Among patients who responded poorly (due to CRIM-negative status, antibody titer, or other as yet undetermined factors), the likelihood of experiencing an event (death or invasive ventilation) increased over time, regardless of the

manufacturing scale from which the alglucosidase alfa was derived, suggesting an accumulated disease burden.

- In the Pivotal Study and US Expanded Access Study, there was a trend towards a reduction or stabilization of LVM Z-scores throughout the course of treatment, regardless of the manufacturing scale from which the alglucosidase alfa was derived.

- In the Pivotal Study, motor response was maintained in the vast majority (88%) of patients after the switch from 160 L to 2000 L alglucosidase alfa. Motor response was not evaluated in the US Expanded Access Study.

The lack of evidence supporting a meaningful difference in efficacy between 160 L and 2000 L lots of alglucosidase alfa is consistent with the comparative analysis of pharmacokinetics for patients in AGLU01602/02403, in which there was insufficient evidence supporting a meaningful difference in alglucosidase alfa pharmacokinetics between lots manufactured at the160 L and 2000 L scale (**Section 6.2**).

### 6.1.1 Overall Survival and Ventilator Free Survival In Patients Treated with alglucosidase alfa From Each Manufacturing Scale

Invasive ventilator-free survival at the initial treatment scale was evaluated from the time of first infusion of alglucosidase. Eighteen patients in the Pivotal Study and 16 patients in AGLU01702 (excluding 5 patients who were invasively-ventilated at Baseline) who received initial treatment with 160 L alglucosidase alfa, and 8 age-matched patients in the US Expanded Access Study (excluding 2 patients who were invasively ventilated at Baseline) who received initial treatment with 2000 L alglucosidase alfa, were included in the analysis.

No marked difference in invasive ventilator-free survival was observed between patients receiving initial treatment with 160 L versus 2000 L alglucosidase alfa. At 18 months of age (the primary efficacy time point in the Pivotal Study), the Kaplan-Meier invasive ventilator-free survival probability estimate was 88% for patients receiving 2000 L product in the US Expanded Access Study and 83% and 69% for patients receiving 160 L product in the Pivotal Study and AGLU01702, respectively. In order to place these results in context, survival curves from birth for untreated historical control / reference

patients were depicted along with invasive ventilator-free survival curves from birth for alglucosidase alfa-treated patients. As shown in **Figure 6-2**, alglucosidase alfa significantly extended patients' invasive ventilator-free survival, regardless of the manufacturing scale from which the alglucosidase alfa was derived, compared with that of untreated historical cohorts from the Pivotal Study and AGLU01702, in which less than 10% of patients survived beyond 24 months of age.

**Figure 6-2: Kaplan-Meier Estimate of Invasive Ventilator-Free Survival From Time of Birth for Alglucosidase Alfa-Treated Patients and Untreated Historical Control / Reference Patients**
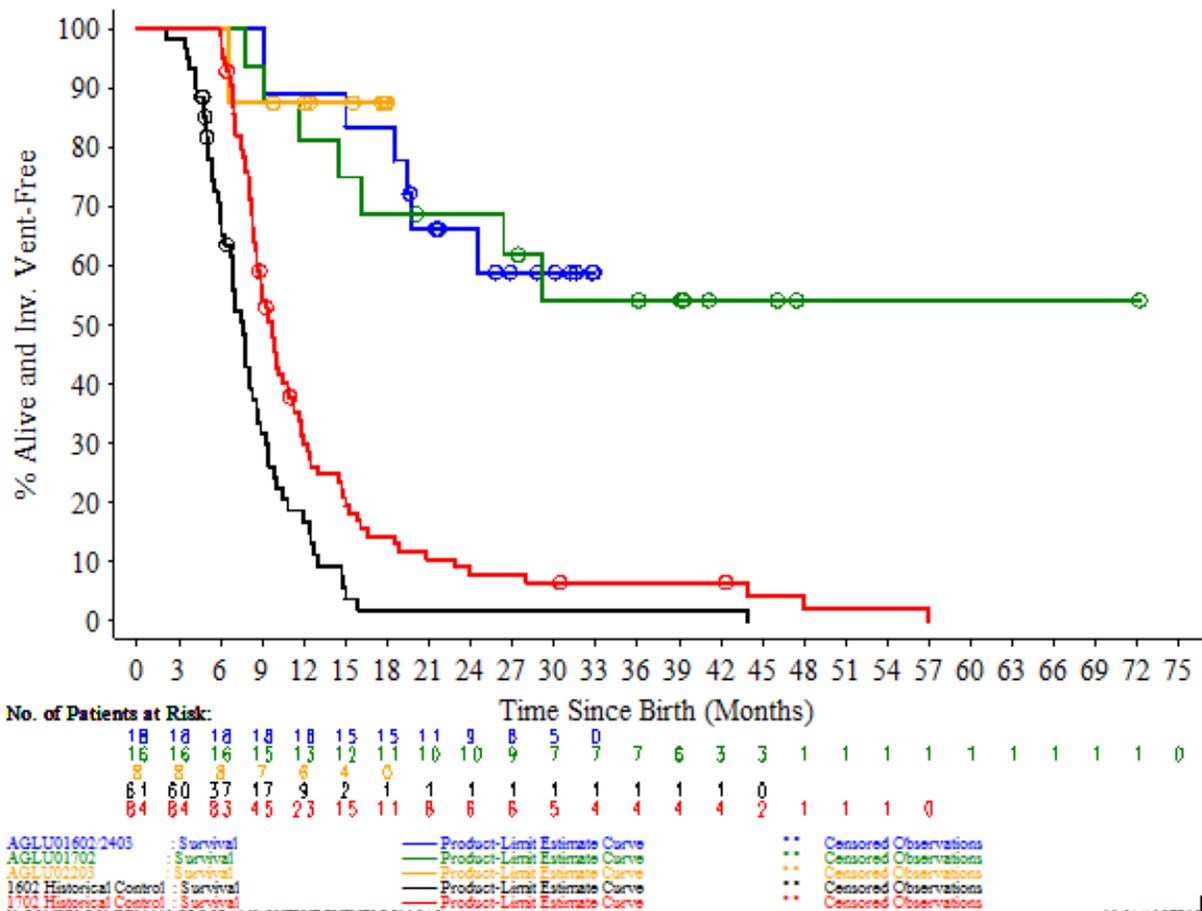


Following the original submission of clinical comparative data, FDA recommended that clinical outcomes data be evaluated for patients in the US Expanded Access Study who transitioned to 160 L commercial alglucosidase alfa after the study completed in July 2006, to provide an evaluation of efficacy over a longer duration of exposure. The

agency further suggested that the comparative analyses focus on a comparison of the invasive ventilator-free survival rate at 18 months for patients in the Pivotal Study (where this was the primary efficacy endpoint) versus patients with comparable Baseline characteristics in the US Expanded Access Study.  Accordingly, in January 2008, Genzyme solicited information from treating physicians on the survival and invasive ventilation status of each of the 12 patients who were included in the subset of US Expanded Access Study patients identified by Genzyme and/or by FDA (refer to **Figure 6-1**).  Results presented in this briefing package are based primarily upon the larger cohort of patients identified by Genzyme, and similar results were obtained for the 7-patient cohort identified by FDA.

**Figure 6-3** presents by-patient exposure to 160 L and 2000 L alglucosidase alfa and age at time of invasive ventilator dependence or death for patients in the Pivotal Study.  Similar by-patient data are presented for the US Expanded Access Study, both for patients identified by Genzyme (**Figure 6-4**) and patients identified by FDA (**Figure 6-5**).  Baseline clinical characteristics that were thought to potentially influence outcomes are also presented in these figures, including age at first infusion, CRIM status, and each patient's last anti-rhGAA IgG antibody titer.  In infantile-onset patients, CRIM-negative status has been observed to negatively impact response to treatment with alglucosidase alfa, and poor outcomes in these patients appear to be due in part to the development of high anti-rhGAA IgG titers.  Given the rapidly progressive nature of 'classic' infantile-onset Pompe disease (see **Section 3.1**), age at onset of treatment may also influence clinical outcome.

**Figure 6-3: Patient Exposure and Timing of Events in the Pivotal Study (AGLU01602/AGLU2403)[1]**
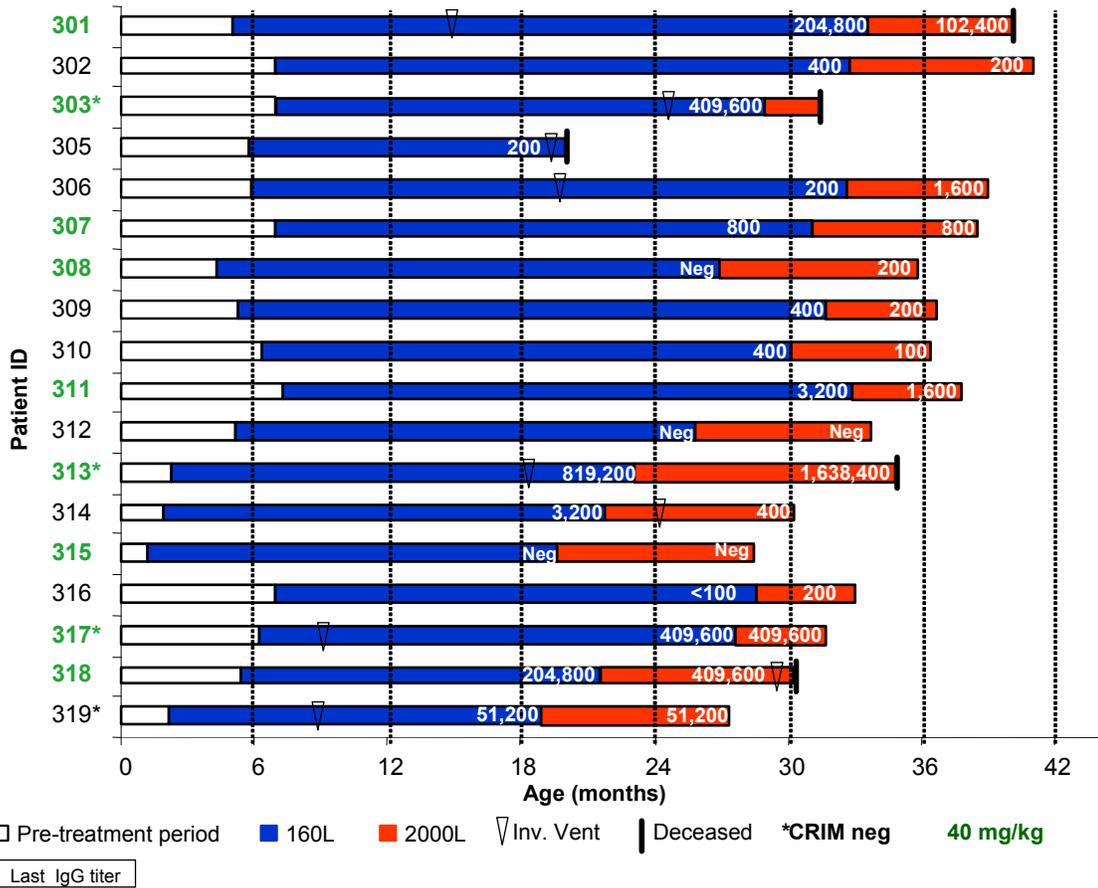


[1] Last titer available at the end of study exposure to alglucosidase alfa derived from each scale is shown. Note: After completion of treatment under AGLU01602, Patient 303 continued to receive treatment in International EAP (with 2000 L product, according to shipping records) and died approximately 3 months after starting commercial therapy, according to a spontaneous report received by Genzyme Pharmacovigilance.

