

**Food and Drug Administration
Center for Drug Evaluation and Research**

**Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) to
Evaluate Myozyme (alglucosidase alfa) for the Treatment of Late Onset Pompe Disease**

October 21, 2008

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**Food and Drug Administration
Center for Drug Evaluation and Research**

**The Endocrinologic and Metabolic Drugs Advisory Committee Meeting
October 21, 2008**

CLINICAL BACKGROUND MATERIALS

Alglucosidase alfa 2000 L Product

For the treatment of Late-Onset Pompe Disease

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1 Executive Summary

1.1 Statement of Purpose

The purpose of the Advisory Committee meeting is to obtain advice from the Committee regarding the efficacy, safety, indication, and use of alglucosidase alfa manufactured at the 2000 Liter scale production process (2000 L product). Genzyme (the Applicant) has proposed the following indication for the 2000 L product: “for long-term use in patients with late-onset Pompe disease (GAA deficiency). Alglucosidase alfa (2000 L) has been shown to improve distance walked and stabilize pulmonary function in patients with late-onset Pompe disease.” The proposed dose is 20mg/kg/dose given intravenously (IV) every other week.

1.2 Background

Pompe disease is a rare, genetic disorder of glycogen metabolism caused by the absence or marked deficiency of the lysosomal enzyme acid- α -glucosidase (GAA). Deficiency of this enzyme results in the accumulation of glycogen in the lysosomes of a variety of cells, but predominantly in skeletal muscle. This accumulation of glycogen in skeletal muscle lysosomes results in progressive muscle weakness, affecting motor and respiratory function. Death in all forms is usually a result of cardiorespiratory failure. Three clinical forms of Pompe disease are described: infantile-, juvenile- and adult-onset forms.

Infantile-onset patients generally have lower GAA activity (% normal) compared with both the juvenile and adult-onset forms, however, there is some overlap. The degree of enzyme deficiency does not correlate completely with clinical severity. Nevertheless, the infantile-onset form leads to severe cardiomyopathy, muscle weakness and death in almost all patients by 18 months of age; it is the most rapidly progressive form of the disease.

Patients with the juvenile-onset form of the disease have an intermediate phenotype between infantile-onset and adult-onset Pompe patients. Juvenile and adult-onset patients develop skeletal muscle weakness without cardiomyopathy, and have a slower progression of disease than the infantile-onset patients. Juvenile-onset patients tend to have faster progression than the adult-onset patients. Patients with the adult-onset form tend to have later age of onset of symptoms, as well as slower progression compared to both the infantile-onset and juvenile-onset forms. However, the classification of juvenile and adult-onset forms is a continuum, and therefore a specific age cut-off between juvenile and adult-onset forms is difficult to clinically define. Therefore, the term late-onset Pompe disease has been used by the Applicant to describe any patient with onset of disease over 12 months of age and without cardiac involvement. For the purposes of this review, juvenile-onset Pompe disease patients have been defined as patients with onset of symptoms before the age of 18 years.

The Applicant manufactures alglucosidase alfa for use in the United States (US) in two production scales, a 160 liter production scale (160 L product), and a 2000 liter scale (2000 L product). Currently, the only treatment approved in the US for Pompe disease is alglucosidase alfa 160 L product (Myozyme®). The 160 L product was approved in the US based on a single clinical trial (n=18) that demonstrated improved ventilator-free survival in patients with infantile-onset Pompe disease (age \leq 7months at the time of first infusion) as compared to an

age-matched, untreated historical control. Approval of the 160 L product in the US for all forms of Pompe disease was based solely on this infantile-onset trial; there have been no controlled studies that have evaluated the efficacy of 160 L product in late-onset Pompe disease. The 2000 L product was approved for use in Canada, Europe, and a number of other countries throughout the world; however, given the inability to establish product comparability based on chemistry, manufacturing and controls (CMC), pharmacokinetic, or clinical data, the 160 L and 2000 L alglucosidase alfa products were deemed to be different products by the US Food and Drug Administration (FDA) in April, 2008. Therefore, the FDA required the Applicant to submit efficacy and safety data to support separate licensure of the 2000 L product. Production of the 160 L product has not been able to meet the demand for the 160 L product in the US and a drug shortage exists. The Applicant has limited access to the 160 L product to patients less than 18 years of age, with the 2000 L product available to adult patients on a case-by-case basis through an Applicant-supported temporary access program (under the IND).

The Applicant has submitted one clinical study in support of the efficacy of 2000 L product. Study AGLU02704 (Late-Onset Treatment Study, LOTS) was a multinational, multicenter, randomized, double-blind, placebo-controlled study in 90 late-onset Pompe disease ages 8 to 70 years. Patients must have been able to ambulate at least 40 meters during a six-minute walk test (6MWT). Additionally, patients must not have required invasive (endotracheal) ventilation, and have had a percent predicted forced vital capacity (% predicted FVC) in the upright position of less than 80%. Patients were to be treated with 2000 L product 20 mg/kg/dose IV or placebo every other week for 52 weeks. The original co-primary endpoints were: 1) change in distance walked during a 6MWT from baseline to completion of treatment and 2) change in upright % predicted FVC. Of the 90 patients enrolled in the study, 81 patients completed the study.

During the conduct of the study, the Applicant requested that LOTS be changed to an adaptive trial design, and subsequently changed both the primary efficacy endpoints and the method of statistical analysis during the study (see section 5.4.1 and Appendix B). When the Independent Statistical Center completed an adaptive design analysis of the data when 1/3 of enrolled patients had completed 36 weeks of treatment on study, they recommended extending the length of the study to 78 weeks. The co-primary endpoints were changed from the original endpoints to the final co-primary endpoints of the study: 1) rate of change (slope) in distance walked during a 6MWT; and 2) rate of change in upright % predicted FVC. When the study was completed and the final data were analyzed, the Applicant discovered that the assumptions of the pre-specified statistical model were violated and again changed the statistical analysis plan to correct for these violations (see section 5.4.1, and Appendix B).

On September 1, 2008, 3 months into the review cycle, the Applicant submitted data regarding 11 infantile-onset Pompe disease patients who received treatment with the 2000 L product at a single center in Taiwan. There was insufficient time to review these data for inclusion in the FDA Advisory Committee briefing package, but it should be noted that these data were retrospectively collected and summarized as an uncontrolled case series. These infantile-onset Pompe disease data, which were not collected as part of a Good Clinical Practices (GCP) study, do not support the Applicant's proposed indication for the 2000 L product to treat late-onset patients only.

Safety data submitted in support of the 2000 L product include comprehensive safety data collected as part of the LOTS study. The Applicant has also submitted other safety data on 154 patients who have received 2000 L product from 3 clinical studies, 2 expanded access programs, and uncontrolled data from postmarketing reports. Safety data from LOTS are reviewed in this background package; however, due to the late submission of safety data other than LOTS to FDA (submitted September 1, 2008); there was insufficient time to review these data for inclusion in this briefing package.

1.3 Clinical Summary

1.3.1 Efficacy

The efficacy of the 2000 L product was assessed by the Applicant, after changing the primary endpoints, based on the effect of treatment on two co-primary endpoints: 1) rate of change over the course of the study in distance walked during a six-minute walk test (6MWT); and 2) rate of change over the course of the study in upright percent predicted forced vital capacity (FVC). These were not the study's original planned co-primary endpoints. For reasons discussed later, FDA's assessment of the 6MWT and FVC rely on results from analyses of covariance (see Section 5.4.1 and Appendix B) of the originally planned primary endpoints. The acceptance of these co-primary endpoints for the original version of protocol was based on the previous use of these same primary endpoints for the approval of two other enzyme replacement therapies for lysosomal storage diseases; Aldurazyme® (laronidase) for the treatment of Mucopolysaccharidosis type I (MPS I) and Elaprase® (idursulfase) for the treatment of Mucopolysaccharidosis type II (MPS II). The mean change from baseline distance walked was 35 ± 14 meters ($p = 0.01$, ANCOVA) for Elaprase, and for Aldurazyme, the median change from baseline distance walked was 39 meters (-2 to 79, 95% CI) ($p=0.07$, Wilcoxon Rank Sum Test). However, it should be noted that MPS I and MPS II present with substantially different clinical manifestations compared with Pompe disease. The clinical phenotype of MPS I and II includes hepatosplenomegaly, skeletal deformities, joint stiffness, cardiomyopathy, and pulmonary hypertension. Death is generally related to cardiopulmonary failure. While the Agency has agreed to use these endpoints in evaluating efficacy of these enzyme replacement therapies, neither of these co-primary endpoints are established in Pompe disease, or for any other lysosomal storage disorder, as surrogate markers for a clinical benefit outcome, such as time to death or ventilator dependency.

The results from the originally planned efficacy analysis for LOTS, utilizing the original planned endpoints, show a difference of 28.1 meters in the estimated mean change in distance walked from baseline to last observation during a six-minute walk test (6MWT) between the 2000 L treatment group and placebo in favor of the 2000 L product. The difference was statistically significant ($p=0.035$), by analysis of covariance (ANCOVA), which adjusted for variables used to stratify the randomization and for a patient's baseline 6MWT. Table 1 shows summary statistics for the 6MWT and the results from the ANCOVA.

Tab 1**Table 1: Change from baseline in distance walked in 6MWT in meters**

	2000 L N=60	Placebo N=30	Difference
<i>Summary statistics:</i>			
Mean (\pm SD) distance walked at baseline	332.2 (128.0)	314.06 (131.4)	n/a
Mean (\pm SD) change from baseline to last observation in distance walked	26.13 (51.3)	0.43 (37.76)	25.70
Median change from baseline to last observation in distance walked	16	0	16
<i>Results of ANCOVA*:</i>			
Mean (\pm SE) change from baseline to last observation in distance walked, adjusted for baseline 6MWT stratification, FVC stratification, their interaction and baseline 6MWT	25.13 (7.57) 95% CI: (10.1, 40.1)	-2.99 (10.64) 95% CI: (-24.1, 18.1)	28.12 (13.10) 95% CI: (2.1, 54.1)

*Copied from Applicant Clinical Study Report pg. 106/1841

There is also a statistically significant difference in the estimated mean change from baseline to last observation in upright FVC (% predicted). The 2000 L treatment group demonstrated a 3.4% increase in upright FVC compared with the placebo group ($p=0.006$); see Table 2.

Table 2: Change from baseline in upright FVC (% predicted)

	2000 L N=60	Placebo N=30	Difference
<i>Summary statistics:</i>			
Mean (\pm SD) FVC at baseline	55.58 (14.5)	53.36 (15.4)	n/a
Mean (\pm SD) change from baseline to last observation in FVC	1.37 (5.0)	-1.82 (4.4)	3.19
<i>Results of ANCOVA*:</i>			
Mean (\pm SE) change from baseline to last observation in FVC, adjusted for baseline 6MWT stratification, FVC stratification, their interaction and baseline FVC	1.20 (0.68) 95% CI: (-0.16, 2.57)	-2.20 (.97) 95% CI: (-4.12, -0.28)	3.40 (1.19) 95% CI: (1.03, 5.77)

*Copied from Applicant Clinical Study Report pg. 112/1841

Despite the demonstration of a statistically significant difference between the 2000 L and placebo groups in both primary efficacy endpoints, the clinical significance of the magnitude of these differences remains unclear. Although the 6MWT has been used as an efficacy endpoint for the approval of enzyme replacement therapies as described above, this test was originally designed to objectively assess functional exercise capacity and response to medical interventions in patients with moderate to severe heart or lung disease, such as chronic obstructive pulmonary disease (COPD). There is one published study that evaluated the correlation between the change in distance walked during a 6MWT and subjective clinical improvement in COPD patients.¹

Tab 1

This study found that a mean change in distance walked of 40 meters was required for patients to stop rating themselves as “about the same” and start rating themselves as “a little bit better” and the mean 6MWT difference was -70 meters for patients to stop rating themselves as “about the same” and start rating themselves² as “a little bit worse.” Similarly, measurements of pulmonary function such as % predicted FVC were designed to objectively assess clinical response in obstructive pulmonary diseases. One consensus statement presented by the American Thoracic Society states that a year-to-year difference in % predicted FVC in COPD patients should be at least 15% to be considered clinically meaningful.² There are no data correlating the change in % predicted FVC or 6MWT and clinical response in Pompe disease. Therefore, the magnitude of change in these endpoints that should be considered clinically meaningful for Pompe disease patients is unknown.

1.3.2 Age

Although patients with Pompe disease 8 years and older were eligible to participate in LOTS, very few patients less than 18 year of age at the time of diagnosis and/or onset of symptoms were actually enrolled. This substantially limited the trials ability to support the efficacy of 2000 L in juvenile-onset patients. Only four patients (two patients in the 2000 L treatment group, and two patients in the placebo treatment group) were less than 18 years of age at the time of enrollment. There were 11 additional patients (8 patients in the 2000 L treatment group and three patients in the placebo treatment group) who, though older than 18, had been diagnosed prior to the age of 18. Finally, there were 14 patients (7 in the 2000 L treatment group and 7 in the placebo group) in the study who were over the age of 18 at the time of diagnosis, but reported that they had first had disease symptoms when they were less than 18 years of age. Thus, it appears that there were insufficient numbers of patients less than 18 years of age in this study to determine the efficacy of the 2000 L product in this younger age group of juvenile-onset patients.

1.3.3 Immunogenicity

All patients treated with 2000 L product developed anti-rhGAA IgG antibodies by 12 weeks, compared with 0 patients in the placebo group. Additionally, 18 patients in the 2000 L treatment group developed inhibitory antibody to 2000 L product. Exploratory analyses suggest that efficacy of the 2000 L product may differ for patients with low (<1%) GAA activity (% normal), and patients with specific anti-rhGAA antibody profiles. All patients with GAA activity < 1% developed inhibitory antibodies to 2000 L product, and this group demonstrated no improvement in either 6MWT or % predicted FVC at the last observation (see section 5.4.5). A subgroup of patients treated with 2000 L product with persistently rising IgG titers, especially in patients with both rising IgG titers and inhibitory antibodies, appeared to have experienced diminished efficacy compared to other patients treated with 2000 L product. It should be noted that given the small size of the study, the subgroup analyses were not powered adequately to demonstrate statistical significance. Despite this limitation, the findings are presented to aid the Advisory Committee in their discussions.

1.3.4 Safety

Anaphylaxis, allergic adverse events and infusion-associated reactions are the major safety concerns for the 2000 L product. There was a 5% incidence of anaphylaxis noted in the clinical trial leading to the approval of the 160 L product, which carries a boxed warning for anaphylaxis in the labeling. Anaphylaxis was also reported in LOTS. According to the FDA review of the

Tab 1

safety data from LOTS, there were 4 patients who met the definition of anaphylaxis (6.7%) in the 2000 L treatment group compared with 0 patients in the placebo treatment group. Additionally, 2/4 (50%) patients identified as developing anaphylaxis withdrew from the study because of this adverse event. No deaths occurred as a consequence of anaphylaxis.

The incidence of infusion-associated reactions (IARs) with the 2000 L product is also an important safety concern. IARs were defined by the Applicant as any AE that occurred during either the infusion or in the 2 hour observation period following the infusion that was assessed by the Investigator as related to the study drug (i.e., possibly, probably, or definitely related). In LOTS, the medical reviewer identified a total of 297 IARs, 78% occurred in patients receiving 2000 L product compared with 22% in the placebo group (table 3). There were important differences in the types of IARs reported between the two groups. In the placebo treatment group, the majority of IARs included headache and nausea, and there were no hypersensitivity-related IARs. However, in the 2000 L group, notable IARs included hypersensitivity reactions such as urticaria, wheezing, hypotension, chest discomfort, throat tightness, decreased oxygen saturation, and skin reactions, including urticaria, and paresthesias.

Table 3 : Number of Infusion of Associated Reactions by treatment group as classified by medical reviewer

	2000 L (% of total) N=60	Placebo (% of total) N=30	Total N=90
AEs occurring during or within 2 hours of completion of infusion	232 (78.1)	65 (21.9)	297
Number of patients experiencing	29 (48)	15 (50)	44

Delayed-onset infusion reactions, occurring from 2-48 hours after the infusion, are also a safety concern, since there have been reports of delayed-onset infusion reactions in patients receiving 160 L product (and other intravenously administered protein products). Delayed-onset anaphylaxis has recently been reported, and may be of concern with the 2000 L product. The medical reviewer uncovered one episode of delayed-onset anaphylaxis in a patient treated with 2000 L product. This event occurred in patient 18713, a patient who developed several episodes of anaphylaxis during the course of the study. Two patients developed urticaria 24-48 hours after completion of the infusion; these patients were in the 2000 L treatment group. There were no episodes of delayed-onset anaphylaxis or urticaria identified in the placebo group. The most common delayed-onset AEs in the placebo group were headache and dysgeusia.

Chronic exposure to 160 L product has led to the development of immune mediated adverse events including skin rashes and at least one report of immune-mediated glomerulonephritis. In LOTS, both skin reactions and urinary abnormalities were noted in higher frequency in the 2000 L treatment group compared with placebo. Eighty-nine percent (89%) of the skin reactions reported in the study occurred in the 2000 L treatment group, and up to 54% (53/98 events) of these skin reactions have a potential immunologic basis (e.g. urticaria, angioneurotic edema, skin nodule); they were seen exclusively in the 2000 L treatment group. Seven patients in the 2000 L treatment group were reported to have hematuria and/or proteinuria compared with two patients in the placebo group. However, these data may not represent the true incidence of immune-mediated skin and renal complications as these adverse events may take months or years to develop.

1.3.5 Additional Safety Observations

Other important adverse events that occurred in LOTS included one patient death, and 26 nonfatal serious adverse events (SAEs). The death occurred in a 33 year-old female patient randomized to receive 2000 L product. She developed brain stem ischemia due to cerebral aneurysms, and her death was determined to be related to her underlying disease and not to the study medication. SAEs led to 2 patient dropouts (anaphylaxis) in the 2000 L group, and 1 patient dropout (headache) in the placebo group.

2 Summary

In summary, the 2000 L product produces a 28.1 meters ($p=0.035$) increase in estimated change from baseline distance walked during the 6MWT and a 3.4% ($p=0.006$) increase in estimated change from baseline in % predicted upright FVC compared to placebo in patients with Pompe disease over a 78-week period. However, an important limitation of LOTS was the failure to enroll sufficient numbers of juvenile-onset patients to demonstrate efficacy in this group of Pompe disease patients. Differences in efficacy may also be present in certain subgroups of patients, including those with low GAA activity, and patients with specific anti-rhGAA IgG antibody profiles. Exploratory analyses suggest that patients with persistently rising anti-rhGAA IgG antibody titers, especially those who also develop inhibitory IgG antibodies may not respond as well. Immunogenicity of the 2000 L product is concerning, as 100% of 2000 L-treated patients developed anti-rhGAA IgG antibodies, and all patients with GAA activity <1% developed inhibitory antibodies.

Important clinical safety issues include those related to the immunogenicity of the 2000 L product. Anaphylaxis, as well as immediate and delayed-onset infusion associated reactions, occur at higher rates than placebo. Chronic exposure to 2000 L product has not been adequately studied, but both skin reactions and urinary abnormalities reported in LOTS suggest that, as with the 160 L product, immune mediated reactions may occur with chronic exposure.

3 Points for Discussion by the Advisory Committee

Based on the clinical review of the 2000 L product, the following discussion points are raised to the Advisory Committee:

1. Discuss the use of the 6MWT and % predicted FVC to assess clinical efficacy for the 2000 L product. Discuss the magnitude of change in these endpoints that constitutes a clinically meaningful response in Pompe disease patients.
2. Discuss the adequacy of the long-term efficacy and safety data for the 2000 L product and whether additional studies should be required to assess the durability of response, and to assess the safety associated with chronic exposure.
3. Discuss the clinical indication of the 2000 L product and whether the product should be limited to adult-onset Pompe disease patients. Is there an age below which patients should be treated with 160 L product instead of the 2000 L product?
4. Although the approved indication for the 160 L product is not restricted to a particular sub-type of Pompe disease in the US, it is currently reserved exclusively for patients less than 18 years of age. The Applicant's proposed indication for the 2000 L product is for "late-onset" Pompe disease only. If there is an age limit below which the committee believes treatment with the 2000 L product should be restricted, then what safeguards should be implemented to avoid use of the 2000 L product in younger patients. Discuss how patients, practitioners, and the public should be informed of these differences.
5. Discuss the role of immunogenicity in the overall efficacy and safety of 2000 L product.
6. The primary efficacy endpoints and method of statistical analysis were changed during the conduct of this trial. In addition, when the final data were analyzed, the Applicant discovered that the assumptions of the pre-specified statistical model were violated. Discuss the implications of changing primary efficacy endpoints during the course of the study and the changes to the statistical analysis plan on the robustness of the conclusions drawn from this trial.

4 Background Information

4.1 Clinical Description of Pompe Disease

Pompe disease, also known as Glycogen Storage Disease Type II (GSD II) or acid maltase deficiency (AMD) is a rare, autosomal recessive disorder of glycogen metabolism caused by the absence or marked deficiency of the lysosomal enzyme acid- α -glucosidase (GAA). Patients with deficiency of this enzyme develop accumulation of lysosomal glycogen. This accumulation of lysosomal glycogen produces effects in various tissues, particularly in cardiac and skeletal muscle, and hepatic tissues, resulting in development of severe and progressive muscle weakness, cardiomyopathy, and impairment of respiratory function. Three clinical forms of Pompe disease are described: infantile-, juvenile- and adult-onset forms. The infantile-onset form leads to severe cardiomyopathy, muscle weakness and death usually by 18 months of age. The juvenile- and adult-onset forms are generally more attenuated, with symptoms developing in childhood or early adulthood and progressing over years to decades. In the juvenile- and adult-onset forms, deficiency of this enzyme results in the accumulation of glycogen in the lysosomes of a variety of cells, but predominantly in skeletal muscle. This accumulation of glycogen in skeletal muscle lysosomes results in progressive muscle weakness. Death in all forms is usually a result of respiratory failure. The frequency of this disease varies between ethnic groups and clinical forms. The frequency of infantile-onset appears to be highest in African-Americans 1/14,000 and Chinese 1/40-50,000. The frequency of late-onset disease is approximately 1/60,000 in Caucasian populations.

Deficiency of acid- α -glucosidase is a *sine qua non* of Pompe disease. Acid- α -glucosidase is a lysosomal enzyme that catalyzes the hydrolysis of α 1,4- and α 1,6-glucosidic linkages at acid pH, leading to the complete hydrolysis of glycogen. The enzyme is transcribed as a 110kD membrane bound precursor in the endoplasmic reticulum and undergoes extensive post-translational modifications. All of the seven potential glycosylation sites are utilized for glycosylation and subsequent phosphorylation of mannose residues within the Golgi apparatus, providing the mannose-6-phosphate recognition marker for targeting to lysosomes. Proteolytic cleavage to the 70kD mature enzyme occurs within lysosomes. The enzyme functions as a glycosyl hydrolase, and hydrolyzes glycogen at acid pH (3.0-4.0). Pompe disease patients have variable activity of the enzyme. In general, infantile-onset patients have undetectable enzyme activity in muscle tissue. Late-onset patients have activity that is reduced to a lesser extent than in infantile-onset patients. Interestingly, residual enzyme activity between juvenile and adult-onset patient may overlap and suggests that residual activity is not the sole determinant of the clinical phenotype.³

4.2 Clinical History of Alglucosidase alfa

Enzyme replacement therapy for lysosomal storage disease was conceived in the early 1960's⁴ but it was not until 1974 when purified glucocerebrosidase in the treatment of Gaucher disease was first published.⁵ Enzyme replacement therapies are now available in the US for several lysosomal storage diseases including Gaucher (Cerezyme and Ceredase), Mucopolysaccharidosis

I (Aldurazyme), II (Elaprase), and VI (Naglazyme), Fabry (Fabrazyme), and Pompe disease (Myozyme).

Alglucosidase alfa (rh-GAA) is the recombinant form of acid alpha-glucosidase and is intended for long-term use as an enzyme replacement therapy (ERT) for patients with Pompe disease. Alglucosidase alfa is a purified analog of the naturally occurring, endogenous lysosomal GAA. The rationale for this therapy is that exogenous administration of alglucosidase alfa should theoretically replace the deficiency of endogenous enzyme in Pompe disease patients. Alglucosidase alfa is produced by recombinant DNA technology developed in a Chinese hamster ovary (CHO) cell line, and has a molecular weight of approximately 109 kD. After intravenous administration, alglucosidase alfa is internalized by cells via cellular membrane mannose-6-phosphate receptors binding to enzyme mannose-6-phosphate residues. The enzyme is then taken up by lysosomes and undergoes proteolytic cleavage resulting in increased enzymatic activity. It then exerts enzymatic activity in cleaving glycogen present in lysosomes.

Alglucosidase alfa 160 L product was approved by the FDA in April, 2006 for the following indication: “Myozyme (alglucosidase alfa 160 L) is indicated for use in patients with Pompe disease (GAA deficiency). Myozyme has been shown to improve ventilator-free survival in patients with infantile-onset Pompe disease as compared to an untreated historical control, whereas use of Myozyme in patients with other forms of Pompe disease has not been adequately studied to assure safety and efficacy.” The 160 L product is currently the only commercially available treatment in the US for patients with Pompe disease.

4.3 Regulatory History of Alglucosidase alfa

The Applicant, Genzyme, submitted the original Biologics Licensing Agreement (BLA) for alglucosidase alfa (STN 125,141/0) on July 29, 2005. For the original BLA, Genzyme requested approval of both the 160 L and 2000 L production scales for alglucosidase alfa, although patients treated in the clinical studies in support of this BLA were treated with the 160 L product only. However, upon Agency review, the 160 L and 2000 L products were not shown to be comparable by Chemistry, Manufacturing, and Controls (CMC), nonclinical, and clinical pharmacology assessments. Genzyme, therefore, withdrew the 2000 L scale manufacturing process from BLA 125141 on December 12, 2005. The Agency approved the 160 L production scale of this product on April 28, 2006, and Myozyme was the trade name for the 160 L product in the US. It should be noted that the trial reviewed in support of the 160 L product was performed on 18 infantile-onset disease patients only. The primary efficacy endpoint that was measured in this trial was alglucosidase alfa effect on ventilator-free survival. There was a statistically significant difference in the ventilator-free survival at 18 months when compared to an historical control. Juvenile and adult-onset Pompe disease patients were not enrolled in the clinical trial. However, the FDA noted that no other commercially available products were approved for use in Pompe disease in the US, and therefore, the 160 L product was approved for use in all Pompe disease patients.

