CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125291

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	BLA 125291
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Priority or Standard	Complete Response Resubmission
Submit Date(s)	16 December 2009
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Division / Office	Division of Gastroenterology Products
Reviewer Name(s)	Christine Mueller, DO
Acting Clinical Team Leader	Lynne Yao, MD
Review Completion Date	7 April 2010
Established Name	Alglucosidase alfa
(Proposed) Trade Name	Lumizyme
Therapeutic Class	Enzyme Replacement Therapy
Applicant	Genzyme
Formulation(s)	Intravenous Injection
Dosing Regimen	20mg/kg every other week
Indication(s)	Treatment of Pompe Disease (glycogen storage disease type II, acid maltase deficiency)
Intended Population(s)	Late-onset Pompe Disease

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Recommend regular approval of this application after agreement with the Applicant to revise proposed labeling, to perform post-marketing commitments (PMCs) and post-marketing requirements (PMRs), and to implement a Risk Evaluation and Mitigation Strategy (REMS). It is recommended that Lumizyme (alglucosidase alfa, 4000L production scale) treatment be restricted to patients with late onset (non-infantile) Pompe disease 8 years of age and older, who do not have evidence of cardiac hypertrophy.

1.2 Risk Benefit Assessment

The current submission relies on the biochemical comparability between the 2000 L and 4000 L products. Therefore, the establishment of comparability between these products by the chemistry, manufacturing and controls (CMC) Reviewer was the major focus of the current review cycle. However, the Applicant was required to submit available clinical safety information on the 4000 L product. The clinical safety data included in the current submission are from one open-label, uncontrolled, expanded access protocol, and from post-marketing surveillance data in Europe, where the 4000 L product was approved in February 2009. A review of these safety data suggest that the incidence of anaphylaxis and allergic reactions appears to be similar to the safety findings of the previous reviews of the BLA 125291 in patients treated with the 2000 L product, and no new safety signals were noted.

This Reviewer concludes that the overall safety of the 4000 L product appears to be consistent with the overall safety of the 2000 L product. Additionally, based on the comparability of the 2000 L and 4000 L products in drug substance, drug product, and pharmacokinetic and pharmacodynamic properties, the 4000 L product appears to be comparable to the 2000 L product. Therefore, this Reviewer concludes that the 4000 L product provides an acceptable overall risk/benefit profile for patients with Pompe disease 8 years of age and older. However, based on the serious known and potential risks uncovered in previous reviews, this Reviewer recommends that a REMS be established as a condition of approval to ensure that the benefits of the 4000 L product outweigh the risks. Additionally, several clinical post-marketing requirement (PMRs) and commitment studies (PMCs) should also be agreed upon to obtain long-term safety and efficacy information with the 4000 L product.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Based on the potential for serious allergic reactions, including anaphylaxis, and to ensure that the administration of Lumizyme is limited to the intended population, the Agency recommends that a REMS is necessary for Lumizyme. The goals of the REMS are to mitigate the potential risk of rapid disease progression in infantile-onset Pompe disease patients and patients with late (non-infantile) onset disease less than 8 years of age for whom the safety and effectiveness of Lumizyme have not been evaluated, and to ensure that the known risks of anaphylaxis and severe allergic reactions associated with the use of Lumizyme are communicated to patients and prescribers, and to ensure that the potential risks of severe cutaneous and systemic immune complex-mediated reactions to Lumizyme are communicated to patients and prescribers. The REMS has been successfully negotiated. The Lumizyme Access, Control, and Education (ACE) Program includes all components of a REMS to ensure that the benefits of Lumizyme outweigh the risk. Please see the final REMS proposal and supporting document for details of the requirements.

1.4 Recommendations for Postmarket Requirements and Commitments

The Applicant formally agreed to all clinical post-marketing requirements (PMRs) and post-marketing commitments (PMCs) proposed by the Agency during the previous review cycle. There are no new clinical PMR/PMCs included in this submission.

Based on the review of the safety data provided by the Applicant, serious adverse reactions, including anaphylaxis and immunologically mediated reactions have been noted. In order to more fully characterize these safety findings, the two postmarketing studies required of the Applicant under section 505(0)(3) of the Food Drug and Cosmetics Act are:

1) A retrospective immunogenicity study based on the pattern of antibody responses that may predict the development of anaphylaxis, allergic reactions, and immune-complex mediated reactions in patients enrolled in the Late Onset Treatment Study (LOTS) and LOTS Extension Studies.

2) A prospective safety study conducted within the ongoing Pompe Registry to assess the known serious risks of anaphylaxis and severe allergic reactions, and signals of severe cutaneous and systemic immune complex-mediated reactions with Lumizyme (alglucosidase alfa) treatment.

There are 3 clinical PMCs agreed to by the Applicant. These PMCs were agreed upon during the last review cycle, and the Applicant has again agreed to these clinical PMCs during the current review cycle.

1) A retrospective study of patients enrolled in the LOTS and LOTS Extension Studies whose efficacy responses (i.e., high performance or poor performance) as assessed by the

6 minute walk test (6MWT) and/or % predicted forced vital capacity (FVC) appeared to have been affected by the pattern of their antibody response.

2) A long-term follow-up study of patients in LOTS and LOTS Extension Studies whose response to Lumizyme (alglucosidase alfa) is associated with substantial improvement over baseline in the 6MWT results. This study will be conducted as a sub-study within the ongoing Pompe Registry.

3) As part of the ongoing Pompe Registry, prospective outcome data will be collected in patients enrolled in the Registry to assess the long-term efficacy of Lumizyme (alglucosidase alfa). The effect of antibody responses (e.g., timing and pattern of antibody responses), and available CRIM analysis in patients treated with Lumizyme (alglucosidase alfa) and their long- term outcome will be assessed.

There were several new CMC PMCs negotiated with the Applicant during the current review cycle. The first three PMCs were previously agreed upon during the last review cycle. The next 8 PMCs were negotiated based on the information on the 4000 L product that was reviewed as part of the current review cycle. In total, there are 11 CMC PMCs agreed to by the Applicant:

1. To evaluate the use of the [redacted] (b) (4) method as a release test for glycan profiling of the drug substance.

2. To develop an analytical method to monitor [redacted] (b) (4) and evaluate risk to product quality and proposed risk mitigation strategies.

3. To establish in process control limits for cell viability during the [redacted] (b) (4) period using the data collected from four upcoming 4000 L cell culture runs.

4. To develop and qualify an in-house 4000 L reference standard.

5. To develop and implement more sensitive and quantitative methods to enhance the detectability and quantitation of degradation products of rhGAA protein, as well as [redacted] (b) (4)

6. To add the [redacted] (b) (4) test to the stability specifications for 4000 L drug substance.

7. To add the [redacted] (b) (4) test to the release and stability specifications for 4000 L drug product.

8. To re-evaluate and optimize the [redacted] (b) (4) hold time to improve [redacted] (b) (4) species for the 4000 L product.

9. To re-evaluate and revise the acceptance criterion for Km measured by the [redacted] (b) (4) [redacted] (b) (4) assay.

10. To include in the annual rhGAA Drug Product stability protocol, derived from drug substance produced at the 4000 L scale, an accelerated storage condition of 25 ± 2°C and 60 ± 5% relative humidity (RH).

11. To qualify the [redacted] (b) (4) for its intended use by performing an equivalency test between the D value of [redacted] (b) (4) and [redacted] (b) (4) [redacted]

There was one clinical pharmacology PMC agreed to by the Applicant. This PMC was agreed upon during the last review cycle, and the Applicant has again agreed to this clinical pharmacology PMC during the current review cycle.

1. A prospective pharmacokinetic (PK) study conducted within the ongoing Pompe Registry study to characterize the pharmacokinetics of Lumizyme in pediatric patients in the age range of 8 years to 18 years.

2 Introduction and Regulatory Background

2.1 Product Information

Lumizyme (alglucosidase alfa) is a recombinant human form of the enzyme acid alpha-glucosidase (rhGAA) that is produced by recombinant DNA technology in a Chinese hamster ovary cell line at a 4000L bioreactor scale. Lumizyme is intended for use as an enzyme replacement therapy to treat patients with severe deficiency of acid alpha-glucosidase (GAA), or Pompe disease (also known as acid maltase deficiency, or glycogen storage disease type II).[1] Pompe disease is an autosomal recessive disorder of glycogen metabolism caused by the absence or marked deficiency of GAA. Alglucosidase alfa provides an exogenous source of GAA and is taken up into cells and transported into lysosomes where the enzyme acts to hydrolyze glycogen. Glycogen accumulation in various tissues leads to the development of progressive muscle weakness, including impairment of respiratory function in all patients, as well as hypertrophic cardiomyopathy in patients with infantile-onset Pompe disease.[1] Pompe disease patients have variable activity of the enzyme with infantile-onset patients having undetectable enzyme activity in muscle tissue and in late-onset patients activity is reduced to a lesser extent. However, 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. The infantile onset form leads to severe cardiomyopathy, muscle weakness and death in almost all patients by 18 months of age. Juvenile and adult-onset patients develop skeletal muscle weakness without cardiomyopathy, and have a slower progression of disease. However, the classification of juvenile and adult-onset forms is a continuum, and therefore a specific age cut-off between the juvenile and adult-onset forms is difficult to 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.

Prior to 2006, the only treatment available for patients with Pompe disease was palliative. Myozyme, another member of the class of alglucosidase alfa biologic products, is the only approved treatment for Pompe disease. It is produced at a 160 L bioreactor scale, and was approved for the treatment of all patients with Pompe disease on April 28, 2006 based on a single clinical trial (n=18) that demonstrated improved ventilator-free survival in patients with infantile-onset Pompe disease (age less than 7 months at the time of first infusion) as compared to an age-matched, untreated historical control cohort. Approval of Myozyme in the US for all forms of Pompe disease was on this infantile-onset trial and there have been no controlled studies that have evaluated its efficacy in late-onset Pompe disease.

Regulatory History

The Agency approved Myozyme, alglucosidase alfa manufactured at the 160 L production scale, in 2006. It is currently the only approved treatment for Pompe disease. In April 2008, the Agency determined that a 2000 L product was not comparable to the 160 L product based on CMC, pharmacokinetic, and clinical data, and required the Applicant to submit efficacy and safety data to support separate licensure of their 2000 L product. The original BLA 125291 was submitted on May 30, 2008 and included one clinical study to support the efficacy of the 2000 L product.

Previous submissions

For a detailed review of the previous submissions to this BLA, please see the clinical reviews by L. Yao (February 23, 2009) and C. Mueller (November 9, 2009).

Original submission

The original BLA was submitted on May 30, 2008 with a PDUFA goal date of February 27, 2009. The clinical study submitted in the original BLA was a randomized, double-blind, placebo-controlled trial that evaluated the efficacy and safety of the 2000 L product in 90 patients with late-onset Pompe disease, Late Onset Treatment Study (LOTS). The major study objectives of LOTS were to evaluate the effect of the 2000 L product on functional endurance as measured by the six minute walk test (6MWT) and to evaluate its effect on respiratory muscle weakness as measured by percent predicted forced vital capacity (% predicted FVC). Treatment demonstrated a benefit of 3.4% (p=0.004) in % predicted FVC at 78 weeks. A benefit of 28.1 meters in the 6MWT was demonstrated at 78 weeks (p=0.06). There were no patients enrolled in LOTS less than 8 years of age, therefore, efficacy in this age group could not be established. Important clinical safety issues were noted including acute and chronic allergic and immunologically-mediated reactions and anaphylaxis. Chronic exposure was not adequately studied, but both skin reactions and urinary abnormalities reported in LOTS suggested that, as with Myozyme, immune-mediated reactions may occur with chronic exposure. These risks were similar to those found with Myozyme. Thus, the clinical review for the initial BLA submission supported approval at the 2000 L production scale under 21 CFR 601 Subpart E approval (accelerated approval) for the agreed upon labeled indication, "patients 8 years and older with late-onset (non-infantile) Pompe disease (GAA deficiency) who do not have evidence of cardiac hypertrophy." However, the effectiveness was based on stabilization of % predicted FVC and improvements in survival or ventilator-free survival were not evaluated; therefore, the product

could not be approved under 21 CFR 601 Subpart E without agreement from the Applicant to conduct an appropriate verification study to confirm that treatment was associated with clinical benefit. An appropriate verification study was not successfully negotiated with the Applicant during the original review cycle.

During the original review cycle, a REMS was required by the Applicant to mitigate the potential risk of rapid disease progression in infantile-onset Pompe disease patients and patients with late (non-infantile) onset disease less than 8 years of age for whom the safety and effectiveness of Lumizyme have not been evaluated, and to ensure that the known risks of anaphylaxis and severe allergic reactions, and the potential risks of severe cutaneous and systemic immune-mediated reactions to Lumizyme are communicated to patients and prescribers. While significant portions of the REMS were successfully negotiated, a finalized REMS was not completed at the end of the review cycle.

There were substantive facility deficiencies uncovered during the New England District Office's inspection of the Applicant's Allston Landing facility that ultimately lead to the issuance of a Warning Letter by the Office of Compliance on February 27, 2009, citing the following deficiencies: (b) (4) (b) (4) (b) (4) The Office of Compliance recommended that a withhold approval action be taken. In addition to the manufacturing deficiencies, the following CMC deficiencies were also cited: 1) inadequate cell viability monitoring; 2) lack of an established reference standard; 3) inadequate product acceptance criteria; 4) inadequate system suitability criteria. Two clinical deficiencies were also cited: 1) the inability to agree upon a verification study required for 21 CFR 601 Subpart E approval and 2) the inability to agree on a complete Risk Evaluation and Mitigation Strategy (REMS). Thus, a Complete Response Letter was issued by the Agency on February 27, 2009.