**Figure 6-4:  Patient Exposure and Timing of Events in the US Expanded Access
Study (AGLU02203): Patients Identified by Genzyme[1]**
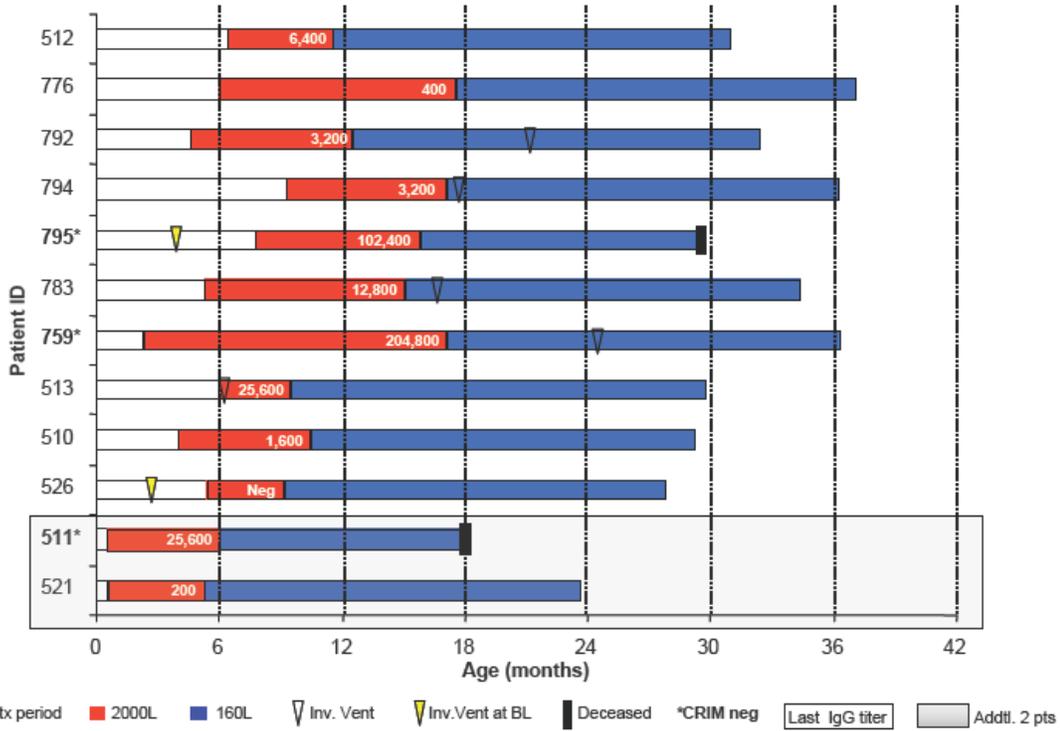


[1] Last titer available during study at end of 2000 L alglucosidase alfa exposure is shown
Note: Patient 2203-511 and Patient 2203-795 were confirmed CRIM-negative by Western blot, while
Patient 2203-759 was predicted to be CRIM-negative based on genotype analysis (Western blot data were
not available for this patient).
Note: Data for Patient 2203-511 and Patient 2203-521 (see box at bottom of figure) were included for
informational purposes; data for these patients were not included in statistical analyses.

**Figure 6-5: Patient Exposure and Timing of Events in the US Expanded Access Study (AGLU02203): Patients Identified By FDA[1]**
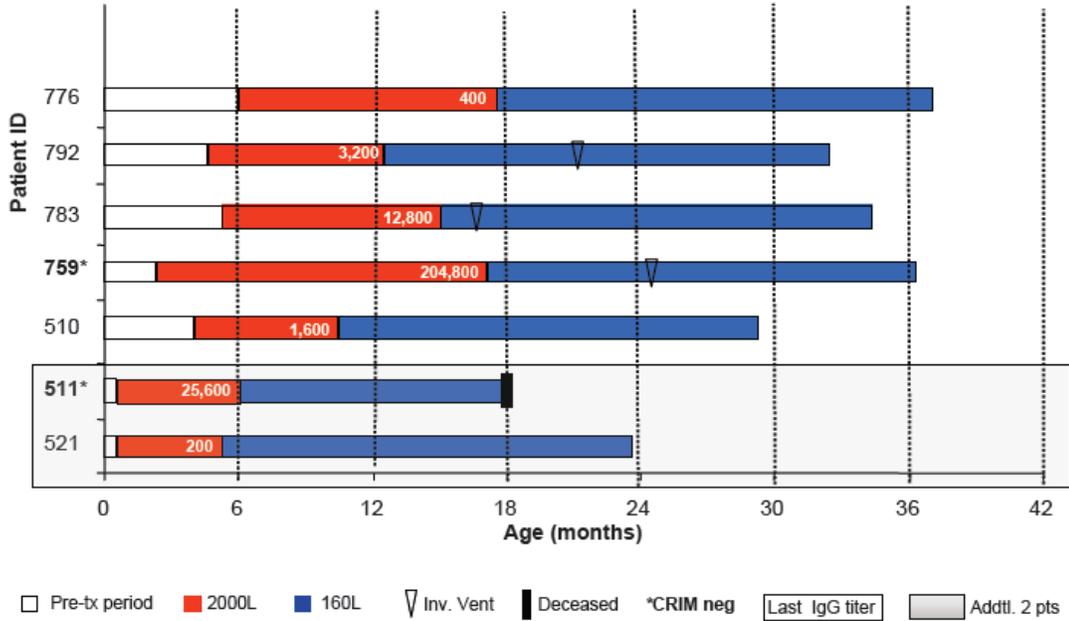


[1] Last titer available during study at end of 2000 L exposure is shown.

As shown in the above figures, a small number of patients respond poorly to treatment. Among these patients, events such as death or invasive ventilation occurred later in treatment, independent of the scale used to derive the alglucosidase alfa administered at treatment initiation and during the 'switch' period. In the Pivotal Study, 3 events occurred prior to age 16.6 months (the midpoint of the average age at last follow up), while 11 events occurred past that age, with events occurring almost equally in patients receiving treatment with alglucosidase alfa derived from each scale. Among the 10 age-matched US Expanded Access Study patients identified by Genzyme, 1 event occurred prior to age 16.1 months (the midpoint of average age at last follow up), while 5 events occurred past that age, with a majority of events occurring while patients were receiving 160 L product. A similar trend was observed among the 7 US Expanded Access Study patients identified by FDA. The order of scale exposure is a confounding variable in assessing outcomes, given the longer duration of exposure to 160 L alglucosidase alfa compared with 2000 L alglucosidase alfa in each study (**Table 6-2**).

However, these findings suggest that events in poor responders are occurring when disease progression reaches a critical threshold, rather than as a circumstance of the scale used to derive the alglucosidase alfa that the patient received.

Table 6-3 and Table 6-4 show individual patient ID color coded by scale at time of events of death, invasive ventilation, and death or invasive ventilation in the Pivotal Study and the US Expanded Access Study, respectively.  Events were summarized for all 18 patients receiving treatment under the Pivotal Study.  For the US Expanded Access Study, events of death were summarized for 10 age-matched patients identified by Genzyme and events of invasive ventilation /death or invasive ventilation alone were summarized for the subset of 8 age-matched patients who were not invasively ventilated at Baseline (i.e., excluding 2203-795 and 2203-526).  These data are consistent with the interpretation that among the patients who respond poorly to treatment, disease burden accumulates over time, regardless of the manufacturing scale from which the alglucosidase alfa was derived.

**Table 6-3: By-Patient Summary of Death and Invasive Ventilator Events by Scale For Patients in the Pivotal Study (AGLU01602/AGLU2403) (N=18)[1,2]**

| Event | 12 m | 18 m | 24 m | 30 m | 36 m | 42 m | Any Age (Total) |
|---|---|---|---|---|---|---|---|
| **Deceased** | NA | NA | 305 | NA | 303*, 313*, 318 | 301 | 305, 303*, 313*, 318, 301 |
| **Invasively Vented** | 317*, 319* | 301 | 305, 306, 313* | 303*, 318, 314, | NA | NA | 317*, 319*, 301, 305, 306, 313*, 303*, 318, 314, |
| **Deceased or Invasively Vented[3]** | 317*, 319* | 301 | 305, 306, 313* | 303*, 318, 314, | NA | NA | 317*, 319*, 301, 305, 306, 313*, 303*, 318, 314, |

m=months of age; 160 L = blue; 2000 L = red; NA= not applicable, i.e., no new events were recorded at this age milestone
1. After completion of treatment under AGLU01602, Patient 303 continued to receive treatment in International EAP (with 2000 L product, according to shipping records) and died approximately 3 months after starting commercial therapy, according to a spontaneous report received by Genzyme Pharmacovigilance.
2. Patients 303, 313, 317, and 319 were CRIM-negative by Western blot. These patients are also denoted by asterisks (*).
3. Patients 301 and 313 are shown in mixed scale color, as invasive ventilation occurred at one scale (160 L) and death at another scale (2000 L).

**Table 6-4:  By-Patient Summary of Death and Invasive Ventilator Events by Scale For Patients in the US Expanded Access Study (AGLU02203) (N=10)**

| Event | 12 m | 18 m | 24 m | 30 m | 36 m | Any Age (Total) |
|---|---|---|---|---|---|---|
| **Deceased[1]** | NA | NA | NA | 795* | NA | 795* |
| **Invasively Vented[2]** | 513 | 783, 794 | 792 | 759* | NA | 513, 783, 794, 792, 759* |
| **Deceased or Invasively Vented[2]** | 513 | 783, 794 | 792 | 759* | NA | 513, 783, 794, 792, 759* |

m=months of age; 160 L = blue; 2000 L = red; NA= not applicable, i.e., no new events were recorded at this age milestone

1. Patient 2203-795 was CRIM-negative by Western blot, and Patient 2203-759 was predicted to be CRIM-negative based on genotype analysis.  These patients are also denoted by asterisks (*).

2. Excluded 2 patients who were invasively ventilated at Baseline (2203-795 and 2203-526).

The small number of subjects in both studies poses a challenge to the interpretation of the data. Over the course of time on treatment, changes in survival among a small sample size have a deeper impact on the proportion of patients remaining alive and ventilator-free. Therefore, statistical analyses were performed to further evaluate the potential impact of alglucosidase alfa manufacturing scale on clinical outcomes. For the Pivotal Study, these analyses were performed using data from all 18 treated patients. For the US Expanded Access Study, these analyses were performed using data from 8 age-matched patients identified by Genzyme (excluding 2 patients who were invasively ventilated at Baseline and thus did not match the Baseline characteristics of patients in the Pivotal Study), as well as with data for the 7 patients whom FDA identified as being comparable in Baseline characteristics to patients in the Pivotal Study.

After 18 months of age, the binomial proportion of survival was higher among patients in the Pivotal Study than in the US Expanded Access Study. However, the 95% CI overlapped between the 2 study cohorts at all age milestones. Results through 24 months of age (the last time point when follow-up data were available for all patients) are presented in **Table 6-5**.

The Cox proportional hazards model was also employed to evaluate whether the risk of death and becoming invasively ventilated was higher while patients were receiving 2000 L versus 160 L lots. Time of 160 L or 2000 L use (a time-varying covariate) and age at first infusion were included as covariates in the model, and study protocol was included as a stratification variable. CRIM status was not included as a covariate in the statistical model (although CRIM status has prognostic value on patient outcome), because CRIM testing by Western blot was not performed for each of the 8 age-matched patients from the US Expanded Access Study that were included in this analysis. The results (p=0.866, Hazard Ratio=1.18 comparing 2000 L to 160 L, 95% CI: 0.18 - 7.85) do not provide evidence in support of a difference in the risk of death or becoming invasively ventilated between patients receiving 160 L and 2000 L alglucosidase alfa. Similar results were obtained for an analysis including the 7 patients identified by FDA.

Baseline characteristics with the potential to influence survival outcome were also analyzed for patients who were alive and invasive ventilator-free versus patients who did not survive or became invasively ventilated during treatment. CRIM status appeared to be most important factor influencing the development of sustained high antibody titers

and poor outcome regardless of the manufacturing scales. In the Pivotal Study AGLU01602/AGLU2403, all 4 patients who were CRIM-negative by Western blot developed high and sustained anti-rhGAA IgG antibody titers and responded poorly to treatment. Although CRIM status was not determined for the 8 age-matched patients in the US Expanded Access Study evaluated for survival, the 1 patient who was predicted to be CRIM negative based on GAA gene mutation analysis (Patient 2203-759) was also among those with poor clinical outcomes. In contrast, for CRIM-positive patients in the Pivotal Study, 5 of 14 patients were noted to have poor clinical outcome, 2 of whom had high and sustained anti-rhGAA antibody titers. The magnitude of the immune response among patients with poor clinical outcomes seems comparable between patients exposed initially to 160 L (Pivotal Study) or 2000 L (US Expanded Access Study). The seroconversion rate was comparable for patients in the Pivotal Study (89%; 16 of 18 patients) and patients in the US Expanded Access Study (90%; 9 of 10 patients). No meaningful differences were observed in IgG titer levels among naïve patients who were treated initially with 160 L (Pivotal study) or 2000 L (Expanded access study) or after the switch from 160 L to 2000 L.

Other characteristics such as age at first infusion, heart size at Baseline (as determined by left ventricular mass [LVM] Z-score), and the dose of alglucosidase alfa administered (40 or 20 mg/kg in the Pivotal Study), did not appear to be differentiating features in outcome. It should be noted, however, that the analysis of age at first infusion was limited by the narrow age range of patients in both the Pivotal Study (1.2-7.3 months) and the US Expanded Access Study (2.3-9.3 months). As discussed in **Section 5.2.1.5**, the clinical hypothesis for ERT would suggest that early initiation of treatment may likely influence the extent of functional recovery that can be achieved.