Genzyme then submitted a supplement for BLA 125,141 (BLA125,141/65) in October, 2007, with biochemical, nonclinical, and clinical data, which was intended to show comparability of the 2000 L manufacturing process to the 160 L process. Following review of this supplement, the Agency found that there was insufficient information available to establish the comparability

Tab 1

of the 160 L and 2000 L products. In particular, there were very limited clinical data available with the 2000 L process product that would have allowed the Agency to make a reasonable assessment of comparability to the 160 L process product. The Agency also had concerns that due to manufacturing differences for the two products, the 2000 L product may be less potent than the 160 L product, although this could not be definitively established given the limitations of the data. Therefore, on April 15, 2008, FDA advised Genzyme to submit a new BLA with clinical data to support a separate licensure of the 2000 L Myozyme product from the 160 L product. It should be noted that the 2000 L product was approved in Canada, Europe and other countries throughout the world, and is also marketed under the trade name Myozyme. The Agency also advised the Applicant that an Advisory Committee meeting would be convened to discuss the efficacy, safety, and quality issues regarding the 2000 L product, and that a six-month, priority review would be granted for this BLA.

Genzyme has now submitted BLA (STN 125,291; dated 28-May-2008) seeking approval of the 2000 L production process for Myozyme for a new indication, the treatment of non-infantile-onset Pompe disease. The BLA submission relies on the data from one double-blind, placebo-controlled study in ninety patients with non-infantile-onset Pompe disease, and the product used in this study is derived exclusively from the 2000 L manufacturing process.

This BLA (STN 125,291) included study AGLU02704, Late-Onset Treatment Study (LOTS). LOTS evaluated the efficacy of 2000 L Myozyme in sixty non-infantile-onset Pompe disease patients (age 8 -70 years) compared with thirty non-infantile-onset Pompe disease patients randomized to placebo. The primary efficacy endpoints of LOTS were measurement of a six minute walk test (6MWT), and measurement of forced vital capacity (FVC). An open-label, six-month extension of this study (AGLU03206, LOTS extension) is also ongoing. Interim efficacy data from the study is to be submitted after the Advisory Committee convenes (October 31, 2008). Safety data from LOTS were also included in the initial BLA submission. In addition, an integrated safety summary that includes patients receiving alglucosidase alfa as part of the AGLU03206 study, a Genzyme sponsored Myozyme temporary access program (AGLU03907, MTAP), several small studies using 2000 L product; (AGLU2603 - 8 patients), (AGLU2804 - 5 patients), (AGLU3105 - 5 patients), and postmarketing safety data was submitted to FDA on September 1, 2008.

5 Overview of Clinical Data in BLA 125291

5.1 Clinical Indication

The Applicant is proposing that alglucosidase alfa 2000 L product receive the following indication:

“Alglucosidase alfa 2000 L is indicated for long-term use in patients with late-onset Pompe disease (GAA deficiency). Alglucosidase alfa has been shown to improve distance walked and stabilize pulmonary function in patients with late-onset Pompe disease.”

5.2 Clinical Efficacy Studies Submitted

Study AGLU02704, “A randomized, double-blind, placebo-controlled, adaptive, multicenter, multinational, placebo-controlled study of the safety, efficacy, and pharmacokinetics of Myozyme, recombinant Human Acid alpha-Glucosidase (rhGAA), treatment in patients with late-onset Pompe Disease”, is the only study that was submitted to support the efficacy of the 2000 L product for the Applicant’s requested indication. The remainder of this document will use “LOTS” to refer to Study AGLU02704.

The Applicant has also agreed to submit efficacy data (through week 26) from the LOTS extension study on October 31, 2008. These data will not be available for review during the Advisory Committee Meeting.

Additionally, on September 1, 2008, the Applicant submitted data to the Agency on eleven infantile-onset Pompe patients from Taiwan who received 2000 L product. These data summarize the clinical experience of a single treatment center, and were collected retrospectively as an uncontrolled case series. These data were not submitted in time for the Agency to perform a thorough review of the findings and include the results in the briefing package. Also, since the Applicant is seeking approval of the 2000 L product in late-onset disease patients only, the data obtained in infantile-onset patients in Taiwan are not felt to be supportive of the proposed indication in late-onset patients, and would be of limited value for the Advisory Committee deliberations. Therefore, the Taiwanese data will not be further discussed by the Agency in support of the efficacy of the 2000 L product.

5.3 Clinical Safety Studies Submitted

The primary source for clinical safety data of the 2000 L product was LOTS and the safety review performed by the Agency for the Advisory Committee was limited to the safety information from LOTS. The Applicant submitted 5 other studies (see section 6.1) to the Agency as part of an Integrated Summary of Safety. However, since these data were submitted late in the review cycle, there was insufficient time for these studies to be adequately reviewed prior to the submission of the Advisory Committee briefing package and therefore, a review of these safety data was not included in this briefing package. A brief listing of the submissions comprising the Integrated Summary of Safety is included below:

Safety Data submissions

- May 31, 2008: Safety data: LOTS; n=90
- September 1, 2008: LOTS extension study (through April 15, 2008)
- September 1, 2008: US expanded access program; n=9
- September 1, 2008: EU open label late-onset study; n=5
- September 1, 2008: EU open label, advanced late onset study; n=5
- September 1, 2008: US Myozyme Temporary Access Program; n=135

6 Clinical Trial Design of Study AGLU02704, LOTS

6.1 General Study Design

LOTS was a randomized, double-blind, placebo-controlled, multicenter (n=8), multinational (5 US sites and 3 international sites) study of the safety, efficacy, and pharmacokinetics of 2000 L product in 90 patients with non-infantile onset Pompe disease, ages 8 to 70 years. Patients must have been able to ambulate at least 40 meters during a 6MWT. Additionally, patients must not have required invasive (endotracheal) ventilation, and have had a % predicted FVC less than 80%. In the original protocol, patients were randomized to receive either 2000 L product infusions (20mg/kg) or placebo infusions every other week (qow) for 52 weeks.

The Applicant requested that LOTS be changed to an adaptive trial design, and in order to do so, the Applicant changed both the primary efficacy measures and method of statistical analysis during the study (see section 6.10). The treatment length was extended to 78 weeks after an Independent Statistical Center completed an adaptive design analysis of the data and recommended increasing the length of the treatment period to 18 months (78 weeks).

6.2 Study Objectives

The primary objectives of LOTS included the following:

1. Assess the effect of repeated infusions of 2000 L product over 78 weeks in late-onset Pompe disease patients on functional endurance and respiratory muscle weakness, as measured by the 6MWT and % predicted FVC.
2. Assess the safety of repeated infusions of 2000 L product over 78 weeks in late-onset Pompe disease patients.

6.3 Eligibility Criteria

Major inclusion criteria include the following:

1. The patient must have a diagnosis of Pompe disease based on deficient endogenous GAA activity in cultured skin fibroblasts of $\leq 40\%$ of the normal mean of the testing laboratory and 2 GAA gene mutations.
2. The patient must be ≥ 8 years of age at the time of enrollment.
3. The patient must be able to ambulate 40 meters (approximately 130 feet) in 6 minutes on each test performed on 2 consecutive days (use of assistive devices such as a walker, cane, or crutches, is permitted).
4. The patient must have an FVC of $>30\%$ and $< 80\%$ predicted in the upright position.
5. The patient must have a postural drop in FVC (liters) of at least 10% from the upright to the supine position $[(\text{FVC supine (L)} - \text{FVC upright (L)})/\text{FVC upright (L)}] * 100\%$.

Major exclusion criteria include the following:

1. Patients who require the use of invasive ventilatory support. Invasive ventilation is defined as any form of ventilatory support applied with the use of an endotracheal tube.
2. Patients who require the use of noninvasive ventilatory support while awake and in an upright position. Noninvasive ventilation is defined as any form of ventilatory support applied without the use of an endotracheal tube. For example, patients receiving positive-pressure ventilation support through a facemask or nose piece are considered as ventilated through noninvasive methods.
3. Patients who have received enzyme replacement therapy with GAA from any source, or who have received an investigational drug within 30 days of study enrollment.

6.4 Concomitant Medications

There were no restrictions to concomitant medications administered with the exception of use of enzyme replacement therapy with GAA or use of an investigational product within 30 days prior to study enrollment as described above in the exclusion criteria. The Applicant recorded all medications and therapies taken by the patient in the 30 days prior to the screening/baseline evaluation. All concomitant medications taken by subjects during the course of the study were recorded. Assistive device use was also recorded as a concomitant therapy.

6.5 Visits and Procedures

Study visits and procedures are shown in Tables 4-6 (tables were electronically copied from Applicant Protocol dated 16 August 2006, pgs. 30-34/84)

Table 4: Schedule of Study Events: Screening Period

Study Event [†]	Pre-Screening ¹	Screening/Baseline	
		Day 1	Day 2
Written Informed Consent	X	X ²	
Inclusion/Exclusion Criteria		X	
Urine pregnancy test ³	X	X	
Medical/Surgical History	X	X ²	
Six Minute Walk Test (6MWT)	X ^{4,5}	X ^{6,6}	X ^{6,6}
Pulmonary Function Testing (PFT)	X ⁴	X ⁶	X ⁶
Quantitative Muscle Testing (QMT)	X ⁴	X ⁶	X ⁶
Manual Muscle Testing (MMT)	X ⁴	X ⁶	
Functional Activities Assessment (FAA)	X ⁴	X ⁶	
SF-36 Health Survey (SF-36) ⁷			X
Fatigue Severity Scale (FSS) ⁷			X
Rotterdam 9-Item Handicap Scale ⁷			X
Late-Onset Pompe Disease Questionnaire ⁸			X
GAA Gene Mutation Analysis	X ⁹		
GAA Activity in skin fibroblasts	X ⁹		
GAA Activity in blood			X ¹⁰
Pompe Disease history/ family history		X	
Physical Examination		X	
Height		X	
Vital signs		X	
Hearing testing			X ¹¹
Serum chemistry and hematology			X
Urinalysis			X
Oligosaccharides in blood			X
Oligosaccharides in urine			X
12-lead electrocardiogram			X ¹¹
Echocardiogram			X ¹¹
Weight for Dosage Calculation			X
Adverse Event Assessment	Continuous Monitoring		
Concomitant and Pre-Infusion Medication/Therapy Monitoring ¹²	Continuous Monitoring		

¹ A pre-screening evaluation will be performed for patients who did not participate in AGLU02303, or in the AGLU02905 screening protocol and a clinical evaluator reliability testing session. Additionally, patients that participated in AGLU02303 may be pre-screened at the Investigator's discretion with permission from Genzyme. The pre-screening visit must occur a minimum of 2 weeks (14 days) before the Screening/Baseline visit.

² These study events will be performed during the Screening/Baseline visit for patients who did not have a pre-screening evaluation.

³ For female patients of child bearing potential only.

⁴ Performed on patients who have not previously been exposed to the test

⁵ One test will be administered on a single day during the Pre-screening visit and 2 tests will be administered during the Screening/Baseline period, 1 on each of 2 consecutive days.

⁶ Portions of these assessments may be videotaped in a subset of patients. Refer to the SOM for details.

⁷ Patients 14 years of age and older at the time of evaluation will complete the questionnaires.

⁸ Patients 14 years of age and older at the time of evaluation will complete the questionnaire. Questionnaire will be completed by parent or legal guardian if the patient is less than 14 years of age.

⁹ Performed on patients for whom a testable sample has not been obtained. Results obtained in study AGLU02303 or screening protocol AGLU02905 will be carried over.

¹⁰ GAA activity analysis in blood does not need to be repeated if performed previously in study AGLU02303.

¹¹ Hearing testing, 12-lead electrocardiogram, and echocardiogram are performed after Screening/Baseline Day 1 and before the day of first infusion (Day 0).

¹² This includes the use (if any) of mechanical ventilation (including both invasive and noninvasive) and assistive devices (e.g., walker, cane, crutches).

Table 5: Schedule of Study Events: Treatment Period

Study Event ^{1*}	D 0 ²	W 2	W 4	W 6	W 8	W 10	W 12	W 14	W 16	W 18	W 20	W 22	W 24	W 26	W 28	W 30	W 32	W 34	W 36	W 38	W 40	W 42	W 44	W 46	W 48	W 50	W 52
Six Minute Walk Test (6MWT) ³						X ⁴							X ⁴							X ⁴							X ⁴
Pulmonary Function Testing (PFT)						X ⁴							X ⁴							X ⁴							X ^{4,5}
Quantitative Muscle Testing (QMT)						X ⁴							X ⁴							X ⁴							X ^{4,5}
Manual Muscle Testing (MMT)						X ⁴							X ⁴							X ⁴							X ⁴
Functional Activities Assessment (FAA)						X ⁴							X ⁴							X ⁴							X ⁴
SF-36 Health Survey (SF-36) ⁶														X						X							X
Fatigue Severity Scale (FSS) ⁶														X						X							X
Rotterdam 9-Item Handicap Scale ⁶													X							X							X
Urine pregnancy test ⁷	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination		X	X	X	X	X	X						X	X						X	X						X
Serum chemistry and hematology		X	X	X	X	X	X						X	X						X	X						X
Urinalysis		X	X	X	X	X	X		X				X	X						X	X						X
Oligosaccharides in blood			X	X	X	X	X						X	X						X	X						X
Oligosaccharides in urine			X	X	X	X	X						X	X						X	X						X
Anti-αGAA antibody (IgG)	X	X	X	X	X	X	X		X				X	X						X	X						X
Pharmacokinetics testing ⁸	X					X																					X
Height						X																					X
Hearing testing																											X
12-lead electrocardiogram														X													X
Echocardiogram																											X
Weight for Dosage Calculation						X							X							X							X
Vital signs ⁹	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Infusion of study drug ¹⁰	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ventilator Use Diary																											
Adverse Event Assessment																											
Concomitant and Pre-Infusion Medication/Therapy Monitoring ¹¹																											

Table 6: Schedule of Study Events—Treatment Period from week 54-week 78/End of Study

Study Event ^{1*}	W 54	W 56	W 58	W 60	W 62	W 64	W 66	W 68	W 70	W 72	W 74	W 76	W 78/ EOS ¹²
Six Minute Walk Test (6MWT) ³						X ⁴							X ^{4,13}
Pulmonary Function Testing (PFT)						X ⁴							X ^{4,13}
Quantitative Muscle Testing (QMT)						X ⁴							X ^{4,13}
Manual Muscle Testing (MMT)						X ⁴							X ^{4,13}
Functional Activities Assessment (FAA)						X ⁴							X ^{4,13}
SF-36 Health Survey (SF-36) ⁵						X							X ¹³
Fatigue Severity Scale (FSS) ⁵						X							X ¹³
Rotterdam 9-Item Handicap Scale ⁵						X							X ¹³
Urine pregnancy test ⁷	X		X		X		X		X		X		X
Physical Examination						X							X
Serum chemistry and hematology						X							X
Urinalysis	X		X		X		X		X		X		X
Oligosaccharides in blood						X							X
Oligosaccharides in urine						X							X
Anti-rhGAA antibody (IgG)						X							X
Height						X							X ¹³
Hearing testing													X ¹³
12-lead electrocardiogram													X ¹³
Echocardiogram													X ¹³
Weight for Dosage Calculation						X							X ¹⁴
Vital signs ⁹	X	X	X	X	X	X	X	X	X	X	X	X	X
Infusion of study drug ¹⁰	X	X	X	X	X	X	X	X	X	X	X	X	X ¹⁴
Ventilator Use Diary	Continuous Monitoring												
Adverse Event Assessment	Continuous Monitoring												
Concomitant and Pre-Infusion Medication/Therapy Monitoring ¹¹	Continuous Monitoring												

D=day; W=week

¹ Unless otherwise specified, all study assessments had a window of ± 14 days.

² Patients were contacted on Day 1 and Day 7 to assess for AEs following first infusion.

³ Two tests were administered, 1 on each of 2 consecutive days.

⁴ Portions of these assessments could be videotaped in a subset of patients.

⁵ QMT and PFT assessments were repeated on each of 2 consecutive days for reliability testing.

⁶ Patients 14 years of age and older at the time of evaluation completed the questionnaires.

⁷ For female patients of child bearing potential only.

⁸ For patients who participated in PK assessments, blood samples for the measurement of plasma rhGAA activity were collected at each of the following time points: 0 (before the start of the infusion), 1 and 2 hours after the start of infusion, end of the infusion, and then 0.25, 0.5, 1, 2, 3, 4, 8, 12, and 16 hours after the end of the infusion (with a window of ± 5 minutes for time points after the start of infusion).

⁹ Vital signs were collected immediately prior to each infusion, every 30 minutes during the infusion, immediately prior to any infusion change (if the time point was different), as well as after completion of the post-infusion observation period (with a window of ± 15 minutes for time points after the start of infusion).

¹⁰ The initial day of infusion was designated as Day 0. Subsequent infusion visits were calculated from Day 0 in 14 day increments (with a window of ± 7 days). Prior to each infusion the patient was assessed by the Investigator or appropriate designee to determine if the patient was free of acute illness and was clinically stable to receive the infusion.

¹¹ This includes the use (if any) of mechanical ventilation (including both invasive and noninvasive) and assistive devices (e.g., walker, cane, crutches).

¹² Week 78 or End of Study (EOS).

¹³ If not performed within the last 6 weeks. However, patients with abnormal ECG performed within 6 weeks of the EOS visit needed to have repeat ECG at EOS.

¹⁴ In case of withdrawal, weight for dose calculation and infusion of study drug were not applicable.

Electronically copied from Applicant Protocol dated 16 August 2006, pgs. 30-34/84

6.6 Randomization and controls

LOTS was conducted as a double-blind, placebo-controlled study with randomization in a 2:1 ratio of 2000 L product to placebo. A total of 90 patients were enrolled at eight primary investigational study centers in the US and Europe. Each patient was to receive either 2000 L product at a dose of 20mg/kg every other week (qow) or placebo as an IV infusion. Patients were randomized using a minimization algorithm. The statistical analysis plan states that this algorithm examined the current distribution of treatment assignments to derive the next treatment arm to assign with the goal of achieving the proposed 2:1 treatment allocation across sites, baseline 6MWT, and baseline FVC upright (% predicted). Stratification levels for the 6MWT and FVC (% predicted) used for treatment allocation were as follows: A) baseline 6MWT \leq 300 meters B) baseline 6MWT $>$ 300 meters, A) baseline FVC \leq 55% predicted B) baseline FVC $>$ 55% predicted. The rationale for the Applicant's choice in these cut points were based on observed median values for the measurements from a set of patients in an observational study of late-onset Pompe disease (AGLU02303). Allocation to treatment assignment was performed using an Interactive Voice Response System (IVRS).

6.7 Study Medication Dose Selection

The selection and timing of 2000 L product dosing was based on prior nonclinical and clinical studies. Dose ranging studies were performed as part of Phase I/II drug development plan and included studies in patients with infantile-onset Pompe disease (AGLU01602, AGLU01702, AGLU2003, and AGLU02203) and in patients with late-onset Pompe disease (AGLU02103, AGLU02503, and AGLU01702). The approved commercial dose of 160 L product is 20mg/kg every other week, and the same dose was selected for use of the 2000 L product in LOTS. No other doses of 2000 L product were used in this study.

6.8 Efficacy and Endpoint Measures

For the purposes of the Advisory Committee meeting, this background package presents information relevant to the approval and labeling of 2000 L product. Therefore, only the substantive analyses of the primary efficacy measures are included. However, the entire list of efficacy and endpoint measures is provided for review in Appendix 1. The co-primary efficacy endpoints for LOTS were:

1. The mean monthly change in distance walked during a 6MWT
2. The mean monthly change in upright FVC (% predicted).

The study was to be considered to have met its primary efficacy objective if a statistically significant treatment effect of Myozyme over placebo was demonstrated in the 6MWT. FVC testing was to be performed if statistical significance was achieved upon analysis of 6MWT results.

The intent to treat (ITT) population, or full analysis population, included all 60 patients enrolled in the 2000 L product arm and all 30 patients in the placebo arm of LOTS. All efficacy and safety analyses in this review were performed on the full analysis population. All data to a cutoff

of the Week 78 study visit were analyzed for the study. Further efficacy data from these patients was obtained in the LOTS extension study; however, efficacy data from the LOTS extension study will not be available until October 31, 2008.

6.9 Safety Assessments

All patients who received at least one dose of study medication or placebo, the ITT, comprised the population evaluated for safety. Safety was assessed by types and incidence of AEs, deaths, discontinuations due to AEs, and drug-related, serious and severe AEs, and changes from baseline in physical exams (including vital signs), and clinical laboratory assessments including clinical chemistry, hematology and urinalysis. Physical examination and urinalysis, urine pregnancy testing (when applicable) and testing for anti-rhGAA IgG antibody titers were to be performed at each infusion. Of note, when the protocol was amended to extend the study to 78 weeks, anti-rhGAA IgG testing was decreased to once at Week 64 and again at Week 78. Other clinical laboratory assessments were to be made at each infusion for the first four infusions, and then every six weeks afterward. ECG testing was to be performed at three study points during the study.

Adverse events were categorized as mild, moderate or severe based on the assessment of the investigator at each site. Serious adverse event (SAE) data were also collected and reported to the Applicant within 24 hours of the Investigator's first knowledge of the event. Written documentation was also sent to the Applicant regarding any serious adverse event. New ventilator use was also documented as a part of the safety assessment. Requirement for ventilatory support greater than 3 days was reported as an SAE. Infusion associated reactions were defined as adverse events that occurred during the infusion period or the 2-hour observation period following the infusion. Relationship to the study drug was classified as either possibly, probably, or definitely by the Investigator. Adverse events that occurred after the infusion and observation period could also be considered an infusion associated reaction at the discretion of the Investigator.

Immunologic testing was performed on all study patients. Routine anti-rhGAA IgG antibody testing was performed pre-infusion and at specified intervals during the study. Inhibitory IgG antibody testing was also performed after Week 78 on all serum samples of patients who developed anti-rhGAA IgG antibody titers during the study. Two assays were used: measurement of inhibition of rhGAA enzymatic activity and measurement of inhibition of the uptake of rhGAA. Both of these *in vitro* assays were performed in fibroblast cells. Each assay was performed from the point of seroconversion and approximately quarterly thereafter.

An independent Data Safety Monitoring Board (DSMB) periodically reviewed safety data, and on an *ad hoc* basis reviewed expedited safety concerns including the following:

1. Death or life-threatening, causally related event in 1 patient.
2. Occurrence of the same serious, unexpected, causally related event in at least 2 patients (excluding death or life-threatening as described above).
3. Two or more occurrences of the same serious, unexpected, causally related event in any single patient.
4. Occurrence of any other safety-related issues identified by the Applicant's pharmacovigilance that posed a medical concern.

Recommendations for discontinuation of the study drug were to be made by the DSMB with the final decision regarding study drug discontinuation made by the Applicant.

6.10 Protocol and Statistical Analysis Plan Amendments

Three protocol amendments and three statistical analysis plan amendments were submitted by the Applicant during the course of LOTS (see figure 1). The major changes in each protocol amendment were summarized by the Applicant:

Protocol Amendment 1 dated 15 September 2005

- This amendment was submitted around the time of the first patient enrollment into LOTS.
- Patients who transferred to regional investigational sites after 6 months of treatment could complete the remaining infusion visits at the transfer site. The Week 38 and Week 52 or yearly withdrawal infusions were no longer required to be done at the primary site.
- Conduct of the 6MWT at Screening/Baseline was changed from 2 tests performed on the same day to testing on 2 consecutive days.
- Inclusion criterion #8, which required the patient to have a forced expiratory volume in the first second of the FVC maneuver (FEV1)/FVC value of $\geq 70\%$ predicted in the upright position, was deleted. The purpose of this criterion was to identify patients with confounding obstructive disease that was NOT related to Pompe disease. However, weakness in the supporting respiratory muscles could prevent patients from exhaling sufficient volume in the first second of the FVC maneuver (FEV1), causing what appears to be mild obstructive involvement in addition to the restrictive involvement caused by diaphragmatic weakness.
- Exclusion for major congenital anomaly was limited to those that in the judgment of the Investigator would significantly interfere with study compliance, including all prescribed evaluations and follow-up activities.

Protocol Amendment 2 dated 26 May 2006

- This amendment was submitted after 33 patients had completed at least 36 weeks of the study.
- The infusion rate schedule was adjusted to a maximum rate of approximately 7 mg/kg/hr to assist in IAR management, consistent with infantile-onset studies of Pompe disease conducted by Genzyme. In Protocol Amendment 3, this infusion rate schedule was subsequently designated as “recommended” to allow investigator discretion in setting the infusion rate.
- Amendment 2 proposed an adaptive design that required a change in the primary efficacy measures from mean change from baseline to a rate of change per month for 6MWT and % predicted FVC.

Protocol Amendment 3 dated 16 August 2006

- The infusion rate schedule as adjusted in Amendment 2 was designated as “recommended” to allow investigator discretion in setting the infusion rate.

- Amendment 3 outlined a revised adaptive design strategy that was fully detailed in the Statistical Analysis Plan (SAP) version dated 29 September 2006 (see below).

The statistical analysis plan was also amended three times, and the major changes to this plan are summarized below:

Original Statistical Analysis Plan, dated 27 September 2005

- Co-primary efficacy variables:
 - Number of meters walked in 6 minutes at Week 52, adjusted for baseline number of meters walked.
 - FVC upright (% predicted) at Week 52, adjusted for baseline FVC upright (% predicted).
- Changes at 52 weeks among subjects randomized to 2000 L product compared with changes at 52 weeks among subjects randomized to placebo to be analyzed using a repeated measures linear model with covariates:
 - Independent variables are site, distance walked at baseline (or FVC at baseline), treatment, time of assessment, time-by-treatment interaction.
 - Response covariance is modeled by a compound symmetry structure.