First Complete Response resubmission

Discussions regarding the design of an appropriate verification study required for 21 CFR 601 Subpart E approval (accelerated approval) were held between the Agency and the Applicant between February 2009 and May 2009. New data were submitted by the Applicant that included retrospective clinical outcome data in infantile-onset Pompe patients from the Pompe Registry, a multinational disease registry. After review of these data, the Agency agreed that the Applicant could submit data from the Registry for review to establish the clinical effectiveness of the 2000 L product in late-onset Pompe patients to support full approval. A review of the Registry data included 25 infantile-onset patients who were age and disease-matched to a historical control cohort. This historical control cohort was the same cohort used to compare the effect of Myozyme in the clinical trial that led to the approval of Myozyme in 2006. The Registry data suggests that there is improvement in survival in 2000 L-treated patients, 18-month survival of 57%, compared with the historical control group, 18-month survival of 1.9%. A safety update was also submitted by the Applicant, which included data from the completed Late-Onset treatment Study (LOTS) and the LOTS extension studies, the Myozyme temporary

access program (MTAP), and postmarketing information. The incidence of anaphylaxis and allergic reactions remained similar to the safety findings of the original BLA 125291 submission reviewed by L. Yao. Thus, the totality of the clinical data supported the regular approval of the 2000 L product. However, because of the limitations of the Registry data, the insufficient numbers of patients age 8 years and younger treated in clinical trials with the 2000 L product, and the availability of Myozyme for these younger patients, the clinical recommendation was that treatment with the 2000 L product be restricted to patients with late onset (non-infantile) Pompe disease 8 years of age and older, who do not have evidence of cardiac hypertrophy.

The Applicant also provided responses to all of the CMC deficiencies, and the facility was re-inspected in late May 2009, and again in October 2009. All of the CMC deficiencies were satisfactorily addressed by the Applicant based on the review of F. Mills, PhD, the Product Quality Reviewer.

During the review cycle of this BLA submission, the Applicant and Agency also held discussions on a 4000 L manufacturing process for which product quality information was submitted under the Myozyme IND (IND 10,780). The 4000 L product was approved in the European Union (EU) based on comparability studies on March 3, 2009. On July 27, 2009 the Applicant submitted drug substance and drug product data as part of their submission for revision of the Myozyme Temporary Access Program (MTAP) to include the investigational use of the 4000 L product in adults in the Alglucosidase Alfa Temporary Access Program (ATAP). In their review of ATAP, J. Liu, CMC Reviewer through E. Lacana, and B. Cherney, noted that the 4000 L material appeared to be biochemically comparable with the 2000 L product. Therefore, they recommended proceeding with introduction of the 4000 L product into the ATAP program. However, they could not fully assess the comparability of the two products based on the information supplied, and requested additional information regarding biochemical comparability from the Applicant. Specifically, the Applicant was asked to provide an assessment of the effect of the [redacted] (b) (4) content on pharmacokinetic/pharmacodynamic properties and biodistribution in support of the biochemical comparability in the 4000 L product submission.

However, inspections of the Allston manufacturing site on May 19, 2009 and October 6, 2009 determined that the facility did not comply with requirements set forth in the 21 CFR 601.20 (a) and (d) and there was not satisfactory resolution of all CGMP deficiencies identified during the initial inspection. Therefore, a Complete Response letter was issued by the Agency on November 13, 2009. This letter stated that the Allston manufacturing facility, the site that produces the 2000 L product, has not yet received a satisfactory compliance status, and therefore, the manufacturing deficiencies at the Allston Landing facility must be resolved as part of the Complete Response.

Current submission (Second Complete Response resubmission)
Although the Complete Response letter issued in November stated that the manufacturing deficiencies at the Allston Landing facility must be resolved as part of the complete response submission, the Agency understood that the 4000 L product was manufactured at the Geel, Belgium facility and filled and finished at the Waterford, Ireland facility. Thus, the 4000 L

product is not produced, filled, or finished at the Allston Landing facility. Furthermore, the Applicant provided information to the IND (IND 10,780) allowing the comparability of the 2000 L product to the 4000 L product to be assessed. Additionally, the Geel, Belgium facility was recently inspected by the Agency on September 21-29, 2009 and the Waterford, Ireland facility on October 21-30, 2009. Therefore, during negotiations between the Applicant and the Agency after the Complete Response Letter was issued, the Agency agreed that submission of comparability data between the 2000 L and 4000 L bioreactor production scales could be submitted to support the Complete Response by the Applicant because the 4000 L product is produced at the Waterford, Ireland facility and the manufacturing deficiencies at the Allston Landing facility would not apply to this facility.

The Applicant submitted information on December 16, 2009 in response to the November 13, 2009 Complete Response letter, which included the following: 1) information on the 4000 L product drug substance manufacturing process at Genzyme Flanders in Geel, Belgium, 2) information on the 4000 L drug product fill and finish processes at the Genzyme manufacturing facility in Waterford, Ireland, 3) pharmacology and pharmacokinetic comparability assessments for the 4000 L and 2000 L products, 4) clinical safety information on the 4000 L product. This Clinical Review focuses primarily on the safety information submitted by the Applicant of the 4000 L product, which will be referred to throughout the remaining review as Lumizyme. The safety update submitted by the Applicant includes data from ATAP and postmarketing information in patients treated with the 4000 L product.

2.2 Tables of Currently Available Treatments for Proposed Indications

Alglucosidase alfa 160 L (Myozyme) is the only approved, marketed drug in the United States (US) for the treatment of Pompe disease (see Table 1). The 4000 L product was approved in the European Union (EU) on March 3, 2009.

Table 1: Currently Available Treatments for the Proposed Indications

Drug (trade name)	Indication	Manufacturer
Alglucosidase alfa 160 L product (Myozyme)	Treatment of Pompe disease	Genzyme

2.3 Availability of Proposed Active Ingredient in the United States

The proposed active ingredient, alglucosidase alfa, produced at the 4000 L bioreactor scale, has not been approved for use in the US. It is available under IND 10,780.

2.4 Important Safety Issues With Consideration to Related Drugs

The development of enzyme replacement therapy for lysosomal storage disease began in the early 1960s, and in 1974 the use of purified glucocerbrosidase for the treatment of Gaucher disease was first published.[2,3] There are now several enzyme replacement therapies available in

the US for lysosomal storage diseases including Gaucher (Cerezyme and Ceredase), Mucopolysaccharidosis (MPS) I (Aldurazyme), MPS II (Elaprase), and MPS VI (Naglazyme), Fabry (Fabrazyme), and Pompe (Myozyme). All of these therapies are associated with immunogenicity, which may lead to important safety concerns including the development of allergic reactions and anaphlaxis.[4] Boxed warnings for the risk of anaphylaxis were required in the labeling for Aldurazyme and Elaprase. A boxed warning for the risk of anaphylaxis was placed on the label for Myozyme based on a 5% incidence of anaphylaxis, and is part of the proposed labeling for Lumizyme. Delayed-onset infusion reactions have also been seen with Myozyme and chronic immune-mediated skin reactions and glomerulonephritis have also been reported.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The reader is also referred to previous clinical reviews by L. Yao and C. Mueller.

The Complete Response letter issued in November stated that the manufacturing deficiencies at the Allston Landing facility must be resolved as part of the complete response submission. However, the Agency understood that the 4000 L product was manufactured at the Geel, Belgium facility and filled and finished at the Waterford, Ireland facility. Thus, the 4000 L product is not produced, filled, or finished at the Allston Landing facility. Furthermore, the Applicant provided information to IND 10,780 allowing the comparability of the 2000 L product to the 4000 L product to be assessed. Therefore, during negotiations between the Applicant and the Agency after the Complete Response Letter was issued, the Agency agreed that submission of comparability data between the 2000 L and 4000 L bioreactor production scales could be submitted to support the Complete Response by the Applicant because the 4000 L product is produced at the Waterford, Ireland facility and the manufacturing deficiencies at the Allston Landing facility would not apply to this facility.

The Applicant submitted information on December 16, 2009 in response to the November 13, 2009 Complete Response letter, which included the following: 1) information on the 4000 L product drug substance manufacturing process at Genzyme Flanders in Geel, Belgium, 2) information on the 4000 L drug product fill and finish processes at the Genzyme manufacturing facility in Waterford, Ireland, 3) pharmacology and pharmacokinetic comparability assessments for the 4000 L and 2000 L products, 4) clinical safety information on the 4000 L product. This Clinical Review focuses primarily on the safety information submitted by the Applicant of the 4000 L product, which will be referred to throughout the remaining review as Lumizyme. The safety update submitted by the Applicant includes data from ATAP and postmarketing information in patients treated with the 4000 L product.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Previous review cycles

The overall quality of the data submitted by the Applicant was adequate for comprehensive review of the data, and the integrity of the investigators and the conduct of the trial were found to be acceptable by the Division of Scientific Investigation (DSI) during the first cycle review.

Current submission
There were no clinical efficacy studies included in the current submission. The only clinical information included in the current submission is safety data from an open-label, uncontrolled, expanded access protocol. Therefore, DSI inspections were not performed during this review cycle.

3.2 Compliance with Good Clinical Practices

Previous review cycles and current submission
The Applicant stated that all clinical studies included for review were conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP) regulations and clinical research guidelines established by the principles defined in the U.S. 21 CFR Part 312, and ICH E6 "Guideline for Good Clinical Practice, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use."

3.3 Financial Disclosures

Previous review cycles
The reader is referred to the original review by L. Yao for review of financial disclosure information.

Current submission
There were no clinical efficacy studies included in the current submission. The only clinical information included in the current submission is safety data from an open-label, uncontrolled, expanded access protocol. Therefore, financial disclosures were not required as part of the current submission.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Current submission
The reader is referred to the CMC review by J. Liu, PhD for a complete review of CMC issues with this submission. A summary of the CMC findings is presented below.

The CMC review focused on the comparison of the 2000 L and 4000 L manufacturing processes and the potential impacts of these changes on the critical attributes of the 4000 L drug substance.

Their conclusions are that the manufacturing validation data indicate the 4000 L manufacturing process is robust. In addition, drug substance characterization and comparability data indicate that the physicochemical properties of the 4000 L scale drug substance are comparable to that of the 2000 L scale drug substance, with improvements of several attributes critical for product quality and that overall the 4000 L product is much improved over the 2000 L product.

4.2 Clinical Microbiology

Clinical microbiology considerations do not apply to this application because Lumizyme is not an antimicrobial agent.

4.3 Preclinical Pharmacology/Toxicology

There are no Preclinical Pharmacology/Toxicology issues with this submission to the Complete Response.

4.4 Clinical Pharmacology

There are no Clinical Pharmacology issues with this submission to the Complete Response.

4.4.1 Mechanism of Action

Acid alpha-glucosidase is a hydrolase that degrades lysosomal glycogen to glucose. During trafficking to the lysosome, acid alpha-glucosidase is proteolytically processed, which results in the formation of an enzymatically active multi-subunit complex. Acid alpha-glucosidase degrades glycogen by catalyzing the hydrolysis of α-1,4 and α-1,6 glycosidic linkages of lysosomal glycogen. Pompe disease is due to the deficiency of acid alpha-glucosidase, which results in the accumulation of glycogen in the lysosomes of a variety of cells, predominantly in skeletal muscle. This accumulation in skeletal muscle lysosomes results in progressive muscle weakness, affecting motor and respiratory function, and death in all forms of the disease is usually a result of cardiorespiratory failure.

Alglucosidase alfa (rhGAA) is the recombinant form of acid alpha-glucosidase and is intended for long-term use as an enzyme replacement therapy (ERT) for the treatment of Pompe disease. It is produced by recombinant DNA technology developed in a Chinese hamster ovary (CHO) cell line. The rationale for therapy is that exogenous administration of the enzyme should replace the deficiency in Pompe disease patients. After intravenous administration, alglucosidase alfa is internalized by cells via cellular membrane mannose-6-phosphate receptors binding to enzyme mannose-6-phosphate residues. It is then taken up by lysosomes where it undergoes proteolytic cleavage resulting in increased enzymatic activity, allowing for the cleavage of glycogen in the lysosomes.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The following table (see Table 2) lists the clinical studies submitted by the Applicant in support of this Complete Response for Clinical Review in support of the safety of Lumizyme at the 4000L production scale. The only study submitted for review in the current submission is the ATAP. This study is designed as an open-label, uncontrolled, treatment protocol to allow patients access to treatment due to a shortage of the 160 L (Myozyme) product in the U.S.

Table 2: Table of Clinical Studies

Study	Trial Design	Comments
AGLU3907	ATAP: open label, expanded access protocol to treat US patients over age 18, n=176	Only safety data for patients who have been treated with 4000L product.

5.2 Review Strategy

For an overview of the clinical development program, the reader is referred to the first cycle clinical review by L. Yao. This Reviewer's safety review strategies are outlined in Section 7 below.

5.3 Discussion of Individual Studies/Clinical Trials

See Section 7 for a detailed outline of the studies used for safety review in this submission.

6 Review of Efficacy

Efficacy Summary

The reader is referred to previous clinical reviews by L. Yao and C. Mueller for details of efficacy information reviewed in the original BLA submission and the first Complete Response resubmission.

The clinical review for the initial submission under this BLA for the 2000 L product supported under Subpart E Accelerated approval regulations for the agreed upon labeled indication, "patients 8 years and older with late-onset (non-infantile) Pompe disease (GAA deficiency) who do not have evidence of cardiac hypertrophy." However, effectiveness was based on stabilization of % predicted forced vital capacity in 60 non-infantile-onset Pompe patients randomized to placebo in the Late-Onset Treatment Study (LOTS). Therefore, the product could not be approved under Subpart E without agreement from the Applicant to conduct an appropriate verification study to confirm that treatment is associated with clinical benefit.

Subsequent review of Pompe Registry data demonstrated an improvement in survival in infantile-onset patients treated with the 2000 L product compared with an untreated infantile-onset historical control cohort. Thus, the totality of the clinical data supported the clinical effectiveness of the 2000 L product. However, because of the limitations of the Pompe Registry data, the insufficient numbers of patients age 8 years and younger treated in clinical trials, and the availability of Myozyme (160 L product) in the US to treat younger patients, the clinical Reviewers recommended that treatment with the 2000 L product be restricted to patients with late onset (non-infantile) Pompe disease 8 years of age and older, who do not have evidence of cardiac hypertrophy.

The information provided to support of the efficacy of the 4000 L product in the current submission relies on the biochemical comparability between the 2000 L product and the 4000 L product. Therefore, no additional clinical studies were submitted in support of the clinical effectiveness of the 4000 L product.

7 Review of Safety

Safety Summary

Previous review cycles
The reader is referred to the previous clinical safety reviews by L. Yao and C. Mueller for a complete review of previously submitted safety information.