**Table 6-5: Proportion of Patients Deceased or Invasively Ventilated by Milestone Age in the Pivotal Study (AGLU01602/02403) and the US Expanded Access Study (AGLU02203)**

| | 12 months | | | 18 months | | | 24 months[2] | | |
|---|---|---|---|---|---|---|---|---|---|
| | **N** | **%** | **95% CI** | **N** | **%** | **95% CI** | **N** | **%** | **95% CI** |
| **Pivotal Study (**N=18) | | | | | | | | | |
| Deceased or Ventilated | 2 | 11 | 1, 35 | 3 | 17 | 4, 41 | 6 | 33 | 13, 59 |
| **US Expanded Access Study (Patients Identified by Genzyme,** N=8[1]) | | | | | | | | | |
| Deceased or Ventilated | 1 | 13 | 0, 53 | 3 | 38 | 9, 76 | 4 | 50 | 16, 84 |
| **US Expanded Access Study (Patients Identified by FDA,** N=7) | | | | | | | | | |
| Deceased or Ventilated | 0 | 0 | NA | 2 | 29 | 4, 71 | 3 | 43 | 10, 82 |

NA = not applicable
1. Two of the 10 age-matched patients identified by Genzyme were invasively ventilated at Baseline and were therefore excluded from this analysis
2. Rate beyond age 24 months is not presented because not all patients had follow-up data beyond this time point.

In summary, these clinical comparative analyses suggest that the likelihood of experiencing an event (death or invasive ventilation) is independent of the manufacturing scale from which the alglucosidase alfa is derived. Rather, among patients who responded poorly due to CRIM-negative status, antibody titer, or other as yet undetermined factors, the occurrence of events appears to be largely dependent on disease burden accumulated over time.

**6.1.2    Cardiac Response In Patients Treated with Alglucosidase Alfa From Each Manufacturing Scale**

Improvement in LVM is an important feature of alglucosidase alfa response likely contributing to prolonged survival in patients with infantile onset Pompe disease (Kishnani, 2007, *Neurology*). For the clinical comparative analyses, the change in LVM Z-score was evaluated over time for patients with 2D echocardiographic data.

In the Pivotal Study, echocardiograms were obtained at regular intervals according to procedures specified in a central cardiology manual, and LVM was calculated via 2D mode measurements by a central cardiologist reader. All 18 patients in the study provided 2D echocardiographic data. For these 18 patients, there was a reduction of

LVM Z-scores following initiation of alglucosidase alfa treatment and subsequent stabilization with continued treatment.  Furthermore, no marked changes in cardiac response were observed after switch from 160 L to 2000 L alglucosidase alfa for the 16 patients in the Pivotal Study who received treatment with product from both scales. Mean LVM Z-score was near the normal range (+2 to -2 Z-scores) at the last visit prior to switching (2.8 ± 1.8; N=16) and through Week 26 after switch from 160 L to 2000 L alglucosidase alfa (3.1 ± 2.0; N=8).  While there was a slight increase in mean LVM Z-score at Week 38 after scale switch (mean 4.0 ± 2.8), LVM Z-scores were only available for 3 patients at this time point:  Patients 302 and 315 exhibited increases in LVM Z-score before scale switch and Patient 319, who was CRIM-negative, had persistent high anti-rhGAA antibody titers that are thought to have contributed to the observed increase in LVM Z-score after scale switch.

In the US Expanded Access Study, echocardiograms were obtained according to local site protocols (i.e., not centrally standardized), and LVM was calculated by 2D or M-mode by the local site cardiologist.  Given the differences in echocardiogram acquisition and the fact that data were not read by central cardiologist, no formal comparative analyses were performed.  However, data were plotted for informational purposes for the 18 patients in the total study population who had 2D echocardiographic data, 7 of whom were in the age-matched cohort identified by Genzyme (refer to **Figure 6-1**).  As shown in **Figure 6-6**, a majority of these 18 patients showed a reduction or stabilization in LVM Z-scores over time, despite the relatively short and variable period of exposure to alglucosidase alfa (160 L and/or 2000 L) and the generally more advanced cardiac disease at Baseline in these patients relative to patients in the Pivotal Study (i.e., LVM Z-scores in the US Expanded Access Study were approximately 1.5 Z-scores higher, on average, than in the Pivotal Study).  Among the 6 patients who received treatment with alglucosidase alfa derived from both scales (and had available data for both scales), LVM Z-score remained stable or continued to decline after the switch.

Together, these data suggest that cardiac response, as measured by LVM Z-score, is relatively sensitive to ERT and does not differ significantly for patients treated with alglucosidase alfa produced at the 160 L and 2000 L scales.

**Figure 6-6: LVM Z-score Over Time for Patients in the US Expanded Access Study (AGLU02203)**
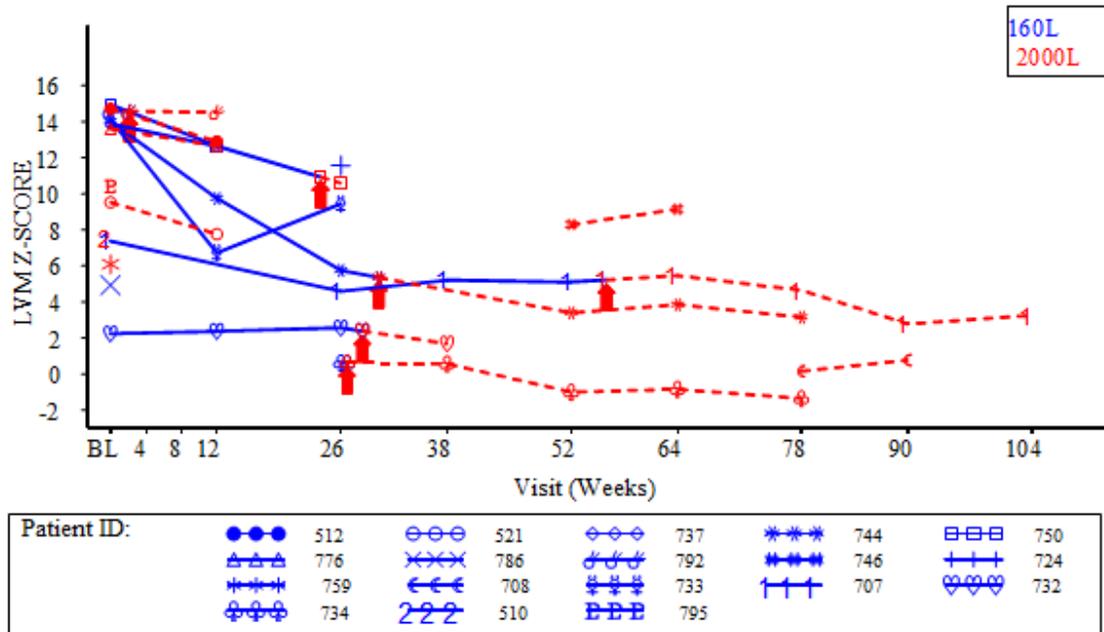


† represents the first 2000L infusion and it is based on the actual week from the first infusion.

Blue = 160 L; Red = 2000 L
Note: Only partial data are available for some patients, as echocardiographic measurements of LVM were missing and/or calculated by M-mode at other time points.

### 6.1.3    Motor Response In Patients Treated with Alglucosidase Alfa From Each Manufacturing Scale

In the Pivotal Study, the Alberta Infant Motor Scale (AIMS) was used to assess motor development. The AIMS was developed to assess normal patterns of motor development in infants from birth through 18 months of age. Table 6-6 shows a by-patient summary of 3 motor response categories for the 16 patients in the Pivotal Study who switched from treatment with 160 L alglucosidase alfa to 2000 L alglucosidase alfa. These categories are defined by Genzyme as follows:

- **Walker:** patient ambulates independently (AIMS Standing subscale score $\geq$ 12)

- **Functional sitter:** patient cannot ambulate but can sit independently with functional use of the trunk and arms (AIMS Standing subscale score < 12 and AIMS Sitting subscale score $\geq$ 8)

- **Motor non-responder:** patient is unable to walk or sit independently (AIMS Standing subscale scores < 12 and AIMS Sitting subscale scores < 8)

As shown in **Table 6-6**, all but 2 (Patients 313 and 314) maintained their motor response category after alglucosidase alfa scale switch.

**Table 6-6**: **By-Patient Summary of Motor Response Category After alglucosidase alfa Scale Switch For Patients in the Pivotal Study (AGLU01602/AGLU2403)**

| Motor Response | 160 L[1] | 2000 L[1] |
|---|---|---|
| Walker | 302, 307, 308, 309, 310, **314**, 315, 316 | 302, 307, 308, 309, 310, 315, 316 |
| Functional Sitter | 311, 312, **313***, 318 | 311, 312, **314**, 318 |
| Motor Non-Responder | 301, 306, 317*, 319* | 301, 306, **313***, 317*, 319* |

Blue = 160 L; Red = 2000 L
Note: Bolded text represents patients who have changed motor response category.
[1]Mean exposure was 95 weeks for 160 L and 29 weeks for 2000 L.
2. Patients 313, 317, and 319 were CRIM-negative by Western blot. These patients are denoted by asterisks (*).

Patient 313, who was CRIM-negative and developed high anti-rhGAA IgG antibody titers, met criteria for a "Functional Sitter" at the time of the transition to 2000 L material but thereafter experienced a rapid decline in motor function and a subsequent need for invasive ventilation at Week 70. By Week 78 (age 20.3 months), the patient had lost motor function relative to Baseline, including all prone skills, the ability to roll, and all anti-gravity movement in legs, but was still able to sit independently. At the time of transition to 2000 L alglucosidase alfa at Week 90 (age 23.0 months), this patient had declined further, and lost all unsupported sitting skills.

Patient 314, who was a CRIM-positive patient, had acquired motor skills since starting treatment and met criteria for a "Walker" at Week 78 (age 19.9 months), just prior to the transition to 2000 L material. After transition to 2000 L alglucosidase alfa, the patient experienced a decline in respiratory function due to pneumonia, and by Week 98 (age 24.5 months) the patient was invasively ventilated and had lost previously acquired motor milestones. By Week 116 (age 28.6 months), the last motor assessment performed in the study, Patient 314 had lost virtually all prone skills, but was still able to sit independently and met criteria for a "Functional Sitter."

A similar assessment of motor response was not performed for the US Expanded Access Study as the AIMS assessment was not performed per protocol due to heterogeneity in patient age and clinical status at Baseline.

## 6.2        Clinical Comparative Analyses of Pharmacokinetics

A pharmacokinetic comparison of alglucosidase alfa lots produced at the 160 L and 2000 L scales was performed using pharmacokinetic data derived from a limited subset of 12 patients in the Pivotal Study who were switched from 160 L lots to 2000 L lots of alglucosidase alfa.

Per the Pivotal Study protocol, plasma GAA activity was measured after administration of the last dose of 160 L alglucosidase alfa and again at the time of the first or second dose of 2000 L alglucosidase alfa to facilitate a comparison of the pharmacokinetics of alglucosidase alfa produced at these 2 scales.  An additional set of blood samples were obtained after the patient had received treatment with 2000 L alglucosidase alfa for a minimum of 12 weeks, i.e., 6 doses (referred to as the "2000 L Repeat" sample).

The pharmacokinetic parameters for 160 L, 2000 L, and 2000 L Repeat are summarized in **Table 6-7**.  A comparison of alglucosidase alfa Cmax (the maximal observed concentration) and AUC(0-$\infty$) (the area under the concentration-time curve (AUC) from time zero to infinity) between 160 L and 2000 L lots was performed using an analysis of variance statistical model with dose, patient, and scale as the classification variables, using the natural logarithms of the data.

As shown in **Table 6-8**, all point estimates for the geometric mean ratios for AUC(0-$\infty$) were within the standard bioequivalence limits for the 90% CIs, i.e., 80% to 125% (FDA Guidance *Statistical Approaches to Establishing Bioequivalence, 2001)* with the exception of the repeat 2000 L vs. 160 L comparison; however, the 90% CIs for the comparisons were not contained within the 80% to 125% equivalence range, likely due to the small sample size (n=11 to 12).  Furthermore, there were no statistically significant differences among the geometric least squares means for any of the individual AUC contrasts or for the combined 2000 L lots vs. the 160 L lot, providing further support that exposure to alglucosidase alfa is independent of the manufacturing scale from which the drug product is derived.

The geometric mean ratios for Cmax ranged from 77% to 140% and none of the 90% CIs fell within the 80% to 125% equivalence window.  Significant differences among the geometric least squares means for Cmax were noted for some of the contrasts (**Table 6-8**).  However, Cmax is dependent not only on the dose of enzyme administered, but also on the time over which that dose is infused.  The time over which the dose was administered varied both among and within patients, making the comparisons of this parameter among the 3 lots used more qualitative than quantitative.  In addition, the difference in Cmax may have been skewed by the inclusion of one patient with Cmax values for the 160 L lot and 2000 L repeat lot that were considerably smaller than those of other patients; the reason for the low concentrations was unknown.  Removal of this outlier improved the precision of the CIs of the geometric mean ratios and made the point estimates themselves closer to each other (**Table 6-9**).

Finally, an evaluation of individual patient values for Cmax and AUC(0-∞) across the 160 L, 2000 L, and 2000 L Repeat showed these parameters to be comparable for a majority of patients (data not shown), again suggesting a lack of any meaningful difference in alglucosidase alfa pharmacokinetics between drug product lots manufactured at the160 L and 2000 L scale.