Statistical Analysis Plan Amendment, dated 29 September 2006

- This amendment was submitted after 33 patients had completed at least 36 weeks of the study.
- Methods and plans for implementation of adaptive information-based design are provided.
- Co-primary efficacy variables changed to slopes (average monthly increase) to accommodate the adaptive design
 - Average monthly increase in 6MWT.
 - Average monthly increase in FVC upright (% predicted).
- Changes in average monthly increases in 6MWT (and FVC upright) among subjects randomized to 2000 L product compared with changes in average monthly increases in 6MWT (and FVC upright) among subjects randomized to placebo to be analyzed using a linear mixed effects (LME) model:
 - Independent variables are site, treatment, time, and treatment-by-time interaction.
 - Outcome vector contains the observed measurements of 6MWT (or FVC upright) collected at baseline and at study visits.
 - Model to be fit using restricted maximum likelihood estimation.
 - Model to use unstructured variance-covariance matrix for the random effects (i.e., intercept and slope).
 - Model will be used to estimate the rate of change for each subject.
- Specifies the assumption of linear rate of change and other modeling assumptions will be assessed.

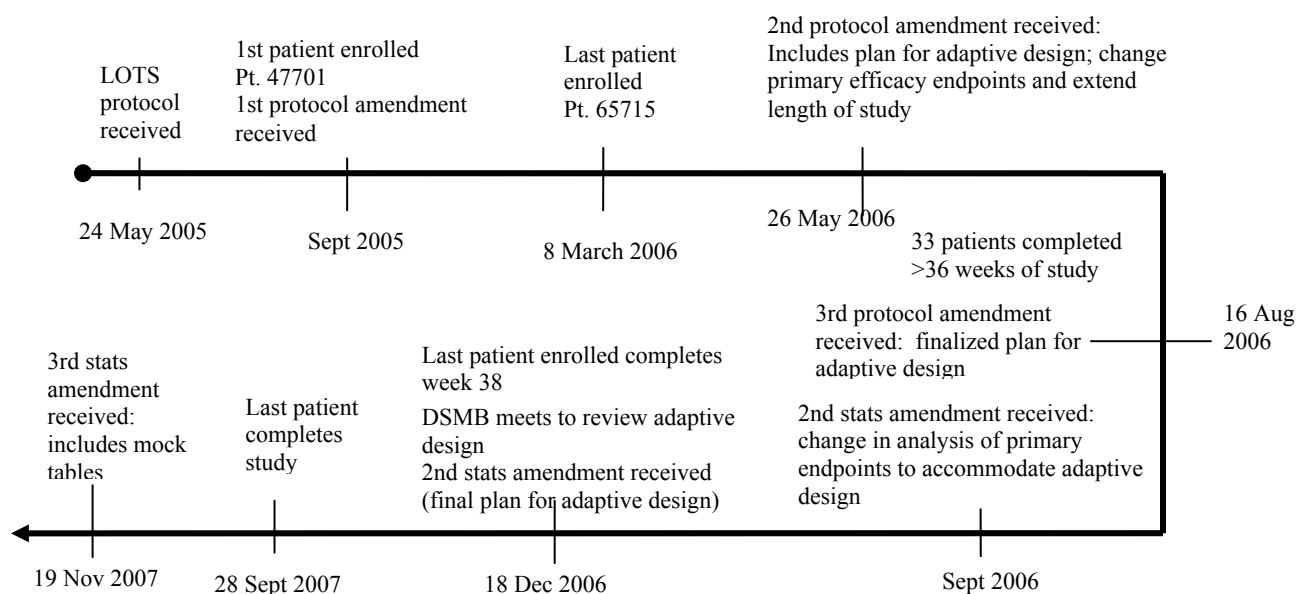
Statistical Analysis Plan Amendment, dated 07 December 2006

- This amendment was submitted just prior to all patients completing 38 weeks of the study.
- Revisions reflect feedback from FDA regarding the interim analysis to be done by the ISC.

Statistical Analysis Plan Amendment, dated 19 November 2007

- Final statistical plan, includes mock tables.

Figure 1: Timeline of Protocol and Statistical Analysis Plan Amendments



7 Efficacy Review

7.1 Methods

The efficacy information available for review for the Advisory Committee meeting includes clinical efficacy or outcomes measures from one clinical study, LOTS. Efficacy data were available in 90 patients (60 patients randomized to 2000 L product and 30 patients randomized to placebo), all of whom had late-onset Pompe disease.

7.2 Demographics

A review of the demographic data was performed to evaluate for any possible imbalances in baseline characteristics of the patients studied in LOTS. Two important findings arise from the review of the demographic data:

- 1) Small numbers of juvenile-onset patients were enrolled in the study
- 2) A gender imbalance was present between treatment groups

In order to evaluate possible differences between the juvenile-onset and adult-onset Pompe disease population, review of the patient age at time of enrollment was performed. While the mean age at first infusions was not different between groups (table 8), the age at first infusion was weighted toward patients ≥ 40 years of age, with 71% of the patients in the 2000 L treatment group aged 40 years or older at the time of the first infusion, and a slightly lower percent of patients aged 40 years and older in the placebo group (66%). There were very few patients enrolled in the study who would be classified as juvenile-onset patients (<18 years of age) at the time of enrollment: only two patients in the 2000 L treatment group were less than 18 years of age at the time of the first infusion, and two patients in the placebo group were less than 18 years of age at the time of enrollment (table 7).

Table 7: Age at first infusion, by treatment group

Age at First Infusion	Number in 2000 L treatment group (% of total)	Number in Placebo group (%)
8-18 years	2 (3.3)	2 (6.6)
18-30 years	3 (5)	1 (3.3)
30-40 years	12 (20)	7 (23.3)
40-50 years	20 (33.3)	12 (40)
50-60 years	17 (28.3)	7 (23.3)
60-70 years	6 (10)	1 (3.3)
Total	60 (100)	30 (100)

Other demographic data from LOTS are presented in table 8 below. A gender imbalance is noted between the treatment groups. The placebo group had a higher percentage of women and a lower percentage of men compared to the 2000 L product. The majority of both placebo and 2000 L treatment groups were Caucasian ($>90\%$ of patients in the study overall). This is expected based on the higher frequency of late-onset Pompe disease in Caucasian populations.

Table 8: Patient Demographics and Baseline Characteristics

	Myozyme (N=60)	Placebo (N=30)
Age at first infusion (years)	45.3±12.37 (15.9, 70.0)	42.6±11.63 (10.1, 68.4)
Sex		
Male	34 (57%)	11 (37%)
Female	26 (43%)	19 (63%)
Ethnicity		
Caucasian	57 (95%)	27 (90%)
Black	0	0
Hispanic	1 (1.7%)	1 (3.3%)
Asian	1 (1.7%)	1 (3.3%)
Other	1 (1.7%)	1 (3.3%)
Height (cm)	170.6±11.04 (146.8, 196.1)	167.6±11.89 (130.8, 186.9)
Weight (kg)	73.7±17.42 (39.2, 118.8)	73.3±18.57 (20.3, 107.2)

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*Myozyme refers to the 2000 L product

In summary, there were important demographic imbalances in LOTS. Most notably, very few patients were juvenile-onset patients based on their age at the time of enrollment. Therefore, efficacy of the 2000 L product in this Pompe disease population cannot be definitively determined. Further analysis of the juvenile-onset subgroup is presented in section 7.4.4.1.

7.3 Patient Disposition

A total of 108 patients with late-onset Pompe disease signed the informed consent form, and were eligible for screening (figure 2). A total of 90 patients qualified for the study. Eighteen patients signed consent for the study but were not enrolled due to the following reasons:

- Failed to meet enrollment criteria based on investigator's discretion (10 patients)
- Failed to qualify based on pre-screening results (5 patients)
- Investigational site was already fully enrolled at the time patients were consented (2 patients)
- Chose not to participate after consenting, but prior to screening (1 patient)

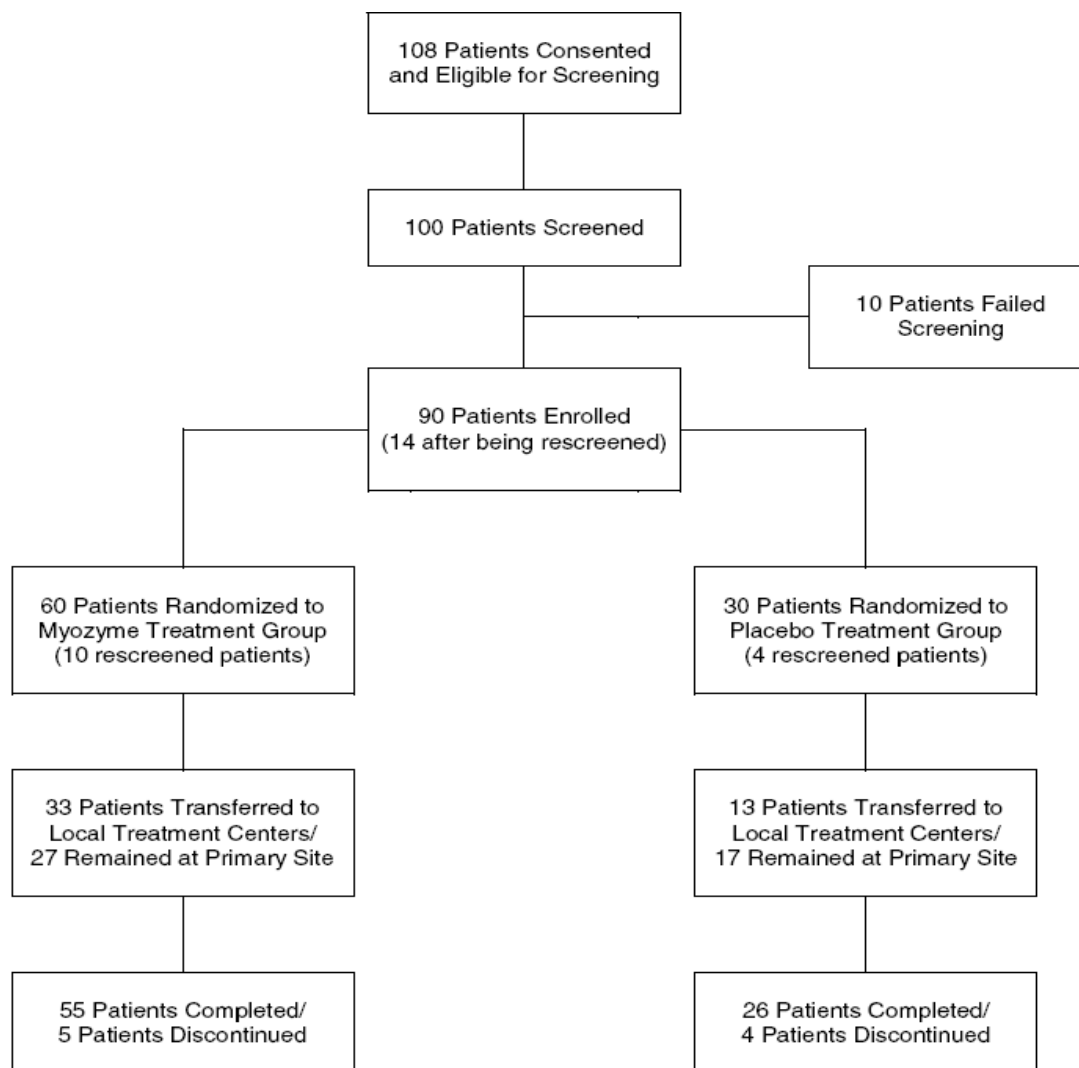
Additionally, fourteen patients (10 patients in the treatment group, 4 patients in the placebo group) failed initial screening based on reliability criteria for FVC and/or (Quantitative Muscle Testing) QMT assessment, but upon rescreening after written approval by the Applicant's Medical Monitor, these patients qualified for randomization. Reasons for initial screen failure for these patients are as follows:

- Postural drop in FVC from sitting to supine of < 10% (4 patients)

- Variability in unilateral QMT knee extensors > 10% from day 1 to day 2 (4 patients)
- Inability to generate sufficient force against test strap during QMT (2 patients)
- FVC upright (% predicted) > 80% (2 patients)
- FVC upright (% predicted) < 30% (1 patient)
- Variability in FVC upright value (% predicted) > 10% from day1 to day 2 (1 patient)

A total of 81 patients successfully completed the study; 55/60 patients in the treatment group, and 26/30 in the placebo group. Detailed information regarding patient drop outs and discontinuations is provided in section 6.2.3.

Figure 2: Patient Disposition ALGU02704



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7.4 Analysis of Primary Endpoints

The co-primary efficacy endpoints were (1) the mean monthly change in distance walked during a 6MWT and (2) the mean monthly change in upright FVC (% predicted). To preserve an overall 5% level of significance when comparing 2000 L product with placebo, a fixed sequence test procedure was used. If the test for 6MWT (the first test in the sequence) was significant at the 5% significance level, then a formal test for upright FVC (% predicted) at the 5% significance level would be performed; otherwise, there would be no formal significance testing of upright FVC (% predicted).

7.4.1 Statistical methods

As stated in section 6.9, the Applicant amended the protocol and statistical analysis plan three times during the course of the study. Initially, the Applicant chose to use the change from baseline for 6MWT and FVC upright (% predicted) at Week 26 and Week 52, but in the second amendment to the protocol and statistical analysis plan, changed the primary efficacy endpoint to a rate of change in distance walked per month in order to change LOTS to an adaptive trial design. The Agency agreed to this protocol change with the caveat that no further amendments to the primary efficacy endpoint would be permitted. Ultimately, the Applicant chose a linear mixed effects (LME) model as the primary statistical method for comparing differences between the 2000 L treatment group and the placebo group in the mean monthly change for the 6MWT and for upright FVC (% predicted). However, because assumptions important to the pre-specified LME models were violated upon analysis of the data, the Applicant submitted additional post-hoc analyses of the data including the LME with robust variance. For a more complete discussion of the statistical methods, see Appendix B.

The FDA statistical reviewer agrees with the Applicant's decision to use a robust variance estimator for the variance-covariance parameters in the LME model. The estimates of treatment effect and other parameters in the LME model remain the same. What changes is the standard error of the estimates, as reflected by changes in confidence intervals and p-values. For thoroughness, the briefing package presents the results from both approaches. However, because of the numerous assumptions that underlie the LME model and because the model was changed after the data were analyzed, we are placing greater emphasis on the ANCOVA. The discussion below is limited to the LME models and the ANCOVA.

7.4.2 Six-Minute Walk Test

7.4.2.1 Description

The 6MWT is used to objectively assess functional exercise capacity and response to medical interventions in patients with moderate to severe heart or lung disease. Patients are asked to walk along a 100 ft. corridor at their own pace for six minutes. It does not provide specific information on the function of different organs involved during exercise, rather it evaluates the global and integrated responses of the systems involved during exercise (i.e. pulmonary, cardiovascular, circulation, neuromuscular units, and muscle metabolism).⁶ Normal ranges for health adults range from 500-580 meters, with men walking slightly longer than women. Healthy adolescents may walk up to 700 meters, and trained athletes may walk up to 1500 meters during the test.

Use of the 6MWT as a clinical outcome measure has formed the basis for approval of other enzyme replacement therapies, including Aldurazyme for the treatment of MPS type I, and Elaprase for treatment of MPS type II. As stated earlier, MPS I and MPS II present with substantially different clinical manifestations compared with Pompe disease. The clinical phenotype of MPS I and II includes hepatosplenomegaly, skeletal deformities, joint stiffness, cardiomyopathy, and pulmonary hypertension. Death is generally related to cardiopulmonary failure. In these two treatments, the clinical efficacy endpoints that led to their approval included the change in distance walked from baseline during a 6MWT. The mean change from baseline distance walked was 35 ± 14 meters ($p = 0.01$, ANCOVA) for Elaprase, and for Aldurazyme, the median change from baseline distance walked was 39 meters (-2 to 79, 95% CI) ($p=0.07$, Wilcoxon Rank Sum Test).^{7, 8}

While the Agency has agreed to use these endpoints in evaluating efficacy of these enzyme replacement therapies, neither of these co-primary endpoints are established in Pompe disease, or for any other lysosomal storage disorder, as surrogate markers for a clinical benefit outcome, such as time to death or ventilator dependency.

7.4.2.2 Results

7.4.2.2.1 Summary statistics

A review of the primary efficacy data from the 6MWT was performed to determine differences between the 2000 L ($n=60$) and placebo treatment groups ($n=30$). Patients were tested at baseline, and at several time points between baseline and Week 78 (see section 4.4). As stated in the Applicant's original statistical analysis plan, LOTS was designed to have 80% power to detect a treatment effect of 52.5 meters in the 6MWT (assuming a standard deviation in change from baseline 6MWT of 70 meters). However, this efficacy endpoint analysis was changed to rate of change per month in the 6MWT. Given the statistical analysis problems encountered with this change in efficacy endpoint analysis as described above, table 9 shows summary statistics based on the original statistical plan. Baseline data for distance walked between the 2000 L and placebo treatment groups was not different. On average, patients in the 2000 L treatment group could walk 26 meters more at the end of treatment than at the beginning of treatment (table 9). This average increase among subjects in the 2000 L treatment group was greater than the average increase of 0.4 meters for a subject in the placebo treatment group. In table 9, a difference between the "*mean distance walked at baseline*" and "*median distance walked at baseline*" should be noted. In the 2000 L treatment group, the median distance walked of 16 meters is lower than the mean distance walked of 26.1 meters because the *mean* distance walked was shifted upward due to a three patients that improved by over 100 meters. A discussion of these patients is presented in section 7.4.5.2. Additionally, there is a difference in the calculation of the "*mean change from baseline*" between the medical reviewer and the Applicant. The "*mean change from baseline analyzed by ANCOVA*" (the Applicant's statistical analysis) is 25.16 (2000 L group) and -2.99 (placebo group), and the "*mean change from baseline*" (the Reviewer's analysis) is 26.13 (2000 L group) and 0.43 (placebo group). These differences are based on the Applicant's baseline stratifications used as part of the ANCOVA as described in table 9.

Table 9: Change from baseline in distance walked in 6MWT in meters

	2000 L N=60	Placebo N=30	Difference
<i>Summary statistics:</i>			
Mean (SD) distance walked at baseline	332.2 (128.0)	314.06 (131.4)	n/a
Mean (SD) change from baseline to last observation in distance walked	26.13 (51.3)	0.43 (37.76)	25.70
Median change from baseline to last observation in distance walked	16	0	16
<i>Results of ANCOVA*:</i>			
Mean (SE) change from baseline to last observation in distance walked, adjusted for baseline 6MWT stratification, FVC stratification, their interaction and baseline 6MWT	25.13 (7.57) 95% CI: (10.1, 40.1)	-2.99 (10.64) 95% CI: (-24.1, 18.1)	28.12 (13.10) 95% CI: (2.1, 54.1)

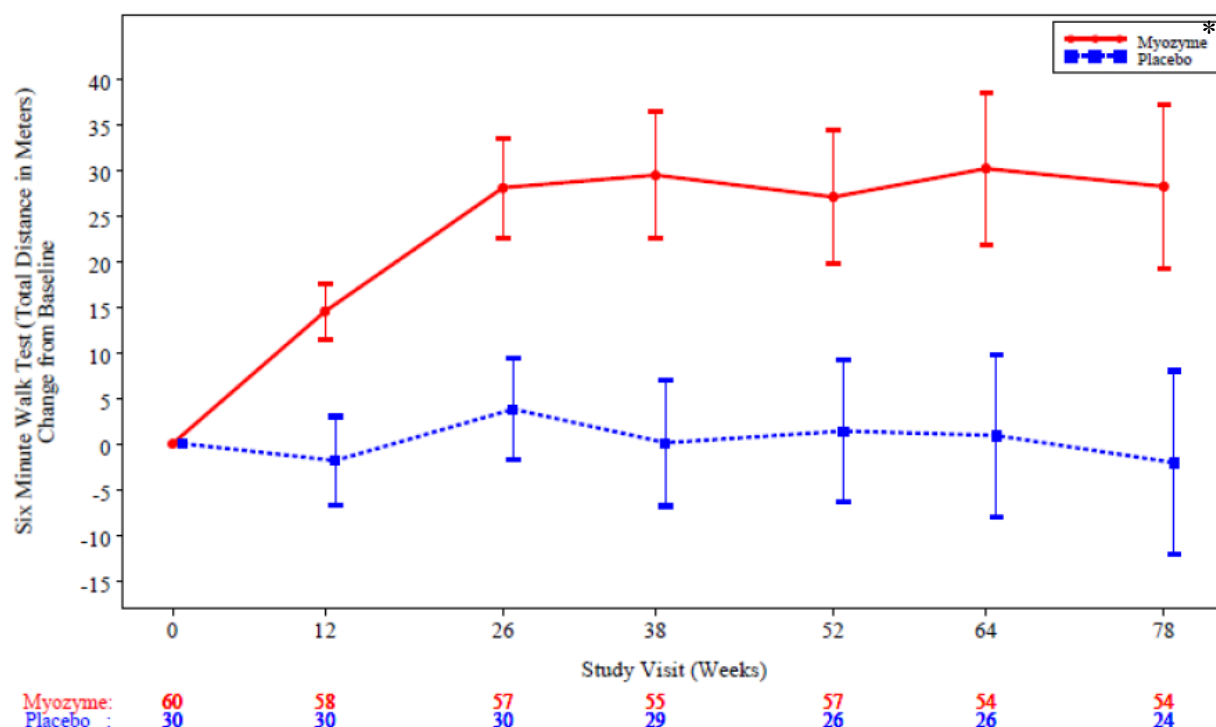
*Copied from Applicant Clinical Study Report pg. 106/1841

In order to descriptively examine the time course of the changes in distance walked from baseline, the change from baseline to various time points are summarized in Table 10 and depicted in Figure 3. Among subjects in the 2000 L product treatment group, the change in distance walked from baseline appears to increase early in treatment and by Week 26, the improvement appears to plateau. The placebo treatment group appears to have a small improvement at Week 26 that is lost by the last observation. The Applicant hypothesizes that the plateau in effect, as well as the variable effect in individual patients overall, may be related to the degree of irreversible muscle damage present at the time of treatment. Therefore, patients may only improve to the degree that muscle may be restored to its baseline contractile state. Replacement of muscle by fat in advanced Pompe disease has previously been described.⁹

Table 10: Mean/median change from baseline (± SD) 6MWT to last observation in meters

Visit	2000 L	Placebo
Screening/Baseline		
Week 12	14.65/12 (23.4)	-1.83/0 (26.5)
Week 26	28.05/21 (41.0)	5.93/4 (28.6)
Week 38	29.44/23 (51.4)	1.07/4 (38.4)
Week 52	27.7/175 (55.1)	1.38/0 (39.9)
Week 64	30.16/13 (61.3)	0.88/-1.5 (45.4)
Week 78/Early Termination	27.10/15.5 (65.6)	-4.96/-7 (47.7)

Figure 3: Change from Baseline 6MWT 2000 L vs. Placebo



*Myozyme = 2000 L product

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7.4.2.3 Statistical analyses

Using the LME model, which adjusted for baseline 6MWT stratification, FVC stratification, and their interaction, the estimated average change in distance walked per month was 1.18 meters for the 2000 L treatment group and -0.06 meters for the placebo group, or about an increase of 21 meters in 78 weeks for the 2000 L treatment group and a decrease of 1 meter in 78 weeks for the placebo treatment group. The treatment effect was 1.24 meters (23 meters in 78 weeks). With 95% confidence, the true treatment effect for the 2000 L product could range from -0.21 meters to 2.70 meters more per month by the LME model with model-based variance estimation, however, this difference was not statistically significant ($p=0.093$). The true treatment effect for the 2000 L product would range from 0.02 meters to 2.47 meters more per month by the LME model with robust variance estimation, which reached statistical significance ($p=0.046$); see table 11.

Table 11: Monthly change in distance walked (m) 6MWT LME with model based variance and robust variance estimation

Parameter	Summary Statistic	Placebo (N= 30)	Myozyme (N= 60)	Difference
Six Minute Walk Test Monthly Change (meters)				
LME	Estimate	-0.06	1.18	1.24
	SE	0.61	0.43	0.74
	95% CI	-1.26, 1.14	0.34, 2.03	-0.21, 2.70
	p-value	0.9217	0.0063	0.0931
LME with robust variance estimation	Estimate	-0.06	1.18	1.24
	SE	0.43	0.47	0.62
	95% CI	-0.90, 0.78	0.26, 2.11	0.02, 2.47
	p-value	0.8683	0.0124	0.0464

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The results from the ANCOVA were consistent with the findings from the LME models. The change in distance walked from baseline to the end of the study was 28.1 meters, which was significantly greater for the 2000 L treatment group compared with the placebo treatment group ($p=.035$). With 95% confidence, at the end of treatment subjects randomized to 2000 L improved from 2 meters to 54 meters more than subjects randomized to placebo; see Table 12:

Table 12: Statistical analysis (ANCOVA) of Change in distance walked from baseline to last observation during 6MWT

Parameter	Summary Statistic	Placebo (N= 30)	Myozyme (N= 60)	Difference*
Change from Baseline ANCOVA model	Estimate	-2.99	25.13	28.12
	SE	10.64	7.57	13.10
	95% CI	-24.16, 18.18	10.07, 40.19	2.07, 54.17
	p-value	0.7794	0.0013	0.0347

* Myozyme = 2000 L product

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7.4.2.4 Summary of results for the 6MWT

Although the difference between the 2000 L product and placebo in average change over time is not statistically significant ($p=0.093$) at the 5% level for the pre-specified 6MWT endpoint as assessed by the LME model with the model-based variance estimates (table 11), the Applicant determined that the model violated an important assumption for the variance of the observations. When robust variance estimates are used, the difference in average change over time is significant ($p=.046$) at the 5% level of significance. Because the LME models assume a linear increase over time in the 6MWT, which was not the case in this study, the models are likely not appropriate for these data.