Important clinical safety issues that were seen in late-onset Pompe disease patients treated with the 2000 L product in review of LOTS/LOTS extension and postmarketing data from previous submissions to this BLA included acute and chronic allergic and immunologically-mediated reactions and anaphylaxis. Chronic exposure could not be adequately assessed based on the studies reviewed, but both the skin reactions and urinary abnormalities reported suggested that, as with Myozyme, immune-mediated reactions may occur with chronic exposure.

Current submission
The Applicant has provided safety data in patients who have received the 4000 L product in the ongoing ATAP and from ex-US commercial use. The known risks of anaphylaxis and infusion reactions were seen in patients in this safety update. Additionally, potential immunologically-mediated reactions including chronic skin and kidney reactions were noted in the initial review. Skin reactions and urinary abnormalities were not reported in patients in this safety update. No new safety issues were observed in the analyses of the additional safety data reviewed.

7.1 Methods

A safety update submitted as part of the Complete Response includes the following data:

1) Cumulative interim safety data in patients who have received the 4000 L product in the ongoing clinical study AGLU03907, the Alglucosidase alfa Temporary Access Program

(ATAP) as reported to Genzyme Global Patient Safety and Risk Management (GPS-RM);

2) Ex-US postmarketing experience using the 4000 L product as reported to GPS-RM.

Patients in ATAP had prior commercial exposure to the 2000 L product and the types and quality of safety data collected were variable. The post-marketing safety data were collected predominantly through spontaneous report of Serious Adverse Events (SAEs) outside of the US.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

A summary of the studies used to evaluate safety is provided in Table 3.

Table 3: Overview of Reporting Intervals for Safety Update

Source of Safety Data	Data Analysis Start Date	Data Analysis Cut-off Date	Late-Breaking Information Cut-off Date	Safety Data[1]
AGLU03907 (ATAP)	October 19, 2009	November 24, 2009	None	SAEs and IARs[2]
Spontaneous Post-Marketing Cases	December 29, 2009 (1 day after data cut-off for the previous safety update submitted on May 15, 2009	September 28, 2009	November 24, 2009	Serious case reports, IARs[3] Deaths, Anaphylactic/significant allergic reactions Immune complex-mediated reactions

1-Based on events reported to GPS-RM.
2 -Represents events with an onset after the first infusion of 4000 L alglucosidase alfa.
3 –Includes events in both serious and non-serious case reports.

Electronically copied from Applicant submission Summary of Clinical Safety, page 5

7.1.2 Categorization of Adverse Events

The Applicant coded adverse events (AEs) by System Organ Class (SOC) and AE preferred terms using the Medical Dictionary for Regulatory Activities 12.0 (MedDRA). The MedDRA coding system contains greater than 15,000 AE preferred terms that can result in substantial granularity, fragmentation, and dilution of AE terms. AE preferred terms and SOC terms were revised by this Reviewer so that related AE terms were combined to allow for a more meaningful description of the AE profile. For example, abdominal discomfort, abdominal pain, abdominal pain lower and upper, were all classified as abdominal pain by this Reviewer.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The patient safety data from ATAP and postmarketing experience were collected predominantly through spontaneous report of Serious Adverse Events (SAEs) received by Genzyme GPS-RM, and thus were not collected as part of a GCP study, thus they have not been pooled.

7.2 Adequacy of Safety Assessments

ATAP, AGLU3907, is a temporary access treatment protocol to allow patients 18 years of and older to be treated with Lumizyme due to a drug shortage of the approved product, Myozyme. The planned dose for all patients treated in this program is 20 mg/kg qow. The safety information provided by the Applicant in previous submissions reflected data from the start of the study on May 25, 2007 to the data cut-off date of October 15, 2008 for patients treated with the 2000 L product. The current submission contains data beginning on October 19, 2009 when patients in ATAP began receiving the 4000 L product to a cut-off of November 24, 2009, which was agreed upon with the Agency for this complete response submission. Of the 184 patients enrolled in ATAP, 128 have received 1 or more infusions at the 4000 L scale. Physicians treating patients in ATAP are required to perform a standard schedule of assessments and are strongly encouraged to follow a minimum schedule of recommended assessments to facilitate consistent and thorough clinical evaluations to reveal additional changes or stability in a patient's clinical status and provide information for a global patient database. Safety assessments in ATAP that are recommended to occur at specified intervals include laboratory, physical examination, echocardiography, and immunologic measurements. These assessments appear to be adequate to evaluate the safety profile of the drug.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The date of first infusion of the 4000 L product is based on verbal communication with the treating physician, and the maximum exposure to the 4000 L product was estimated by the Applicant to be 3 infusions for this safety update. In contrast, the range of exposure to the 2000 L product is estimated to be 2 to 133 infusions with exposures of 4 to 267 weeks. The majority of patients in ATAP also had prior commercial exposure to the 160 L before treatment with the 2000 L product.

7.2.2 Explorations for Dose Response

No explorations of dose response were included in this submission.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or *in vitro* testing was conducted.

7.2.4 Routine Clinical Testing

No explorations of routine safety laboratory studies were included in this submission.

7.2.5 Metabolic, Clearance, and Interaction Workup

Studies evaluating metabolic, clearance, and interaction were not conducted.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Enzyme replacement therapy is approved for use in several metabolic diseases including Mucopolysaccharidoses I, II, VI, Gaucher disease, and Fabry disease. These therapies all have significant potential to produce anaphylaxis and other severe hypersensitivity reactions and have led to a boxed warning for each of these therapies. Myozyme, which was approved in April, 2006 for treatment of Pompe disease, also carries a boxed warning for anaphylaxis. Infusion reactions (IRs) are also commonly found in these treatments. The labeling for Myozyme also includes a warning of the risk of cardiac failure and immune-mediated skin reactions and kidney disease. In the pivotal clinical trial leading to the approval of Myozyme, only infantile-onset patients were studied, a form of Pompe disease that is associated with the development of hypertrophic cardiomyopathy. However, patients studied in LOTS, LOTS extension, and ATAP (formerly MTAP, Myozyme Temporary Access Program) all had late-onset Pompe disease and do not have this same underlying risk for hypertrophic cardiomyopathy, but late-onset patients would be expected to have the potential for development of immune-mediated skin reactions and kidney disease.

7.3 Major Safety Results

Adverse events continue to be collected and monitored in this ongoing study; therefore, these data are based on interim reporting. A serious adverse event (SAE) was defined as an AE that resulted in any of the following outcomes: death; life-threatening experience; required prolonged inpatient hospitalization; persistent or significant disability/incapacity; congenital anomaly; or important medical events that may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above. All SAEs, regardless of relationship to treatment, were reported to the Applicant within 24 hours of the Investigator's knowledge of the event. The Applicant did not provide an analysis of common AEs from ATAP with 4000 L exposure for this safety update, which is reasonable due to the short duration of treatment.

7.3.1 Deaths

There were no patient deaths reported for patients receiving the 4000 L product in ATAP.

7.3.2 Nonfatal Serious Adverse Events

The definition used by the Applicant to define SAEs is consistent with the regulatory definition of SAEs as noted in the International Conference on Harmonization (ICH E2A). The medical Reviewer agrees with the classification of SAEs by the Applicant.

The Applicant reported one SAE out of the 128 patients who received at least one infusion of the 4000 L product. The patient was a 55 year old female with late-onset Pompe disease who experienced multiple episodes of vomiting and diarrhea two days after her first infusion and was subsequently hospitalized and diagnosed with viral gastroenteritis and deemed unlikely to be related to treatment.

7.3.3 Dropouts and/or Discontinuations

There were no patient dropouts or discontinuations reported for patients receiving the 4000 L product in ATAP.

7.3.4 Significant Adverse Events

Infusion Reactions
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). However, elevated IgE antibody titers are not required to establish the clinical diagnosis of anaphylaxis. The pathogenesis of non-anaphylactic, acute infusion reactions (IRs) that develop during or shortly after an infusion is less clear.[7] The National Cancer Institute has developed terminology, published as Common Terminology Criteria for Adverse Events v3.0 (CTCAE), to distinguish between hypersensitivity reactions and acute IRs.[8] There is clear overlap between the clinical definitions of anaphylaxis and IRs.

IRs were defined by the Applicant as any AE that occurred during either the infusion or the post-infusion observation period following the infusion, which were assessed by the Investigator as treatment-related (i.e., possibly, probably, or definitely related). During the safety update period, 1 of the 128 patients who received at least one infusion of the 4000 L product experienced events characterized as infusion-associated reactions. The patient is a 44 year-old female with late-onset Pompe disease who was previously treated in LOTS (29708) who had a prior history of IRs including infusion site pruritus, local swelling, paresthesia, peripheral edema, chest pain, erythema, urticaria, hypotension, and pyrexia, which Dr. Yao classified as anaphylaxis in the initial review of the 2000 L product. The patient had been receiving 2000 L product at a dose of 10 mg/kg weekly under a desensitization protocol since June 3, 2009, after testing positive for IgE antibodies and complement activation. During her first infusion of 4000 L on November 4, 2009, she experienced local swelling, pain in extremity, catheter site swelling, and skin tightness. The infusion was stopped and restarted twice with a decrease in pain. In the opinion of the investigator, the events were considered non-serious, moderate, and definitely related to treatment, and this Reviewer agrees with that assessment.

Anaphylaxis
Anaphylaxis as seen in other enzyme replacement therapies is the primary safety concern with Lumizyme treatment. A boxed warning for the risk of anaphylaxis was placed in the label for Myozyme based on a 5% incidence of anaphylaxis in the clinical trial of 18 infantile-onset patients who received Myozyme. This Reviewer used a definition for anaphylaxis based on the consensus statement written by the Second Symposium on the Definition and Management of Anaphylaxis (Table 13). The participants of this Symposium agreed that the definition should be made based on clinical criteria, and that laboratory test results such as IgE antibody presence or skin testing do not play a role in making the diagnosis of anaphylaxis.[6] The Applicant reports that no events reported to Genzyme GPS-RM during the safety update reporting period were determined to be anaphylaxis or considered significant hypersensitivity reactions.

Skin Reactions and other Potential Immune-mediated AEs
Other significant adverse events that were uncovered during the original review of the 2000 L product include the possibility of chronic immune-mediated skin and kidney adverse reactions. Skin reactions have also been noted in postmarketing safety data collected for Myozyme, and the Myozyme labeling has been updated to reflect this safety finding. The Applicant reports that no events of glomerulonephritis, hematuria, proteinuria, vasculitis, skin lesion, skin necrosis, arthralgia, myalgia, arthropathy, lymphadenopathy, serum sickness, type II immune-complex mediated reaction, or influenza-like symptoms in patients given the 4000 L product.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The Applicant did not provide an analysis of common AEs from ATAP with 4000 L exposure for this safety update, which is reasonable due to the short duration of treatment and inability to assess the frequency of events. However, it was noted in previous reviews of ATAP safety data that there was a substantially lower percentage of patients reporting adverse events, as well as a substantially lower incidence of adverse events in this study compared with other clinical studies evaluating the safety of alglucosidase alfa treatment. This finding may be related to potential underreporting of AEs in ATAP, since it is a treatment protocol, and intended only to obtain "standard of care" assessments. Therefore, this Reviewer recommends that labeling of common adverse events should be based on information reviewed in previous submissions.

7.4.2 Laboratory Findings

Analysis of laboratory testing was not performed for the current safety update.

7.4.3 Vital Signs

Analysis of vital signs was not performed for the current safety update.

7.4.4 Electrocardiograms (ECGs)

Analysis of ECGs was not performed for the current safety update.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were conducted.

7.4.6 Immunogenicity

See section 7.3.4 (anaphylaxis and infusion reactions)

7.5 Other Safety Explorations

No other safety explorations were performed.

7.5.1 Dose Dependency for Adverse Events

No safety explorations on dose dependency were conducted by the Applicant.

7.5.2 Time Dependency for Adverse Events

No time dependency studies were conducted by the Applicant.

7.5.3 Drug-Demographic Interactions

No drug-demographic interaction studies were conducted by the Applicant.

7.5.4 Drug-Disease Interactions

No drug-disease interaction studies were conducted by the Applicant.

7.5.5 Drug-Drug Interactions

No drug-drug interaction studies were conducted by the Applicant.

7.6 Additional Safety Evaluations

No additional safety evaluations were performed with this submission.

7.6.1 Human Carcinogenicity

No animal or human studies were conducted to assess the carcinogenic or mutagenic potential.

7.6.2 Human Reproduction and Pregnancy Data

No formal studies have been conducted in pregnant women, and there are no reports of pregnancy in any patients treated to date.

7.6.3 Pediatrics and Assessment of Effects on Growth

Growth was not assessed as a primary efficacy endpoint in any of the studies submitted thus far by the Applicant. Only two patients under the age of 18 received treatment with the 2000 L product in LOTS/LOTS extension, therefore, no conclusions can be made regarding pediatric patients.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There have been no withdrawal/rebound phenomena or abuse potential issues identified. There have been no reports of overdose.

7.7 Additional Submissions / Safety Issues

There were no additional submissions reviewed for this application.

8 Postmarketing Experience

The previous postmarketing safety data reviewed for the 2000 L product included data provided by the Applicant to a cutoff of late-breaking information up to March 16, 2009. This submission includes postmarketing data from December 29, 2008 through September 28, 2009 with narratives for late-breaking reports through November 24, 2009 for patients treated outside the US, where the 2000 L and 4000 L product are available for commercial use. The 4000 L product has been available to patients outside the US as of March 3, 2009. Postmarketing experience data are available for both infantile and late-onset Pompe disease patients and were presented by the Applicant by manufacturing scale as estimated based on country-specific dates for shipment of the 4000 L product. If the date of onset of the adverse event was missing, the adverse event onset date was set to the 15th day of the month reported. Adverse events with a missing date of onset were reported as "unknown scale". In some countries the 2000 L product continued to be distributed for commercial use for a short period of time after the first shipment of the 4000 L product, therefore it is possible that some events reported in association with the 4000 L product occurred prior to the first infusion of the 4000 L product. The Applicant estimated that the total worldwide exposure to the 2000 L and 4000 L products was (b) (4) patients through the end of the current safety update and (b) (4) through the late-breaking reporting period. The Applicant estimates that approximately 698 patients received at least one infusion of the 4000 L product with a duration of exposure from 1 to 6 months, with an estimated (b) (4) patients receiving the 4000 L product through the late-breaking reporting period.