**Table 6-7: Summary of Pharmacokinetic Parameters for Alglucosidase Alfa after IV Administration of 160 L and 2000 L Lots in AGLU02403**

| Parameter [1] | 160 L [2] | 2000 L [2] | 2000 L Repeat [2] |
|---|---|---|---|
| **20 mg/kg** | | | |
| Weight (kg) | 12.6 ± 1.43 (7) | 12.9 ± 1.16 (6) | 12.9 ± 1.48 (6) |
| K10 (h$^{-1}$) | 0.307 ± 0.066 (7) | 0.288 ± 0.073 (5) | 0.325 ± 0.061 (6) |
| V | | | |
|   (mL) | 1,430 ± 1,015 (7) | 870 ± 377 (5) | 1,347 ± 1,064 (6) |
|   (mL/kg) | 111 ± 74.1 (7) | 67.3 ± 27.3 (5) | 103.6 ± 77.2 (6) |
| CL | | | |
|   (mL/h) | 483 ± 461 (7) | 254 ± 131 (5) | 416 ± 297 (6) |
|   (mL/h/kg) | 37.4 ± 34.1 (7) | 19.5 ± 9.56 (5) | 31.9 ± 21.4 (6) |
| Cmax (ng/mL) | 168,0969 ± 96,968 (7) | 269,269 ± 232,608 (6) | 176,119 ± 71,640 (6) |
| AUC(inf) (h•ng/mL) | 815,347 ± 418,759 (7) | 1,238,280 ± 619,243 (5) | 777,156 ± 284,476 (6) |
| MRT (h) | 3.28 ± 0.56 (7) | 3.31 ± 0.58 (5) | 2.96 ± 0.34 (6) |
| t½ (h) | 2.36 ± 0.56 (7) | 2.53 ± 0.64 (5) | 2.21 ± 0.46 (6) |
| **40 mg/kg** | | | |
| Weight (kg) | 13.0 ± 2.55 (5) | 13.0 ± 2.57 (5) | 13.3 ± 2.59 (5) |
| K10 (h$^{-1}$) | 0.344 ± 0.068 (5) | 0.323 ± 0.047 (4) | 0.361 ± 0.052 (5) |
| V | | | |
|   (mL) | 1,016 ± 660 (5) | 844 ± 195 (4) | 919 ± 299 (5) |
|   (mL/kg) | 81.3 ± 57.2 (5) | 69.9 ± 9.06 (4) | 68.8 ± 17.9 (5) |
| CL | | | |
|   (mL/h) | 329 ± 158 (5) | 266 ± 35.0 (4) | 324 ± 88.1 (5) |
|   (mL/h/kg) | 25.8 ± 13.5 (5) | 22.3 ± 2.5 (4) | 24.3 ± 3.84 (5) |
| Cmax (ng/mL) | 268,512 ± 88,454 (5) | 291,130 ± 56,283 (5) | 254,288 ± 42,055 (5) |
| AUC(inf) (h•ng/mL) | 1,796,195 ± 566,697 (5) | 1,806,667 ± 200,625 (4) | 1,678,773 ± 246,453 (5) |
| MRT (h) | 2.99 ± 0.57 (5) | 3.15 ± 0.51 (4) | 2.81 ± 0.37 (5) |
| t½ (h) | 2.08 ± 0.39 (5) | 2.19 ± 0.36 (4) | 1.95 ± 0.25 (5) |

[1] Arithmetic mean ± standard deviation (N)
[2] PK was evaluated after the last dose of 160 L (160 L), after the first or second dose of 2000 L (2000 L), and after the 6th dose of 2000 L (2000 L Repeat).

**Table 6-8:  Statistical analysis of pharmacokinetic parameters for Alglucosidase Alfa after IV administration of 160 L and 2000 L lots in AGLU02403**

| Parameter | Geometric Means | | Geometric Mean Ratio[1] | | Within-Subject CV (%) |
|---|---|---|---|---|---|
| | Test | Reference | Estimate | 90% Confidence Interval | |
| 2000 L (Combined) vs. 160 L | | | | | |
| Cmax | 224,789 | 182,318 | 123.3 | 104.5 → 145.5 | 27.1 |
| AUC(0-∝) | 1,203,790 | 1,073,844 | 112.1 | 97.1 → 129.4 | 22.6 |
| | | | | | |
| 2000 L vs 160 L | | | | | |
| Cmax | 255,520 | 182,318 | 140.2 | 115.5 → 170.1 | 27.1 |
| AUC(0-∝) | 1,326,502 | 1,073,844 | 123.5 | 103.5 → 147.4 | 22.6 |
| | | | | | |
| 2000 L (R) vs. 160 L | | | | | |
| Cmax | 197,755 | 255,520 | 108.5 | 89.4 → 131.6 | 27.1 |
| AUC(0-∝) | 1,092,431 | 1,073,844 | 101.7 | 86.4 →119.8 | 22.6 |
| | | | | | |
| 2000 L (R) vs. 2000 L | | | | | |
| Cmax | 197,755 | 255,520 | 77.4 | 63.3 → 94.6 | 27.1 |
| AUC(0-∝) | 1,092,431 | 1,326,502 | 82.4 | 68.6 → 98.9 | 22.6 |

[1]  Based on analysis of log-transformed data

**Table 6-9:  Statistical analysis of pharmacokinetic parameters for Alglucosidase Alfa after IV administration of 160 L and 2000 L lots in AGLU02403— Patient 2403-316 Excluded**

| Parameter | Geometric Means | | Geometric Mean Ratio[1] | | Within-Subject CV (%) |
|---|---|---|---|---|---|
| | Test | Reference | Estimate | 90% Confidence Interval | |
| 2000 L (Combined) vs. 160 L | | | | | |
| Cmax | 241,858 | 211,239 | 114.5 | 98.7 → 132.8 | 22.9 |
| AUC(0-∝) | 1,316,547 | 1,206,554 | 109.1 | 94.3 →126.3 | 22.2 |
| | | | | | |
| 2000 L vs 160 L | | | | | |
| Cmax | 270,350 | 211,239 | 128.0 | 107.6 → 152.2 | 22.9 |
| AUC(0-∝) | 1,465,412 | 1,206,554 | 121.5 | 101.9 → 144.8 | 22.2 |
| | | | | | |
| 2000 L (R) vs. 160 L | | | | | |
| Cmax | 216,368 | 211,239 | 102.4 | 86.1 → 121.8 | 22.9 |
| AUC(0-∝) | 1,182,206 | 1,206,544 | 98.0 | 82.8 → 116.1 | 22.2 |
| | | | | | |
| 2000 L (R) vs. 2000 L | | | | | |
| Cmax | 216,368 | 270,350 | 80.0 | 66.9 → 95.8 | 22.9 |
| AUC(0-∝) | 1,182,806 | 1,465,412 | 80.7 | 67.2 → 96.9 | 22.2 |

[1]  Based on analysis of log-transformed data

**7          CLINICAL EXPERIENCE WITH 2000 L ALGLUCOSIDASE ALFA IN INFANTILE-ONSET POMPE DISEASE**

Although Genzyme is seeking approval for a late-onset indication only for 2000 L alglucosidase alfa, efficacy and safety data from infantile-onset patients treated in a single-center, investigator-sponsored study in Taiwan (hereafter referred to as the 'Taiwan Study') are also included in this briefing package to support the efficacy and safety of the 2000 L product in patients with this rapidly progressive form of Pompe disease. Efficacy and safety assessments in this study were prospectively defined based on the schedule of assessments in AGLU01602 (the pivotal study supporting approval of 160 L alglucosidase alfa in the US), and data are available for all patients for whom assessments were age-appropriate.

Eleven patients with a confirmed diagnosis of infantile-onset Pompe disease, who were identified either through the National Taiwan University Hospital (NTUH) newborn screening program (6 patients) or based on clinical symptoms of Pompe disease (5 patients), received treatment with alglucosidase alfa in this study. Six patients (54.5%) were male and 5 (45.5%) were female; all (100.0%) were Taiwanese. The median age at first symptoms was 2.0 months (range of 0.2 to 5.0 months), and median age at initial diagnosis of Pompe disease was 1.3 months (range of 0.2 to 5.8 months). All patients were predicted to be CRIM-positive based on GAA mutation analysis.

All patients exclusively received alglucosidase alfa produced at the 2000 L scale. Ten patients received alglucosidase alfa at a dose of 20 mg/kg qow, and 1 patient received alglucosidase alfa at a dose of 40 mg/kg qow. As of the data cutoff of 28 May 2008, median duration of treatment with alglucosidase alfa was 16.5 months (range 5.1 to 27.0 months). The median age at first alglucosidase alfa infusion was 3.3 months (range: 0.4 to 14.0 months). A majority of patients (9 patients; 81.8%) received alglucosidase alfa treatment for at least 26 weeks, and 7 (63.6%) patients received treatment for at least 52 weeks. As of 02 June 2008, all 11 patients were continuing to receive alglucosidase alfa treatment.

Efficacy data presented in this briefing package include survival, ventilator status, cardiac status, and motor development (**Section 7.1**). Safety data presented in this briefing package include spontaneously reported AEs, routine laboratory tests (clinical chemistry: aspartate aminotransferase, alanine aminotransferase, and creatine kinase; hematology;

urinalysis), and monitoring for anti-rhGAA IgG antibodies (**Section** 7.2). These efficacy and safety parameters have been summarized in the briefing package given their similarity to outcome measures assessed in the infantile-onset pivotal study of alglucosidase alfa AGLU01602, on which the US prescribing information for 160 L product is based. Histopathological changes in skeletal muscle are also presented for selected patients.

Additional efficacy assessments (i.e., cognitive development) and safety assessments (i.e., vital signs, physical examination, ECGs, and hearing tests) were performed in this investigator-sponsored study, but these data were not collected by Genzyme Corporation.

## 7.1 Summary of Efficacy in Infantile-Onset Patients Treated in Taiwan

The Kaplan-Meier estimate of the percentage of patients alive and free of ventilator support is displayed in **Figure 7-1**. All 11 patients (100.0%) were alive and free of ventilator support at the time of their last follow-up visit, with a median age at last follow-up of 23.7 months (range 5.5 to 31.1 months), which is consistent with the prolongation of ventilator-free survival observed for infantile-onset patients treated with alglucosidase alfa in AGLU01602 and the subsequent extension study AGLU02403 (also shown in **Figure 7-1**). In contrast, in an untreated historical control population of 61 infantile-onset patients, which was initially selected for comparison with treated patients in AGLU01602 and included cases from NTUH, only 16.8% patients were alive at 12 months of age and only 1.9% patients were alive at 18 months of age (**Figure 7-1**). Of note, survival was similar between Asian and non-Asian patients in this historical control cohort. Therefore, the ventilation-free survival of the 11 Taiwanese patients represents a dramatic departure from the rapid progression to death that is typically observed in untreated 'classical' infantile-onset patients.

**Figure 7-1:  Kaplan-Meier Estimate of Percentage of Patients Alive and Free of Ventilator Support in the Taiwan Study Versus AGLU01602 Patients and Untreated Patients**
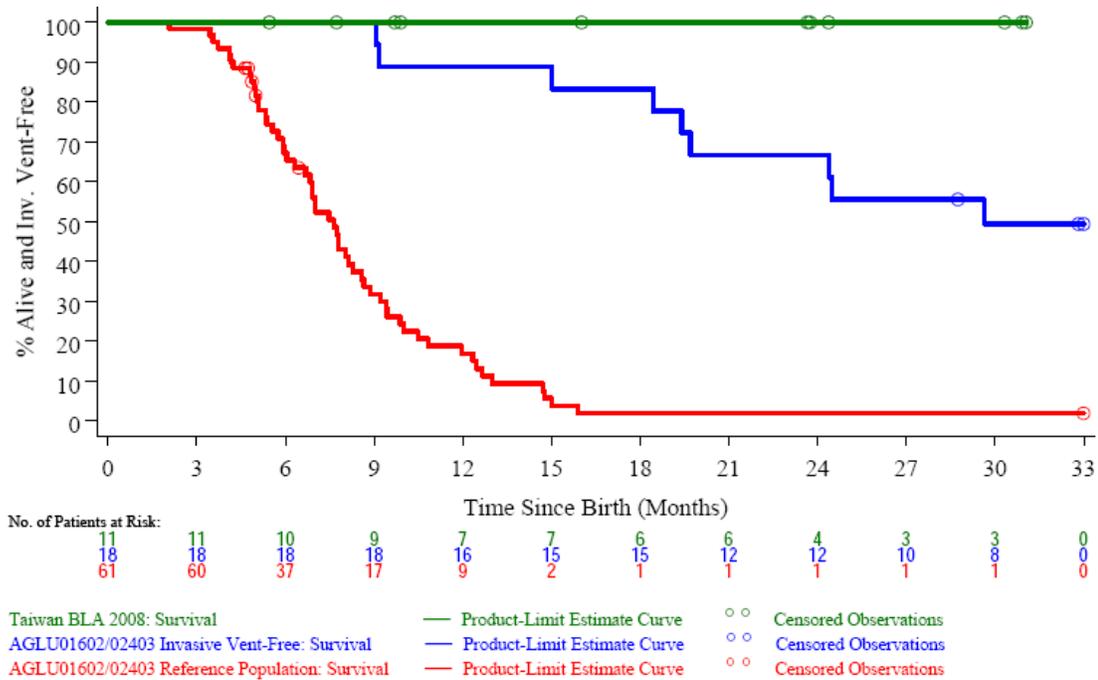


As stated previously, infantile-onset Pompe disease is characterized by rapidly progressive hypertrophic cardiomyopathy, manifested by increased myocardial mass (LVM).  Echocardiographic 2D LVM Z-score data were available for 10 of the 11 Taiwanese patients, all of whom had hypertrophic cardiomyopathy at their initial examinations.  Nine (90%) of the 10 patients demonstrated decreases in LVM Z-scores over time, representing improvement in cardiac function, and a significant departure from the natural progression of cardiac involvement in patients with untreated Pompe disease. One patient (Patient 10380) had no Baseline data and fluctuations in LVM Z-scores throughout the study.  Individual patient changes are presented in **Figure 7-2**.