Analysis of covariance (ANCOVA) is more appropriate for these data. ANCOVA showed that the change in distance walked from baseline to the end of the study was significantly greater for the 2000 L treatment group compared with the placebo treatment group ($p=.035$). With 95%

confidence, at the end of treatment, patients randomized to 2000 L treatment walked from 2 meters to 54 meters more than patients randomized to placebo during the 6MWT.

Despite the demonstration of a statistically significant difference between the 2000 L and placebo groups in both primary efficacy endpoints, the clinical significance of the magnitude of these differences remains unclear. Although the 6MWT has been used as an efficacy endpoint for the approval of enzyme replacement therapies, the test was originally designed to objectively assess functional exercise capacity and response to medical interventions in patients with moderate to severe heart or lung disease, such as chronic obstructive pulmonary disease (COPD). There are no data correlating the change in 6MWT and clinical response in Pompe disease. Therefore, the magnitude of change in these endpoints that should be considered clinically meaningful for Pompe disease patients is unknown. Alternatively, absence of deterioration in a progressive condition such as Pompe disease could be considered clinically meaningful.

7.4.3 Forced Vital Capacity (% predicted)

Forced Vital Capacity (FVC) is a test of pulmonary function that is used to evaluate the adequacy of respiratory effort exerted. It is the measurement of the volume of air exhaled from the deepest inspiration possible to the end of exhalation.¹⁰ FVC is generally reported in units of volume, and normal values vary based on age, gender, and height. Therefore, FVC is often reported as percent predicted value based on established normal values that have been determined in healthy populations. Normal % predicted FVC values are generally considered to be at least 80% of the predicted normal value. There are also differences in FVC normally between the upright and supine position. This difference may be larger in patients with muscle weakness as the effect of gravity is decreased in the supine position.¹¹ Normal values have not been established for patients with Pompe disease or other lysosomal storage diseases, but it has been used as a clinical efficacy endpoint in other enzyme replacement therapy trials, including Aldurazyme. Again, it is important to note that measurement of FVC or % predicted FVC is not a clinical outcome measure, or even a surrogate marker for a clinical outcome. There has been no correlation described to date between FVC and any clinical outcome in Pompe disease.

The Applicant proceeded with a full statistical analysis of the co-primary endpoint, FVC (% predicted) based on the statistically significant difference demonstrated in the 6MWT data. As stated earlier, the Applicant's statistical analysis plan stated that if the test on 6MWT (the first test in the sequence) was not significant at the 5% significance level, then there would be no formal significance testing on FVC upright.

Based on the ITT (full analysis population), the change in upright FVC (% predicted) per month using the LME model was 0.03 for the 2000 L treatment group and -0.16 for the placebo group. The difference in monthly change in FVC (% predicted) was 0.18 (tables 13 and 14). Unlike the data reviewed for the 6MWT, the data for the change from baseline for FVC measured in upright position (% predicted) is statistically significant with all methods used to analyze the data. However, the clinical meaning of the rate of monthly change in upright FVC between 2000 L product treated and placebo of 0.18% is unclear.

Table 13: FVC Upright (% Predicted)

	Myozyme * N = 60	Placebo N = 30	Difference	P value
Estimates/Tests of Monthly Change in % Predicted FVC (Repeated Measures Analyses)				
LME, % predicted (95% CI)	0.03 (-0.05, 0.10)	-0.16 (-0.27, -0.05)	0.18 (0.05, 0.31)	0.0084
LME, with robust variance estimation % predicted (95% CI)	0.03 (-0.05, 0.10)	-0.16 (-0.25, -0.06)	0.18 (0.06, 0.30)	0.0041
GEE, % predicted (95% CI)	0.03 (-0.05, 0.11)	-0.17 (-0.26, -0.07)	0.20 (0.07, 0.32)	0.0019
Wei-Lachin test				0.0009
Estimates/Tests of Change in % Predicted FVC From Baseline to Last Observation				
ANCOVA—Mean Change, % Predicted (95% CI)	1.20 (-0.16, 2.57)	-2.20 (-4.12, -0.28)	3.40 (1.03, 5.77)	0.0055
Nonparametric Inference—Median Change, % Predicted (95% CI)	0.00 (-1.00, 3.00)	-3.00 (-5.00, 0.00)		
Wilcoxon-Mann-Whitney test				0.0026
ANCOVA—Mean Relative Change, % of % predicted (95% CI)	1.94 (-0.62, 4.50)	-3.79 (-7.40, -0.19)		

* Myozyme = 2000 L product

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Table 14: Change from baseline in upright FVC (% predicted)

	2000 L N=60	Placebo N=30	Difference
<i>Summary statistics:</i>			
Mean (± SD) FVC at baseline	55.58 (14.5)	53.36 (15.4)	n/a
Mean (± SD) change from baseline to last observation in FVC	1.37 (5.0)	-1.82 (4.4)	3.19
<i>Results of ANCOVA*:</i>			
Mean (± SE) change from baseline to last observation in FVC, adjusted for baseline 6MWT stratification, FVC stratification, their interaction and baseline FVC	1.20 (0.68) 95% CI: (-0.16, 2.57)	-2.20 (.97) 95% CI: (-4.12, -0.28)	3.40 (1.19) 95% CI: (1.03, 5.77)

*Copied from Applicant Clinical Study Report pg. 112/1841

The effect of 2000 L product on the change in % predicted FVC from baseline increases very early in treatment and by week 12, the improvement appears to plateau. Again, the time course of this change from baseline is similar to the change seen in the 6MWT. The placebo group also appears to have a small, but persistent decline in FVC throughout the course of the study (table 15).

Table 15: Mean (± SD) Change in FVC (% predicted) from baseline by visit

Visit	2000 L	Placebo
Screening/Baseline		
Week 12	1.77 (3.8)	-0.83 (4.0)
Week 26	1.56 (4.3)	-0.38 (3.7)
Week 38	1.35 (4.8)	-2.56 (4.7)
Week 52	1.60 (5.1)	-1.96 (4.5)
Week 64	0.48 (6.1)	-3.04 (5.2)
Week 78/Early Termination	1.41 (5.6)	-2.41 (4.3)

It should be noted that the estimated mean change in % predicted FVC from baseline was 3.4% and is similar, but smaller, to the change seen for other enzyme replacement therapies. In the clinical trial for Aldurazyme in the treatment of MPS I, change in % predicted FVC from baseline was used as a primary efficacy endpoint, and there was a statistically significant mean improvement of 4.5% in FVC (% predicted) with Aldurazyme treatment compared with placebo. However, the validity of FVC, and other tests of pulmonary function, as a clinical outcome measure in the approval of enzyme replacement therapies has not been established. To date, there have been no published studies validating the measurement of FVC as a clinical outcome measure in lysosomal storage diseases. Therefore, it is unclear whether the measurement of FVC is useful as a surrogate of measurement of clinical effect.

7.4.4 Exploratory Analyses

7.4.4.1 Effect of Age

Age at Diagnosis of Disease

As stated in section 7.2, only four patients under the age of 18 at the time of enrollment participated in LOTS. However, grouping patients by age at the time of enrollment may miss some patients with juvenile-onset disease. Therefore, the medical reviewer also reviewed the Applicant's demographic data sets to determine the number of patients with the diagnosis of Pompe disease before the age of 18. There were 11 patients in whom the diagnosis of Pompe disease was made prior to the age of 18. Of the 11 patients less than 18 years of age at diagnosis who were enrolled in the study, 8 patients were in the 2000 L group, and 3 patients were in the placebo group. Their demographic data are presented in table 16. It should also be noted that 2 patients in the 2000 L treatment group (18710 and 26710) were over the age of 18 at the time of first symptoms despite their diagnosis being made prior to the age of 18 years.

Table 16: Demographic characteristics of patients with diagnosis of Pompe disease prior to age 18 (n=11)

Patient ID	Treatment group	Age at Diagnosis (years)	Age at first symptoms (years)	Age at enrollment (years)
4701	2000 L	5.8	5.3	15.9
65706	2000 L	11.6	10.6	28.2
18710	2000 L	12.0	28.3	36.9
65707	2000 L	14.2	9.8	20.7
26710	2000 L	14.6	22.6	30.3
29712	2000 L	15.3	8.9	17.5
16708	2000 L	16.0	16.0	31.7
29701	2000 L	17.2	16.4	25.8
4705	Placebo	7.5	7.4	10.1
29711	Placebo	8.3	6.3	14.8
29714	Placebo	12.3	2.7	38.3

Age at First Symptoms

Juvenile-onset can also be defined as patients with onset of symptoms less than 18 years of age. There were 14 patients with age at first symptoms less than 18 years of age but with the diagnosis of Pompe disease after the age of 18 years in LOTS (table 17). These 14 patients represent a clearly distinct group from the 9 patients who were both symptomatic and were diagnosed before the age of 18. Of the 14 patients who reported symptoms before the age of 18, 8 patients were over 40 years of age at the time of enrollment in LOTS, and 3 patients were over the age of 50. Furthermore, 9 of the 14 patients were diagnosed with Pompe disease over the age of 25. Therefore, most of these 14 patients do not appear to represent juvenile-onset patients as the progression of their disease is clearly attenuated. Thus, juvenile-onset patients, defined clinically by a younger age at onset of symptoms, faster progression of disease, and lower GAA activity compared with adult-onset patients, appear not be represented in LOTS in sufficient numbers to assess efficacy of the 2000 L product.

Tab 1

Table 17: Demographic characteristics of patients with diagnosis of Pompe disease prior to age 18 (n=11)

Patient ID	Treatment Group	Age at first symptoms (years)	Age at Diagnosis (years)	Age at enrollment (years)
26708	Placebo	15.8	22.8	27.5
26723	Myozyme	12.3	18.3	31.8
16709	Myozyme	17.8	27.8	32.6
47702	Placebo	10.1	26.8	33.3
26721	Placebo	14.7	24.8	35.3
29702	Myozyme	9.9	28.3	40.3
65715	Myozyme	10.2	34.2	41.9
29707	Placebo	7.6	27.3	44.9
18703	Myozyme	17.3	31.1	48.0
90710	Myozyme	17.9	39.3	48.5
16701	Myozyme	16.1	42.8	49.7
16707	Placebo	16.3	49.3	50.9
65702	Placebo	11.42	20.50	52.0
29704	Placebo	13.67	37.67	59.1

Additional exploratory analyses were also performed in subgroups of patients based on age at enrollment, age at diagnosis, age of first symptoms. All of these analyses demonstrated a treatment effect in the 2000 L treatment group compared to placebo, but overall younger patients had smaller changes from baseline compared to older patients. For detailed analyses of these subgroups, see Appendix C.

In summary, based on the demographic characteristics of the juvenile-onset Pompe disease patients using the different definitions explored above (e.g., age at diagnosis, age at first symptoms), it appears that most of these patients had attenuated disease most consistent with adult-onset presentations. There were insufficient numbers of juvenile-onset patients in this study to determine the efficacy of the 2000 L product. Furthermore, LOTS was not designed to study juvenile-onset patients less than 8 years of age, who would be expected to have more rapidly progressive disease. Thus, given the concerns regarding the potency of 2000 L product compared with 160 L product, the potential for increased immunogenicity of 2000 L product (see section 7.4.5), and the lack of data regarding efficacy of 2000 L product in the juvenile-onset patients, strong consideration should be given to limiting the indication of 2000 L product to adult-onset patients only.

7.4.5 Immunogenicity

7.4.5.1 Effect of anti-GAA IgG antibody status

An important safety consideration with all enzyme replacement therapies for lysosomal storage diseases is the development of immune responses to the infused enzyme. These immune responses can be associated with the development of allergic/hypersensitivity reactions as well as altered effectiveness of treatment. In the LOTS study, anti-rhGAA IgG antibodies were measured throughout the course of the study at specific time points. All of the 2000 L treated

Tab 1

patients developed anti-rhGAA IgG antibodies by week 20 of the study. Below tables 18 and 19 demonstrate the effect of mean and max anti-rhGAA IgG titers on the primary efficacy endpoints. Based on these data, increasing anti-rhGAA IgG titer is actually associated with an improved response in both 6MWT and FVC.

Table 18: Effect of Mean IgG titer category on 6MWT and FVC

Parameter	Mean IgG Titer Category for Myozyme Patients who Seroconverted (N = 59)			
	Quartile 1 124.1-581.0	Quartile 2 729.4-1449.2	Quartile 3 1458.8-3736.8	Quartile 4 4098.6-135117.6
6MWT change in meters walked from Baseline to last observation	-6.9±48.15 median -8.0	25.2±41.61 median 17.0	24.2±46.18 median 16.0	59.7±94.17 median 23.0
FVC change in % predicted from Baseline to last observation	-0.6±4.96 median -1.0	2.4±5.72 median 2.0	1.5±5.18 median 1.0	1.7±6.33 median 0.0

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Table 19: Effect of Peak IgG titer category on 6MWT and FVC

Parameter	Peak IgG Titer Category for Myozyme Patients who Seroconverted (N = 59)			
	Quartile 1 200-1600	Quartile 2 3200-3200	Quartile 3 6400-12800	Quartile 4 25600-819200
6MWT change in meters walked from Baseline to last observation	6.1±53.67 median 5.0	16.0±24.98 median 9.0	34.8±76.60 median 16.5	49.1±79.91 median 19.5
FVC change in % predicted from Baseline to last observation	0.8±5.68 median 0.0	1.8±5.29 median 3.0	1.5±5.73 median 0.5	1.1±5.95 median 0.0

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The overall mean and maximum anti-rhGAA IgG titer may not reflect the true nature of the risk of the effect of immunogenicity on efficacy in the 2000 L product. Most patients receiving enzyme replacement therapies develop antibody responses, but most also develop “tolerance” to the treatment and these antibody responses decline over time. Therefore, patients who have declining anti-rhGAA IgG titers over time regardless of the maximum titer are less likely to have changes in the effectiveness or safety profile of 2000 L product. However, patients who fail to develop tolerance to the 2000 L product, that is, patients who have a continually rising anti-rhGAA IgG antibody titer, may be at risk for both decreases in efficacy and increases in immunologically mediated safety concerns. Therefore, the 2000 L treatment group was explored based on the presence of a persistently rising IgG titer rather than peak IgG titer. Nine of 60 patients who developed positive IgG titers during the study had a persistently elevated IgG titer

Tab 1

at the end of the study. The demographics of these 9 patients are presented below (table 20). This subgroup's overall improvement was approximately 7.4 meters less than the overall 2000 L treatment group (table 21 and table 22). Additionally, there is a loss of treatment effect in this group of patients after Week 52 (table 22). Because this is an exploratory analysis of a small subgroup of patients, statistically significant conclusions cannot be made, but these findings suggest a difference in treatment effect in patients with persistently rising anti-rhGAA antibody titers and the overall 2000 L treatment group.

Table 20: Demographic characteristics of patients without decline in IgG titer at week 78 (n=9)

Patient ID	Gender	Age at first symptoms	Age at Diagnosis	Disease Duration	Age at enrollment
4701	Male	5.25	5.75	9.92	15.92
18701	Female	35.50	40.42	1.75	42.25
18704	Male	34.50	35.25	16.58	51.83
18710	Male	28.33	12.00	24.83	36.92
26712	Male	29.33	39.75	10.00	50.00
29713	Female	40.08	41.58	3.67	45.42
47713	Female	39.83	39.83	3.25	43.17
65701	Male	36.33	39.08	0.50	39.83
90705	Male	48.33	61.33	7.50	68.92

Table 21: Mean change from baseline 6MWT in 9 patients with rising IgG titer at week 78

	2000 L Overall (n=60)	Rising IgG at week 78 (n=9)
Mean Change from baseline in meters (±SD)	26.13 (51.3)	18.76 (25.0)
Difference in Change from baseline	7.40	

Table 22: Mean (± SD) change from baseline 6MWT in patients without decline in IgG titer at week 78 (n=9)

Visit	Mean (M)
Screening/Baseline	
Week 12	12.44 (19.9)
Week 26	21.75 (16.9)
Week 38	19.125 (20.0)
Week 52	26.25 (23.2)
Week 64	16 (29.3)
Week 78/Early Termination	17.75 (40.2)

2000 L product, as with all of the currently studied enzyme replacement therapies, is associated with development of immunogenicity. A published review of immune responses in enzyme replacement therapy notes that humoral immune responses developed in all six of the currently available enzyme replacement therapies. A summary table from this review is presented below

Tab 1

(table 23).¹² Development of immunologic responses to rhGAA may be related, in part, to the degree of endogenous enzyme present, or cross reacting immunologic material (CRIM). One study suggests that CRIM-negative patients may be more likely to develop a higher, more sustained immunologic response against rhGAA than CRIM-positive patients, and potentially a more limited duration of clinical benefit after rhGAA administration.¹³ Infantile-onset patients are more likely to be CRIM-negative. CRIM status was not tested in LOTS as non-infantile onset patients are generally CRIM-positive. In the clinical trial supporting the approval of the 160 L product, 89% of infantile-onset patients developed anti-rhGAA IgG antibodies. This compares with 100% of patients in LOTS who develop antibody. This finding is unexpected, since infantile-onset patients tend to have little or no endogenous enzyme, and are at higher risk of developing antibodies to exogenous enzyme compared to patients with partial enzyme deficiencies (i.e., late-onset patients). Furthermore, of the infantile-onset patients who developed anti-rhGAA IgG antibodies, only 10% developed *in vitro* neutralizing antibodies.

Table 23: Immune responses in patients receiving enzyme replacement therapy

Table 1 Immune responses to replacement lysosomal enzymes					
Disease	Product	Enzyme	Product status	Patients with IgG antibody (%)	Reference
Gaucher's	Ceredase	Alglucerase	Licensed	12.8	18
	Cerezyme	Imiglucerase	Licensed	13.8	Product label
Fabry's	Fabrazyme	Agalsidase beta	Licensed	90	20
Hurler's (MPS I)	Aldurazyme	α -L-iduronidase	Licensed	91	55
Pompe's	Myozyme	Acid- α -glucosidase	Licensed	89	Product label
Hunter's (MPS II)	Elaprase	Iduronate-2-sulfatase	Licensed	51	Product label
Maroteaux-Lamy (MPS VI)	Naglazyme arylsulfatase B	N-acetylgalactosamine-4-sulfatase	Phase 3 completed	97	87

MPS, mucopolysaccharidosis.

Electronically copied from Wang J, Lozier J, Johnson G, et al., Neutralizing antibodies to therapeutic enzymes: considerations for testing, prevention and treatment, Natur Biotech, 2008, 26: 901-908

In summary, all patients who received treatment with 2000 L product developed anti-rhGAA IgG antibodies, as compared with 0 patients in the placebo group. In addition, the incidence of development of anti-rhGAA antibody titers is higher in the 2000 L product than that seen with the 160 L product in infantile-onset patients. Exploratory analyses of presence of anti-rhGAA IgG antibody suggest that patients with persistently rising anti-rhGAA antibody titers may have an attenuated response to 2000 L product. These findings may suggest a higher immunogenicity of the 2000 L product compared to the 160 L product.

7.4.5.2 Effect of GAA Inhibitory Antibody Status

Inhibitory antibody production was tested by the Applicant using two assays; one to measure inhibition of rhGAA enzymatic activity by antibody and one to measure inhibition of the uptake of rhGAA by fibroblast cells *in vitro*. Development of inhibitory antibodies may play an important role in both decreases in efficacy and increases in safety concerns, as these antibodies may affect either the ability of the drug to reach its target location within the lysosome or the activity of the drug. It should also be noted that these assays are performed *in vitro* and may not reflect the same response *in vivo*.

Tab 1

Eighteen patients (30%) developed inhibitory antibodies to 2000 L product during the study. This compares with 2.5% of infantile-onset patients treated with 160 L product. The demographic characteristics of these patients are listed below in table 34. Eight of the patients were female and 10 were male patients. The average age of these patients was not different between female and male patients, nor was the mean age at time of diagnosis, or the mean age of disease duration (table 24 and 25).

Table 24: Pompe disease characteristics for 18 patients testing positive for inhibitory antibody

Gender	N	Mean age in years of first symptoms	Mean age in years at diagnosis	Mean Disease Duration in years	Mean age in years at enrollment
Female	8	31.51	35.25	8.11	43.54
Male	10	33.37	37.97	11	49.08

Table 25: Demographic characteristics of 18 patients with positive inhibitory antibodies

Patient	Gender	Age at first symptoms (years)	Age at Diagnosis (years)	Disease duration (years)	Age at enrollment (years)
18701	Female	35.50	40.42	1.75	42.25
18703	Female	17.33	31.08	16.58	48.00
26705	Female	35.17	42.67	1.00	43.83
26715	Female	36.33	36.83	14.75	51.67
29701	Female	16.42	17.17	8.58	25.83
29713	Female	40.08	41.58	3.67	45.42
47713	Female	39.83	39.83	3.25	43.17
65709	Female	31.42	32.42	15.33	48.17
18704	Male	34.50	35.25	16.58	51.83
18713	Male	41.17	48.92	6.83	55.92
26712	Male	29.33	39.75	10.00	50.00
26718	Male	26.25	29.25	18.50	47.83
29709	Male	18.58	22.58	7.42	30.00
47706	Male	34.92	35.25	15.92	51.25
47711	Male	37.42	39.00	15.67	54.92
65701	Male	36.33	39.08	0.50	39.83
90703	Male	26.83	29.25	11.08	40.33
90705	Male	48.33	61.33	7.50	68.92

The presence of inhibitory antibodies in these 18 patients and its effect on the primary efficacy endpoint, 6MWT was reviewed. Overall, a positive and paradoxical correlation between the presence of inhibitory antibody and change from baseline in the 6MWT is seen. Patients who developed inhibitory antibodies had a mean change from baseline at the end of the study of 39 meters (table 26). This is unexpected as patients who develop inhibitory antibodies generally develop attenuated response to treatment and also are at risk for more immunologic side effects. However, close examination of the data reveals that the median improvement in this group of patients was only 16 meters, and the standard deviation of the mean improvement was large (83.9 meters), suggesting an upward skew of the data by a small number of patients. Thus, this

Tab 1

subgroup of inhibitory antibody positive patients was evaluated more closely to examine possible explanations for this response.

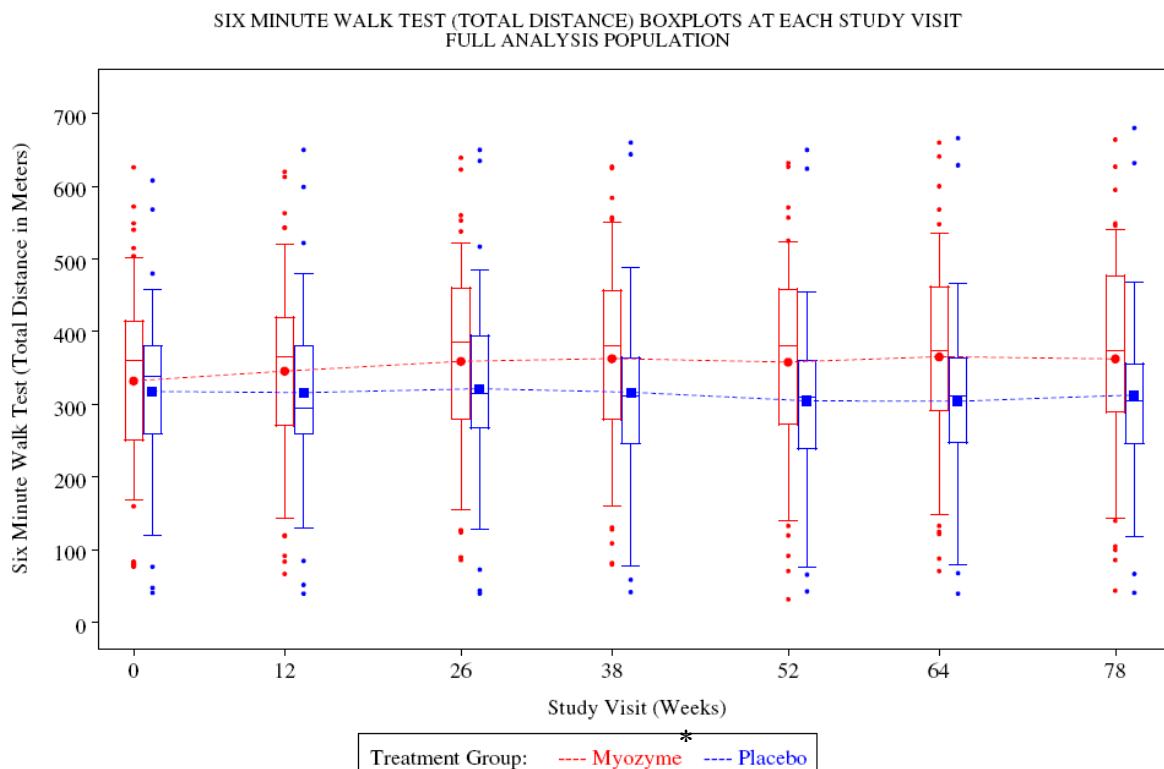
Table 26: Mean change (\pm SD) from baseline 6MWT in meters; inhibitory antibody positive patients (n=18)

Visit	Mean
Screening/Baseline	
Week 12	16.28 (25.9)
Week 26	41 (63.4)
Week 38	46 (72.5)
Week 52	41.47 (78.4)
Week 64	40.71 (79.3)
Week 78/Early Termination	39.12 (83.9)

“High performers”

A small group of patients in the 2000 L treated group performed much better than expected and walked much longer during the 6MWT, with only five patients during the study who sustained an improvement in 6MWT from baseline of over 100 meters. This boxplot graph below (figure 4) demonstrates the presence of the median, 25th (lower box), 75th (upper box) and 1.5 times these points (whiskers). Therefore, any data points outside these limits may be considered to be statistical outliers, and can help identify patients who are performing substantially better or worse than their counterparts. Furthermore, if each patient's 6MWT is examined over time, there are four patients in the treatment group that performed substantially better over time than the rest of the group (figure 5).