The Genzyme GPS-RM database was used by the Applicant as the source for spontaneously reported AEs, with coding performed using MedDRA version 12.0. The Applicant states that the

exact incidence for these AEs cannot be determined because the total number of patients evaluated is based on an estimate. Datasets for postmarketing adverse events were not provided, therefore, a complete review of these data was not possible. A summary of the safety update from the postmarketing setting is provided below.

Deaths

During the safety update reporting period, 30 patient deaths were reported. The Applicant reports that 16 deaths occurred during treatment with the 2000 L product; 13 patients with infantile-onset Pompe disease and 3 patients with late-onset Pompe disease. Seven deaths occurred during treatment with the 4000 L product; 4 patients with infantile-onset disease and 3 patients with late-onset disease. Seven were reported as occurring with unknown product scale, 4 patients with infantile-onset, 2 patients with late-onset, and 1 patient with unknown phentoype. Although late-onset Pompe disease is more prevalent than the infantile-onset form, more deaths were reported in the infantile-onset patients. This finding was expected given the more severe phenotype of infantile-onset disease.

Eighteen infantile-onset patient deaths were reported due to cardiac and/or respiratory causes, two were unknown, and one was reported as 'disease progression'. The cause of death for seven of the late-onset patients were reported as cardiac and/or respiratory, and one was reported as withdrawal of life support at patient's request. The majority of deaths were assessed as being related to the underlying Pompe disease in both patient populations and the Applicant assessed these deaths as unrelated to treatment.

Serious Adverse Events

Spontaneous AEs are provided to the Applicant on a voluntary basis. Thus, it is difficult to accurately assess incidence rates for adverse events reported in the post-marketing setting. Additionally, the relationship to treatment is not always included in case reports. For this safety update, a total of 289 SAEs and 119 non-serious AEs were reported in 87 patients.

One hundred and seventy-four SAEs were reported during treatment with the 2000 L product; 134 in infantile-onset Pompe patients and 40 in late-onset patients. Seventy SAEs were reported during treatment with the 4000 L product; 37 in infantile-onset patients and 33 in late-onset Pompe patients. In patients with infantile-onset Pompe disease, SAEs reported in more than two patients included pneumonia, pyrexia, respiratory failure, respiratory tract infection, cardiac failure, diarrhea, irritability, no therapeutic response, oxygen saturation decreased, rash and wheezing. In patients with late-onset Pompe disease, SAEs reported in more than one patient included respiratory distress, pneumonia, septic shock, cough, and respiratory disorder. Overall, the post-marketing SAEs reported in both treatment groups were consistent with those previously reported in clinical trials. There were six patients who the Applicant identified as having serious IRs, three of which the Applicant reported as anaphylaxis based on their presentation of SAEs. One of the three patients with anaphylaxis had recurrent anaphylactic reactions during 2000 L infusions and also experienced IRs during one 4000 L infusion; one patient had an anaphylactic reaction during infusion with 4000 L; and one patient had an anaphylactic reaction during 2000 L infusion and continued to experience IRs during 4000 L infusions. The Applicant also reported that there were no cases suggestive of immune-complex mediated reactions involving the skin or

kidneys. The Reviewer is unable to confirm the Applicant's assessment of relationship to treatment and overall occurrence of anaphylaxis or immune-complex mediated reactions, as there were no post-marketing safety datasets included in the submission.

Submission Specific Primary Safety Concerns

Important clinical safety issues were seen in previous reviews of the most comprehensive safety data of the GCP-compliant LOTS and LOTS extension studies, ATAP, and postmarketing experience in patients treated with the 2000 L product. The main safety concerns with Lumizyme continue to be those related to immunogenicity, anaphylaxis and infusion reactions. Immune-mediated skin and kidney reactions were not reported with this submission, but should be considered potential long-term safety issues. Common adverse events reported in the postmarketing setting appear similar to those reported in the initial reviews of the 2000 L product, and will need to continue to be monitored in ATAP. No new safety issues were observed in the analyses of the additional safety data reviewed using the 4000 L product.

This Reviewer concludes that the overall safety of the 4000 L product appears to be consistent with the overall safety of the 2000 L product. Therefore, this Reviewer concludes that the 4000 L product provides an acceptable overall risk/benefit profile. However, based on the serious known and potential risks uncovered in previous reviews, this Reviewer recommends that a REMS be established as a condition of approval to ensure that the benefits of the 4000 L product outweigh the risks. Additionally, several clinical post-marketing requirement (PMRs) and commitment studies (PMCs) should also be agreed upon to obtain long-term safety and efficacy information with the 4000 L product.

9 Appendices

9.1 Literature Review/References

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[8] 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

[9] Hunley TE, Corzo D, Dudek M, et al, Nephrotic syndrome complicating alpha-glucosidase replacement therapy for Pompe disease, Pediatrics. 2004 Oct; I 14(4):e532-535
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9.2 Labeling Recommendations

Labeling has been negotiated successfully in previous review cycles. The reader is referred to the clinical reviews by L. Yao and C. Mueller for details of previous labeling negotiations.

The final labeling contains all revisions negotiated with the Applicant. During the current review cycle, only minor labeling edits were negotiated. The indication, as negotiated during the previous review cycle should be, "Lumizyme (alglucosidase alfa) is a lysosomal glycogen-specific enzyme indicated for patients 8 years and older with late (non-infantile) onset Pompe disease (acid α-glucosidase (GAA) deficiency) who do not have evidence of cardiac

hypertrophy. The safety and efficacy of Lumizyme have not been evaluated in controlled clinical trials in infantile-onset patients, or in late (non-infantile) onset patients less than 8 years of age"

Highlights of Lumizyme labeling include a boxed warning for the risk of anaphylaxis. The Warnings and Precautions section includes the risk of anaphylaxis, severe allergic and immune-mediated reactions, (b) (4)

9.3 Advisory Committee Meeting

There was no Advisory Committee Meeting with this submission.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 13, 2009
TO: BLA STN 125291 Lumizyme (alglucosidase alfa)
Genzyme Corporation

FROM: Julie Beitz, MD
Director, Office of Drug Evaluation III

SUBJECT: Complete Response Action

Lumizyme (alglucosidase alfa) consists of the human enzyme acid α-glucosidase (GAA) and is produced by recombinant DNA technology in a Chinese hamster ovary cell line at a 2000 L bioreactor scale. In contrast, Myozyme, another member of the class of alglucosidase alfa biologic products, is produced at a 160 L bioreactor scale. Both Lumizyme (alglucosidase alfa) and Myozyme (alglucosidase alfa) provide an exogenous source of GAA that is taken up into cells and is transported into lysosomes where the enzyme acts to hydrolyze glycogen. These products have been evaluated in Pompe disease, an inherited disorder of glycogen metabolism caused by the absence or marked deficiency of GAA. Glycogen accumulation in various tissues leads to the development of progressive muscle weakness, including impairment of respiratory function in all patients, as well as hypertrophic cardiomyopathy in patients with infantile-onset Pompe disease. When Pompe disease presents in infants, it is rapidly progressive resulting in cardiorespiratory failure and death before the age of 2 years; the course of the disease in late (non-infantile) onset patients is more slowly progressive.

Apart from Myozyme (alglucosidase alfa), which has been shown to improve ventilator-free survival in infantile-onset patients, there are no other approved treatments for Pompe disease. Due to manufacturing constraints, Genzyme has limited access to Myozyme to patients less than 18 years of age. Lumizyme (alglucosidase alfa) has been made available to approximately 175 adult US patients 18 years and older via a temporary access program (under IND 10,780), although recent manufacturing problems have resulted in the need for dose conservation strategies in these patients. Since April 2008, the temporary access program has been closed to new patient enrollment.

This memorandum documents my concurrence with the Division of Gastroenterology Product's (DGP's) recommendation for a complete response action for Lumizyme (alglucosidase alfa), for the treatment of patients 8 years and older with late (non-infantile) onset Pompe disease who do not have evidence of cardiac hypertrophy, due to CGMP deficiencies identified at Genzyme's Allston Landing, MA, manufacturing facility. As of this writing, negotiation of postmarketing commitments, and review of the product labeling and of Genzyme's proposed risk evaluation and mitigation strategy, or REMS, are nearly complete. Discussions regarding postmarketing study requirements are complete.

REGULATORY HISTORY

BLA 125291 was originally submitted on May 30, 2008, and granted a priority review. The application was discussed before the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) on October 21, 2008. A major amendment submitted on November 21, 2008, extended the review clock by three months. In closed session, the Advisory Committee was briefed on the biochemical differences between Lumizyme (alglucosidase alfa) and Myozyme (alglucosidase alfa), and their potential impact on the relative efficacy and safety of the two products. In open session, deliberations centered on the demonstration of efficacy based on effects of Lumizyme (alglucosidase alfa) on the 6-minute walk test (6MWT) in a single placebo-controlled study. A majority of Committee members voted in favor of accelerated approval of Lumizyme (alglucosidase alfa) based on its effects on a surrogate endpoint, percent of predicted forced vital capacity (FVC), arguing that a positive effect on the 6MWT had not be demonstrated.

On February 27, 2009, a complete response action was taken. The action letter stated that before the application may be approved, Genzyme must 1) address CGMP deficiencies identified during FDA's October 2008 inspection of the Allston Landing, MA, manufacturing facility, 2) address CMC deficiencies in the BLA, 3) reach agreement with FDA on the design of the post-approval study to be conducted under accelerated approval regulations to verify the clinical benefit of Lumizyme (alglucosidase alfa), and 4) submit a revised proposed REMS. In addition, discussions regarding product labeling and postmarketing study requirements and commitments would need to be resolved. A Warning Letter issued on February 27, 2009 that provided further details regarding the CGMP deficiencies identified during the Allston Landing inspection.

On May 15, 2009, Genzyme responded to FDA's February 2009 complete response letter. The applicant also implemented some corrective actions to address the issues raised in the Warning Letter. Re-inspections of the Allston Landing, MA, facility in May 2009, and again in October and November 2009, however, led to the identification of several 483 deficiencies. On November 6, 2009, the Office of Compliance recommended that approval of the BLA be withheld. (See additional discussion under **Product Issues**.)

EFFICACY

Lumizyme (alglucosidase alfa) was studied in a multicenter, double-blind, placebo-controlled study of 90 late-onset Pompe disease patients (Late-Onset Treatment Study or LOTS). Enrollment was restricted to patients 8 years and older who were naïve to enzyme replacement therapy, ambulatory, did not require invasive ventilatory support, and had an FVC between 30 and 79% of the predicted normal value in a healthy population. Patients were allocated 2:1 to either 20 mg/kg administered intravenously every two weeks or placebo for a total of 78 weeks.

Several statistical issues were raised by the FDA regarding the interpretation of the efficacy results for LOTS. Using FDA's preferred analysis (ANCOVA), the mean change from baseline to last observation in % predicted upright FVC was 1.2% for

Lumizyme-treated patients as compared to -2.2% for placebo-treated patients. This resulted in a treatment difference of 3.4% (95% CI: 1.3, 5.5). The mean change from baseline to last observation in distance walked in the 6MWT was 25 meters for Lumizyme-treated patients and -3 meters for placebo-treated patients. This resulted in a treatment difference of 28 meters (95% CI: -1, 52; p=0.06).[1]

Based on these results, the Advisory Committee voted 16-1 that the effectiveness of Lumizyme (alglucosidase alfa) had been demonstrated in patients with late (non-infantile) onset Pompe disease, ages 8 years and older, who do not have evidence of cardiac hypertrophy. Eleven members recommended that accelerated approval be granted based on the results for the surrogate endpoint of % predicted FVC. Following this advice, FDA's complete response letter indicated that marketing approval may be granted based on a surrogate endpoint under the accelerated approval regulations.[2] Approval would be subject to the requirement that the applicant study the drug further to verify and describe its clinical benefit.

In the weeks that followed the complete response action, a series of discussions were held with the applicant to determine an optimal design for a post-approval study that would verify the clinical benefit of Lumizyme (alglucosidase alfa). At DGP's request, the applicant submitted data collected in the Pompe Registry from *infantile-onset* patients who received Lumizyme (alglucosidase alfa) commercially outside the U.S. The Pompe Registry is a multi-center, multi-national, voluntary, observational disease registry. Fifteen infantile-onset patients enrolled in the registry that had received Lumizyme (alglucosidase alfa) prior to 6 months of age were matched to an untreated historical control group (the same historical control group that was used to base the original approval of Myozyme).

The median duration of Lumizyme (alglucosidase alfa) treatment in these infantile-onset patients was 15 months (range 3-48 months). Estimated survival in Lumizyme-treated patients was 57% at 18 months and 37% at 36 months, compared to 2% in the historical control group at both time points. The median age of death or last follow-up was 19 months (range 5-51 months). DGP concluded, and I concurred, that the survival data in Lumizyme-treated infantile-onset patients could be used to support the findings from LOTS and provide sufficient evidence of efficacy for Lumizyme (alglucosidase alfa) for the treatment of patients 8 years and older with late-onset Pompe disease, without the need for an additional study.

It should be noted that we do not believe that the efficacy findings from LOTS and the survival data in Lumizyme-treated infantile-onset patients from the Pompe registry support approval of Lumizyme (alglucosidase alfa) for all ages. The reasons for this determination include: 1) Pompe disease patients less than 8 years of age are at risk for rapid disease progression, 2) there are residual concerns that the biochemical differences

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[1] First cycle clinical and statistical reviews, including my review dated February 27, 2009, further describe the statistical issues that were identified in LOTS and discussed at the October 21, 2008 Advisory Committee meeting.
[2] 21 CFR 601.41-46

between Lumizyme and Myozyme may lead to differences in potency, 3) the clinical information on patients enrolled in the Pompe registry is limited, and 4) the potential exists for selection bias, that is, patients with improved survival may more likely be included in the registry. In accordance with this determination, Lumizyme (alglucosidase alfa), if approved, will have a REMS designed to ensure that Lumizyme is used exclusively for the treatment of late (non-infantile) onset Pompe disease patients 8 years and older who do not have evidence of cardiac hypertrophy.

CLINICAL PHARMACOLOGY

The pharmacokinetics of alglucosidase alfa was studied in 32 patients enrolled in LOTS ranging in age from 21 to 70 years. The declining portion of the concentration-time profile appears biphasic; the half-life for the first phase is 2.4 hours. Concentrations of alglucosidase alfa were not sampled long enough to adequately determine the half-life for the second phase. Genzyme has agreed to perform a post-approval pharmacokinetic study in at least 20 Pompe disease patients aged 8-18 years enrolled in the Pompe Registry.