**Figure 7-2: LVM Z-Score Over Time in Taiwanese Patients (N=10)[1]**
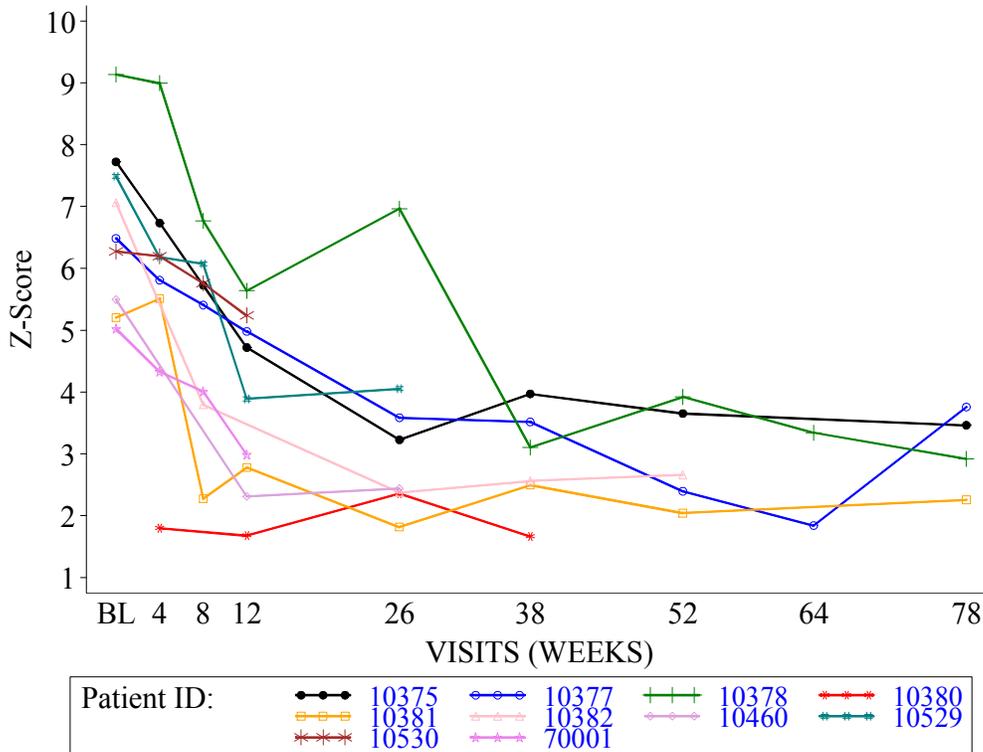


[1] Patient 10528 had no recorded cardiac data

The AIMS was developed to assess normal patterns of motor development in infants from birth through 18 months of age. Age-equivalent scores can be determined from available AIMS norm-referencing data (Piper, 1994, *Motor Assessment of the Developing Infant*), and are used to relate subject scores to the motor development of normally developing age-matched peers. In the Taiwan Study, patients were classified by Genzyme as Walkers, Functional Sitters, or Motor Non-Responders according to the definitions previously provided in **Section 6.1.3**.

AIMS data were available for 10 of the 11 Taiwanese patients, and are presented in **Figure 7-3**. At the last assessment, 5 patients were classified as Walkers, 1 patient was classified as a Functional Sitter, and the remaining 4 patients could not be classified because they were ≤ 6 months of age at the time of their last assessment, and therefore too early in their motor development to define a functional category based on their gross motor milestones.

**Figure 7-3: AIMS Total Scores Over Time in Taiwanese Patients (N=10)[1]**
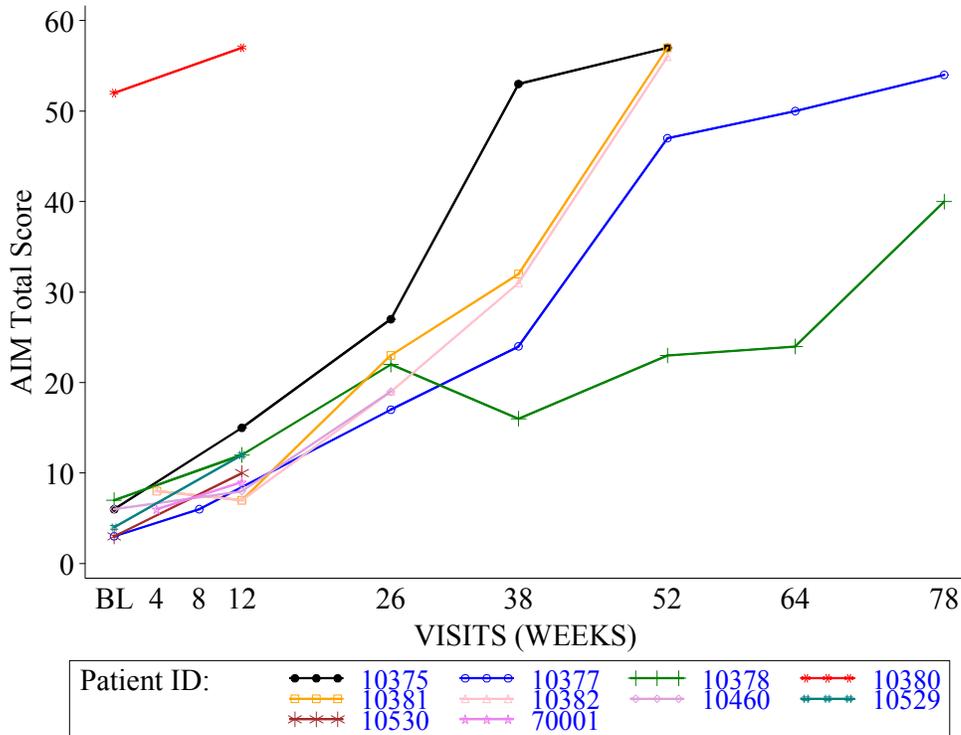


[1] Patient 10528 had no recorded AIMS data

Improvements in motor function were paralleled by changes in skeletal muscle cyto-architecture and glycogen load, as observed on histological evaluation of alternating quadriceps muscle biopsies taken from patients at the time of diagnosis, i.e., before initiation of treatment (**Figure 7-4**), and after 6 months of treatment with 2000 L alglucosidase alfa (**Figure 7-5**). Biopsy slides from 3 of 11 patients treated in this study are shown in these figures. Comparison of these pre- and post-treatment biopsies shows clearance of glycogen by Periodic acid-Schiff (PAS) staining and restoration of cellular ultrastructure (i.e., repair or myofibrils, the contractile apparatus of the cell) by electron microscopy. Similar histopathologic improvements with ERT have been reported previously (Thurberg, 2006, *Lab Invest*) and were also observed in muscle biopsies taken from infantile-onset patients who received treatment with 160 L alglucosidase alfa in AGLU01602.

**Figure 7-4: Quadriceps Muscle Histology at Diagnosis: Patients 10381 (NBS2), 10377 (NBS3) and 10382 (NBS4)**
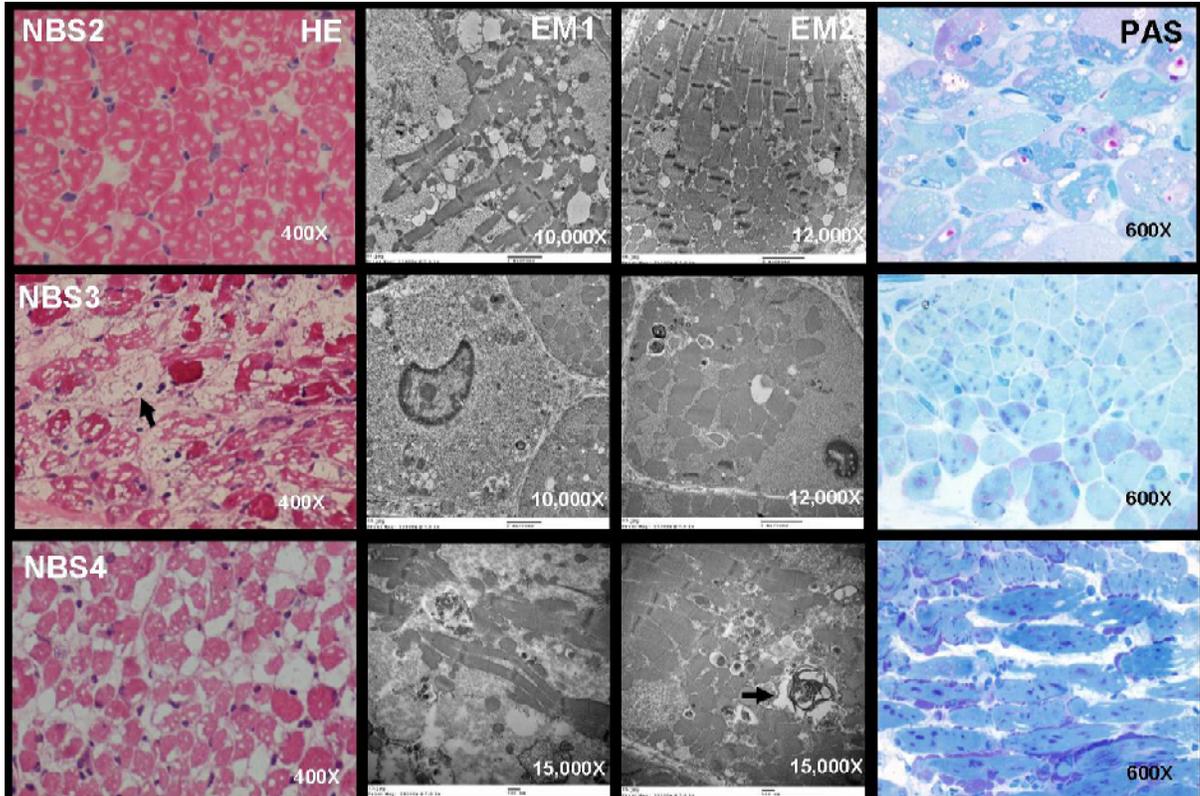


HE= hematoxylin and eosin (H&E) stain; EM1 and EM2=electromicroscopy; PAS=high resolution light microscopy PAS stain

**Figure 7-5: Quadriceps Muscle Histology After 6 Months of Treatment with 2000 L Alglucosidase Alfa: Patients Patients 10381 (NBS2), 10377 (NBS3) and 10382 (NBS4)**
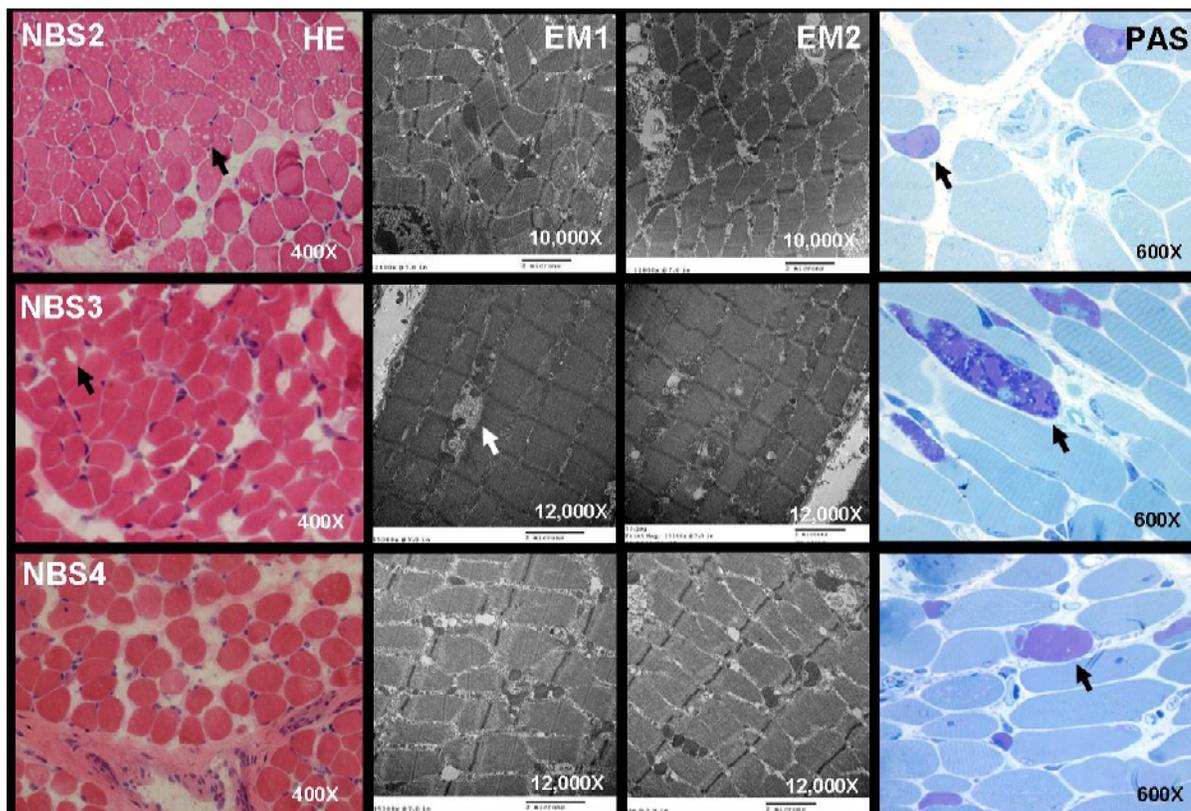