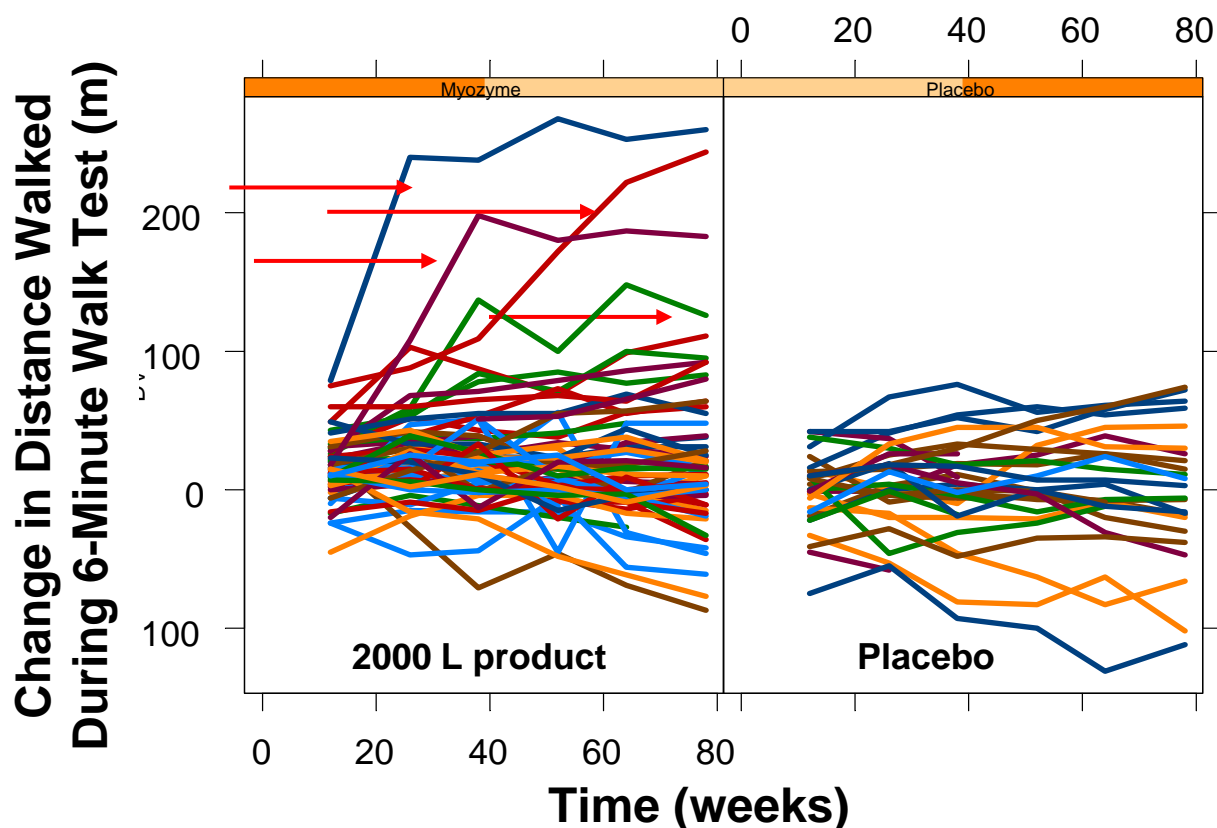
Figure 4: Boxplot graph of total distance walked during 6MWT full analysis population.



* Myozyme = 2000 L product

Electronically copied from Applicant Clinical Study Report, pg 104/1841

Figure 5: Individual 6MWT data



Clinical and demographic characteristics of the four patients identified as high performers in figure 5 were reviewed. Interestingly, three of these “high performers” had inhibitory antibody titers to 2000 L product, and another patient with inhibitory antibody. Thus, presence of inhibitory antibody appears to be associated with a dramatic improvement in at least three patients treated with 2000 L product. The individual 6MWT test data on these three patients is presented below in table 27. The overall mean improvement in these three patients was 194 meters. Interestingly, all three of these patients are male, and none of these patients had a rising IgG titer at the end of the study. Indeed, it has been previously reported that neutralizing or inhibitory antibodies may actually enhance enzyme effect in certain patients. In a study evaluating the effect of neutralizing antibodies on cytokine activity, injection of neutralizing antibody to the cytokine IL-4 (anti-IL-4 antibody) enhanced the *in vivo* activity of IL-4 in mice.¹⁴ The authors concluded that the presence of the neutralizing antibody may act as a carrier protein, thus increasing the half-life of the cytokine. While the data are extremely limited, patients with dramatic improvements in 6MWT, especially those with inhibitory antibodies, may be a subgroup of patients in which the 2000 L treatment may be especially beneficial.

Table 27: Mean (\pm SD) change from baseline 6MWT in 3 “high performers” with inhibitory antibody

Patient ID	Mean (M)
18713	107 (5.7)
26718	251.8 (12.9)
47711	171.2 (36.0)

“Low performers”

Again, as stated previously, patients who develop inhibitory antibodies exogenous enzyme generally develop attenuated response to treatment and also are at risk for more immunologic side effects. Therefore, another subgroup of patients with inhibitory antibody was evaluated based on the status of their anti-rhGAA antibody profile. As described in the previous section, patients with a rising anti-rhGAA antibody titer at the end of the study did not perform as well in the 6MWT when compared to the overall mean. Therefore, a subgroup of patients with rising anti-rhGAA IgG antibody titer *and* the presence of inhibitory antibody titer was evaluated. There were four patients who had both a rising anti-rhGAA IgG titer and the development of inhibitory antibody at the end of the study. The demographics data on these patients is presented below in table 28. There were three female patients and one male patient in this group, and disease characteristics are not significantly different.

Table 28: Demographics of patients with increased IgG titer at week 78 and inhibitory antibody positive

Patient ID	Gender	Age at first symptoms (years)	Age at Diagnosis (years)	Disease duration (years)	Age at enrollment (years)
18701	Female	35.50	40.42	1.75	42.25
26712	Male	29.33	39.75	10.00	50.00
29713	Female	40.08	41.58	3.67	45.42
47713	Female	39.83	39.83	3.25	43.17

These four patients performed substantially worse in both primary efficacy outcomes when compared to the overall 2000 L treated group. This group’s mean change from baseline walked at the end of the study was -8.75 meters (compared with the overall 2000 L treatment group mean at 78 weeks of 27.1 meters). Furthermore, this group performed worse than the placebo group at the end of the study (table 29).

This subgroup of patients with both rising anti-rhGAA antibodies and inhibitory antibodies also performed substantially worse compared to the overall 2000 L treatment group in change in FVC from baseline. Their change from baseline to the last observation worsened in % predicted FVC by 0.5% (table 29). Again, these data are extremely limited, but further monitoring of patients who develop inhibitory antibodies should be performed both to evaluate the potential for further efficacy, as well as to monitor for loss of efficacy.

Table 29: Patients with rising anti-GAA IgG titer at end of study and positive inhibitory antibodies (n=4)

Change in 6MWT (M)	Mean (\pm SD)
Screening/Baseline	
Week 12	6 (6.7)
Week 26	16.25 (10.2)
Week 38	11.75 (3.4)
Week 52	23.25 (22.5)
Week 64	-7 (17.6)
Week 78/Early Termination	-8.75 (28.2)
Change in FVC (% Predicted)	Mean (\pm SD)
Screening/Baseline	
Week 12	1 (4.5)
Week 26	1.25 (5.7)
Week 38	-0.25 (6.0)
Week 52	0.75 (5.0)
Week 64	-1 (8.8)
Week 78/Early Termination	-0.5 (8.4)

In summary, inhibitory antibody formation is increased (30%) in patients receiving 2000 L product compared to infantile-patients that received 160 L product (10%). The development of inhibitory antibodies to the 2000 L product appears to produce two disparate effects; one subgroup of patients with inhibitory antibody appears to improve substantially compared to the overall 2000 L treatment group, while the other group, characterized by development of inhibitory antibody and persistently rising anti-rhGAA IgG antibody titers appears to perform substantially worse than the overall 2000 L treatment group. These subgroups of patients are small, and therefore, clear conclusions from these data cannot be drawn. However, these observations should lead to further examination of the specific role of the increased incidence of inhibitory antibody formation associated with the 2000 L product.

7.4.5.3 Effect of residual acid α -glucosidase (GAA) activity

Measurement of GAA activity is used to assess the degree of enzyme deficiency in patients with Pompe disease. In general, patients with the infantile-onset form of the disease do not have any residual enzyme activity and, therefore, their disease onset is earlier, and their disease manifestations more rapidly progressive. Patients with late-onset (juvenile and adult-onset) Pompe disease have some degree of residual enzyme activity, thus leading to a less rapidly progressive phenotype. However, overlap between GAA activity exists between the juvenile and adult forms of the disease and, furthermore, GAA activity does not always predict clinical course.

GAA activity was measured in all patients at baseline. Ten patients had GAA activity measured at less than 1%. The average age at diagnosis was younger, as well as the age at first symptoms compared to the overall patient average (table 30). The overall average change from baseline in each of the primary efficacy endpoints was worse than the overall average in both treatment groups (table 31). However, the patients in the 2000 L treatment group performed better than

their untreated counterparts. Nevertheless, both groups failed to improve during the course of the study. Another interesting characteristic of this group is that 9/10 of these patients were female, and this finding may at least partially explain the difference in overall performance between female and male patients in this study (section 5.4.6.1). Additionally, lower GAA activity also appears to be associated with younger age.

Table 30: Pompe Disease characteristics, 10 patients with GAA activity < 1%

	Mean(range)
Age at Diagnosis (years)	24.2 (7.5-43.1)
Age at First Symptoms (years)	20.0 (6.3-40.3)
Disease Duration (years)	8.2 (1.8-16.4)

Table 31: Mean Change from Baseline 6MWT and % predicted FVC in patients with 0% GAA activity

	2000 L (n=6)	Placebo (n=4)
Mean Change 6MWT (± SD)	-1.0 (28.4)	-13.1 (22.1)
Mean Change % predicted FVC (± SD)	-1.4 (5.3)	-2.1 (2.8)

Another association uncovered in the analysis of patients with low GAA activity includes the development of immune responses to 2000 L product. Six of ten patients with GAA activity < 1% were randomized to receive 2000 L product. All six patients developed anti-rhGAA IgG antibodies, but mean and maximum anti-rhGAA titers were not increased compared to the overall 2000 L treatment group. However, all six of the patients with GAA activity < 1% (Patients 16708, 18701, 65706, 65707, 90709, and 90710) who received 2000 L product developed inhibitory antibodies to 2000 L product.

Overall, these observations regarding patients with GAA activity <1% are concerning for a population of patients that are younger, may have more severe disease at baseline, may not respond as well to treatment with 2000 L product, and may be at risk for more significant immune responses to the 2000 L product.

7.4.5.4 Overall immunogenicity findings

In summary, the immunogenicity of the 2000 L product remains a concern. All patients treated with 2000 L product in LOTS developed anti-rhGAA IgG antibodies, while none of the patients treated with placebo developed antibodies. This is also increased compared to infantile-onset patients treated with 160 L product (89%). This finding is particularly noteworthy, since infantile-onset patients tend to have little or no endogenous enzyme, and are at higher risk of developing antibodies to exogenous enzyme compared to patients with partial enzyme deficiencies (i.e., late-onset patients). Additionally development of inhibitory antibodies occurred in 30% of patients treated with 2000 L product, and this incidence is substantially higher than the 10% incidence in infantile-onset patients treated with 160 L product. Exploratory analyses of subgroups of patients with persistently rising anti-rhGAA IgG antibody titers, especially in the presence of inhibitory antibody produces a mean decrease in distance walked in the 6MWT as well as a decline in % predicted FVC at the last observation. Also,

Tab 1

patients with low GAA activity (<1%) appear to be at increased risk for development of inhibitory antibody and attenuated response to 2000 L product. Thus, these immunogenicity findings suggest a higher immunogenic potential in the 2000 L product compared with the 160 L product. The higher immunogenicity of the 2000 L product may lead to concerns with long-term efficacy and safety that could not be evaluated in a 78 week trial. Furthermore, younger patients, who may be expected to receive exogenous enzyme treatments the longest, may be at the greatest risk for problems associated with the increased immunogenicity of the 2000 L product.

7.4.5.5 Other exploratory analyses

Effect of gender

Differences in prognosis in Pompe disease based on gender have not been described. However, there are gender differences in baseline 6MWT between men and women. Healthy men, on average, walk farther than healthy women by about 80 meters during the 6MWT. Overall, both male and female patients treated with 2000 L product show larger increases in distance walked compared to placebo treatment. The overall treatment effect for female patients is 35.1 meters and the overall treatment effect for male patients is 16.2 meters, however, much of the increased treatment effect in females is due to the substation deterioration in the female placebo treatment group. Additionally, male patients have higher mean baseline 6MWT test scores compared to female patients in all groups (see table 18). Furthermore, at 78 weeks, male patients in the placebo group showed larger increases in distance walked when compared to the female patients in the 2000 L treatment group (see table 32 and figure 6). These differences are not clearly explained by differences between men and women on duration of disease, time of diagnosis, or baseline 6MWT. Speculatively, differences in muscle mass between men and women may partially explain this difference. Additionally, as discussed in section 7.4.5.3, 9/10 patients with GAA activity (% normal) < 1% were women, and this subgroup performed worse than the overall mean for both treatment groups.

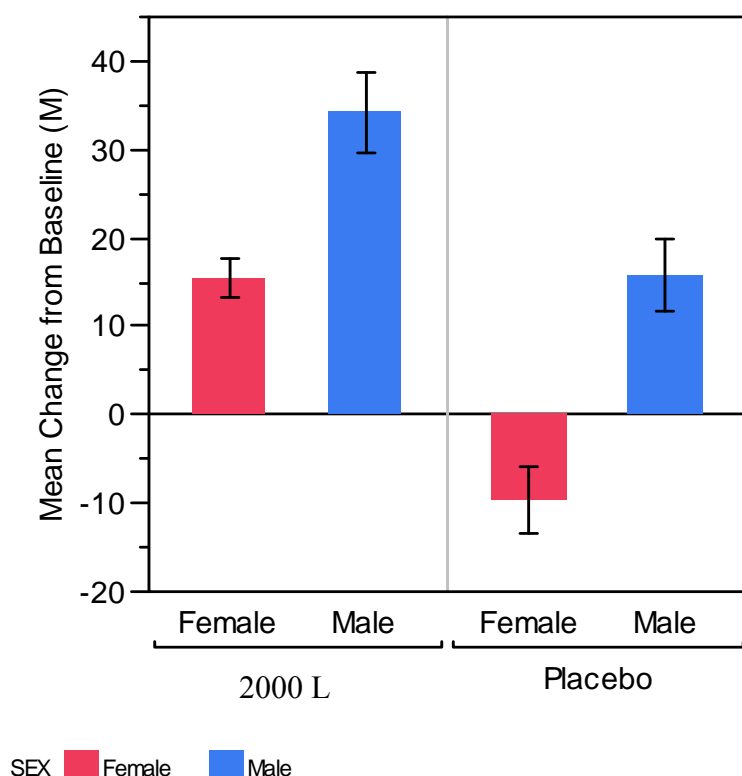
Table 32: Mean (\pm SD) baseline 6MWT based on gender (meters)

Gender	Treatment	Mean
Female (n=45)	2000 L (n=26)	318.42 (117.1)
	Placebo (n=19)	303.42 (119.4)
Male(n=45)	2000 L (n=34)	342.74 (132.6)
	Placebo (n=11)	343 (148.9)

Table 33: 6MWT mean (\pm SD) based on gender at 78 weeks

		Baseline (M)	Change from baseline (M)
Gender	Treatment	Mean	Mean
Female	2000 L (n=25)	337.71 (117.78)	7.25 (36.36)
	Placebo (n=17)	284 (107.08)	-27.85 (43.65)
Male	2000 L (n=34)	382.75 (156.03)	33.64 (79.53)
	Placebo (n=10)	375.9 (168.22)	17.45 (41.70)

Figure 6 : Mean Change from Baseline 6MWT (M) by gender



7.5 Analysis of Secondary Endpoints

For the purposes of the Advisory Committee meeting, only information relevant to the approval and labeling of 2000 L product will be presented. Therefore, substantive analyses of only the primary efficacy endpoints of the study are included in this packet.

7.6 Responder Analysis

Despite the statistical significance of the differences between 2000 L and placebo in the co-primary endpoint (6MWT and % predicted FVC) results, defining the clinical meaningfulness of this difference is challenging. The Applicant attempted to establish pre-defined clinical significance levels as part of the statistical analysis plan. In the original protocol, the Applicant defined a responder based on the change in 6MWT and FVC upright at 52 weeks. A responder was defined as a patient with both 1) an increase in 6MWT of at least 54 meters from baseline to week 52 and 2) an increase in FVC upright (% predicted) of at least 15% from baseline to week 52. Patients who satisfy only condition 1 will be considered walk test responders. The Applicant also described an additional responder analysis that may be repeated using the definition of a responder as a patient with both an 1) increase in 6MWT of at least 37 meters from baseline to week 52 and 2) an increase in FVC upright (% predicted) of at least 15% from baseline to week 52. All other patients will be considered non responders.

In the second statistical analysis plan amendment, the definition for responder was changed to reflect the change in length of the study to 78 weeks. However, in the third statistical analysis

plan that was submitted by the Applicant several weeks after the completion of the study, the Applicant redefined clinical response using less stringent criteria. The definitions of responder change to include all of the following:

1. Increase in 6MWT of at least 54 meters and an increase in FVC upright % predicted of at least 15% over baseline
2. Increase in 6MWT of at least 37 meters and an increase in FVC upright % predicted of at least 15%
3. Increase in 6MWT of at least 30 meters and an increase in FVC upright % predicted of at least 15%
4. Increase in 6MWT of at least 54 meters
5. Increase in 6MWT of at least 37 meters
6. Increase in 6MWT of at least 30 meters
7. Increase in FVC upright % predicted of at least 15%

As discussed previously, these clinical thresholds were derived from a study evaluating the correlation between change in distance walked during 6MWT and subjective clinical improvement in COPD patients. A mean difference of 40 meters was required for patients to stop rating themselves as “about the same” and start rating themselves as “a little bit better”. Additionally, the mean 6MWT difference was -70 meters for patients to stop rating themselves as “about the same” and start rating themselves as “a little bit worse.” However, these two values were not statistically significantly different, and therefore, the authors averaged the difference to provide a “threshold of clinical importance” of 54 meters (37-71, 95% CI).¹⁵ The Applicant used a second clinical threshold of 37 meters based on the lower 95% CI, and a third clinical threshold of 30 meters based on the mean difference in distance walked that corresponded to patients feeling “a little bit better.” Clearly, problems exist in validity of these clinical thresholds in this study based both on the lack of statistical clarity as well as the clinical applicability of this study to Pompe disease.

The clinical thresholds derived for % predicted FVC are also problematic. Again, there has been no study performed in Pompe disease or other lysosomal storage diseases that correlates % predicted FVC with clinical outcome or progression of disease. The Applicant applies a clinical threshold for this study based on criteria developed by the American Thoracic Society.¹⁶ The Applicant chose to use the definition of clinical significant change based on % predicted FVC (year-to-year) of 15% as defined as a clinically meaningful change in % predicted FVC for patients with COPD. The applicability of these thresholds to Pompe disease patients remains unclear.

The overall mean change from baseline for the 6MWT in the 2000 L group was 26.13 meters, and the mean change in upright FVC (% predicted) was 1.41. Clearly, neither of these overall means met the definition of responder at even the least stringent level based on the Applicant’s classification. However, if these definitions are used to evaluate individual patient response, some differences between 2000 L and placebo are apparent. For each responder level of 6MWT established by the Applicant, there were a greater percentage of patients in the 2000 L group who achieved the clinical threshold. In the 2000 L group, 14/60 patients (23.3%) improved at least 54 meters at the last observation, while only 4/30 in the placebo group (13.3%) improved at least 54 meters at the last observation. However, there were no patients in either 2000 L or placebo

Tab 1

group who improved more than 15% in upright FVC (table 42). Two patients in the entire study (one in the 2000 L group, and one in the placebo group each improved by 14% in upright FVC at the last observation.)

Table 34: Number (n) of responders based on clinical threshold definitions

Clinical Threshold	2000 L N (% of total)	Placebo N (% of total)
6MWT		
Change from baseline > 54 m	14 (23.3)	4 (13.3)
Change from baseline > 37 m	16 (26.6)	5 (16.6)
Change from baseline > 30 m	17 (28.3)	6 (20)
Upright FVC % predicted		
Change from baseline > 15%	0	0

In summary, using predefined thresholds to define responders for the 6MWT and FVC, it is difficult to draw conclusions about the clinical meaning of the effect of 2000 L product in Pompe disease patients. Currently, there are no guidelines to assess magnitude of change in either of these clinical measures as clinically meaningful in Pompe disease, or other lysosomal storage diseases.

7.7 Overall Efficacy Conclusions

The 2000 L product produces a statistically significant difference (28.1 meters, $p=0.035$) in estimated change from baseline distance walked during the 6MWT and the statistically significant difference (3.4%, $p=0.006$) in estimated change from baseline in % predicted upright FVC compared to placebo in patients with Pompe disease over a 78 week period. These differences are similar to the differences found in the clinical trials leading to the approval of two other enzyme replacement therapies, Laronidase (Aldurazyme) for MPS I, and Idursulfase (Elaprase) for MPS II.

The Applicant has proposed that the 2000 L product be indicated for late-onset Pompe disease patients. However, only 4 patients were less than 18 years of age at the time of enrollment in the study. Furthermore, based on the demographic characteristics of the juvenile-onset Pompe disease patients using the different definitions explored above (e.g., age at diagnosis, age at first symptoms), it appears that most of these patients had attenuated disease most consistent with adult-onset presentations. Therefore, insufficient numbers of juvenile-onset disease patients were studied in LOTS to conclude efficacy of the 2000 L product in this patient group. Also, LOTS was not designed to study juvenile-onset patients less than 8 years of age, who would be expected to have more rapidly progressive disease. Thus, given the concerns regarding the potency of 2000 L product compared with 160 L product, the potential for increased immunogenicity of 2000 L product (see section 7.4.5), and the lack of data regarding efficacy of 2000 L product in the juvenile-onset patients, strong consideration should be given to limiting the indication of 2000 L product to adult-onset patients only.

Tab 1

Treatment with 2000 L product produces substantial immunologic effects. 100% of patients treated with 2000 L product developed anti-rhGAA IgG antibodies during LOTS. This compares with 0 patients in the placebo group, and 89% of infantile-onset patients in the clinical trial leading to the approval of the 160 L product. Additionally, 30% of patients in the 2000 L treatment group developed inhibitory IgG antibodies to rhGAA uptake. Again, this differs substantially from the 10% of infantile-onset patients who received 160 L product. Differences in phenotype of disease, product attributes, or CRIM status may all play a role in this difference in development of inhibitory antibody. Low GAA activity (<1%) may also be associated with the development of inhibitory antibody. All patients in the 2000 L treatment group who had GAA activity <1% developed inhibitory antibody. These patients also had a smaller treatment effect compared to the overall 2000 L treatment group. Persistently rising IgG titer especially in combination with the presence of inhibitory antibody may attenuate the efficacy of 2000 L product in this specific group of patients. Thus, these immunogenicity findings suggest a higher immunogenic potential in the 2000 L product compared with the 160 L product. The higher immunogenicity of the 2000 L product may lead to concerns with long-term efficacy and safety. Finally, younger patients, who may be expected to receive exogenous enzyme treatments the longest, may be at the greatest risk for problems associated with the increased immunogenicity of the 2000 L product.

8 Safety Review

8.1 Methods

The safety information available for review for the Advisory Committee meeting includes clinical safety data from one clinical study, AGLU02704, Late Onset Treatment Study (LOTS).

Additional safety data on the 2000 L product was submitted to the Agency on September 1, 2008 by the Applicant. Due to the late submission of the following safety data, there was insufficient time for review to be included in this background package.

1. AGLU03206 (n=80) is the open-label extension study of LOTS. This study evaluated the efficacy and safety of patients previously enrolled in LOTS for an additional 6 months, with 2000 L-treated patients continuing on treatment, and the previously placebo-treated patients converting to receive the 2000 L product for 6 months. Preliminary safety data on 80 patients enrolled in this study through April 15, 2008, were submitted.
2. AGLU02603 (n=9) is a US expanded access protocol that provides 2000 L product to severely affected patients (i.e., ventilator-dependent and wheelchair-bound) with non-infantile onset Pompe disease, until commercial therapy was available. Nine patients were enrolled in this study, and 8/9 received 2000 L product only. One patient in the study received 160 L product for the first six infusions and then was switched to 2000 L product. The study was conducted from November 23, 2004 to August 13, 2006.
3. AGLU02804 (n=5) is a single center, open-label study of the safety, pharmacokinetics, and efficacy of 2000 L product treatment in patients with non-infantile onset Pompe disease. Five patients were enrolled in the study center in the Netherlands, and all

Tab 1

patients received 2000 L product, 20mg/kg/dose, every other week for 74 weeks. The study was conducted from February 2, 2005 until July 13, 2006.

4. AGLU03105 (n=5) is a single center, open-label study of the safety and efficacy of 2000 L product with advanced non-infantile onset Pompe disease who are receiving respiratory support. Five patients were enrolled in the study center in France, and all patients received 2000 L product, 20mg/kg/dose, every other week for 52 weeks. The study was conducted from December 12, 2005 until March 30, 2007.
5. AGLU03907 (n=135) is the Myozyme® Temporary Access Program (MTAP). The objective of the study is to provide, under clinical trial monitoring conditions, adult patients (patients over the age of 18) with Pompe disease in the US access to 2000 L product while the product is under review, and to divert the remaining supply of the 160 L product to infantile-onset patients. Safety data on these patients, many of whom have received 160 L product in the past are being treated with 2000 L product, are only partially available at the time of this writing.
6. Postmarketing safety data through April 15, 2008, for the 2000 L product. A total of 32 adverse events reports in late-onset Pompe disease patients were submitted by the Applicant. Because the 2000 L product is not commercially available in the US, these postmarketing data reflect the postmarketing safety data collected in the EU and Canada.