SAFETY

The most common adverse reactions observed with Lumizyme (alglucosidase alfa) administration were infusion reactions. Both acute reactions occurring during or within 2 hours of Lumizyme infusion, and delayed onset reactions occurring within 48 hours of completion of the infusion have been reported. The incidence of acute infusion reactions in LOTS was 50%.

Anaphylaxis and severe allergic reactions were reported in Lumizyme-treated patients during and up to 3 hours after Lumizyme infusion. Some of these reactions were life-threatening and included anaphylactic shock, respiratory arrest, apnea, dyspnea, bradycardia, tachycardia and hypotension. The incidence of anaphylaxis in LOTS was approximately 7%. These events will be highlighted in a Boxed Warning and in the WARNINGS AND PRECAUTIONS section of the product label which advise that appropriate medical support measures be readily available when Lumizyme is administered. If anaphylaxis or severe allergic reactions occur, immediate treatment discontinuation should be considered. Interrupting the infusion, administering antihistamines, corticosteroids, intravenous fluids and/or oxygen may ameliorate the symptoms. Patients who have experienced such reactions should be treated with extreme care if Lumizyme is re-administered.

In addition, serious immune-mediated reactions involving skin and kidney have been reported with Lumizyme and will be highlighted in the Boxed Warning and the WARNINGS AND PRECAUTIONS sections of the product label.

IMMUNOGENICITY

In LOTS, all Lumizyme-treated patients with available samples (n=59) tested positive for IgG antibodies to alglucosidase alfa within the first three months of treatment. There was no apparent association between mean or peak IgG antibody titers and the occurrence of adverse reactions. Although none of the 59 patients tested positive for inhibition of enzyme activity, antibody titers for cellular uptake inhibition were present in 18 of 59 patients by week 78.

Ten patients in LOTS underwent testing for alglucosidase alfa-specific IgE antibodies; two tested positive, both of whom experienced anaphylactic reactions. A small number of Lumizyme-treated patients in the postmarket setting have tested positive for the presence of alglucosidase alfa-specific IgE antibodies, and some of these experienced anaphylaxis. Some patients who tested positive for the presence of alglucosidase alfa-specific IgE antibodies were successfully rechallenged with Lumizyme using a slower infusion rate at lower initial doses and have continued to receive treatment. Patients who developed alglucosidase alfa-specific IgE antibodies appear to be at a higher risk of developing infusion reactions and should be monitored more closely.

PRODUCT ISSUES

Lumizyme (alglucosidase alfa) manufactured in a 2000 L bioreactor differs from Myozyme (alglucosidase alfa) produced in a 160 L bioreactor in several biochemical attributes, including [redacted] (b) (4) (b) (4) These differences were the basis of FDA's recommendation that a separate BLA be filed for the product manufactured in a 2000 L bioreactor.

In its initial review of BLA 125291, the Division of Therapeutic Proteins (DTP) identified several deficiencies involving chemistry, manufacturing and controls that would have to be addressed before the BLA could be approved: 1) in-process controls for bioreactor monitoring, 2) qualification of a reference standard for use in the testing control strategy, 3) evaluation of selected analytic tests used to develop acceptance criteria for drug substance and drug product specifications, and 4) criteria used for the system suitability requirement regarding the precision of the [redacted] (b) (4) assay to better reflect assay performance. The applicant's May 2009 complete response adequately addressed these deficiencies. In addition, Genzyme has agreed to perform the following postmarketing commitments: 1) evaluate use of the [redacted] (b) (4) method as a release test for glycan profiling of the drug substance, 2) develop an analytic method to monitor [redacted] (b) (4) and evaluate its use in the release and stability specifications, (b) (4) [redacted] and 4) establish in-process control limits for cell viability during the [redacted] (b) (4) period using the data collected from four upcoming 4000 L cell culture runs.

Significant deviations from CGMP regulations (21 CFR Parts 210 and 211) were identified during an inspection of the Allston Landing, MA, manufacturing facility and conveyed to Genzyme in a 483 form dated October 10, 2008. Genzyme's response to the 483 did not adequately address the concerns raised, prompting the New England District

(b) (4) to recommend that a Warning Letter be issued. On February 6, 2009, the Office of Compliance recommended a withhold approval action. The Warning Letter, dated February 27, 2009, cited deficiencies in (b) (4) (b) (4) (b) (4) These practices and conditions could affect the quality, safety and/or efficacy of all products manufactured at the Allston Landing facility.

In addition to addressing these deficiencies, Genzyme was investigating the root cause for contamination of bioreactor 7B that occurred at Allston Landing in November 2008.[3] A re-inspection of the Allston Landing site conducted between May 19 and 28, 2009 found that all promised corrective and preventative actions had not been fully implemented or were found to be inadequate. During the inspection, the investigator was informed that Vesivirus 2117 had been identified as a possible contaminant in the bioreactor 7B investigation, and that possible contamination had occurred on May 23, 2009 involving bioreactor 5A. This event necessitated that the Allston Landing facility be closed temporarily for decontamination; dose conservation strategies were implemented for the products manufactured at the site, including Lumizyme. On July 27, 2009, the applicant was informed that re-inspection to verify the firm's corrective and preventative actions and to evaluate their state of compliance would be required.

A re-inspection of the Allston Landing facility was conducted between October 6 and November 13, 2009. The inspectors discussed their preliminary findings and concerns with DGP, ODE III, DTP, ONDQA, and the Office of Compliance in teleconferences held on October 29, and November 4, 2009. Several deficiencies were noted involving aseptic filling of vials, contamination of vials with particulate matter (including metal particles, cotton and polyester fibers, and human hair), media fills, and air flow patterns. It was further noted that these deficiencies were applicable not only to Lumizyme but to all finished dosage forms filled at this site [i.e., Myozyme 160 L (BLA 125141), Cerezyme (NDA 020367), Fabrazyme (BLA 103979), Aldurazyme (BLA 125058), and Thyrogen (NDA 020898)]. A 483 will be issued to the firm upon completion of this inspection. On November 6, 2009, the Office of Compliance recommended that approval of the Lumizyme BLA be withheld.

On February 26, 2009, the European Commission approved the production of Myozyme (alglucosidase alfa) at the 4000 L bioreactor scale at Genzyme's manufacturing facility in Geel, Belgium. As of this writing, US adult Pompe disease patients enrolled in the temporary access program (under IND 10,780) are transitioning from Lumizyme (alglucosidase alfa) 2000 L to the Myozyme (alglucosidase alfa) 4000 L scale material.

RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

[3] A similar investigation was ongoing to determine the root cause for contamination of a 4000 L bioreactor at the Geel, Belgium manufacturing facility in September 2008.

As described in the complete response letter dated February 27, 2009, in accordance with section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA), we have determined that a REMS is necessary for Lumizyme (alglucosidase alfa) to ensure that the benefits of the drug outweigh the potential risk of rapid disease progression in infantile-onset Pompe disease patients and patients with late (non-infantile) onset disease less than 8 years of age for whom the safety and effectiveness of Lumizyme (alglucosidase alfa) have not been evaluated. In addition, we have determined that a REMS is necessary to ensure that the known risks of anaphylaxis and severe allergic reactions associated with the use of Lumizyme (alglucosidase alfa), and the potential risks of severe cutaneous and systemic immune complex-mediated reactions to Lumizyme (alglucosidase alfa) are communicated to patients and prescribers.

As of this writing, review of Genzyme's proposed REMS submitted on November 7, 2008, and amended on February 24 and 25, April 6, May 15, June 30, and September 25, 2009 is nearly complete.

The elements of the REMS will be a communication plan, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

The elements to ensure safe use will include: 1) the requirement for patients, healthcare facilities and prescribers to enroll in the Lumizyme ACE (Alglucosidase Alfa Control and Education) program, 2) a training module for healthcare facilities and prescribers, and 3) a restricted distribution system to ensure that only patients enrolled in the ACE program receive Lumizyme, and that only prescribers and healthcare facilities enrolled in the ACE program are able to prescribe and administer Lumizyme.

As part of the implementation system, Genzyme will be required to 1) maintain a database of certified healthcare facilities and prescribers, and enrolled patients, 2) monitor re-enrollment of participants, and 3) monitor healthcare facilities and prescribers to ensure that Lumizyme is infused only to patients enrolled in the ACE program.

REMS assessments will be required at 6 months, 1 year, and then annually, from the date of approval of the BLA.

POSTMARKET REQUIREMENTS

As described in the complete response letter dated February 27, 2009, FDA has determined that, if BLA 125291 is approved, Genzyme will be required to conduct postmarketing studies of Lumizyme (alglucosidase alfa) to assess the known serious risks of anaphylaxis and severe allergic reactions, and signals of severe cutaneous and systemic immune complex-mediated reactions. Specifically, the studies that will be required, pursuant to section 505(o)(3) of the FDCA, are:

1. A retrospective immunogenicity study based on the pattern of antibody responses in patients enrolled in the Late Onset Treatment Study (LOTS) and LOTS Extension Studies. (b) (4)

(b) (4)

2. A prospective safety study conducted within the ongoing Pompe Registry to assess the known serious risks of anaphylaxis and severe allergic reactions, and signals of severe cutaneous and systemic immune complex-mediated reactions with Lumizyme (alglucosidase alfa) treatment.

TRADENAME REVIEW

The Division of Medication Error Prevention and Analysis has found the proposed tradename "Lumizyme" to be acceptable.

Julie Beitz 11-13-09

Julie Beitz, MD
Director, Office of Drug Evaluation III
CDER, FDA

Cross-Discipline Team Leader Review

Date	November 10, 2009
From	Lynne Yao, M.D., Acting Clinical Team Leader, DGP
Through	Donna J. Griebel, M.D., Director, DGP
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	BLA 125291/0/72 Complete Response Resubmission
Applicant	Genzyme
Date of Submission	May 15, 2009
PDUFA Goal Date	November 14, 2009
Proprietary Name / Established (USAN) names	Lumizyme/Alglucosidase alfa
Dosage forms / Strength/Dose	Intravenous injection/50 mg/10 mL vial (reconstituted)/ 20 mg/kg every other week
Proposed Indication(s)	Late-onset Pompe disease
Recommended:	*Complete Response (CR)*

11/10/09 MD

MD 11/10/09

I. Introduction

This memorandum reviews the information submitted by the Applicant, Genzyme, in response to a Complete Response Letter issued by the Agency on February 27, 2009, for BLA 125291, Lumizyme (alglucosidase alfa), for the treatment of late-onset Pompe disease. This review focuses on the deficiencies cited in the Complete Response Letter issued and the adequacy of the responses provided by the Applicant regarding these deficiencies. The Complete Response Letter noted deficiencies in the manufacturing facilities; chemistry, manufacturing, and controls (CMC); and clinical areas. These deficiencies are briefly outlined below, and are fully reviewed in this document.

There were substantive facility deficiencies uncovered during the Agency's inspection that lead to the issuance of FDA Form 483 on October 10, 2008, by the New England District Office. The deficiencies cited in the Form 483 were not adequately addressed by the Applicant and, therefore, the Office of Compliance issued a Warning Letter on February 27, 2009. The Warning Letter cited the following deficiencies: (b) (4) (b) (4) (b) (4) Additionally, the Office of Compliance recommended that a withhold approval action be taken. The Applicant has provided responses to all of these deficiencies, and the facility was re-inspected in late May 2009, and again in October 2009.

There were four CMC deficiencies cited in the Complete Response Letter. The CMC deficiencies cited were 1) inadequate cell viability monitoring; 2) lack of an established reference standard; 3) inadequate product acceptance criteria; 4) inadequate system suitability

criteria. All of these deficiencies have been satisfactorily addressed by the Applicant based on the review of Frederic Mill, Ph.D., the Product Quality reviewer.

There were two clinical deficiencies cited in the Complete Response Letter. These deficiencies include the inability to agree upon a verification study required for 21 CFR 601 Subpart E approval (accelerated approval), and the inability to agree upon a complete Risk Evaluation and Mitigation Strategy (REMS). Discussions regarding the design of an appropriate verification study were held between the Agency and the Applicant between February, 2009 and May, 2009. New data were submitted by the Applicant that included retrospective clinical outcome data in infantile-onset Pompe patients treated with Lumizyme from the Pompe Registry, a multinational disease registry. After review of these data, the Agency agreed that the Applicant could submit data from the Pompe Registry for review to establish the effectiveness of Lumizyme in late-onset Pompe patients to support regular approval of Lumizyme. Thus, the requirement for a verification study under Subpart E approval could be waived if adequate clinical data were available to support a full approval. A review of the Pompe registry data included 25 infantile-onset patients that were age and disease-matched to an historical control cohort. This historical control cohort was the same cohort used to compare the effect of Myozyme in the clinical trial that led to the approval of Myozyme in 2006. The overall survival and survival at 18 months in Lumizyme-treated patients compares favorably with an age-matched, diseased-matched historical control group. Eighteen month survival for Lumizyme-treated patients was 57% compared with 1.9% in the historical control group.

A REMS was required by the Applicant to mitigate the potential risk of rapid disease progression in infantile-onset Pompe disease patients and patients with late (non-infantile) onset disease less than 8 years of age for whom the safety and effectiveness of Lumizyme have not been evaluated, and to ensure that the known risks of anaphylaxis and severe allergic reactions, and the potential risks of severe cutaneous and systemic immune-mediated reactions to Lumizyme are communicated to patients and prescribers. A satisfactory REMS was negotiated with the Applicant during this review cycle. The Lumizyme Access, Control, and Education (ACE) Program includes all components of a REMS to ensure that the benefits of Lumizyme outweigh the risk. The ACE program includes goals; a communication plan; elements to assure safe use; an implementation system; and a system of assessments. A medication guide was not required because patients would be expected to receive treatment only at specialized infusion centers under the supervision of trained personnel.

The Complete Response provided by the Applicant includes clinical information from the Pompe Registry, a multinational disease registry, to support the full approval of Lumizyme. A safety update, including data from the Applicant's postmarketing pharmacovigilance database, the Alglucosidase Temporary Access Program (ATAP, formerly the Myozyme Temporary Access Program, MTAP), and the completed Late-Onset Treatment Study (LOTS) extension trial were also submitted in the Complete Response. A review of this additional clinical efficacy and safety information is included in this memorandum.