HE= hematoxylin and eosin (H&E) stain; EM1 and EM2=electromicroscopy; PAS=high resolution light microscopy PAS stain

In summary, treatment with 2000 L alglucosidase alfa in this infantile-onset patient cohort was seen to improve survival and the need for ventilator dependence, mitigate the cardiac hypertrophy and cardiomegaly associated with Pompe disease, and enable progressive motor development. These results are in marked contrast to the natural history of disease progression that has been seen in virtually all untreated patients with infantile-onset Pompe disease (Van den Hout, 2003, *Pediatrics*; Kishnani, 2004, *J Pediatr*; Laforet, 2000, *Neurology*; Kishnani, 2007, *Neurology*). Clinical outcomes in this investigator-sponsored study are consistent with those in AGLU01602 where treatment with 160 L alglucosidase alfa prolonged survival and invasive ventilation-free

survival in infantile-onset patients at 18 months of age (83% alive and free of invasive ventilation) compared with an untreated historical patient cohort (1.9%).

## 7.2    Summary of Safety in Infantile-Onset Patients Treated in Taiwan

Three (27%) of the 11 Taiwanese patients experienced a total of 25 spontaneously reported AEs, including 19 SAEs and 6 non-serious AEs.  The most frequently reported AEs were rash (including rash papular, 3 events in 2 patients), wheezing (2 events in 1 patient), rhinorrhoea (2 events in 1 patient), urticaria (2 events in 1 patient), and erythema (including generalized erythema; 2 events in 1 patient).

Nine (36%) of the 25 AEs were mild or moderate; 7 (28%) were severe, and 9 (26%) were of unknown severity.

Sixteen (64%) of 25 AEs were assessed as related (definitely, probably, or possibly related) to alglucosidase alfa therapy, all of which were characterized as IARs.  Fifteen of the 16 IARs were experienced by 1 patient (Patient 10529) who tested positive for anti-rhGAA IgE antibodies, and who experienced a potential anaphylactic reaction.  The remaining IAR occurred in Patient 10460.

Nineteen (76%) AEs in 2 patients were assessed as serious.  Patient 10529, an 8-month old male, experienced 12 SAEs that were IgE-mediated reactions, including 2 events of urticaria and single events of oxygen saturation decreased, eyelid oedema, facial oedema, hypersensitivity, wheezing, rash papular, generalized erythema, irritability, rhinorrhoea, and tachypnoea.  This patient also experienced 5 non-serious events of cough, rash, rhinorrhoea, erythema, and wheezing.  All 17 events were mild or moderate in severity and 15 of the events were characterized as IARs (excluding the episode of cough and a non-serious AE of rhinorrhoea).  This patient was successfully rechallenged using desensitization protocols of lower dose (10 mg/kg qow) at slower infusion rates, and continued to receive treatment.  Patient 10378 experienced 7 SAEs, all of which were reported as severe and unlikely related to alglucosidase alfa: atelectasis, bronchiolitis, respiratory failure, left ventricular hypertrophy, torsade de pointes, catheter-related infection, and gastric haemorrhage.

Abnormalities in laboratory parameters were generally consistent with underlying Pompe disease, and no clinically meaningful trends were noted within the limited data available from this study.

Seven of the 11 patients were tested for anti-rhGAA IgG antibodies, although only 1 patient had a Baseline assessment (this patient was negative). Four (57.1%) of the 7 patients tested seroconverted during treatment. Patient 10529, who experienced 15 of the 16 IARs, seroconverted at Week 12 (titer 6,400) and remained seropositive through the last assessment at Week 26 (titer 3,200), the time point at which a majority of the IARs occurred. The remaining 3 patients had peak titers ranging from 200 to 800, and 1 patient was reported as seronegative at their last assessment at Week 64.

## 8            ALGLUCOSIDASE ALFA RISK / BENEFIT PROFILE

Pompe disease is a rare, progressive, and ultimately fatal disorder.  Patients with Pompe disease have a genetic mutation in the gene encoding the enzyme GAA, which results in the accumulation of tissue glycogen secondary to insufficient enzyme activity.  Most patients present with progressive weakness in proximal limb and respiratory muscles, leading to loss of mobility and declining pulmonary function which, without ventilator assistance, results in death due to respiratory failure.  Alglucosidase alfa, a form of recombinant human GAA, is the only therapy that has been proven efficacious for the treatment of this debilitating disease and has an acceptable safety profile.

Alglucosidase alfa produced at the 160 L scale was initially studied in patients with the infantile-onset form of the disease.  The rapidly progressive nature of the disease in this population, who have little to no residual enzyme activity, allowed for the use of ventilator-free survival as the primary efficacy endpoint, with changes to that endpoint occurring within the 18-month duration of the pivotal trial.  Alglucosidase alfa produced at the 160 L scale is approved in the US for the treatment of Pompe disease (under the trade name Myozyme), based on demonstrated improvement in ventilator-free survival in patients with infantile-onset Pompe disease compared with an untreated historical control group.  In all other global markets, alglucosidase alfa produced at the 2000 L scale is approved for the treatment of Pompe disease (also under the trade name Myozyme).  With the submission of BLA 125291, Genzyme is seeking US licensure of 2000 L alglucosidase alfa based on 18 months of safety and efficacy data from LOTS, a randomized, double-blind, placebo-controlled study of 90 patients with late-onset Pompe disease.

Efficacy data from the LOTS trial provide clear evidence of the benefits of 2000 L alglucosidase alfa therapy in treating the primary clinical manifestations of late-onset Pompe disease. Alglucosidase alfa produced at the 2000 L scale improved walking ability and stabilized pulmonary function, preventing the disease progression observed in placebo patients.  Alglucosidase alfa-treated patients exhibited a mean increase in 6MWT distance walked from Baseline to last observation of +25.13 meters compared with the lack of any meaningful change in 6MWT distance walked among placebo-treated patients (-2.99 meters) during this same time period (treatment difference=28.12; ANCOVA p=0.0347).  Alglucosidase alfa-treated patients also exhibited an increase of +1.20% in

FVC % predicted from Baseline through the last observation compared with a decline in FVC % predicted for placebo-treated patients (-2.20%) during this same time period (an absolute treatment difference=3.40%; ANCOVA p=0.0055). Endpoints that measure proximal leg strength (QMT leg scores) and respiratory muscle strength (MIP and MEP % predicted) exhibited a consistent pattern of response with 2000 L alglucosidase alfa treatment relative to placebo, and provide further support for the results observed in 6MWT and FVC.

The improvement in walking ability and stabilization of pulmonary function are both important clinical outcomes of 2000 L alglucosidase alfa treatment. The capacity of alglucosidase alfa to halt or significantly slow disease progression represents a clear therapeutic benefit to patients in a disease characterized by relentlessly progressive weakness, loss of functional independence, and increasing dependence on ventilatory support. These benefits of alglucosidase alfa therapy do not appear to be limited to any specific subpopulation.

The LOTS safety data demonstrate an acceptable safety profile for 2000 L alglucosidase alfa in late-onset patients. A majority of reported adverse events in LOTS were non-serious, mild or moderate in severity, and not related to study treatment. The primary risk was the occurrence of IARs, and these events were generally non-serious and mild or moderate in severity. In general, IARs were managed with infusion rate reduction and/or interruption of infusion. Two patients experienced IgE-mediated anaphylactic reactions; both patients were successfully rechallenged and able to continue therapy (1 during the study and 1 in the post-marketing setting). There were no treatment-related deaths during the study (1 patient died of causes unrelated to alglucosidase alfa treatment).

Further supportive evidence of the acceptable safety profile of 2000 L alglucosidase alfa is provided by clinical data from 5 additional completed or ongoing GCP studies in late-onset patients, as well as international post-marketing experience with 2000 L alglucosidase alfa spanning from the initial approval of 2000 L alglucosidase alfa by EMEA on 29 March 2006 through 15 April 2008. Approximately 1% of patients in the post-marketing setting experienced anaphylactic reactions following treatment with alglucosidase alfa, some of which were life threatening. Some of these reactions were IgE mediated. In addition, approximately 2% of patients experienced serious allergic

reactions. The majority of patients recovered and continued to receive treatment with alglucosidase alfa under close clinical supervision.

Given the relentlessly progressive nature of Pompe disease with consequent loss of mobility and death, the overall safety and efficacy profile for 2000 L alglucosidase alfa supports a favorable benefit / risk relationship for alglucosidase alfa produced at the 2000 L scale in patients with late-onset Pompe disease. Pompe disease can be reliably diagnosed with a blood test for enzymatic activity. Enzyme replacement therapy with alglucosidase alfa should only be administered to patients with a confirmed diagnosis of Pompe disease. The totality of the evidence supports the use of ERT in the treatment of Pompe disease. Specifically, data from the randomized double-blind placebo controlled LOTS study demonstrate the efficacy of enzyme produced at the 2000 L scale. Infusion-associated reactions are a well-known adverse effect of enzyme replacement therapies when administered to patients with enzyme deficiencies. The demonstrated improvement in walking ability and prevention of progression of pulmonary deterioration outweigh the risks of the predominantly mild to moderately severe IARs and low risk of anaphylaxis that may occur in some patients. Approval of 2000 L alglucosidase alfa will fill an unmet medical need in this ultra-orphan patient population. The 160 L scale was not designed to meet the global demand for alglucosidase alfa enzyme replacement therapy. It is, however, adequate to meet the demand of the small US infantile-onset Pompe patient population. Without the availability of 2000 L alglucosidase alfa, most of the US patients with the life threatening, albeit later onset, form of the disease will have no treatment option.

**9          CONCLUSIONS AND PROPOSED PATH FORWARD**

**9.1          Conclusions**

In this briefing package, Genzyme has provided the Advisory Committee with a summary of the data supporting approval of 2000 L alglucosidase alfa for the treatment of late-onset Pompe disease.

Data from LOTS, a randomized, double-blind, placebo-controlled trial in 90 patients with late-onset Pompe disease, show that 2000 L alglucosidase alfa is efficacious and has an acceptable safety profile in late-onset patients.  The safety experience with 2000 L alglucosidase alfa in the LOTS Extension and 5 other completed and ongoing clinical studies, as well as the global post-marketing experience in approximately 465 patients receiving exclusively 2000 L alglucosidase alfa, are consistent with observations in LOTS and further support an acceptable safety profile for 2000 L alglucosidase alfa. Specifically:

- Patients treated with 2000 L alglucosidase alfa demonstrated statistically significant improvement in walking ability (6MWT distance walked) and pulmonary function (FVC % predicted) relative to placebo-treated patients during 18 months of treatment in LOTS.  This positive treatment effect of alglucosidase alfa was supported by results for secondary and tertiary efficacy endpoints that measure proximal limb (QMT leg and arm) and respiratory (MIP and MEP) muscle strength.

- The treatment effect size of 2000 L alglucosidase alfa on 6MWT and FVC observed in LOTS is clinically meaningful, and consistent with the observed effect sizes of other recombinant protein products that have been approved for the treatment of orphan diseases (MPS type I, Aldurazyme and MPS type II, Elaprase).

- Infusion-associated reactions were the most frequently reported treatment-related AEs in the clinical studies with 2000 L alglucosidase alfa.  The majority of these reactions were mild to moderate in severity, and were primarily managed with infusion rate reduction and/or interruption of infusion.