8.2 Major Safety Results

8.2.1 Deaths

One death occurred during the LOTS clinical trial. This death occurred in patient 16708, a 33 year-old Caucasian woman enrolled at the –b6----- and randomized to the 2000 L treatment group. The patient has a history of Pompe disease diagnosed at the age of 16. The patient received her first infusion of 2000 L product on February 23, 2006. In October, 2006, the patient developed right arm and leg numbness which prompted an evaluation that led to the diagnosis of two broad-based cerebral aneurysms, one at the junction of the right vertebral and basilar arteries (11mm), and one in the mid-upper basilar artery (9mm). The patient was reported to have had a cerebral MRI performed at the time of diagnosis of Pompe at the age 16 that did not demonstrate these aneurysms. The patient was hospitalized and placed on Clopidogrel bisulfate (Plavix®) and aspirin with the plan to place coils and stents to treat the aneurysms. The stenting procedure was performed on –b6-----, and two coils were placed, one on –b6-----, and the second on –b6-----.

The patient developed dizziness, nausea and sweating on the morning of ---b6-----, 13 days after completing her week 72 infusion. Shortly afterward, she was unable to speak and could not hear out of her right ear. Subsequently, she developed slurred speech and severe dizziness and was hospitalized emergently. She then became unresponsive and required intubation. Emergent cerebral angiogram demonstrated multiple filling defects in her basilar artery consistent with thrombosis. A non-contrast CT scan demonstrated multiple basilar aneurysm coils and redemonstration of old cerebellar and brainstem infarctions. Additionally, MR of the brain with and without contrast demonstrated multiple foci of old hemorrhage

Tab 1

throughout the cerebral hemispheres and cerebellum, prominent cerebellar atrophy, acute and subacute areas of infarction within the right cerebellum and mid-pons, and no abnormal areas of enhancement. These findings were consistent with brain stem ischemia. The patient was not able to speak, but was able to communicate yes/no responses with 100% accuracy. Thus, the patient was diagnosed with locked-in syndrome secondary to brain stem ischemia. The patient communicated to her physician by alphabet board and vertical eye movements that she wished to die and to remove the ventilator and all treatments with the exception of palliative sedation. Elective extubation was performed, and the patient died of cardiac arrest shortly thereafter. No autopsy was performed. In the opinion of the Investigator, the cause of death was brainstem ischemia secondary to basilar artery thrombosis, a known complication in Pompe disease patients, and unrelated to the study drug. The medical reviewer concurs with the Applicant's assessment.

8.2.2 Nonfatal Serious Adverse Events (SAEs)

There was a total of 26 nonfatal serious adverse events recorded during the LOTS trial. Of the 26 events, 19 of the events occurred in the 2000 L treatment group and 7 events occurred in the placebo group. SAEs led to 2 patient dropouts (anaphylaxis) in the 2000 L group, and 1 patient dropout (headache) in the placebo group. A listing of all of the nonfatal serious adverse events is listed by system organ class (SOC) and preferred term (PT) in table 35. Ten of these SAEs (8 in the 2000 L treatment group and 2 in the placebo group) were considered possibly related to treatment by the Applicant, while the other 17 were recorded as not treatment related. It should be noted that the medical reviewer recoded the preferred terms angioneurotic edema, hypersensitivity, chest discomfort and throat tightness under the preferred term anaphylaxis, as these events all meet the definition of anaphylaxis as described in section 6.2.4.1, and will be discussed further in that section. There were five episodes of anaphylaxis that were reported in the treatment group, while none occurred in the placebo group. The medical reviewer agrees with the classification of SAEs by the Applicant.

Table 35: Number (n) of Nonfatal Serious Adverse Events by treatment group

System Organ Class	Preferred Term	2000 L	Placebo
Cardiac disorders	Coronary artery disease	2	0
	Supraventricular tachycardia*	1	0
Gastrointestinal disorders	Abdominal pain	1	1
	Gastroenteritis	1	0
General disorders and administration site conditions	Musculoskeletal chest pain*	1	0
Immune System Disorder	Anaphylaxis*	5	0
Infections and infestations	Pneumonia	1	0
	Diverticulitis	0	1
	Flank pain	0	1
Injury, poisoning and procedural complications	Fall	1	1
	Injury	1	1
Metabolism and nutrition disorders	Dehydration	1	0
Musculoskeletal and connective tissue disorders	Intervertebral disc protrusion	2	0
Nervous system disorders	Headache*	0	1
Respiratory, thoracic and mediastinal disorders	Lung disorder	1	0
Skin and subcutaneous tissue disorders	Septal panniculitis*	0	1
Vascular disorders	Aneurysm	1	0
Total SAEs		19	7

*Assessed by Applicant as possibly related to study drug

8.2.3 Drop outs and Discontinuations

Overall, nine patients dropped out of the study or were discontinued due to adverse events. In the placebo group, one patient was discontinued from the study due to persistent headache, and three patients dropped out wishing to receive commercial product. In the 2000 L treatment group, one patient died (see section 8.2.1), and two patients were discontinued due to serious adverse events (anaphylaxis), one dropped out for personal reasons, and one patient dropped out to receive commercial product (table 36). The non-fatal AEs that led to discontinuation in these patients are briefly summarized below:

- Patient 16709, in the 2000 L product treated group, is a 32 year old Caucasian female, who was diagnosed with Pompe disease at the age of 27.8 years. She developed chest discomfort, throat tightness and urticaria associated with flushing, nausea, decreased oxygen saturation, rash, wheezing, and headache after the second 2000 L product infusion. The patient tested positive for anti-rhGAA IgE antibodies and complement activation with significantly elevated serum trypsin. These criteria fulfill the clinical and laboratory definition of anaphylaxis.
- Patient 90701, in the 2000 L product treated group, is a 61.5 year old Caucasian male, who was diagnosed with Pompe disease at the age of 56.4 years. He developed severe angioneurotic edema after the third 2000 L product infusion, and based on the risk/benefit profile, the Investigator withdrew the patient from the study. There are no other laboratory studies to review for this patient, but it is known that anti-rhGAA IgE antibodies in this patient were negative.

Tab 1

- Patient 29703, in the placebo treated group, is a 25.8 year old Asian female who was diagnosed with Pompe disease at the age of 17.2 years. She developed ongoing, serious headache and missed infusions at weeks 22, 24, 26, 46, and 48. The patient withdrew from the study due to this adverse event.

Table 36: Patient dropout or discontinuation (n=9)

Patient ID	Treatment group	Reason for Drop out or Discontinuation
16708	2000 L	Death
16709	2000 L	Adverse Event (Anaphylaxis)
29706	2000 L	Withdrew for “personal reasons”
65701	2000 L	Wish to receive commercial product
90701	2000 L	Adverse Event (Angioneurotic edema)
4705	Placebo	Wish to receive commercial product
29703	Placebo	Adverse Event (Persistent headache)
29711	Placebo	Wish to receive commercial product
65705	Placebo	Wish to receive commercial product

As shown in Table 36, four patients dropped out of the study (one patient in the 2000 L treatment group and three patients in the placebo group) based on their “wish to receive commercial product”. None of these patients developed infusion associated reactions, and two patients sustained SAEs: patient 4705 developed gastroenteritis and pneumonia, and patient 65701 developed an episode of supraventricular tachycardia. Their overall 6MWT data (table 37) suggests that they were not performing well and it is possible that their poor performance led to some unblinding bias, at least for the patients receiving placebo treatment.

Table 37: Mean change (± SD) from baseline to last observation 6MWT patients who withdrew from the study based on “wish to receive commercial product” (n=4)

	Change from baseline (M)
Screening/Baseline	
Week 12	-17.5 (20.7)
Week 26	12.5 (19.1)
Early Termination	-28 (26.5)

8.2.4 Significant Adverse Events

8.2.4.1 Anaphylaxis

Anaphylaxis and other allergic reactions, as are seen in other enzyme replacement therapies, are the foremost safety concern regarding alglucosidase alfa. A boxed warning for the risk of anaphylaxis was placed in the label for the 160 L product based on a 5% incidence of anaphylaxis in the clinical trial of 18 infantile-onset patients who received 160 L product. The Review Division uses a definition for anaphylaxis based on the consensus statement written by the Second Symposium on the Definition and Management of Anaphylaxis (the Symposium).¹⁷ The participants of this Symposium, convened by the National Institute of Allergy and Infectious Disease, and Food Allergy and Anaphylaxis Network, along with representatives from 16

different international organizations and government bodies, agreed that while there is no universal agreement on the definition of anaphylaxis or criteria for diagnosis, the definition should be made based on clinical criteria. Laboratory test results such as IgE antibody presence or skin testing do not play a role in making a clinical diagnosis of anaphylaxis. The clinical definition established is shown in Table 38.

Table 38: Clinical definition of Anaphylaxis

Anaphylaxis is highly likely when any <u>one</u> of the following 3 criteria are fulfilled:	
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)	
AND AT LEAST ONE OF THE FOLLOWING	
a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)	
b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)	
2. Two or more of the following that occur rapidly after exposure to a <u>likely allergen for that patient</u> (minutes to several hours):	
a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)	
b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)	
c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)	
d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)	
3. Reduced BP after exposure to <u>known allergen for that patient</u> (minutes to several hours):	
a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*	
b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline	

PEF, Peak expiratory flow; BP, blood pressure.
 *Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Table electronically copied from Sampson HA, Munoz-Furlong A, Campbell RL, et al., Second symposium on the definition and management of anaphylaxis: Summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis network symposium, J Allergy Clin. Immunol., 2006, 117(2), 391-397

The Applicant, however, defined anaphylaxis as a subset of infusion associated reactions that were considered related to anaphylaxis, based on an expanded search algorithm using MedDRA version 9.1 and a standardized MedDRA query (SMQ). Using this method, the Applicant found only two patients (16709 and 18713) with anaphylaxis. A third patient was defined by the Applicant as having developed anaphylaxis based on the development of angioneurotic edema. Thus, the Applicant's overall incidence of anaphylaxis was 5% (3/60 patients) for LOTS. However, using the clinical criteria established by the Symposium for the definition of anaphylaxis in conducting an independent safety review of the AE datasets, the medical reviewer found one additional patient who met the definition of anaphylaxis. All of the patients identified with anaphylaxis (4/60, 6.7%) were in the 2000 L treatment group. This compares with 0% incidence of anaphylaxis in the placebo treatment group. Additionally, 2/4 (50%) patients with anaphylaxis withdrew from the study because of this adverse event. No deaths occurred as a consequence of anaphylaxis. There was no correlation observed between peak IgG titers and development of anaphylaxis. The Applicant tested for IgE antibodies to rhGAA, complement activation, and serum tryptase in most patients with infusion associated reactions. These laboratory studies may be positive in patients with anaphylaxis but the diagnosis may be made clinically without positive tests for any of these laboratory tests. Of the four patients with

anaphylaxis, only two had positive IgE antibodies to rhGAA, 3 tested positive for complement activation, and one patient had elevation in serum tryptase (see table 39).

Table 39: Laboratory values in 7 patients with Anaphylaxis

	Anti-rhGAA IgE antibody	Complement activation	Serum tryptase
Patient 16709*	Positive	Positive	Elevated
Patient 18713*	Positive	Positive	Normal
Patient 90701*	Negative	Negative	Normal
Patient 29708	Negative	Positive	Normal

*Patients identified by Applicant with anaphylaxis

8.2.4.2 Infusion Associated Reactions (IARs)

The immunologic mechanisms involved in the pathogenesis of anaphylaxis (hypersensitivity) traditionally have been characterized by IgE mediated release of histamines, leukotrienes, and prostaglandins (Type 1 hypersensitivity), although elevated IgE antibody titers are neither necessary nor sufficient to diagnose anaphylaxis. The pathogenesis of infusion reactions is even less clear. In general, infusion associated reactions that occur with biologic protein administration are adverse reactions that develop during or shortly after the infusion, and may be immune mediated, although the exact underlying mechanism is unclear.

The National Cancer Institute has developed terminology published in as Common Terminology Criteria for Adverse Events v3.0 (CTCAE) to distinguish between hypersensitivity reactions and acute infusion reactions (table 40).¹⁸ There is clear overlap between the clinical definitions of anaphylaxis and infusion associated reactions as noted in table 40. For the purposes of this review, all reactions that fulfill the criteria for anaphylaxis based on the clinical definition described by the Symposium have been classified as anaphylaxis. Infusion associated reactions in this review will include both reactions that may be classified as “hypersensitivity/allergic” and reactions that may involve other mechanisms but do not clearly fulfill the clinical definition of anaphylaxis. In the opinion of the medical reviewer, this definition provides meaningful information to the prescribing clinician regarding the possible infusion associated reactions to patients receiving the drug. Table 41 lists some of the signs and symptoms of infusion associated reactions.¹⁹

Table 40: Grading of Reactions according to the NCI CTCAE

	Grade				
	1	2	3	4	5
Hypersensitivity (allergic reaction)	Transient flushing or rash; drug fever $<38^{\circ}\text{C}$ ($<100.4^{\circ}\text{F}$)	Rash; flushing; urticaria; dyspnea; drug fever $\geq 38^{\circ}\text{C}$ ($\geq 100.4^{\circ}\text{F}$)	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension	Anaphylaxis	Death
Acute infusion reaction (cytokine release syndrome)	Mild reaction; infusion interruption not indicated; intervention not indicated	Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g. antihistamines, NSAIDs, narcotics, i.v. fluids); prophylactic medication indicated for ≥ 24 hours	Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening; pressor or ventilatory support indicated	Death

Electronically copied from National Cancer Institute, Common Terminology Criteria for Adverse Events v3.0 (CTCAE) Publish date August 9, 2006. Available at <http://ctep.cancer.gov/forms/CTCAEv3.pdf>.

Table 41: Possible signs and symptoms of acute infusion reactions

Allergic reaction/hypersensitivity (including drug fever)
Pruritus/itching
Rash/desquamation
Urticaria (hives, welts, wheals)
Rigors/chills
Headache
Arthralgia/myalgia
Tumor pain
Fatigue (asthenia, lethargy, malaise)
Dizziness
Sweating
Nausea/vomiting
Cough
Dyspnea
Bronchospasm
Hypotension/hypertension
Tachycardia

Electronically copied from Lenz HJ, Management and Preparedness for Infusion and Hypersensitivity Reactions, Oncologist, 2007, 12: 601-609.

Tab 1

Infusion associated reactions (IARs) were defined by the Applicant as any AE that occurred during either the infusion or the recommended 2 hour observation period following the infusion that was assessed by the Investigator as related to the study drug (i.e., possibly, probably, or definitely related). The Applicant also submitted data on the timing of the AE in relationship to the infusion and divided the AEs into 4 categories: 1) AE onset during the infusion 2) AE onset within 2 hours of completion of infusion 3) AE onset between 2-24 hours of infusion 4) AE onset between 24-48 hours of infusion.

The relationship of the AE to the study drug was re-evaluated independently by the medical reviewer. Many AEs that occurred during the infusion or within two hours after completion of the infusion were classified as unlikely related to the study medication by the Applicant. The medical reviewer analyzed the clinical context of the AEs and recoded them as possibly related to the study drug if the event occurred during the infusion or within 48 hours after completion of the infusion. The preferred terms that were recoded as possibly related by this Reviewer included: skin rash, pruritis, headache, dizziness, chest discomfort, peripheral edema, pyrexia, hypotension, nausea, chills, respiratory distress, dyspnea, syncope, photosensitivity reaction, blurred vision, malaise, abdominal pain, hematuria, hyperhidrosis, diarrhea, somnolence, Raynaud's syndrome, hematuria, and proteinuria.

Based on the Applicant's classification of IARs found in the electronic dataset, there were a total of 214 IARs, with 167 events occurring in 13 patients in the 2000 L treatment group, and 47 events occurring in 5 patients in the placebo group. Based on the medical reviewer's classification of IARs and relationship to study drug, there were a total of 297 IARs, with 232 events occurring in 29 patients in the 2000 L treatment group and 65 events occurring in 15 patients in the placebo group (table 42).

Table 42: Number of Infusion of Associated Reactions by treatment group

	2000 L (% of total)	Placebo (% of total)	Total
AEs occurring during or within 2 hours of completion of infusion	232 (78.1)	65 (21.9)	297
Number of patients experiencing	29	15	44

The types of AEs differed between the 2000 L treatment group and placebo group. Table 51 lists all of the IARs by system organ class (SOC) and preferred term (PT). Additionally, the types of AEs also differ between the 2000 L treatment group and placebo group. Table 43 lists all of the IARs by system organ class and preferred term. Notable differences between the 2000 L and placebo group included the presence of hypersensitivity (allergic) reactions, skin reactions, including urticaria, and paresthesias that were not present in the placebo group. Headache and nausea, the most common IARs in the placebo group were also noted in the 2000 L treatment group. It should also be noted that one patient (18713) accounted for 107 separate IARs or 36% of the total IARs. Despite this, there was a large discrepancy between the number and type of IARs present between the treatment groups, with the 2000 L group experiencing more potentially immune-mediated IARs.

Table 43: Types of Infusion Associated Reactions and Number (N) by treatment group

System Organ Class (SOC)	Preferred Term (PT)	2000 L	Placebo
Cardiac disorders	Sinus tachycardia	1	0
Ear and labyrinth disorders	Ear discomfort	17	0
	Auricular swelling	1	0
	Hypoacusis	2	0
Eye disorders	Asthenopia	1	0
	Eye irritation	1	0
	Eye pruritus	2	0
	Photophobia	1	0
	Vision blurred	1	0
Gastrointestinal disorders	Nausea	5	36
	Diarrhea	7	0
	Abdominal pain	3	1
	Lip swelling	3	0
	Oral pruritus	1	0
	Swollen tongue	1	0
	Vomiting	4	0
General disorders and administration site conditions	Asthenia	0	2
	Catheter site pain	3	0
	Chest discomfort	6	0
	Chills	1	0
	Fatigue	1	2
	Local swelling	9	0
	Malaise	1	0
	Non-cardiac chest pain	1	0
	Edema peripheral	2	0
	Pyrexia	7	2
Immune system disorders	Hypersensitivity	21	0
Infections and infestations	Sinusitis	1	0
Investigations	Blood pressure increased	2	0
	Oxygen saturation decreased	1	0
Musculoskeletal and connective tissue disorders	Arthralgia	1	0
	Muscle twitching	1	0
	Musculoskeletal chest pain	2	0
	Myalgia	2	4
	Pain in extremity	3	0
	Sensation of heaviness	2	0
Nervous system disorders	Headache	18	16
	Dizziness	5	1
	Paraesthesia	7	0
	Somnolence	1	0
	Syncope vasovagal	1	0
Renal and urinary disorders	Hematuria	2	0
	Proteinuria	1	0
Respiratory, thoracic and mediastinal disorders	Dyspnea	5	1
	Throat tightness	2	0
	Wheezing	1	0
Skin and subcutaneous tissue disorders	Erythema	6	0
	Hyperhidrosis	4	0

Tab 1

	Photosensitivity reaction	1	0
	Pruritus	6	0
	Rash	17	0
	Subcutaneous nodule	21	0
	Urticaria	10	0
Vascular disorders	Flushing	5	0
	Hypotension	1	0
Total		232	65

Delayed-onset infusion associated reactions, defined by the medical reviewer as those occurring from 2-48 hours after the infusion and listed as either possibly or probably related to the infusion are also a safety concern. Delayed, and/or biphasic phase allergic reactions have previously been described with other enzyme replacement therapies and biologic protein therapies.²⁰ Biphasic reactions are characterized by an initial reaction and the onset of a second phase reaction that may occur up to 72 hours after the initial reaction. There have also been reports of delayed-onset infusion reaction in patients receiving 160 L product; infantile-onset patients with underlying cardiorespiratory compromise may be at greater risk for developing delayed-onset infusion reactions. Delayed-onset anaphylaxis may also be of concern in patients receiving 2000 L product.

Based on the medical reviewer's classification of delayed-onset IARs and relationship to study drug, there were a total of 152 delayed IARs, with 66 events occurring in 26 patients in the 2000 L treatment group and 86 events occurring in 15 patients in the placebo group. Table 44 shows the total number of and types of delayed-onset IARs. It should be noted that while there were a greater number of delayed-onset IARs in the placebo group, one patient (29703) accounted for 36 events or 41.8% of the total delayed IARs in the placebo group. The types of AEs also differ between the 2000 L group and placebo group. Table 52 also lists all of the IARs by system organ class and preferred term. The most common delayed-onset IARs in the 2000 L group were headache, dizziness, and diarrhea. However, a concerning finding is the apparent development of one episode of delayed-onset anaphylaxis in a patient treated with 2000 L product. This event occurred in Patient 18713, a patient that developed several episodes of anaphylaxis during the course of the study. Two episodes of urticaria occurred in two patients (16710 and 29705) in the 2000 L treatment group. No episodes of delayed-onset anaphylaxis or urticaria were identified in the placebo group. The most common delayed-onset IARs in the placebo group were headache and dysgeusia.

Table 44: Types of Delayed-Onset Infusion Associated Reactions and Number (N) by treatment group

System Organ Class (SOC)	Preferred Term (PT)	2000 L	Placebo
Cardiac disorders	Angina pectoris	1	0
Ear and labyrinth disorders	Hypoacusis	0	1
Eye disorders	Vision blurred	1	0
	Cataract	0	1
Gastrointestinal disorders	Abdominal pain	2	1
	Diarrhea	7	3
	Nausea	5	2
	Vomiting	3	1
General disorders and administration site conditions	Chest discomfort	2	1
	Chills	1	1
	Fatigue	0	2
	Malaise	1	0
	Local swelling	0	1
	Pyrexia	1	1
	Edema peripheral	0	5
Immune system disorders	Hypersensitivity	1	0
Investigations	Blood urine present	1	0
	Electrocardiogram QT corrected interval prolonged	1	0
Musculoskeletal and connective tissue disorders	Muscle spasms	1	0
	Muscle twitching	1	1
	Myalgia	2	1
	Sensation of heaviness	1	0
Nervous system disorders	Dysgeusia	0	11
	Dizziness	7	2
	Headache	19	40
	Paraesthesia	1	1
Renal and urinary disorders	Proteinuria	1	1
	Urine odor abnormal	1	0
Respiratory, thoracic and mediastinal disorders	Throat irritation	1	0
	Dyspnea	0	2
Skin and subcutaneous tissue disorders	Cold sweat	1	0
	Rash	3	3
	Pruritus	0	1
	Skin nodule	1	0
	Urticaria	2	0
Vascular disorders	Hypotension	0	1
	Phlebitis	0	1
	Raynaud's phenomenon		1
Total		66	86

As stated earlier, a total of 44 patients in the study had IARs, 29 in the 2000 L treated group and 15 in the placebo group. Of these 44 patients, 5 patients had at least 10 IARs (4 of these patients were randomized to the 2000 L group, and 1 patient was in the placebo group). One of the 2000 L treated patients dropped out of the study. It was a concern to the medical reviewer that patients who developed more infusion associated reactions may have “unblinded” the investigator to the treatment arm and thus introduced bias in the conduct of the endpoint

Tab 1

measures. Or, patients themselves might have been “unblinded” and thus performed differently on the 6MWT, a test that is patient-effort dependent. Table 45 shows the mean change from baseline in the 6MWT in all patients reporting at least 10 IARs. Interestingly, patients with more IARs in the placebo treatment group performed much better than the overall placebo treatment group mean, and in fact performed better than patients in the 2000 L treatment group. While no clear conclusions can be drawn from these data, this observation may suggest some introduction of “unblinding” bias in the placebo treatment group since the 6MWT and pulmonary function testing are dependent upon patient effort.

Table 45: Overall change from baseline 6MWT for 5 patients with at least 10 IARs

Treatment	Mean (\pm SD)
2000 L	26.35 (45.6)
Placebo	59.17 (15.3)

8.2.4.3 Skin Reactions and other Potential Immune-mediated AEs

Skin reactions have been noted in postmarketing safety data collected as part of the 160 L product, and the 160 product label has been updated to reflect this safety finding. Some of the skin reactions identified in the postmarketing data collected include reactions that may be immunologically mediated. Therefore, a review of skin findings reported in the LOTS trial was performed using the following preferred terms: Angioneurotic edema, erythema, pruritus, rash (and several subcategories of rash), urticaria, drug eruption, skin nodule, subcutaneous nodule, and septal panniculitis. Clearly, skin reactions are more common in the 2000 L group (89.8%) compared with the placebo group (10.2%). Table 46 lists the various types of skin reactions based on treatment group. It should be noted that the report of “skin nodule” occurred on 21 separate occasions in the same patient (Patient 18713) who also developed several episodes of anaphylaxis. Additionally, 54% (53/98 events) of these skin reactions have a potential immunologic basis (e.g. urticaria, angioneurotic edema, skin nodule).

Table 46: Total number (N) of Skin Reactions by treatment group

Treatment	Preferred Term	N (% of total)
2000 L	Angioneurotic edema	1 (1.0)
	Erythema	5 (5.1)
	Pruritus	15 (15.3)
	Rash	10 (10.2)
	Rash macular	5 (5.1)
	Rash maculo-papular	4 (4.1)
	Rash papular	4 (4.1)
	Rash pruritic	7 (7.1)
	Skin nodule	21 (21.4)
	Subcutaneous nodule	1 (1.0)
	Urticaria	15 (15.3)
	2000 L Total	88 (89.8)
Placebo	Drug eruption	1 (1.0)
	Erythema	1 (1.0)
	Pruritus	1 (1.0)
	Rash	3 (3.0)
	Rash pruritic	3 (3.0)
	Septal panniculitis	1 (1.0)
Placebo Total		10 (10.2)

Tab 1

Additionally, although small in number, there is evidence of possible glomerular injury as manifested by hematuria and/or proteinuria in patients treated with 2000 L product. Seven patients in the 2000 L treatment group developed hematuria and/or proteinuria, and only two patients in the placebo group. Two patients in the 2000 L treatment group and one patient in the placebo group developed both hematuria and proteinuria. Interestingly, patient 18713 (hematuria and proteinuria) and Patient 29705 (hematuria) also developed anaphylaxis. There has been at least one report in the literature of the development of membranous glomerulonephritis associated with treatment with the 160 L product.²¹ While this condition was not observed in the LOTS study, immune mediated kidney disease should be considered as potential long-term safety issue.