The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of the Therapeutic Biologic-Establishment Evaluation Report (TB-EER)

and states that the Allston Landing, MA facility continues to be classified as Official Action Indicated (OAI), an unacceptable compliance status. A facilities re-inspection was performed by the New England District Office (NEDO) in May, 2009. However, the corrective actions to resolve the deficiencies in the Warning Letter were found to be incomplete at the time of this inspection, and therefore, another re-inspection was performed in October, 2009. The New England District Office determined that the facility does not comply with requirements set forth in the 21 CFR 601.20 (a) and (d). As a result of the adverse findings, NEDO updated the firm's GMP profile to "further action indicated" on November 6, 2009. Therefore, the Office of Compliance, Division of Manufacturing and Product Quality (DMPQ) issued a memo recommending a withhold approval action be taken for Lumizyme on November 6, 2009.

There were satisfactory responses to all of the clinical deficiencies cited in the Complete Response Letter, additional clinical evidence provided by the Applicant from the Pompe Registry, and satisfactory responses to all CMC deficiencies. However, the manufacturing deficiencies cited in the Complete Response Letter and the Warning Letter have not been adequately resolved. Therefore, the recommendation from the Office of Compliance is to withhold approval of Lumizyme due to the unacceptable compliance status of the manufacturing facility at Allston Landing, MA. I concur with the recommendation that a Complete Response action be taken for Lumizyme.

II. Background

Clinical Background

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, known collectively as the late-onset form, 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.[1]

[1] Scriver CR, Beaudet AL, Sly WS, et. al. The Metabolic and Molecular Bases of Inherited Disease, eighth ed., McGraw-Hill Medical Publishing, New York, 2001, pg. 3389-3420

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.

Regulatory History

Regulatory History of Lumizyme

The Applicant manufactures alglucosidase alfa for use in the United States (US) in two production scales, a 160 liter (L) production scale (Myozyme), and a 2000 liter (L) production scale (Lumizyme). Currently, the only treatment approved in the US for Pompe disease is Myozyme. Myozyme 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 ≤ 7months at the time of first infusion) as compared to an age-matched, untreated historical control. Approval of Myozyme 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 Myozyme 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 160 L product has not been able to meet the demand for 160 L product in the US and a drug shortage exists. The Applicant has limited access to 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 10,780). However, the Applicant stopped this temporary access program for the 2000 L product as of April 15, 2008, and Pompe patients over 18 years of age in US are not eligible for treatment under any active IND or access program. The Applicant reports that at least 40 patients in the US have directly requested Genzyme to provide access to treatment with Lumizyme, and estimates that there are at least 50-150 adult Pompe patients in the US that are unable to receive treatment due to the drug shortage. It should be noted that Myozyme is the tradename give to the 160 L product within the US, but outside the US, Myozyme is the tradename used for the 2000 L product. However, given the requirement for separate licensure of these two products in the US, the Agency and Applicant have agreed in the US to name the 160 L product, Myozyme, and the 2000 L product, Lumizyme. The 2000 L product will be referred

to as Lumizyme and the 160 L product will be referred to as Myozyme throughout the remainder of this document.

Initial Submission

In May, 2008, Genzyme submitted a separate BLA seeking the approval of the 2000 L product (Lumizyme) because comparability with the 160 L product could not be established based on clinical, nonclinical, or biochemical data. The clinical data submitted for review included one multicenter, randomized, double-blind, placebo-controlled trial of 90 late-onset Pompe disease patients (Late-Onset Treatment Study or LOTS). Numerous statistical analysis issues were identified during the review and led to concerns regarding the Applicant's analysis of the primary endpoints; change in distance walked at 78 weeks in a six-minute walk test (6MWT), and change in % predicted forced vital capacity (% predicted FVC). An Endocrinology and Metabolic Drugs Advisory Committee (EMDAC) was convened on October 21, 2008, to obtain advice regarding statistical and clinical review issues. The committee voted 16 to 1 to approve Lumizyme based on the clinical data presented. However, the majority of the committee recommended approval under 21 CFR 601 Subpart E, accelerated approval, based on improvement in % predicted FVC. Under Accelerated Approval regulations, the Applicant would be required to perform a post-marketing verification study to confirm the clinical effectiveness of Lumizyme. The committee also voted 17 to 0 to require post-marketing safety studies to address the concerns of anaphylaxis, immunogenicity, and potential chronic immune-mediated reactions. The committee members also recommended that a REMS be required to ensure the safe use of Lumizyme.

Despite the EMDAC vote to recommend accelerated approval of Lumizyme, the Agency was unable to approve Lumizyme during the first review cycle because of several deficiencies including:

1. Manufacturing facility deficiencies that led to the issuance of a Warning Letter
2. Product quality (CMC) deficiencies
3. Inability to agree upon a verification study required for Subpart E approval
4. Inability to agree upon a final Risk Evaluation and Mitigation Strategy (REMS)

Thus, a Complete Response Letter was issued on February 27, 2009 by J. Beitz, M.D., Director, Office of Drug Evaluation III.

Current Submission

The Agency and the Applicant held discussions between February and May, 2009, to review the design and conduct of a verification study required for Subpart E approval. The Agency and Applicant agreed that additional information from the Pompe Registry may be sufficient to provide full approval for Lumizyme. The Pompe Registry is a multinational disease registry with clinical outcome data collected in Pompe patients treated with Lumizyme since 2006. Therefore, additional clinical outcome data from the Pompe Registry submitted as part of the Applicant's complete response was believed to offer the potential for the elimination of the requirement for approval under Subpart E, and the requirement to perform a verification study. A safety update was also required as part of the Complete Response and was negotiated with

the Applicant. The Agency and Applicant agreed that additional safety information that would be required with the Complete Response should include:

1. Cumulative, final data from AGLU 03206 (LOTS extension)
2. Cumulative interim safety data from AGLU03907 (ATAP) as reported in IND 10,780 annual report submitted on October 15, 2008, and any additional late-breaking safety information to a cutoff of March 16, 2009
3. Spontaneous post-marketing serious case reports as reported in the periodic AE report from March 29, 2008 through December 28, 2008, with any additional late-breaking safety information to a cutoff of March 16, 2009

Additionally, continued discussions occurred between the Agency and the Applicant regarding product labeling, and revisions to the REMS that would be included as part of the Applicant's Complete Response submission.

The Reviewer also notes the Agency was informed by the Applicant in January 2009, that they intended to seek approval of a 4000 L production scale of alglucosidase alfa in the US during the course of 2009. Genzyme received marketing approval for the 4000 L product in the European Union (EU) based on biochemical comparability in February 2009. The Applicant also informed the Agency in April 2009, that the company was not planning to continue producing Lumizyme in the US after September 2009. Despite this, Genzyme planned to submit a Complete Response to the Lumizyme application so that the 4000 L product could be later submitted as a supplement to the Lumizyme BLA, assuming a favorable outcome of the Lumizyme resubmission. Based on this scenario, the Applicant estimated that a drug shortage for Lumizyme would be likely after September, 2009, if the 4000 L scale product was not approved in the US. Therefore, the Agency agreed to attempt to take an early action after the Applicant's submission of a complete response planned for May 2009. However, a re-inspection of the Allston Landing facility by the New England District Office in May 2009, revealed that the Applicant had not completed all the corrective actions required in the Warning Letter, and that the corrective actions would not be fully in place until September 2009. Therefore, a re-inspection of the Allston Landing facility was scheduled for early October 2009. Thus, despite efforts by the Agency to facilitate an early action to alleviate the drug shortage issue, the Applicant was unable to institute all corrective actions to address the deficiencies cited in the Warning Letter to allow for an action on the Lumizyme resubmission before late October 2009.

The Lumizyme BLA resubmission was dated May 15, 2009. It was classified as a six-month resubmission with a PDUFA deadline of November 11, 2009.

No Advisory Committee meeting was convened to discuss this resubmission; however, an advisory committee was convened during the first cycle review as described above.

The following review disciplines have provided written evaluations and recommendations that were reviewed as part of this document:

Clinical Review by C. Mueller, dated November 9, 2009

Clinical Review by L. Yao, dated November 9, 2009
Chemistry Review (Division of Therapeutic Proteins) by F. Mills, with DTP Deputy Director concurrence by B. Cherney, dated September 23, 2009
Division of Medication Error Prevention and Analysis (DMEPA) Proprietary Name, Label and Labeling Review by Z. Oleszczuk, dated September 14, 2009
Division of Risk Management Review by Y. Choudhry, dated October 21, 2009
Memo, CDER Office of Compliance, Division of Manufacturing and Product Quality, dated November 6, 2009

The reviews should be consulted for more specific details of the application. The reader is also referred to the first cycle CDTL Review by J. Ku dated February 26,2009, as well as to the primary review documents from that cycle. This memorandum summarizes selected information from the review documents, with primary emphasis on the issues to be resolved in the current review cycle.

III. Chemistry, Manufacturing, and Controls

The reader is referred to the CDTL Review by J. Ku, dated February 26, 2009, and the DTP review by F. Mills, dated February 27, 2009, for complete details.

A. General product quality considerations

Aglucosidase alfa is produced as a lyophilized powder that is intended for intravenous injection. The product is provided in a 20 ml vial containing 52.2 mg alglucosidase alfa, along with various excipients. Each vial contains 50 mg of alglucosidase alfa. The drug substance and the drug product are manufacture by Genzyme Corporation (the Applicant) at the Allston Landing, MA facility.

Initial Submission

During the initial review, the CMC Reviewer noted several critical product attributes that differed between Myozyme and Lumizyme. (b) (4) These differences in critical product attributes could potentially contribute to differences in potency and immunogenicity between the two products. Additionally, the CMC review included several deficiencies that were not addressed by the Applicant during the first review cycle and were noted in the Complete Response letter:

1. Cell viability is a critical parameter for controlling product quality during (b) (4) You will need to provide adequate justification for not using cell viability as an in-process control for bioreactor monitoring.

2. An established reference standard for use in your testing control strategy that is representative of the 2000 L process has not been submitted to this BLA. You will need to provide data to support the qualification of a reference standard.

3. The acceptance criteria for drug substance and drug product specifications are not consistent with manufacturing process capability and considerations regarding potential impact on safety

and efficacy. You will need to provide an evaluation on the following analytical tests: (b) (4) (b) (4) assay; SDS-PAGE gel assays; HPLC for measurement of (b) (4) ; HPAEC-PAD for measurement of (b) (4) ; and size exclusion chromatography.

(b) (4)

Current submission

The reader is referred to the Product Quality Review dated September 14, 2009, by F. Mills, Division of Therapeutic Proteins.

The Applicant submitted information to address all four CMC deficiencies.

1. The Applicant has proposed monitoring two cell culture metabolic parameters (b) (4) in place of cell viability monitoring, and to establish in process control limits for cell viability during the (b) (4) period as a post-marketing commitment.

2. The Applicant included data to support the proposed 2000 L reference standard (b) (b) There appears to be consistency in critical quality attributes (i.e., total (b) (4) between (b) (4) and Lumizyme. Additionally, (b) (4) appears to be an in-trend standard for Lumizyme based on silver-stain SDS-PAGE and Western blot data.

3. The Applicant has provided acceptance criteria (b) (4) that have been agreed upon with the Division of Therapeutic Proteins.

4. The Applicant has revised system suitability criterion for % coefficient of variation (CV) (b) (4). This "tighter" % CV will result in improved system suitability for precision.

The Applicant Complete Response to the CMC deficiencies addresses all the deficiencies noted in the Complete Response Letter. Additionally, the Applicant has agreed to perform four post-marketing commitment studies (see section XIII.D; Recommendations for Other Postmarketing Requirements and Commitments) to further evaluate release testing for drug substance, release and stability specifications, drug product stability, and cell viability.

Final Recommendation

Based on acceptable responses by the Applicant to the four CMC deficiencies included in the Complete Response Letter, and the agreement to perform 4 post-marketing commitment studies, the CMC reviewer recommends an approval action for Lumizyme. The Deputy Director for the Division of Therapeutic Proteins concurs with this recommendation.

B. Facilities review/inspection

Initial Submission

The Division of Manufacturing and Product Quality (DMPQ) performed a facility inspection of the Applicant's Allston Landing facility, where Lumizyme is manufactured and this inspection uncovered several deviations from current Good Manufacturing Practices including the following:

(b) (4)

[redacted]

(b) (4)

These deficiencies were cited in an FDA Form 483 issued to the Applicant on October 10, 2008. The Applicant issued a response to these deficiencies; however, the response was deemed inadequate, and the Office of Compliance issued a Warning Letter on February 27, 2009, based on the following deficiencies:

1. Failure to establish and follow written procedures designed to prevent microbiological contamination of drug products
2. Failure to assure that there are written production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess
3. Failure to follow written procedures for the maintenance of equipment used in the manufacture, processing, packaging or holding.
4. Failure to maintain computerized systems in a validated state.

The Office of Compliance also recommended that a withhold approval action be taken.

It should also be noted that during the first review cycle, a 2000 L bioreactor producing Lumizyme crashed (i.e., rapid cell death occurred in the bioreactor) at the Allston Landing facility on November 14, 2008. In addition, a 4000 L alglucosidase alfa bioreactor crash occurred in September, 2009, at their Geel, Belgium facility, and another 2000 L bioreactor crash (during production of Cerezyme, an enzyme replacement therapy for Gaucher disease) occurred in May 2009 at the Allston Landing facility. Subsequently, the Applicant reported that the bioreactor crash was likely due to viral contamination with Vesivirus 2117. These bioreactor crashes have led to further drug shortage issues with Lumizyme, as well as Cerezyme, and Fabrazyme, an enzyme replacement therapy for Fabry disease. All of these treatments are produced at the Allston Landing facility with the 2000 L bioreactor process. An analysis of these bioreactor crashes has thus far failed to determine a root cause; however, the Applicant has stated that a contamination of raw materials used in the manufacturing process may be involved.

Current Submission

The New England District Office re-inspected the Allston Landing facility in May 2009, in follow-up for the deficiencies noted in the Warning Letter. However, this re-inspection was incomplete because the Applicant had not instituted full corrective actions at the facility by the time of the re-inspection. Therefore, a second re-inspection was required and occurred in October 2009. The NEDO inspectors determined that the facility does not comply with requirements set forth in the 21 CFR 601.20 (a) and (d). As a result of the adverse findings, the New England District Office updated the firm's GMP profile to "further action indicated." The adverse findings uncovered by the New England District Office will be issued in a full report; however, the full report is pending at the time of this review. Additionally, based on the adverse findings noted thus far, the Sponsor's CGMP profile continues to be classified as Official Action Indicated (OAI), an unacceptable compliance status. Therefore, the Office of

Compliance issued memo recommending a withhold approval action be taken for Lumizyme on November 6, 2009.