- Anaphylactic reactions have been reported in approximately 1% of patients during 2000 L alglucosidase alfa infusion in clinical studies or the post-marketing setting. Some of these reactions were life threatening and/or IgE-mediated. Additionally, approximately 2% of patients developed serious allergic reactions. The majority of patients recovered and continued to receive treatment with alglucosidase alfa under close clinical supervision.

The efficacy and safety of 2000 L alglucosidase alfa in the treatment of Pompe disease is further supported by additional clinical data, albeit limited, in patients with the more rapidly progressive infantile-onset form of Pompe disease.

- Retrospective clinical analyses in 49 infantile-onset patients receiving initial treatment with 2000 L or 160 L alglucosidase alfa demonstrate that alglucosidase alfa extends invasive ventilator-free survival compared with untreated historical cohorts, regardless of manufacturing scale. Further analyses in infantile-onset patients receiving treatment with both 160 L and 2000 L product show no meaningful difference in the risk of death or invasive ventilation, or in cardiac or motor outcomes, by manufacturing scale. However, the data sets are small and the comparisons are indirect, precluding a more definitive conclusion regarding the relative efficacy of the material produced at the 2 scales.

- Treatment with 2000 L alglucosidase alfa exclusively has been shown to improve invasive ventilation-free survival, mitigate the cardiac hypertrophy and cardiomegaly associated with Pompe disease, and enable progressive motor development in a cohort of 11 infantile-onset patients treated in an investigator-sponsored study in Taiwan. These results are consistent with clinical outcomes in infantile-onset patients treated with 160 L alglucosidase alfa in AGLU01602, and stand in marked contrast to the natural history of disease progression (Van den Hout, 2003, *Pediatrics*; Kishnani, 2004, *J Pediatr*; Laforet, 2000, *Neurology*; Kishnani, 2007, *Neurology*).

In summary, Genzyme believes the results from the LOTS trial and supplemental safety data for 2000 L alglucosidase alfa from other clinical studies and the post-marketing experience in late-onset patients support the following proposed indication:

TRADE NAME (alglucosidase alfa) is indicated for long-term use in patients with late-onset Pompe disease (GAA deficiency). TRADE NAME has been shown to improve distance walked and stabilize pulmonary function in patients with late-onset Pompe disease.

## 9.2 Proposed Path Forward

Genzyme offers the following points for consideration as a path forward to assure a continued supply of commercial alglucosidase alfa for all patients worldwide.

- Genzyme initially believed that the 2000 L alglucosidase alfa could be approved based on comparability with the 160 L scale product. However, based on communications with FDA, Genzyme agrees that given the small clinical dataset in infants, these products should be approved independently. Genzyme is now requesting alglucosidase alfa 2000 L scale material be approved in the US for late-onset Pompe patients under a separate BLA.

- Managing two different products for subgroups (infantile- and late-onset) of the US Pompe patient population is not an ideal situation but Genzyme believes this is manageable since the Pompe physician and patient communities are small and well-connected networks which will make managing communication and distribution of two different products possible.

- Genzyme believes that an important part of the US approval will be the ability to assign the Myozyme trade name to the 2000 L product. Approval of 2000 L alglucosidase alfa in all countries other than the US is under the trade name of Myozyme, so for global pharmacovigilance tracking and reporting of the 2000 L material, and to avoid confusion amongst a worldwide Pompe community, keeping the Myozyme trade name for the 2000 L scale product is essential. Furthermore, the small size and highly visible nature of the US infantile-onset Pompe population, as compared to the much larger global late-onset population who would be using the 2000 L material, makes controlled distribution of a separately named 160 L scale material to this population not only possible, but improved, by the use of a new name for the 160 L material.

- In consideration of the need to manage two alglucosidase alfa products in the US market place and the above proposal to assign the "Myozyme" name to the 2000 L product, while assigning the 160 L product a new trade name, Genzyme proposes to implement a product specific drug distribution plan. This distribution plan will be part of a Risk Evaluation and Mitigation Strategy (REMS) to ensure the appropriate use of each product according to the labeled indication. The components of the overall plan include a program of 160 L product communication about the name change with patients, and physicians, an in-service training and annual certification of physicians treating infantile onset patients with 160 L product, signed disclosure statements of 160 L/2000 L product use, and clear product differentiation by their labeled indication in shipments. Genzyme intends to implement this plan for direct distribution and with contracted preferred drug distributors.

- Genzyme is committed to meeting the global demand for alglucosidase alfa through approval of the 2000 L product and ultimately through scale up to a 4000 L bioreactor scale, which will significantly expand capacity.

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**11          APPENDICES**

**11.1          Appendix 1: LOTS Statistical Analysis Details**

**11.1.1          Details of Six-Minute Walk Test Statistical Analysis**

**11.1.1.1          Linear Mixed Effects Model**

For the co-primary efficacy endpoints (6MWT and FVC (% predicted), the primary measure of efficacy was the monthly rate of change (or slope) from Baseline to Week 78. As described in the SAP, the difference in the rate of changes between treatment groups was to be estimated via a standard LME model. The LME included covariates for the Baseline randomization strata (i.e., based on Baseline 6MWT and FVC results) and linear effects of time and treatment-by-time interaction, as well as random effects for the intercept and for the linear effect of time.

The difference between the slopes in the model, the treatment-by-time interaction, represents the average monthly increase in distance walked in alglucosidase alfa-treated patients compared to placebo-treated patients. This difference in linear slopes was the planned basis for hypothesis testing of the co-primary endpoints. The Wald test statistic for the difference in linear slopes was to be constructed using the estimate of the treatment-by-time interaction and the associated standard error from the model-based variance-covariance matrix estimate.

The SAS code for the LME model is

```
proc mixed method = reml;
  class patid trtgrp;
  model effobs = mwbs300q|fvcbs55q mnth mnth*trtgrp;
  random intercept mnth / type = un subject = patid;
  estimate 'SLOPE / rhGAA' mnth 1 mnth*trtgrp 1 0 / cl;
  estimate 'SLOPE / Placebo' mnth 1 mnth*trtgrp 0 1 / cl;
  estimate 'SLOPE / Difference' mnth*trtgrp 1 -1 / cl;

run;
```

where, **patid** is the patient ID, **trtgrp** is the treatment group (either active treatment or placebo), **effobs** is the observed 6MWT, **mwbs300q** and **fvcbs55q** are the randomization strata variables and **mnth** is the time from 1st infusion in months.

### 11.1.1.2    Checking the Assumptions of the LME model

The validity of the statistical inference pertaining to the treatment effect is dependent on certain assumptions regarding the planned LME model with model-based variance being met.  These assumptions include:

(i)    Linearity of the time trend of the responses

(ii)    Correct specification of the variance-covariance structure of the responses

(iii)    Normal distribution of the responses

If these assumptions are not met the inference from the hypothesis testing may be compromised.

### 11.1.1.2.1    Test of Linearity Assumption

As specified in the SAP, the test of the assumption of linearity was assessed via a forward-selection algorithm applied to the planned LME.  The algorithm sequentially added higher order functions of time based on the likelihood-ratio-test (LRT).  This procedure stopped after a quadratic effect of time ($P < 0.0001$) and a quadratic effect of time-by-treatment interaction ($P = 0.0005$) were added to the LME, indicating statistically significant departures from linearity.  The result of the 2 degree-of-freedom LRT that jointly tests the significance of the quadratic effects of time and time-by-treatment interaction is the following:

|  | -2LL* | Difference | p-value |
|---|---|---|---|
| Planned Linear LME | 5624.6 |  |  |
| Quadratic LME | 5565.7 | 58.9 | < 0.00001 |

*-2LL = -2*log-likelihood using maximum likelihood estimation

Therefore, there is very strong evidence of a statistically significant departure from linearity.

### 11.1.1.2.2    Test of Variance-Covariance Structure

The test of the specification of the variance-covariance structure was based on a LRT that compared the planned LME with random effects for the intercept and slope to an LME

with random effects for the intercept and slope and also with an additional first-order autoregressive correlation structure. The following statement was added to above PROC MIXED SAS code:

```
repeated etvisid / type = ar(1) subject = patid;
```

where **etvisid** is a class variable identifying visit number from Baseline to Week 78.

The result of the 1 degree-of-freedom LRT is the following:

|  | -2LL* | Difference | p-value |
|---|---|---|---|
| Planned Linear LME | 5624.6 |  |  |
| Linear LME with AR(1) | 5569.1 | 55.5 | < 0.00001 |

Therefore, there is very strong evidence that the variance-covariance structure specified by the random intercept and slopes does not adequately capture the within-patient correlation.

### 11.1.1.2.3    Test of Normality

Normality was rejected at the $p < 0.0001$ level of significance based on a pre-specified application of the Wilks-Shapiro test to the patient-specific slopes as well as the within-subject errors.

### 11.1.1.3    LME with Robust Variance Estimation

The failure of these 3 assumptions (linearity, correct specification of variance-covariance structure, and normality) was likely to lead to incorrect calculation of standard errors and invalid statistical inference. Therefore, a robust repeated measures analysis method, which used the same underlying LME model, but which included a standard and commonly-used robust variance estimate that is commonly referred to as the "sandwich" variance estimate (Fitzmaurice, 2004, *Applied Longitudinal Analysis*) was used. This method, the LME with robust variance estimation, uses the pre-specified LME model and thus yields an identical point estimate for the difference in slopes (i.e., treatment difference). However, it provides valid statistical inference about the treatment difference even when model assumptions are violated.

## 11.1.1.4 Complementary Repeated Measures Analyses of the 6MWT Data

To confirm the validity of the primary analysis using the LME model with robust variance estimation, 2 complementary repeated measures analyses were also performed to obtain additional inferences about the treatment difference in slopes for 6MWT distance walked: the GEE method and a profile analysis method with unconstrained covariance structure. These additional repeated measures analyses are arguably even less dependent on the assumption of correct specification of the variance-covariance structure, linearity, and/or normality than the LME with robust variance estimation.

### 11.1.1.4.1 GEE

This method yields a point estimate for the difference of slopes without relying on the normal distributions of the responses to the same extent as the LME, and also utilizes a robust "sandwich" variance estimate based on the standard GEE method. This method employed a compound symmetric working correlation matrix.

### 11.1.1.4.2 Profile Analysis with Linear Contrast and an Unconstrained Covariance Structure:

This repeated measures linear model also yields a point estimate for the difference of slopes. The model includes terms for visit (as a categorical rather than a quantitative variable) and treatment-by-visit interaction, and uses a linear contrast to estimate and test the treatment group difference in slopes. Importantly, the analysis is based on a completely unstructured variance-covariance matrix and an unconstrained model for the patterns of change in the mean response. The use of profile models in longitudinal data analysis has been described by Fitzmaurice et al (Fitzmaurice, 2004, *Applied Longitudinal Analysis*). The profile analysis SAS code was

```
proc mixed method = reml;
  class patid trtgrp etvisid;
  model effobs = mwbs300q|fvcbs55q etvisid etvisid*trtgrp;
  repeated etvisid / type = un subject = patid;
  estimate 'SLOPE / rhGAA' etvisid -3 -2 -1 0 1 2 3
    etvisid*trtgrp -3 -2 -1 0 1 2 3 0 0 0 0 0 0 0  /
    divisor = 84 cl;
  estimate 'SLOPE / Placebo' etvisid -3 -2 -1 0 1 2 3
    etvisid*trtgrp 0 0 0 0 0 0 0 -3 -2 -1 0 1 2 3 /
    divisor = 84 cl;
  estimate 'SLOPE / Difference' etvisid*trtgrp -3 -2 -1 0 1 2 3 3 3 2 1 0
-1 -2 -3 /
    divisor = 84 cl;
run;
```

where `etvisid` is a class variable is a class variable identifying the visit from baseline to Week 78.

The GEE and profile analysis provided 2 additional estimates of the treatment difference in slopes (the basis of the primary analysis), arguably under even weaker assumptions than the LME with robust variance estimation. Both methods provided confirmation of the statistically significant treatment difference in the average monthly rate of change, and there was very good agreement between the GEE method (1.51 meters/month) and the profile analysis method (1.51 meters/month).

## 11.2 Appendix 2: Criteria for Identifying Anaphylactic and Allergic Reactions

A modified version of the Standardized MedDRA 9.1 Query (SMQ) for anaphylactic reactions was used to identify potential anaphylactic and allergic reactions. The SMQ contains a list of preferred terms which are suggestive of anaphylactic and allergic reactions and differentiates them into a number of categories. Given that anaphylactic reactions often manifest themselves in multiple classes of symptoms (e.g., rash and wheezing), symptoms from one category alone are often not sufficient to determine the occurrence of potential anaphylactic and allergic reactions. The algorithm for identifying potential anaphylactic and allergic reaction cases is as outlined below.

An anaphylactic and allergic reaction must have one of the following:

1. At least one AE term from category A
2. At least one AE term from category B and one AE term from category C.
3. At least one AE term from category D and one AE term from category B or category C or category E.

As part of the search criteria, Genzyme reviewed AEs which occurred concurrently on the day of infusion and were assessed as related to administration of study drug.