8.2.4.4 Cataracts

Six patients (4 patient in the 2000 L group and 2 in the placebo group) developed cataracts during the study. The demographic characteristics are listed below in table 47. The mean time to development of the cataracts was not different between placebo treated and 2000 L product. There is also no clear difference between the patients' age at onset of the cataract between the groups. It is unclear whether 2000 L product is associated with the development of cataracts.

Table 47: Characteristics of 6 patients who developed cataracts during the study

Treatment	Patient ID	Gender	Age and Enrollment	Time (weeks) to development of AE
2000 L product	47704	Female	70.0	51.9
2000 L product	47707	Female	43.8	63.9
2000 L product	47708	Male	50.7	63.9
2000 L product	47711	Male	54.9	77.1
Placebo	26701	Male	68.4	52.4
Placebo	47712	Female	45.9	63.9

8.2.4.5 Arrhythmias

One episode of supraventricular tachycardia was noted, as well as one episode each of right bundle branch block and left bundle branch block. All of these arrhythmias occurred in 2000 L product treated patients. There were no arrhythmias noted in the placebo group.

8.3 Other Safety Results

8.3.1 Overall Adverse Events/Common Adverse Events

Overall, 2349 were AEs reported during the study period; 1479 AEs in the 2000 L treatment group, and 870 AEs in the placebo group. 100% of patients in the study reported at least one AE. The relationship of AE to treatment was classified by the site Investigators as definite, possible, probable, remote/unlikely, or not related. Based on these reports, the Applicant noted a total of 442 treatment treatment-related events 298 AEs (67.4%) in the 2000 L group and 144 events (32.6%) in the placebo group). The number of patients reporting AEs is listed in table 57. Based on criteria stated in section 6.2.4.2, relationship of AE to treatment was reassessed by the

Tab 1

medical reviewer. There was a difference between the number of treatment related AEs as defined by the medical reviewer and the Applicant as noted in the table 48. The medical reviewer identified a total of 500 treatment related AEs; 401 in the 2000 L treatment group, and 199 in the placebo group (table 49). These differences do not account for major changes in the overall safety profile of the 2000 L product, however.

Table 48: Overall AE profile by treatment group

	2000 L (n=60) N (%)	Placebo (n=30) N(%)
Patients with Any AE	60 (100)	30 (100)
Patients with Treatment-related AE*	47 (78.3)	21 (70.0)
Patients with SAEs	13 (21.7)	6 (20.0)
Patients who discontinued due to AE	3 (5.0)	1 (3.3)
Patients who Died	1 (1.7)	0 (0)

*This number differs from the Applicant's table, and is based on the medical reviewer's classification of treatment relationship (see section 6.2.4.2)

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Table 49: Number of treatment-related AEs

	Applicant	Medical Reviewer
Total number of treatment-related AEs	442	500
Treatment-related AEs 2000 L group	298	401
Treatment-related AEs placebo group	144	199

The most common AEs (AEs occurring in > 20% of the patients in LOTS) are summarized in table 50. Many of these common AEs were related to the patient's underlying diagnosis of Pompe disease, and therefore, arthralgia, myalgia, and falls were expected to occur in roughly equal percentages between the 2000 L treatment group and the placebo group. Additionally, conditions that would be expected to occur in the general population over the course of the study were also not different (e.g. nasopharyngitis). Incidence of rash more common in the 2000 L treatment group compared with the placebo group.

Table 50: AEs occurring in at least 20% of patients

Preferred term	Number of patients Total (%)	Number of patients 2000 L (%)	Number of patients Placebo (%)
Fall	59 (65.6)	39 (65)	20 (66.6)
Nasopharyngitis	43 (47.8)	27 (45)	16 (53.3)
Headache	39 (43.3)	24 (40)	15 (50)
Arthralgia	29 (32.2)	20 (33.3)	9 (30)
Hypoacusis	27 (30)	20 (33.3)	7 (23.3)
Muscular weakness/myalgia	29 (32.2)	20 (33.3)	9 (30)
Diarrhea	30 (33.3)	17 (28.3)	13 (43.3)
Rash	18 (20)	16 (26.6)	2 (6.6)
Dizziness	22 (24.4)	16 (26.6)	6 (20)
Back pain	22 (24.4)	14 (23.3)	8 (26.6)
Muscle spasms	20 (22.2)	14 (23.3)	6 (20)
Pharyngolaryngeal pain	18 (20)	12 (20)	6 (20)
Nausea	21 (23.3)	11 (18.3)	10 (33.3)
Gastroenteritis	18 (20)	9 (15)	9 (30)

8.4 Overall Safety Conclusions

Based on this review, allergic and immune mediated reactions are the main safety concern with the 2000 L product. The risk of anaphylaxis remains a serious safety concern and proper warning to patients and practitioners should be clearly documented in labeling. Additionally, the risk of delayed-onset anaphylaxis should also be clearly documented in labeling. Safety conclusions may only be made to 78 weeks, and thus, the long term safety profile of the product is unknown. Additionally, unlike acute allergic reactions (anaphylaxis and infusion associated reactions), chronic immune mediated responses are likely to be seen only after long term exposure. Although the safety profile of the 2000 L product is generally similar to the 160 L product and other enzyme replacement therapies for lysosomal storage diseases, there is a suggestion that 2000 L product may be more immunogenic than the 160 L product.

Finally, should the 2000 L product be approved for use in late-onset Pompe disease, administration of 2000 L product in unapproved populations must be avoided. Safeguards are being discussed (a Risk Evaluation and Mitigation Strategy; REMS) with the Applicant in order to avoid misuse of the 2000 L product, should it be approved, to infantile-onset patients, for whom safety and efficacy have not been demonstrated, and for whom 160 L product has previously been approved.

9 Summary

9.1 Efficacy Summary

Based on the amended, pre-specified statistical analysis of the primary efficacy endpoints, there was not a statistically significant difference in the rate of change in the 6MWT between the 2000 L product and placebo. However, based on the original statistical analysis plan, a difference of 28.1 meters in estimated change from baseline in distance walked during a 6MWT between the 2000 L product and placebo was statistically significant ($p=0.035$). Additionally, based on both the pre-specified and original statistical analysis plans, there was a 3.4% difference ($p=0.006$) in % predicted upright FVC in favor of the 2000 L product.

The Applicant has proposed that the 2000 L product be indicated for late-onset Pompe disease patients. However, only 4 patients were less than 18 years of age at the time of enrollment in the study. LOTS was not designed to study juvenile-onset patients less than 8 years of age, who would be expected to have more rapidly progressive disease. Therefore, it appears that insufficient numbers of juvenile-onset disease patients were studied to conclude efficacy of the 2000 L product in this patient group. Currently, the 160 L product is approved in the US for juvenile-onset Pompe disease patients. However, there have been no controlled clinical trials to date evaluating either the 160 L or 2000 L product in juvenile-onset Pompe disease patients. Thus, given the concerns regarding the potency of 2000 L product compared with 160 L product, the potential for increased immunogenicity of 2000 L product, and the lack of data regarding efficacy of 2000 L product in the juvenile-onset patients, strong consideration should be given to limiting the indication of 2000 L product to adult-onset patients only.

While treatment with 2000 L product produces statistically significant differences in the primary endpoints compared to placebo in LOTS, the clinical meaning of these differences remains unclear. Despite the use of these primary efficacy endpoints in LOTS, as agreed upon by the Agency, these endpoints have yet to be established as true surrogate markers for Pompe disease, or other lysosomal storage diseases. Additionally, there has been no study to date that correlates the magnitude of treatment effect observed for the 6MWT with any clinical outcome.

Immunogenicity of the 2000 L product may also contribute to differences in efficacy of the 2000 L product in certain subgroups. All patients treated with 2000 L product developed anti-rhGAA antibodies by 12 weeks, compared with 0 patients in the placebo group. This incidence is also higher compared to infantile-onset patients treated with 160 L product. Additionally, 18 patients in the 2000 L treatment group developed inhibitory antibody. Again, this incidence is higher compared to both the placebo group and to infantile-onset patients treated with 160 L product. Persistently rising IgG titers in a subgroup of patients treated with 2000 L product may attenuate the efficacy, especially in patients with both rising IgG titers and inhibitory antibodies. Differences in phenotype of disease, product attributes, or CRIM status may all play a role in this difference in development of inhibitory antibody. Additionally, patients with GAA activity level <1% all developed inhibitory antibody to 2000 L product, and the treatment effect in these patients ($n=6$) was reduced. Interestingly, a small subgroup of patients who developed inhibitory antibody actually performed substantially better than the overall treatment group. There is no clear explanation for this finding, but this improvement may be related to a protein carrier or targeting effect of the inhibitory antibody in these patients. Further evaluation of this subgroup

of patients may lead to better understanding of the mechanisms of immunogenicity and possibly improved efficacy in the 2000 L product.

Exploratory analyses of the effect of age and gender also demonstrated differences between the 2000 L treatment group and placebo group. However, there was a persistent treatment effect for the 2000 L product present in all of these subgroup analyses. Although some differences were found, subgroup analyses were not intended to be powered adequately to demonstrate statistical significance. Nevertheless, these findings should be considered by the Advisory Committee.

9.2 Safety Summary

Important clinical safety issues include those related to the immunogenicity of the 2000 L product. Anaphylaxis, as well as immediate and delayed-onset infusion associated reactions, occurs at higher rates than placebo. Chronic exposure to 2000 L product has not been adequately studied, but both skin reactions and urinary abnormalities reported in LOTS suggest that, as with the 160 L product, immune mediated reactions may occur with chronic exposure.

Finally, should the 2000 L product be approved for use in late-onset Pompe disease, administration of 2000 L product in unapproved populations must be avoided. Safeguards are being discussed (a Risk Evaluation and Mitigation Strategy; REMS) with the Applicant in order to avoid misuse of the 2000 L product, should it be approved, to infantile-onset patients, for whom safety and efficacy have not been demonstrated, and for whom 160 L product has previously been approved.

10 Appendix A: Secondary, Tertiary, and Exploratory efficacy endpoints for LOTS

Secondary efficacy endpoints

1. Determination of effect of 2000 L product treatment on proximal muscle weakness in the lower limbs as measured by Quantitative Muscle Testing (QMT) in bilateral knee flexors (hamstrings) and knee extensors (quadriceps).
2. Determination of the effect of 2000 L product treatment on health-related quality of life as measured by the Physical Component Summary (PCS) score of the Medical Outcomes Study (MOS) SF-36.
3. Determination of the effect of 2000 L product treatment on functional endurance as measured by the six-minute walk test at the 26-week study time point.
4. Determination of the effect of 2000 L product treatment on respiratory muscle weakness as measured by FVC in the upright position at the 26-week study time point.

Tertiary efficacy endpoints were:

1. Determination of the effect of 2000 L product treatment on inspiratory muscle weakness as measured by Maximal Inspiratory Pressure (MIP).
2. Determination of the effect of 2000 L product treatment on expiratory muscle weakness as measured by Maximal Expiratory Pressure (MEP).
3. Determination of the effect of 2000 L product treatment on proximal muscle weakness in the upper limbs as measured by QMT in bilateral elbow flexors (biceps) and elbow extensors (triceps).

Exploratory efficacy and endpoints

1. Evaluation of the effect of 2000 L product treatment on respiratory function as measured by the number of hours on ventilation (both invasive and non-invasive) per day recorded in a patient diary.
2. Evaluate the effect of 2000 L product treatment on the timed performance of functional activities of daily living, such as walking 10 meters, climbing stairs and getting up from a supine position on the floor.
3. Evaluate the effect of 2000 L product treatment on proximal muscle weakness as measured by QMT in bilateral shoulder adductors (pectoralis) and hip adductors, as well as bilateral grip strength.
4. Evaluate the effect of 2000 L product treatment on muscle strength as assessed by Manual Muscle Testing (MMT).
5. Evaluate the effect of 2000 L product treatment on patient-reported fatigue as measured by Fatigue Severity Scale (FSS).
6. Evaluate the effect of 2000 L product treatment on the patient's functional ability as measured by the Rotterdam 9-item Handicap Scale.
7. Evaluate the effect of 2000 L product treatment on the change in oligosaccharide levels in plasma and urine.

11 Appendix B: Discussion of Final Statistical Analysis Plan

A linear mixed effects (LME) model was the primary statistical method for comparing differences between the 2000 L treatment group and the placebo group in the mean monthly change for the 6MWT and for upright FVC (% predicted). Conceptually, for each patient a linear slope is estimated from all of the measurements of the 6MWT versus the time of the measurement. If a patient's data for 6MWT versus time forms a straight line, then the slope of the line can be thought of as the average change in distance walked as a function of time. In a LME model, each patient has his own slope and intercept, and each value of 6MWT has some measurement error; these are called random effects. The LME model assumes that the average slope for all patients in the treatment group differs from the average slope for all patients in the placebo treatment group by a fixed amount called the effect of treatment. This assumption is equivalent to the treatment effect assessed by analysis of variance or analysis of covariance and is called a fixed effect. When fitting the LME model, assumptions made about the relationship among the subject-level intercept, slope and measurement error, and about the relationship between the 6MWT and time of measurement are important.

In addition to the LME model, which uses all available measurements over time, the protocol specified a supportive analysis of the change from baseline to last available observation; measurements between baseline and last available observation would not be used. The effect of treatment would be assessed by analysis of covariance (ANCOVA), adjusting for baseline 6MWT stratification, FVC stratification, their interaction and baseline observation. Unless there is a compelling reason to model changes over time in an outcome measure, an analysis from baseline to last available observation is acceptable and, in the statistical reviewer's experience, is extremely common. Compared with LME models, ANCOVA benefits from fewer assumptions about the data which, as will be seen below, can be problematic.

As discussed in the Applicant's briefing package, assumptions important to the pre-specified LME models were violated. For the 6MWT, these assumptions are the linear relationship between the 6MWT and time, the specification of variance-covariance structure of the responses, and the normal distribution of the responses and random effects. For FVC, the assumption for the variance-covariance structure of the responses was violated. Because of misspecification of the variance-covariance structure, the Applicant decided to use a "sandwich" variance estimate, which the Applicant calls a robust variance estimate. Although the Applicant used several other types of parametric and nonparametric longitudinal models, this briefing package focuses on the LME longitudinal models.

The FDA statistical reviewer agrees with the Applicant's decision to use a robust variance estimator for the variance-covariance parameters in the LME model. The estimates of treatment effect and other parameters in the LME model remain the same. What changes is the standard error of the estimates, as reflected by changes in confidence intervals and p-values. For thoroughness, the briefing package presents the results from both approaches.

12 Appendix C: Effect of Age on 6MWT results

Treatment effect was evaluated by the medical reviewer based on age at enrollment, as well as age of onset of symptoms, and age at time of diagnosis. The Applicant provided only data on patients less than 45 years compared with patients older than 45 years (45 years is the median age of patients in the study). The Applicant did not perform an analysis of age of onset of disease, only duration of disease and age at enrollment. However, in their analysis of age at enrollment (less than or greater than 45 years) there was a difference in estimated mean treatment effect of 2000 L product between these groups. Patients 45 years and older at the time of enrollment had treatment effect of 40 meters, while patients younger than 45 at the time of enrollment had a treatment effect of only 19 meters. While there is some overlap in the 95% confidence intervals in these groups, there appears to be a smaller treatment effect in younger patients (see table 51).

Table 51: Estimate of mean change from baseline to last observation 6MWT by Age

Factor	2000 L		Placebo		Treatment eff. (95%CI)
	n	Estimate (95%CI)	n	Estimate (95% CI)	
Age ≥ 45	30	40.07 (18.65, 61.50)	12	-0.43 (-34.83, 33.97)	40.50 (0.46, 80.54)
Age < 45	30	11.30 (-10.65, 33.24)	18	-7.31 (-34.95, 20.32)	18.61 (-16.33, 53.55)

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Given variability of phenotype in the non-infantile onset patient population, the medical reviewer evaluated the effect of 2000 L product in smaller subgroups based on age at enrollment, age at diagnosis, and age at first symptoms.

Age at enrollment

Because patients with juvenile-onset Pompe disease generally have earlier onset of symptoms and faster progression of disease, the efficacy of the 2000 L product in this subgroup is of interested.

The medical reviewer initially attempted to divide the age at enrollment based on decade, with the youngest group representing only patients with juvenile-onset Pompe disease (age less than 18 years) at the time of enrollment. However, there were only 4 patients less than 18 years of age at the time of enrollment. Therefore, the age at enrollment was divided into the following subgroups: age < 30 years (table 53), age 30-50 years (table 54), age 50-70 years (table 55). Patients less than 30 years of age appear to have the least improvement with 2000 L treatment. At the time of last observation, there was a mean change in baseline in 6MWT of -4.6 meters compared to the overall average of +27.1 meters. Additionally, the placebo group performance also was worse (-35.5 meters) compared to the overall average of -5.0 meters at 78 weeks (table 52). However, the overall estimated treatment effect (the difference in mean distance walked at last observation between 2000 L and placebo groups) of 2000 L product is 40.1 meters which is consistent with the overall treatment effect.

Table 52: Patients less than 30 years of age 6MWT mean (±SD) change from baseline

Treatment	Visit	Mean (M)
2000 L (n=5)	Week 12	7.56 (17.1)
	Week 26	14.8 (23.9)
	Week 38	-21.3 (88.0)
	Week 52	-6.4 (32.0)
	Week 64	14.8 (21.5)
	Week 78/Early Termination	-4.6 (44.1)
Placebo (n=3)	Week 12	-38 (17.8)
	Week 26	-5.75 (10.2)
	Week 38	2 (2.8)
	Week 52	-1.5 (2.1)
	Week 64	1 (4.2)
	Week 78/Early Termination	-35.5 (25.2)

Individual patient data for the five 2000 L product treated patients less than 30 years of age is listed below in table 22. Patient 4701 was the only patient in this subgroup with a change in baseline walked at or above the average for the entire 2000 L product treated group. It should be noted that patient 4701 also had a substantially longer distance walked at baseline when compared to the total group average.

While the patient population less than 30 years is smaller than the other subgroups, this subgroup appears to have performed worse than expected, and this effect appears to be independent of baseline distance walked as well as age of onset of disease, disease duration, or other demographic characteristics.

Table 53: 2000 L product treated patients < 30 years demographics (n=5)

Patient ID	Age at enrollment	Disease duration	Age at first symptoms	Age at diagnosis	Gender	Baseline 6MWT(M)	Change from baseline 6MWT (M)
4701	15.92	9.92	5.25	5.75	Male	626	36.5
29701	25.83	8.58	16.42	17.17	Female	389	-7.5
29712	17.50	1.92	8.92	15.33	Male	84	18.5
65706	28.17	16.42	10.58	11.58	Female	210	12.5
65707	20.67	6.50	9.83	14.17	Male	280	-83

Table 54: Patients aged 30-49 years 6MWT mean (\pm SD) change from baseline

Treatment	Visit	Mean (M)
2000 L (n=32)	Week 12	7.23 (25.8)
	Week 26	20.03 (47.4)
	Week 38	23.55 (50.2)
	Week 52	26.25 (59.2)
	Week 64	21.88 (70.7)
	Week 78/Early Termination	24.55 (71.24)
Placebo (n=19)	Week 12	-3.21 (30.0)
	Week 26	1.58 (33.1)
	Week 38	-3.33 (43.4)
	Week 52	-9.91 (57.5)
	Week 64	-6.45 (50.1)
	Week 78/Early Termination	-10.48 (53.3)

Table 55: Patients age 50-70 6MWT mean (\pm SD) change from baseline

Treatment	Visit	Mean (M)
2000 L (n=23)	Week 12	13.27 (18.9)
	Week 26	26.82 (34.0)
	Week 38	30.39 (50.9)
	Week 52	17.70 (63.1)
	Week 64	28.88 (56.9)
	Week 78/Early Termination	25.52 (61.9)
Placebo (n=8)	Week 12	-9 (24.1)
	Week 26	-10.81 (35.5)
	Week 38	-4.31 (32.8)
	Week 52	0.56 (32.3)
	Week 64	4 (34.5)
	Week 78/Early Termination	-0.79 (39.6)

Age at Diagnosis of Pompe Disease

As stated above, only two 2000 L-treated patients were less than 18 years of age at the time of enrollment in the study, and only two patients in the placebo group were less than 18 years of age at the time of enrollment. However, there were 11 patients in whom the diagnosis of Pompe disease was made prior to the age of 18. Of the 11 patients less than 18 years of age at diagnosis who were enrolled in the study, 8 patients were in the 2000 L group, and 3 patients were in the placebo group. Two of the placebo treated patients dropped out of the study, leaving only one patient with data at 78 weeks. There was one patient death in the 2000 L treatment group. Also, 2 patients (18710 and 26710) were over the age of 18 at the time of first symptoms despite their diagnosis being made prior to the age of 18 years. The Applicant did not include an analysis of

Tab 1

patients with the diagnosis of Pompe less than 18 years, or for patients with age of onset of symptoms less than 18 years of age.

The mean and median change from baseline distance walked for the 2000 L group was worse than the overall 2000 L treatment group. Additionally, the placebo group performed much worse than the overall mean for their group (see table 56) and if the two patients in the 2000 L treated group that were diagnosed before the age of 18, but did not develop symptoms of the disease until after the age of 18, the results worsen for both groups further (see table 57). Again, it should be noted that the overall treatment effect (difference between mean change from baseline to last observation between 2000 L and placebo treatment groups) for the 2000 L product remains about 38 meters in this group as well.

Table 56: Patients 18 years or younger at the time of diagnosis

Mean (\pm SD) change from baseline in 6MWT and % predicted FVC at each time point

Visit	6MWT (M)		% predicted FVC	
	2000 L (n=7)	Placebo (n=3)	2000 L (n=7)	Placebo (n=3)
Screening/Baseline				
Week 12	9.43 (23.5)	-18 (29.2)	2 (4.5)	0 (3.5)
Week 26	20.71 (25.5)	7 (11.3)	3.29 (4.3)	-0.5 (2.1)
Week 38	15.5 (46.7)	19 (0)	3.83 (5.7)	-3 (0)
Week 52	10.71 (38.2)	18 (0)	1.14 (5.4)	-4 (0)
Week 64	31.33 (41.0)	26 (0)	0.5 (8.0)	-3 (0)
Week 78/Early Termination	18 (55.5)	-20.33 (36.6)	2.33 (7.3)	-1 (2.6)

Table 57: Patients 18 years of age or younger with pts. 18710 and 26710 removed

Mean (\pm SD) change from baseline in 6MWT and % predicted FVC at each time point

Visit	6MWT (M)		% predicted FVC	
	2000 L (n=5)	Placebo (n=3)	2000 L (n=5)	Placebo (n=3)
Screening/Baseline				
Week 12	1.4 (21.3)	-18 (29.2)	0 (3)	0 (3.5)
Week 26	15 (25.9)	7 (11.3)	1.8 (3.8)	-0.5 (2.1)
Week 38	-2.25 (40.6)	19 (0)	2.25 (5.2)	-3 (0)
Week 52	-3.2 (32)	18 (0)	0.2 (5.8)	-4 (0)
Week 64	15.25 (29.8)	26 (0)	-4.25 (3.8)	-3 (0)
Week 78/Early Termination	-0.75 (51.8)	-20.33 (36.6)	-1.5 (4.4)	-1 (2.6)

Age at First Symptoms

Another analysis includes only patient who first developed symptoms prior to the age of 18 years. However, 4 patients were diagnosed with Pompe disease at least 10 years after the age of first symptoms. This group of patients may be considered to be the most clearly defined group of juvenile-onset patients, however, given the long time interval from age at first symptoms, age

Tab 1

at diagnosis and age at enrollment, there may be some recall bias in terms of the actual age at first symptoms. The overall treatment effect of 2000 L product in this subgroup is about 34 meters, but this subgroup of patients has a lower mean improvement when compared to the overall means for each treatment group, or when compared to patients who developed symptoms after the age of 18 years (table 58).

Table 58: Patients with age at first symptoms < 18 years of age 6MWT mean (\pm SD) change from baseline

Treatment	Visit	Mean (M)
2000 L (n=7)	Screening/Baseline	
	Week 12	6.71 (26.0)
	Week 26	18.14 (23.7)
	Week 38	2.29 (32.2)
	Week 52	7.86 (26.8)
	Week 64	25.33 (16.6)
	Week 78/Early Termination	5.43 (38.1)
Placebo (n=7)	Screening/Baseline	
	Week 12	-16.56 (20.4)
	Week 26	-7.75 (21.8)
	Week 38	-17.29 (25.9)
	Week 52	-15 (27.5)
	Week 64	-17.14 (34.3)
	Week 78/Early Termination	-28.29 (27.9)

These exploratory observations suggest that overall, younger patients treated with 2000 L product performed better than the younger placebo treated patients. However, younger patients deteriorate faster as seen in the placebo group data, and overall improvement with 2000 L treatment is attenuated. This subgroup analysis only included small numbers of patients and, therefore, clear conclusions based on these observations cannot be made.

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CLINICAL PHARMACOLOGY SUMMARY

This summary addresses the pharmacokinetics (PK) aspect only based on the data submitted to the BLA.