Final Recommendation
As stated above, the final recommendation from the Office of Compliance is to withhold approval of Lumizyme due to persistent adverse findings leading to an unacceptable compliance status for the Lumizyme manufacturing facility at Allston Landing, MA.

IV. Nonclinical Pharmacology/Toxicology

Initial Submission
The reader is referred to the Pharmacology/Toxicology Review by N. Mehta dated January 30, 2009 for complete information.

Two nonclinical pharmacology/toxicology studies were reviewed during the original review cycle, as well as cross-referenced nonclinical pharmacology/toxicology studies submitted under BLA 125141 for Myozyme. The Reviewer noted that Lumizyme produced similar glycogen clearance as compared with Myozyme but the glycogen clearance assays used in these studies were insufficiently sensitive to establish comparability between the two products. Two other studies suggest that glycogen clearing activity appeared to be directly correlated with mannose-6-phosphate receptor binding affinity. Toxicology studies demonstrated no treatment-related effects on developmental parameters. Based on the results of a 6-month repeat-dose toxicity study of rhGAA in juvenile mice, the NOAEL of rhGAA was 20 mg/kg/every other week. The kidney and the thymus were the primary target organs of toxicity. Five reproductive toxicity studies showed no treatment-related effects on fertility or early embryonic development in mice, or on fetal development in rabbits. A special toxicology study demonstrated that methotrexate induced a long-lived reduction in alglucosidase alfa directed antibody responses.

The Reviewer recommended approval provided agreement could be reached regarding recommended labeling changes. No post-marketing commitments or requirements were recommended.

Current Submission
There were no nonclinical issues cited in the Complete Response letter. Thus, there are no nonclinical issues reviewed in the Applicant's current submission.

V. Clinical Pharmacology/Biopharmaceutics

Initial Submission
The reader is referred to the Clinical Pharmacology Reviews by J. I. Kim and the Pharmacometrics Review by J. Earp, both dated January 7, 2009, for complete information.

General clinical pharmacology and intrinsic factors potentially affecting elimination
Lumizyme is a therapeutic protein product that is disintegrated to amino acid and it is not expected to be excreted.

Multiple-dose pharmacokinetic (PK) parameters of Lumizyme were estimated in 32 patients with late-onset Pompe disease patients in LOTS. PK parameters (Cmax, AUCinf, clearance, Vss, and effective half life) appear to be comparable at Weeks 0, 12, and 52.

Drug-drug interactions
No studies were conducted to evaluate drug-drug interactions.

Through QT (TQT) Study or other QT assessment
Lumizyme is a biologic product. No TQT study or other QT assessment was performed.

Demographic interactions/special populations
No studies were done to evaluate the effects of demographic or special populations on the PK of Lumizyme.

Immunogenicity
All patients in the Lumizyme-treated group tested positive for anti-rhGAA IgG antibodies as assessed by enzyme-linked immunosorption assay (ELISA) and confirmed by radio-immunoprecipitation assay (RIP). The median time to seroconversion was 4 weeks after exposure. Approximately 61% of the patients trended toward decreasing titers from peak to last observation with continued treatment. However, 9 of 59 (15%) of patients who developed positive IgG titers during the study had a persistently elevated IgG titer at the end of the study. The median peak titer was 6,400 (range 200 to 819,000), and the median last titer was 1,600.

None of the 60 IgG positive patients tested positive for inhibition of enzyme activity. However, 10 patients (17%) tested positive, 8 (14%) borderline positive, and 41 (68%) negative for inhibition of cellular uptake into fibroblast cells. Both high anti-rhGAA IgG antibody titers and positive inhibitory antibody status appeared to affect PK: five patients with the highest binding IgG titer also tested positive for inhibitory antibody, and these 5 patients had higher mean CL, lower Cmax, and lower AUC than the 29 patients with negative status. There is insufficient data, however, to indicate whether inhibitory or high IgG antibodies are responsible for the increased clearance.

The Pharmacometrics Reviewer noted that although the data suggested a trend towards higher improvement in the 6 minute walk test (6MWT) with higher IgG titers and possibly also with positive inhibitory antibody status, he felt that the clinical significance of high antibody titers or positive uptake inhibition status remains unclear. No change in % predicted FVC was noted. There was no apparent association between higher anti-rhGAA IgG titers and occurrence of infusion reactions.

The Clinical Pharmacology review team recommended an approval action, provided agreement could be reached regarding the recommended labeling changes. The review team also recommended that additional PK data be collected in Pompe patients less than 21 years of age to further characterize the PK profile in pediatric patients as part of a verification study. This recommendation has been incorporated into a post-marketing commitment (see section XIII.D. Postmarketing Requirements and Commitments).

Current Submission
There were no clinical pharmacology issues cited in the Complete Response letter. Thus, there are no clinical pharmacology issues reviewed in the Applicant's current submission.

VI. Clinical Microbiology

There were no clinical microbiology issues presented in the original review. Thus, there are no clinical microbiology issues reviewed in the Applicant's current submission.

VII. Clinical/Statistical- Efficacy

Initial Submission
The reader is referred to the CDTL Review by J. Ku dated February, 26, 2009, and the Clinical Review by L. Yao dated February 26, 2009, and the statistical review by L. Kammerman, dated February 9, 2009, for complete information.

Lumizyme was studied in a multicenter randomized, double-blind, placebo-controlled trial of 90 late-onset Pompe disease patients (Late-Onset Treatment Study or LOTS). Enrollment was restricted to patients 8 years and older who were naïve to enzyme replacement therapy, ambulatory, did not require invasive ventilatory support, and had an FVC between 30 and 79% of the predicted normal value in a healthy population. Patients were randomized 2:1 to either 20 mg/kg administered intravenously every two weeks or placebo.

The original design of LOTS was a 52 week trial with the co-primary endpoints of 1) distance (meters) walked during the 6MWT at 52 weeks, adjusted for the baseline, and 2) upright % of predicted FVC at 52 weeks, adjusted for the baseline. The 6MWT was to be examined first; if the treatment effect was statistically significant, then the effect on % of predicted FVC would be evaluated. A computerized minimization algorithm, rather than blocked randomization, was used to randomize the patients. While the study was ongoing, the design was revised to an adaptive strategy in order to determine, through an interim analysis, the optimal duration of the study, and compare the two treatments over the course of the study rather than focusing on comparisons at 52 weeks. Adoption of this strategy resulted in an extension of the trial to 78 weeks, changes in the definition of the primary endpoints, and a decision to use a linear effects model that assumed the 6MWT and FVC results would change linearly over time.

When the trial was completed and data were unblinded, it was observed that patients experienced improvement in the 6MWT from baseline to week 26 and then plateaued rather than continuously improved throughout the 78 weeks. Thus, the results had not satisfied the model assumption of linearity. Additionally, assumptions about the variance were also violated. To mitigate the violation of these assumptions, the applicant presented statistical models that were not pre-specified. Further complicating the analysis of the results was the use of a minimization algorithm to maintain a 2:1 ratio (Lumizyme: placebo) within study sites and within strata defined by baseline values for the 6MWT and FVC. Re-randomization tests are the appropriate approach for assessing statistical significance when a minimization

algorithm is used. Usually, the result from using re-randomizations tests is similar to the result from using classical tests. This was not the case in LOTS. For example, for the ANCOVA of the 6MWT, the p-value changed from 0.035 to 0.06 with re-randomization. Based on these complications, the statistical Reviewer concluded that the most appropriate analytic method to use to analyze the results from LOTS was an analysis of covariance model (ANCOVA).

Thus, the results from LOTS as analyzed using ANCOVA demonstrate that after 78 weeks, the mean 6MWT increased by 25 meters for Lumizyme-treated patients and decreased by 3 meters for placebo-treated patients, indicating a treatment difference of 28 meters (p=0.06) (see Table 1). Additionally, the mean % predicted FVC at 78 weeks increased by 1.2% for Lumizyme-treated patients and decreased by 2.2% for placebo-treated patients indicating a treatment difference of 3.4% (95% CI: 1.0, 5.8%, p=0.004) (see Table 2).

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

	Lumizyme N=60	Placebo N=30	Difference
Summary statistics:			
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
Results of ANCOVA:*			
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)

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

	Lumizyme N=60	Placebo N=30	Difference
Summary statistics:			
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
Results of ANCOVA:*			
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)

An Endocrinology and Metabolic Drugs Advisory Committee (EMDAC) was convened to obtain advice regarding the statistical and clinical review issues. The Advisory Committee voted 16-1 that the effectiveness of Lumizyme had been demonstrated in LOTS, however, twelve members recommended that accelerated approval be granted based on the FVC findings. Under Accelerated Approval regulations, the Applicant would be required to perform a post-marketing verification study to confirm the clinical effectiveness of Lumizyme. Additionally, the committee voted 17 to 0 to require post-marketing safety studies to address the concerns of anaphylaxis, immunogenicity, and potential chronic immune-mediated reactions. The committee members also recommended that a REMS be required to ensure the safe use of Lumizyme.

Current Submission

The reader is referred to the Clinical Review by C. Mueller for complete information.

As stated above, the Agency and Applicant agreed that additional information from the Pompe Registry, a multinational disease registry with clinical information collected in Pompe patients treated with Lumizyme since 2006 may provide sufficient clinical outcome information to support regular approval for Lumizyme. Therefore, additional clinical data from the Pompe Registry submitted as part of the Applicant's Complete Response might eliminate the requirement for approval under Subpart E, and the requirement to perform a verification study as stated in the Complete Response Letter issued on February 27, 2009. Thus, additional data submitted by the Applicant in their Complete Response includes clinical outcomes data from the Pompe Registry.

The Pompe Registry is a disease registry that was established as a post-marketing commitment as a condition for approval of Myozyme in 2006. The Registry was designed as a multi-center, multi-national, observational program, and was initiated in September, 2006. The primary objectives of this voluntary registry were to evaluate the long-term effectiveness and safety of available treatment options, including ERT, in patients with Pompe disease, and to enhance the understanding of the natural history of Pompe disease. The data collected are based on standard of care clinical assessments as determined by the patient's physician, but include recommended assessments such as demographic information, clinical examination and laboratory assessments, cognitive, motor, and developmental assessments, quality of life assessments, antibody testing for patients receiving ERT, and neuron-imaging studies. Long-term clinical outcomes such as survival, ventilator-free survival are also collected. It should be noted that the registry includes both prospectively and retrospectively collected data.

The Applicant submitted clinical data from the Pompe registry comparing clinical outcome in a subset of infantile-onset Pompe patients treated exclusively with Lumizyme with an age and diseased-matched historical control. The clinical outcome of primary interest was survival, but ventilator-free survival was also included. Use of an age and disease-matched cohort of infantile-onset patients would be expected to provide more definitive outcomes over an 18 to 24 month period as compared with late-onset patients, whose clinical course would not be expected to decline as rapidly. Additionally, the Applicant was aware of a cohort of infantile-onset patients treated exclusively with Lumizyme because Lumizyme has been approved for use in all Pompe patients outside the U.S. since 2006. Thus, evaluation of clinical outcomes in

a cohort of infantile-onset Pompe patients from the Pompe registry was performed to establish supportive clinical efficacy of Lumizyme.

The Applicant reviewed the Pompe registry for infantile-onset patients who matched inclusion criteria for AGLU1602, the Phase 3 trial that led to the approval of Myozyme. These criteria included:

1. Onset of symptoms of Pompe disease on or before 6 months of age
2. Confirmed diagnosis based on GAA activity
3. Evidence of hypertrophic cardiomyopathy
4. Initiation of treatment prior to 6 months of age

Overall, there were 48 patients enrolled in the Pompe registry meeting these inclusion criteria. However, only 25 of these patients had not been previously studied or reported by the Applicant, or had received Lumizyme or Myozyme exclusively. Of these 25 patients, 10 US patients received Myozyme exclusively, and 15 ex-US patients received Lumizyme exclusively. The median duration of treatment, median age at first infusion, and median age at death or last follow-up were similar between the Myozyme and Lumizyme treatment groups.

Survival

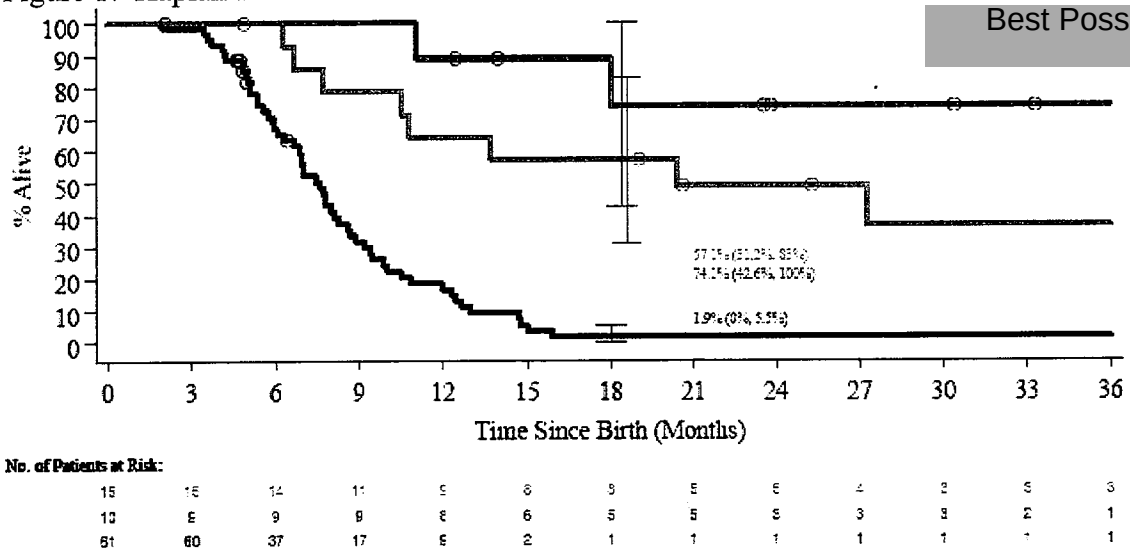
Based on data from natural history studies in infantile-onset Pompe disease, only 3% of patients survive past the age of 18 months. Therefore, the Applicant evaluated survival and ventilator-free survival at 18 months in Lumizyme and Myozyme treated patients compared to this historical control population. There appears to be an increase in survival at 18 months in both the Lumizyme and Myozyme treatment groups compared with the historical control. Table 3 shows the overall survival by treatment group. The reviewer also notes an increase in survival in the Myozyme treatment group compared with the Lumizyme group, however, this analysis included only a small numbers of patients and, therefore, clear conclusions based on these observations cannot be made.