The following is a list of categories with corresponding AE preferred terms:

| Category | SMQ Terms |
|----------|-----------|
| A | Anaphylactic reaction |
| | Anaphylactic shock |
| | Anaphylactoid reaction |
| | Anaphylactoid shock |
| | Circulatory collapse |
| | Shock |
| | Type I hypersensitivity |
| | |
| B | Acute respiratory failure |
| | Asthma |
| | Bronchial oedema |
| | Bronchospasm |
| | Cardio-respiratory distress |
| | Chest discomfort |
| | Choking |
| | Choking sensation |
| | Cough |
| | Dyspnoea |
| | Hyperventilation |
| | Laryngeal dyspnoea |
| | Laryngeal oedema |
| | Laryngospasm |
| | Laryngotracheal oedema |
| | Oedema mouth |
| | Oropharyngeal spasm |
| | Oropharyngeal swelling |
| | Respiratory arrest |
| | Respiratory distress |
| | Respiratory dyskinesia |
| | Respiratory failure |

Reversible airways obstruction
Sensation of foreign body
Sneezing
Stridor
Swollen tongue
Throat tightness
Tongue oedema
Tracheal obstruction
Tracheal oedema
Wheezing


C                        Allergic oedema
Angioneurotic oedema
Erythema
Eye oedema
Eye swelling
Eyelid oedema
Face oedema
Fixed eruption
Flushing
Generalised erythema
Lip oedema
Lip swelling
Oedema
Periorbital oedema
Pruritus
Pruritus allergic
Pruritus generalised
Rash
Rash erythematous
Rash generalised
Rash pruritic
Skin swelling
Swelling
Swelling face
Urticaria
Urticaria generalised
Urticaria papular

D                        Blood pressure decreased
Blood pressure diastolic decreased
Blood pressure systolic decreased

Cardiac arrest
Cardio-respiratory arrest
Cardiovascular insufficiency
Diastolic hypotension
Hypotension

E           Abdominal pain
Agitation
Convulsion
Incontinence
Palpitations
Paraesthesia

Vomiting

**11.3  Appendix 3: Listing of Serious Post-Marketing Reports of Potential Allergic or Anaphylactic Reactions as Identified by MedDRA SMQ**

| Patient ID | Case ID | Age at Event/ Gender | Dosage | IgE/IgG and other testing | Days Since First Dose | Time to onset of reaction from infusion start | Preferred Term | Severity | Action taken regarding the infusion | Outcome | Life Threatening Assessed by Reporter | Assessment for anaphylactic reaction |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Infantile-Onset Pompe Disease** | | | | | | | | | | | | |
| PV 02 | POMP-11264 | 24 mo./M | 20 mg/kg qow | Not tested /204800 | Unknown | During infusion | Cyanosis | Unknown | Unknown | Recovered | No | No |
| | | | | | | | Hypotension | Unknown | Unknown | Recovered | | |
| | | | | | | | Rash | Unknown | Unknown | Recovered | | |
| | | | | | | | Tachypnoea | Unknown | Unknown | Recovered | | |
| | | | | | | | Cardiac hypertrophy[1] | Unknown | Unknown | Not yet recovered | | |
| | | | | | | | Catheter related infection[1] | Unknown | Unknown | Unknown | | |
| | | | | | | | Cough[1] | Unknown | Unknown | Not yet recovered | | |
| | | | | | | | Disease progression[1] | Unknown | Unknown | Unknown | | |
| | | | | | | | Hypotonia[1] | Unknown | Unknown | Not yet recovered | | |
| | | | | | | | Pneumonia[1] | Unknown | Unknown | Unknown | | |
| | | | | | | | Electromyogram abnormal[1] | Unknown | Unknown | Unknown | | |
| | | | | | | | Respiratory syncytial virus infection[1] | Unknown | Unknown | Unknown | | |
| | | | | | | | Deafness neurosensory[1] | Unknown | Unknown | Not yet recovered | | |
| PV09 | POMP-10891 | 5mo./F | 20 mg/kg qow | +/- | 99 days | A few minutes | Bronchospasm | Severe | Interrupted | Recovered | No | Yes |
| | | | | | | | Urticaria | Severe | Interrupted | Recovered | | |
| | | | | | | | Restlessness | Moderate | Interrupted | Recovered | | |

**Available for Public Disclosure**

| Patient ID | Case ID | Age at Event/ Gender | Dosage | IgE/IgG and other testing | Days Since First Dose | Time to onset of reaction from infusion start | Preferred Term | Severity | Action taken regarding the infusion | Outcome | Life Threatening Assessed by Reporter | Assessment for anaphylactic reaction |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PV48 | POMP-1000046 | 6mo./F | 20 mg/kg qow | Not tested /Not tested | 168 days | Late in infusion (when the infusion rate was increased to 12.9 ml/hour) | Dyspnoea | Moderate | Interrupted | Recovered | Yes | No |
| | | | | | | | Crying | Moderate | Interrupted | Recovered | | |
| | | | | | | | Pyrexia | Moderate | Interrupted | Recovered | | |
| | | | | | | | Moaning | Moderate | Interrupted | Recovered | | |
| | | | | | | | Nervousness | Moderate | Interrupted | Recovered | | |
| | | | | | | | Tachypnoea | Moderate | Interrupted | Recovered | | |
| | | | | | | | Tachycardia | Moderate | Interrupted | Recovered | | |
| | | | | | | | Erythema | Moderate | Interrupted | Recovered | | |
| | | | | | 182 days | After 30 minutes | Apnoea | Severe | Interrupted | Recovered | | |
| | | | | | | | Tachycardia | Severe | Interrupted | Recovered | | |
| | | | | | | | Cyanosis | Severe | Interrupted | Recovered | | |
| PV63 | POMP-10930 | 9mo./F | 20 mg/kg qow | Not tested/ Not tested | 98 days | During infusion | Respiratory arrest | Severe | None | Recovered | Yes | No |
| | | | | | | | Bradycardia | Severe | None | Recovered | | |
| | | | | | | | Hypotension | Severe | None | Recovered | | |
| | | | | | | | Leukocytosis[1] | Severe | None | Unknown | | |
| | | | | | | | Anemia[1] | Unknown | None | Unknown | | |
| | | | | | | | Anisocytosis[1] | Unknown | None | Unknown | | |
| | | | | | | | Microcytosis[1] | Unknown | None | Unknown | | |
| PV71 | POMP-1000078 | 8mo./M | 20 mg/kg qow | Not tested/ Not tested | 26 days | 10 hours after completion of the infusion | Convulsion | Severe | None | Unknown | No | No |
| | | | | | | | Cyanosis | Severe | None | Unknown | | |
| | | | | | | | Diarrhoea | Severe | None | Unknown | | |
| | | | | | | | Circulatory collapse | Severe | None | Unknown | | |
| | | | | | | 11 days | Cardiac arrest | Severe | None | Fatal (unrelated)2 | | |

| Patient ID | Case ID | Age at Event/ Gender | Dosage | IgE/IgG and other testing | Days Since First Dose | Time to onset of reaction from infusion start | Preferred Term | Severity | Action taken regarding the infusion | Outcome | Life Threatening Assessed by Reporter | Assessment for anaphylactic reaction |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Late-Onset Pompe Disease** | | | | | | | | | | | | |
| PV10 | POMP-10807 | 28yr./F | Unk | -/Not tested | 15 days | 5 minutes | Dyspnoea | Severe | Permanently Discontinued[4] | Unknown | Yes[5] | No |
| | | | | | | | Rash | Severe | Permanently Discontinued[4] | Unknown | | |
| PV 55 | POMP-10999 | 58yr./F | 20 mg/kg qow | Not tested /Not tested | 126 days | Unspecified | Chest discomfort | Moderate | Interrupted | Recovered | No | No |
| | | | | | | | Bronchospasm | Moderate | Interrupted | Recovered | | |
| | | | | | | | Tachycardia | Moderate | Interrupted | Recovered | | |
| | | | | | | | Erythema | Moderate | Interrupted | Recovered | | |
| | | | | | 154 days | Unspecified | Oxygen saturation decreased | Moderate | Interrupted | Recovered | | |
| | | | | | | | Dyspnoea | Moderate | Interrupted | Recovered | | |
| PV32 | POMP-11022 | 59yr./M | 20 mg/kg qow | -/800 | 238 days | Shortly after the start of infusion | Hypersensitivity | Moderate | Interrupted | Recovered | No | No |
| | | | | | | | Dyspnoea | Moderate | Interrupted | Recovered | | |
| | | | | | | | Erythema | Moderate | Interrupted | Recovered | | |
| | | | | | 252 days | Shortly after the start of infusion | Hypersensitivity | Severe[3] | Interrupted | Recovered | | |
| | | | | | | | Dyspnoea | Severe[3] | Interrupted | Recovered | | |
| | | | | | | | Cyanosis | Severe | Interrupted | Recovered | | |
| PV35 | POMP-11023 | 51yr./F | 20 mg/kg qow | Not tested /Not tested | 240 days | Shortly after the start of infusion | Hypersensitivity | Moderate | Interrupted | Recovered | No | No |
| | | | | | | | Hypotension | Moderate | Interrupted | Recovered | | |
| | | | | | | | Erythema | Moderate | Interrupted | Recovered | | |
| PV37 | POMP-10860 | 45yr./F | 20 mg/kg qow | -/Not tested | 154 days | Ten minutes | Anaphylactic shock | Severe | Interrupted | Recovered | Yes | Yes |
| | | | | | | | Back pain | Mild | Interrupted | Recovered | | |
| | | | | | | | Flushing | Mild | Interrupted | Recovered | | |
| | | | | | | | Nausea | Mild | Interrupted | Recovered | | |

| Patient ID | Case ID | Age at Event/ Gender | Dosage | IgE/IgG and other testing | Days Since First Dose | Time to onset of reaction from infusion start | Preferred Term | Severity | Action taken regarding the infusion | Outcome | Life Threatening Assessed by Reporter | Assessment for anaphylactic reaction |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PV41 | POMP-10915 | 43yr./F | 20 mg/kg qow | +/51200 | 224 days | One minute | Anaphylactic reaction | Severe | Interrupted | Recovered | Yes | Yes |
| | | | | | | | Dyspnoea | Severe | Interrupted | Recovered | | |
| | | | | | | | Chest pain | Severe | Interrupted | Recovered | | |
| | | | | | | | Peripheral coldness | Severe | Interrupted | Recovered | | |
| | | | | | | | Dizziness | Severe | Interrupted | Recovered | | |
| | | | | | | | Headache | Severe | Interrupted | Recovered | | |
| | | | | | | | Hypertension | Severe | Interrupted | Recovered | | |
| | | | | | | | Pallor | Severe | Interrupted | Recovered | | |
| | | | | | | | Hyperhidrosis | Severe | Interrupted | Recovered | | |
| | | | | | | | Tachycardia | Severe | Interrupted | Recovered | | |
| PV43 | POMP-1000011 | 49yr./F | 20 mg/kg qow | Not tested /Not tested | 60 days | Ten minutes | Chest pain | Moderate | Interrupted | Recovered | No | No |
| | | | | | | | Chest discomfort | Moderate | Interrupted | Recovered | | |
| | | | | | | | Flushing | Moderate | Interrupted | Recovered | | |
| | | | | | | After about 800 mg alglucosidase alfa had been infused | Paraesthesia | Moderate | Interrupted | Recovered | | |
| | | | | | | | Pruritus | Moderate | Interrupted | Recovered | | |
| | | | | | | | Circumoral oedema | Moderate | Interrupted | Recovered | | |
| | | | | | | | Paraesthesia oral | Moderate | Interrupted | Recovered | | |

| Patient ID | Case ID | Age at Event/ Gender | Dosage | IgE/IgG and other testing | Days Since First Dose | Time to onset of reaction from infusion start | Preferred Term | Severity | Action taken regarding the infusion | Outcome | Life Threatening Assessed by Reporter | Assessment for anaphylactic reaction |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Pompe Disease of Unknown Phenotype** | | | | | | | | | | | | |
| PV66 | POMP-11278 | Unk/F | Unk | Not tested /Not tested | Unknown | Unspecified | Anaphylactic reaction | Severe | Interrupted | Recovered | Yes | Yes |
| PV75 | POMP-11271 | 10yr./M | Unk | Not tested /Not tested | 192 days | Within 45 minutes | Erythema | Unknown | Interrupted | Recovered | No | No |
| | | | | | | | Dysphagia | Unknown | Interrupted | Recovered | | |
| | | | | | | | Throat tightness | Unknown | Interrupted | Recovered | | |

[1] These events were assessed as unrelated to alglucosidase alfa therapy infusion and excluded for this section analysis.

[2] This fatality was assessed as unrelated to alglucosidase alfa therapy.

[3] Assessment severity was upgraded by the reporter from moderate to severe after data cut-off

[4] This patient permanently discontinued treatment on a later date for an unspecified reason.

[5] This case was assessed by the treating physician as life threatening. However, provided information is not sufficient to confirm the life threatening nature of the case