PK data: The sponsor submitted PK data obtained from Study AGLU02704. This was a randomized, double-blind, placebo-controlled, multicenter, multinational study of the safety, efficacy, and PK of alglucosidase alfa (rhGAA; 2000 L product) treatment in patients with late-onset Pompe disease. Eligible patients were randomized in a 2:1 ratio to receive intravenous (IV) infusions of 20 mg/kg rhGAA or placebo every other week (qow) up to 78 weeks based on an adaptive clinical trial design. A total of 90 patients were enrolled in the study. PK assessment was performed on a subgroup of patients (N=32). Serial blood samples for the measurement of plasma rhGAA activity were collected on Day 0 (Week 0), Week 12, and Week 52.

PK analysis: The PK analysis utilized a 2-compartment linear model with a zero-order input that was calculated based on the individual's alglucosidase alfa infusion rate. In general, the model described the data well. The model fitting for each individual was then used to determine the individual's Clearance values from which AUC was calculated. Observed concentrations were used to determine the C_{max} .

Results

PK Parameters: Mean alglucosidase alfa PK parameters are listed in Table 1.

Table 59. PK Parameters at Weeks 0, 12 and 52 in patients receiving Alglucosidase Alpha 20 mg/kg qow

Parameter	Week 0	Week 12	Week 52
C _{max} (mcg/mL)	385 ± 106	349 ± 79	370 ± 88
AUC(0-∞) (mcg*h/mL)	2672 ± 1140	2387 ± 555	2700 ± 1000
CL (mL/h)	633 ± 175	700 ± 244	645 ± 198
V _{ss} (L)	69 ± 92	70 ± 91	70 ± 92
Effective Half-life(h)	2.4 ± 0.4	2.4 ± 0.3	2.5 ± 0.4

Impact of antibody titer on PK (as reflected by systemic clearance):

Although the sponsor claims no difference in systemic clearance with antibody titer, clearance appears to increase at high antibody titer concentrations (Figures 1&2). The upper quartile (Q4) in Figure 2 contained six subjects. Of these six, 5 were positive for inhibitory antibody status. These were the only 5 subjects with positive inhibitory antibody status at the time of PK sampling in the study. The profiles of clearance over time in these 5 subjects are shown in Figure 3. There is a clear increase in clearance in 4 of the 5 subjects between week 0 and week 52 while one had similar clearance between Week 0 and Week 52. Of the 4 subjects with increased clearance on Week 52, one had an increase by as much as 100% (from ~600 to ~1200 mL/h).

Figure 1. Smoothed Trend Line Depicts the Tendency of Clearance to Increase with Antibody Titer

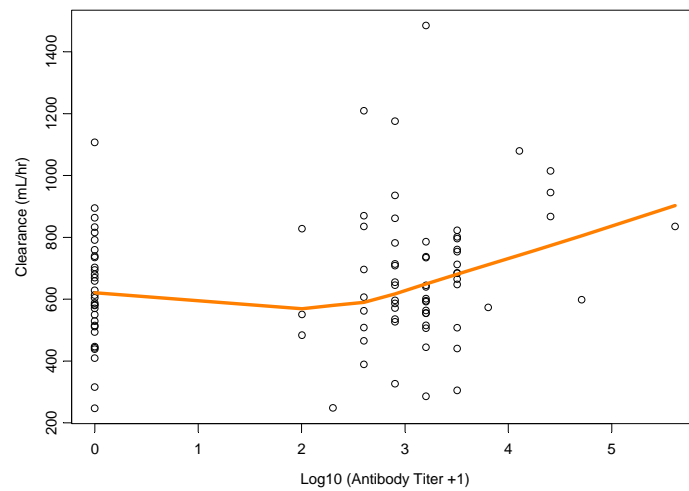
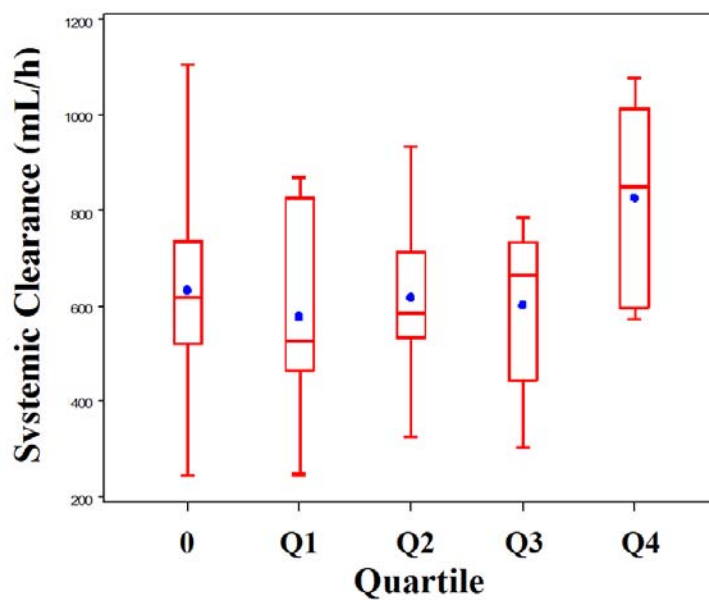
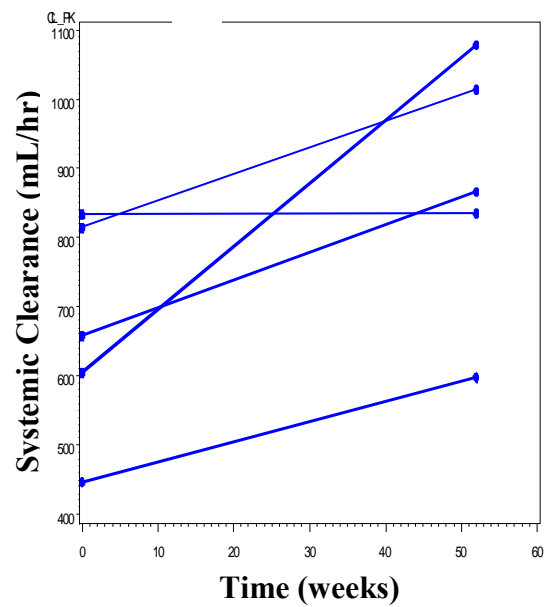


Figure 2. Systemic Clearance versus Antibody Titer Quartile



Note: 0 quartile denotes patients at baseline (i.e., before developing immunogenicity)

Figure 3. Time Course of Clearance for Individuals with High IgG Antibody Titer and Positive Inhibitory Antibody Status at Week 52.



OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Is the sponsor's pharmacokinetic model accurate and sound in its description?

The reviewer's analysis obtained nearly the same final pharmacokinetic parameters estimates as those provided by the sponsor. The model is well defined based on the rich pharmacokinetic sampling. The model lacks in accounting for antibody effects on clearance.

1.1.2 Does the IgG- or inhibitory-antibody titer affect the pharmacokinetics of recombinant alglucosidase alfa?

High IgG antibody titer and inhibitory antibodies are both indicative of an increased clearance of alglucosidase alfa. Inhibitory antibodies coincide with highest IgG titers. The five patients with the highest antibody titer also had inhibitory antibodies. However the existing data is not sufficient to indicate whether inhibitory or high IgG antibodies are responsible for the increased clearance.

1.1.3 Are the labeling statements regarding the pharmacokinetics of recombinant alglucosidase alfa accurate?

The labeling statements regarding the pharmacokinetics of alglucosidase alfa are not accurate with regards to patients with high IgG antibody titer. For individuals with high IgG titer the distinction that clearance increases with antibody titer needs to be emphasized. For individuals with average/low antibody titer the pharmacokinetics are well-described and not time-dependent between weeks 0, 12, and 52.

2 PERTINENT REGULATORY BACKGROUND

"Genzyme is submitting a Biologics License Application (BLA) for alglucosidase alfa, recombinant human acid alpha-glucosidase (rhGAA) for the treatment of late-onset Pompe disease. This product has been studied under BB-IND 10780. Genzyme is filing this second BLA for alglucosidase alfa in order to obtain licensure for the product produced at the 2000 L manufacturing scale. Alglucosidase alfa (Myozyme®) produced at the 160 L scale is approved under BLA 125141 for the treatment of patients with Pompe disease and this product has been in short supply since early 2007. A treatment protocol referred to as the Myozyme Temporary Access Program (MTAP) was initiated in accordance with 21 CFR 312.34 in May 2007 to provide adult patients with access to alglucosidase alfa produced at the 2000 L scale. Approximately 140 patients have been treated to date via MTAP. Genzyme requests priority review of this application for 2000 L alglucosidase alfa given the intended indication for the treatment of a serious, life-threatening disease, the extremely limited supply of alglucosidase alfa 160 L commercial product, and the scope and duration of the MTAP treatment protocol to provide patients with access to drug." (Source: Sponsor's Original Submission Cover Letter)

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Pharmacokinetics

3.1.1 Study Design

“Study AGLU02704 was a randomized, double-blind, placebo-controlled, multicenter, multinational study of the safety, efficacy, and pharmacokinetics of Myozyme treatment in patients with late-onset Pompe disease [2]. Eligible patients were randomized in a 2:1 ratio to receive intravenous (IV) infusions of 20 mg/kg Myozyme or placebo every other week (qow) up to 78 weeks based on an adaptive clinical trial design.”

“A total of 90 patients, who provided signed written informed consent and met all the inclusion criteria and none of the exclusion criteria, were enrolled in the study.

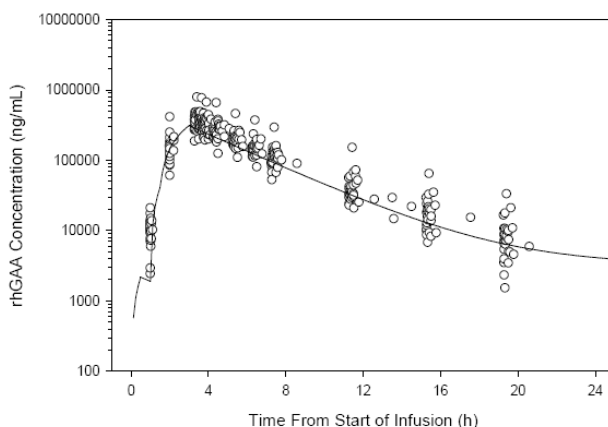
“Assessment of pharmacokinetics was performed on a subgroup of patients. The subgroup of patients for whom pharmacokinetic samples were obtained was based on those study sites that could accommodate pharmacokinetic sampling needs. Blood samples for the measurement of plasma rhGAA activity were collected on Day 0, Week 12, and Week 52 at each of the following time-points: 0 (before the start of the infusion), 1 and 2 hours after the start of infusion, end of the infusion, and then 0.25, 0.5, 1, 2, 3, 4, 8, 12, and 16 hours after the end of the infusion (with a 5-minute window for time-points after the start of infusion).”

(Source: Sponsor's Pharmacokinetic Report, Section 3)

3.1.2 Pharmacokinetic Model

The sponsor applied a 2-compartment linear pharmacokinetic model with a zero-order input that was calculated based on the individual's alglucosidase alpha infusion rate. In general, the model described the data well (Figure 7). The model fitting for each individual was then used to determine the individual's Clearance values (Table 60) from which AUC was calculated. Observed concentrations were used to determine the C_{max} . Non-compartmental analysis was not used to present the pharmacokinetic parameters of the individuals in the population studied.

Figure 7. Sponsor's Final Pharmacokinetic Model Fitting at Week 0.



(Source: Sponsor's Pharmacokinetic Report)

Table 60. Alglucosidase Alpha Model-Based Pharmacokinetic Parameters

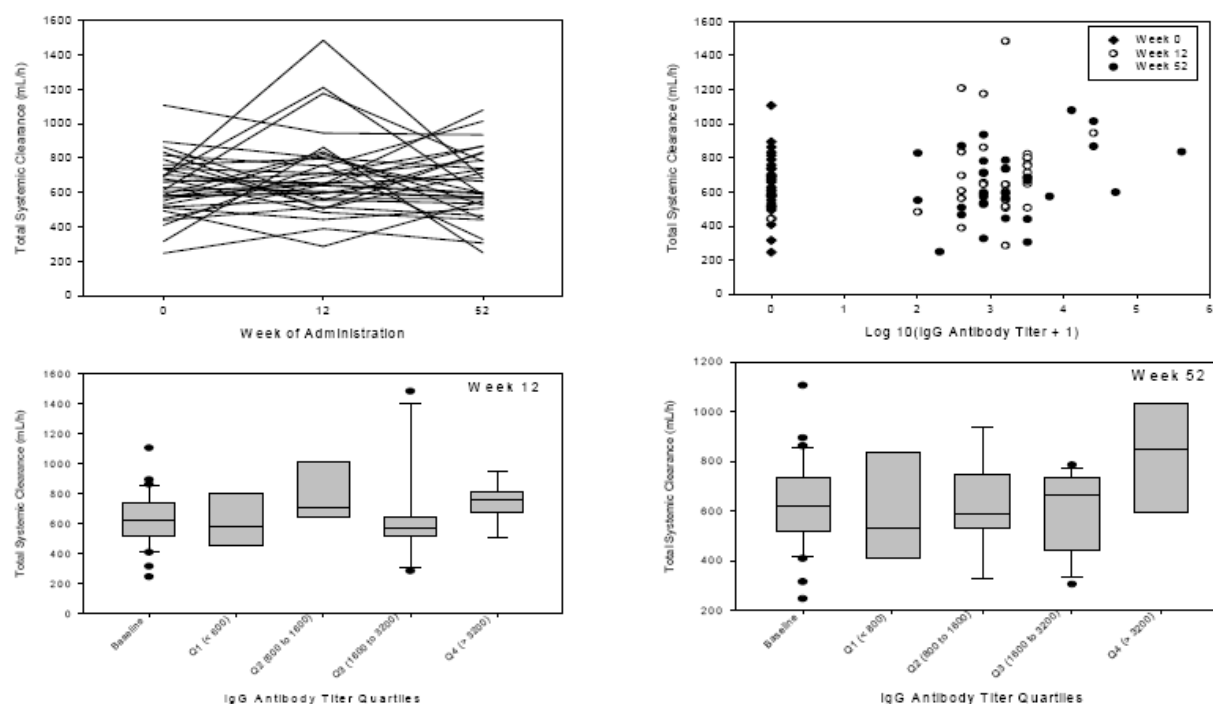
Parameter	Week 0	Week 12	Week 52
C _{max} (mcg/mL)	385 ± 106	349 ± 79	370 ± 88
AUC(0-∞) (mcg*h/mL)	2672 ± 1140	2387 ± 555	2700 ± 1000
CL (mL/h)	633 ± 175	700 ± 244	645 ± 198
V _{ss} (L)	69 ± 92	70 ± 91	70 ± 92
Effective Half-life(h)	2.4 ± 0.4	2.4 ± 0.3	2.5 ± 0.4

(Source: Sponsor's Proposed Label Document)

3.1.3 Do IgG antibodies Change the Clearance of Alglucosidase Alpha?

Based on the graphs in Figure 8, Genzyme suggests that clearance is not affected by the individual's IgG antibody titer.

Figure 8. Sponsor's Presentation of IgG antibody Impact on Systemic Clearance.

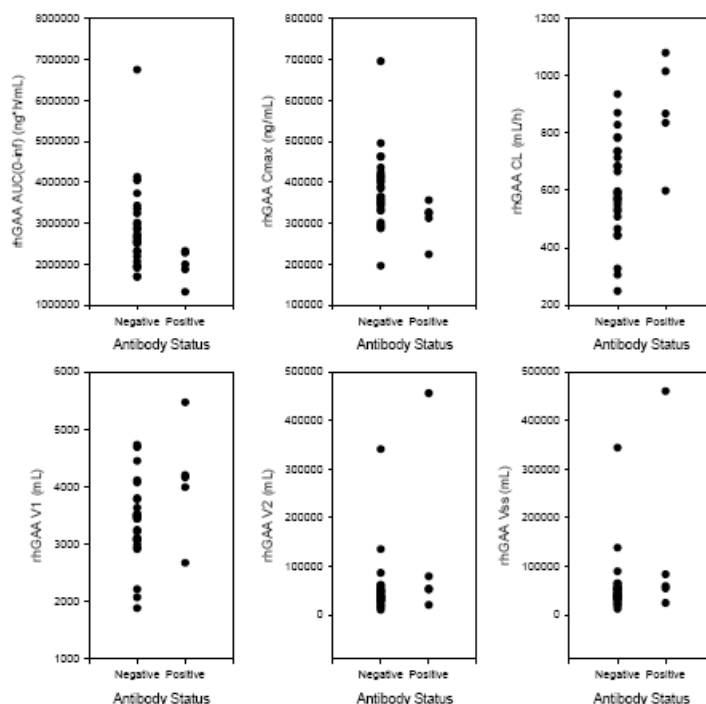


(Source: Sponsor's Pharmacokinetic Report)

Reviewer's Comments: Although the sponsor claims no difference in systemic clearance with antibody titer, clearance appears to increase at much higher antibody titer concentrations. This is most visible at week 52 in the 4th quartile -- there is a higher median. In the log 10 antibody titer versus systemic clearance plot, clearance appears to increase at the higher antibody titer amounts. There is no apparent difference in AUC across the weeks and across different amounts of antibody titer. However, AUC should not be used as a secondary parameter as dosing is weight and tolearence dependent and not all individuals are expected to have the same AUC following dosing and across different weeks.

The sponsor goes on to show that the pharmacokinetics of the 5 patients that tested positive for inhibitory antibodies have lower AUC and higher clearance values than in the population that tested negative (Figure 9).

Figure 9. Week 52 Pharmacokinetics in Patients who Tested Negative or Positive for Inhibitory Antibodies.



(Source: Sponsor's Pharmacokinetic Report)

Reviewer's Comments: This plot shows there is a clear difference in the CL, AUC, Cmax of the patients with inhibitory antibody titers. What this plot does not distinguish is if 1) the pharmacokinetics of these individuals was different than the population before drug administration at week 0 and 2) intrinsic factors such as body weight, age, or gender can explain these differences.

4 REVIEWER'S ANALYSIS

4.1 Introduction

Genzyme presented the pharmacokinetics of alglucosidase alpha as stationary and unaffected by higher IgG antibody titer concentrations. However, there appeared to be higher clearance in the upper quartile of antibody titer at week 52. A further look at the patients with the highest antibody titer was done to test whether clearance increased with 1) antibody titer in these individuals and 2) patients positive for inhibitory antibodies.

4.2 Objectives

Analysis objectives are:

1. Test the accuracy of the sponsor's final population pharmacokinetic model.
2. Examine the relationship between IgG antibody titer and clearance on an individual basis.
3. Examine the relationship between inhibitory antibody titer and clearance.

4.3 Methods

The sponsor's NONMEM VI code was run with their pharmacokinetic dataset to test the results of the model fitting. Parameters were compared with reported values. A model simulation of the time course of alglucosidase alpha concentrations was done to test if accumulation should be visible between weeks 0, 12, and 52.

Relationships between antibody titer and modeled clearance in each individual were evaluated using S-plus software by generating plots that might suggest there is a correlation between titer and clearance.

4.3.1 Data Sets

Data sets used are summarized in Table 61.

Table 61. Analysis Data Sets

Study Number	Name	Link to EDR
Aglu2704	pkconc5.xpt	\\cbsap58\M\CTD_Submissions\STN125291\0000\m5\datasets\aglu02704\analysis

4.3.2 Software

NONMEM VI was used to test the sponsor's pharmacokinetic model with their dataset. S-plus (Insightful, Inc.) was used to create graphs and summarize data.

4.4 Results

4.4.1 Is the sponsor's pharmacokinetic model accurate and sound in its description?

The final parameter estimates from both the sponsor's and agency's NONMEM fittings are shown in Table 62. There was no apparent difference in the parameter estimates though slight differences were noted in the estimates of the parameter and inter-occasion variances.

Table 62. Comparison of Sponsor's and Reviewers Pharmacokinetic Estimates.

Parameter	Sponsor's Estimate	Sponsor's Standard Error	Reviewer's Estimate	Reviewer's Standard Error
CL (mL/hr)	613	156	613	152
V ₁ (mL)	3400	133	3400	133
Q (mL/hr)	334	153	334	150
V ₂ (mL)	46900	44900	46800	44300
θ_5	0.683	0.131	0.683	0.128
BPV (CL)	30.3%		29.6%	
BPV (V ₁)	20.4%		13.8%	
BPV (Q)	23.4%		25.7%	
BPV (V ₂)	107%		87.3%	
IOV (CL)	17.9%		17.8%	
IOV (V ₁)	14.2%		14.1%	
σ^2	19.9%		19.7%	

The model adequately described the observed pharmacokinetics data. Determination of clearance from the model is reasonable. The kinetics appeared stationary for the entire population. However, for biologics the development of immunogenicity against the drug is

always of concern. Immunogenicity is different between individuals and kinetics in one person may vary greatly from what the population predicts. The remainder of the pharmacokinetic review attempts to address the impact of high antibody titer on the clearance of alglucosidase alpha.

4.4.2 Does the IgG titer or inhibitory antibody status affect the pharmacokinetics of recombinant alglucosidase alpha?

The sponsor's plot of clearance versus antibody titer (Figure 8) was remade with a smoothed trend line through the data (Figure 10) to better show the clearance-antibody titer relationship. There is a clear upslope in the clearance estimate at antibody titers at or above 10000. This would suggest that clearance increases with higher antibody titers.

Figure 10. Smoothed Trend Line Depicts the Tendency of Clearance to Increase with Antibody Titer.

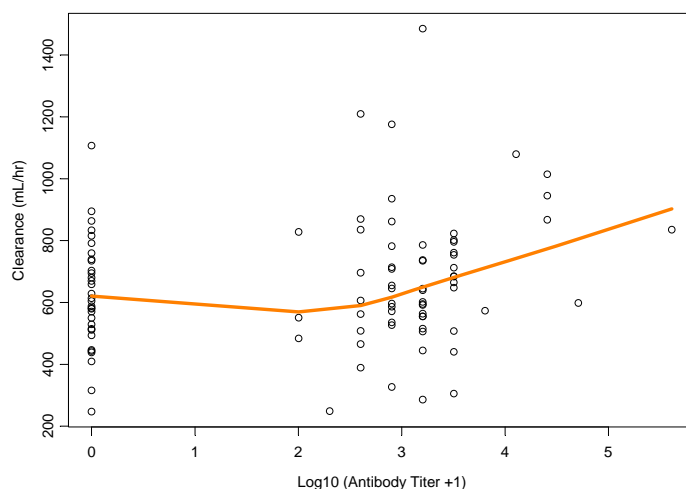
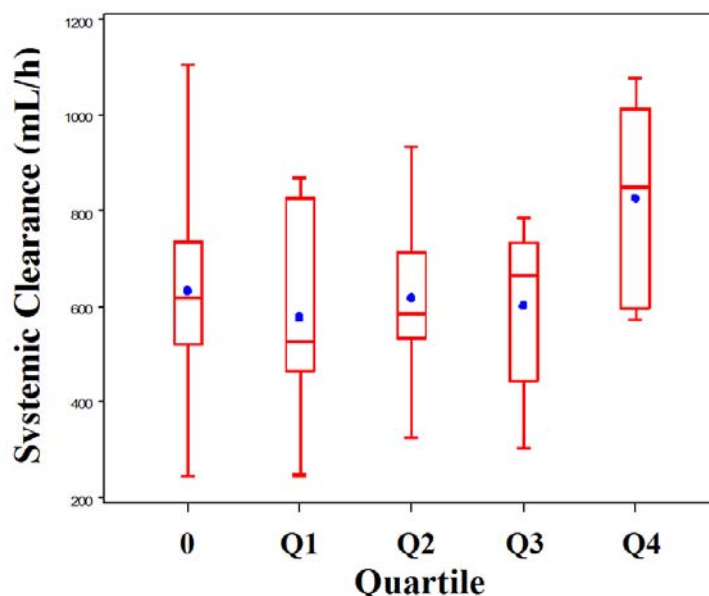


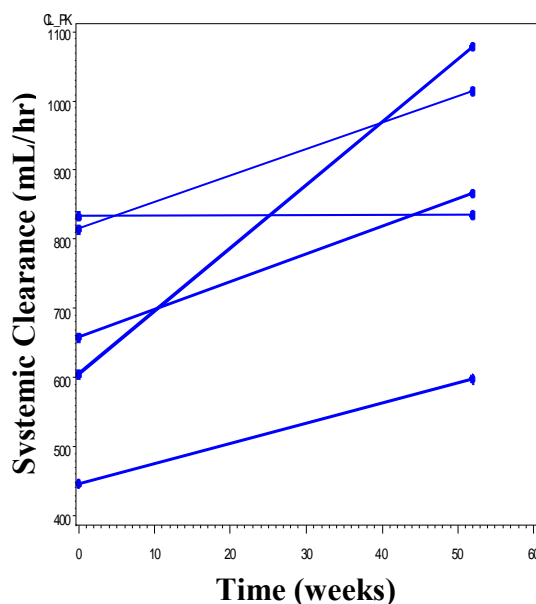
Figure 11 is similar to Figure 10 and the sponsor's depiction of the data (Figure 8). Here the mean (blue dots) is shown in addition to the median (solid red line across each bar) for each quartile of antibody titer. Clearance appears to be greater at the higher quartile.

Figure 11. Systemic Clearance versus Antibody Titer Quartile.



The upper quartile in Figure 11 contained 6 subjects. Of these 6 subjects 5 were positive for inhibitory antibody status. These were the only 5 subjects with positive inhibitory antibody status at the time of pharmacokinetic sampling in the study. The profiles of clearance over time in these individuals is shown in Figure 12. There is a clear increase in 4 individuals between week 0 and week 52. In one patient the clearance increases by as much as 100% (from ~600 to ~1200 mL/h).

Figure 12. Time Course of Clearance for Individuals with High IgG Antibody Titer and Positive Inhibitory Antibody Status at Week 52.



The results in Figure 12 clearly indicate that the onset of inhibitory antibodies increases the clearance of alglucosidase alpha. It should also be noted that the 5 inhibitory positive individuals

Tab 3

also had the highest IgG antibody titer in the study. This second observation makes it unclear whether IgG antibodies or inhibitory antibodies are the cause for increased clearance. It can only be stated then that inhibitory antibody status appears to coincide with high IgG antibody titer.