Table 3: Overall Survival

Survival	Lumizyme (%)	Myozyme (%)	Historical control (%)
Alive	5 (33)	8 (80)	1 (2)
Deceased	10 (67)	2 (20)	60 (98)
Total	15	10	61

As stated above, evaluation of survival at 18 months was of interest as this was the clinical endpoint used in AGLU1602. The Kaplan Meier estimate demonstrates a difference in survival at 18 months between patients treated with Myozyme or Lumizyme and the historical control group (see Figure 1). Again, it is difficult to draw clear conclusions from these data based on the limited sample size, however, it should be noted that the 95% confidence intervals for the treated groups do not overlap with the historical control group, suggesting a substantive difference in survival. Table 3 shows *overall survival,* not survival at 18 months, and the reviewer also noted that (data not shown in the table 3) only 1/15 Lumizyme treated patients and 3/10 Myozyme patients were alive, but had not reached 18 months of age.

Figure 1: Kaplan-Meier estimate of time to death from date of birth



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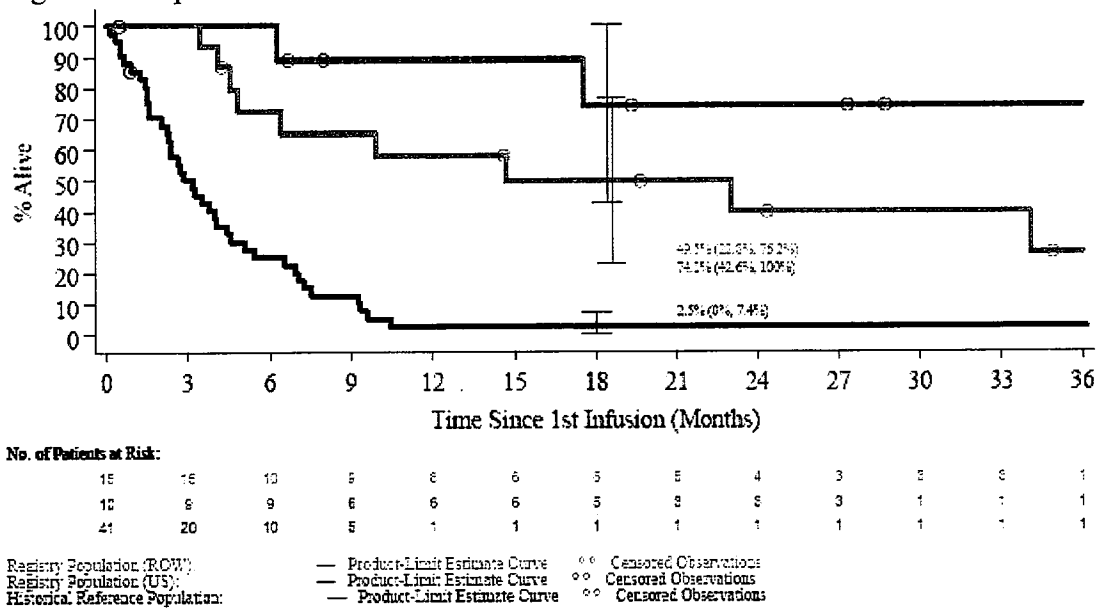
Additionally, the Applicant evaluated the overall survival and survival at 18 months based on the time from the first treatment. The reviewer included this analysis because time of death from initiation of treatment would be more likely to assess the effect of treatment on overall survival than time from birth. However, all patients began treatment before 6 months of age, and therefore, differences in time from first treatment or birth are relatively small. Figure 2 shows the Kaplan-Meier estimate of the time of death from the date of the first infusion. There do not appear to be substantive differences between survival based on date of birth or date of first infusion.

Figure 2: Kaplan-Meier estimate of time to death from date of first infusion



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Although ventilator-free survival was also evaluated as a clinical outcome measure, there were insufficient numbers of patients to assess this outcome measure. Only three patients received invasive ventilation, and two of these patients were receiving invasive ventilation prior to initiation of treatment with alglucosidase alfa. Therefore, only one patient received invasive ventilation prior to death, and thus, invasive ventilator-free survival as an outcome measure separate from overall survival does not reflect a meaningful outcome measure in these registry data. It is this reviewer's opinion that these findings may be explained by the fact that physicians may be counseling families against initiation of invasive ventilation in patients with progressive disease. However, this opinion cannot be confirmed.

Immunogenicity

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 Lumizyme-treated patients developed anti-rhGAA IgG antibodies by week 20 of the study. Of the 25 patients from the Pompe registry evaluated, only 17 patients had antibody information reported. Thus, it is not possible to evaluate the effect of immunogenicity on either safety or efficacy in these patients since this information was collected in a minority of patients evaluated. Only 8/25 patients had antibody data reported, and the majority of these patients (7/8) were treated with Myozyme in the US. However, in 8 patients for whom antibody data is available, 3 of 4 patients with antibody titer > 100,000 (range 102,400-409,600) died, while all patients (4/4) with antibody titers < 100,000 (range 100-51,200) survived. These data suggest that patients with higher antibody responses to alglucosidase alfa had worse outcome, however, the numbers of patients is too small to make clear conclusions regarding immunogenicity and outcome.

CRIM status

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.[2] Infantile-onset patients are more likely to be CRIM-negative. CRIM status for the 25 patients from the Pompe Registry included in the Complete Response was reviewed. The reviewer noted that 5/15 patients (33%) were CRIM negative in the Lumizyme group, and 1/10 patients (10%) were CRIM negative in the Myozyme group. CRIM status was not available in 6/15 (40%) patients in the Lumizyme group, and 3/10 (30%) of patients in the Myozyme group. Overall survival in CRIM negative patients was 20% (1/5 patients) in the Lumizyme group, whereas 100% of CRIM negative patients in the Myozyme group were alive. Additionally, 4/10 (40%) of the patients who died in the Lumizyme group were CRIM negative, whereas none of the patients who died in the Myozyme group were CRIM negative. These data suggest that differences in

[2] Kishnani PS, Corzo D, Nicolino M, et al., Recombinant human acid α-glucosidase: Major clinical benefits in infantile-onset Pompe disease, Neurol, 2007, 68:99-109

CRIM status may contribute to the increase in mortality in the Lumizyme group, however, the numbers of patients is too small to establish clear conclusions regarding these data.

Conclusions/Recommendations
The original Complete Response letter identifies one clinical deficiency; the inability to provide an adequately designed verification study required for Subpart E approval. However, during discussions with the Applicant after the Complete Response letter was issued, it was agreed that if sufficient evidence of clinical effectiveness were available based on a subset of Pompe Registry patients treated with Lumizyme, regular approval may be considered. The clinical information provided by the Applicant provides additional clinical outcome information to support full approval for Lumizyme. Specifically, the Applicant provides information from 25 infantile-onset patients from the Pompe Registry to support the overall clinical efficacy of Lumizyme. The overall survival and survival at 18 months in Lumizyme-treated patients compares favorably with an age-matched, diseased-matched historical control group. Eighteen month survival for Lumizyme-treated patients was 57% compared with 1.9% in the historical control group.

There are several concerns regarding the reliance of the Pompe Registry data in support of the clinical effectiveness of Lumizyme. The Pompe Registry includes both prospectively and retrospectively obtained data and thus, inclusion of some patients retrospectively may be biased toward patients who had improved survival. Additionally, the overall numbers of patients are small, and there were no prospectively designed endpoints or statistical analysis plans. Therefore, despite the use of a cohort of infantile-onset patients treated with Lumizyme outside the US, it is the opinion of the Reviewer that the limitations of the Pompe Registry data prevent a recommendation for approval of Lumizyme in the US for all ages. The data from the only randomized, double-blind, placebo controlled trial evaluating the safety and efficacy of Lumizyme (LOTS) did not study patients less than 8 years of age. Therefore, Lumizyme should be limited to patients 8 years of age and older. Myozyme, approved for all Pompe patients, should be exclusively reserved for infantile-onset patients and late-onset patients less than 8 years of age for whom the efficacy and safety of Lumizyme has not been established. Additionally, as stated above, Lumizyme and Myozyme were determined to be different products based on important biochemical differences that may lead to differences in potency.

VIII. Safety

A. Clinical Site Inspections

Initial Submission
The Division of Scientific Investigations (DSI) performed clinical site inspections at 3 sites participating in LOTS and LOTS extension studies (Site #26 Erasmus Medical Center, the Netherlands; Site #4 Sophia's Children Hospital, the Netherlands; Site #29 Tower Hematology Oncology Medical Group, US). The DSI inspector found that the data from the three sites inspected are reliable and can be used in support of the BLA (see section XI.A. for further details).

Current Submission

There were no issues cited in the Complete Response letter by the Division of Scientific Investigations. Thus, there were no clinical site inspections performed for this submission.

B. Safety

Initial Submission

The reader is referred to the CDTL Review by Joanna Ku dated February, 26, 2009, and the clinical review by L. Yao dated February 26, 2009, for complete information.

The primary safety information included data from LOTS, the only placebo-controlled study of Lumizyme. Additional safety data as supportive evidence included interim safety data from the LOTS Extension Study (n=80) through April 15, 2008; data from 3 small open label studies of late (non-infantile) onset patients; data from the Myozyme Temporary Access Program (MTAP) (n=135); and data from world-wide post marketing safety reporting through April 15, 2008.

One death occurred, reported in a 33 year old woman who died of brain stem ischemia secondary to basilar artery thrombosis, a known complication of Pompe disease. The Reviewer concurred with the Applicant's assessment that the death was unrelated to the study drug.

Nine patients dropped out of the study (n=4 in the placebo group, and n=5 in the Lumizyme treated group). In the placebo group, one patient was discontinued due to persistent headache, and three patients dropped out "wishing to receive commercial product." In the Lumizyme group, one patient died from brain stem ischemia; two patients were discontinued due to infusion reactions that were serious adverse events (anaphylaxis); one dropped out for personal reasons; and, one dropped out to receive commercial product. In the two patients who withdrew due to anaphylaxis as infusion reactions, one patient had anaphylaxis with laboratory confirmation of IgE mediated anaphylaxis, and the other developed severe angioneurotic edema after the third Lumizyme dose, and based on the risk/benefit profile, the Investigator withdrew the patient from the study.

There was a total of 27 serious adverse events (SAEs), occurring in 19 patients. The SAEs that occurred at a higher incidence in the Lumizyme group than placebo included anaphylaxis, brain stem ischemia, coronary artery disease, angioneurotic edema, throat tightness, intervertebral disc protrusion, cerebral aneurysm, supraventricular tachycardia, gastroenteritis, chest pain/discomfort, pneumonia, and dehydration.

Anaphylaxis, allergic adverse reactions, and infusion reactions are the major safety concerns for Lumizyme. Four cases of anaphylaxis were identified in LOTS, for an overall incidence anaphylaxis of Lumizyme treated patients of 4/60, or 6.7 %, compared with no cases in the placebo group. Anaphylaxis and severe allergic reactions have been observed in patients during and up to 3 hours after Lumizyme infusion.

Infusions reactions were also noted to be the most common adverse reaction with Lumizyme. Notable infusion reactions that occurred in an incidence of at least 5% greater in the Lumizyme treatment group compared with placebo include anaphylaxis, urticaria, diarrhea,

vomiting, dyspnea, rash, hematuria, and chest discomfort. Additionally, delayed infusion reactions, occurring up to 48 hours after the infusion include urticaria, dizziness, musculoskeletal weakness and pain. As some reactions occurred up to 48 hours after the infusion, they highlight the need for longer monitoring for delayed onset reactions. Additionally, the initial review also uncovered potential immune-mediated adverse reactions involving skin and kidney. There has been at least one report in the literature of the development of membranous glomerulonephritis associated with Myozyme treatment.

A review of the data submitted for review during the first cycle also includes interim data from the LOTS extension study, MTAP, and the Applicant's post-marketing pharmacovigilance database. There were no substantive differences in the types of adverse reactions noted in the primary review.

Current Submission
The reader is referred to the Clinical Review by C. Mueller for full details of the safety analysis.

The safety information submitted by the Applicant in the Complete Response included the following:

1. Cumulative, final data from AGLU 03206 (LOTS extension)
2. Cumulative interim safety data from AGLU03907 (MTAP) as reported in IND 10,780 annual report submitted on October 15, 2008, and any additional late-breaking safety information to a cutoff of March 16, 2009
3. Spontaneous post-marketing serious case reports as reported in the periodic AE report from March 29, 2008 through December 28, 2008, with any additional late-breaking safety information to a cutoff of March 16, 2009.

The submission of this additional safety data to the Complete Response was determined to be adequate to evaluate any new safety information collected by the Applicant from the end of the first review cycle to the submission of the Complete Response. The most relevant safety data submitted were from AGLU03206, LOTS extension. This study was conducted as an open-label, extension study for AGLU02704, LOTS, a double-blind, randomized, placebo-controlled study in 90 late-onset Pompe patients. In LOTS extension, 30 patients previously randomized to receive placebo, were started on treatment with Lumizyme. Comparisons between these patients and patients treated with Lumizyme in LOTS can be made. Safety data from the other sources (i.e., MTAP and spontaneous post-marketing reports) are uncontrolled, and therefore, these data cannot be used to determine incidence rates for adverse events. However, these data were included to evaluate for any potential new safety signals from longer-term use of Lumizyme.

Overall, the Applicant estimates that approximately (b) (4) patients have received Lumizyme exclusively in clinical trials and the postmarketing setting. LOTS extension includes 81 patients; all patients that completed LOTS also completed LOTS extension. Fifty-five patients were randomized in LOTS to receive Lumizyme and continued to receive Lumizyme in LOTS extension, and 26 patients were randomized in LOTS to receive placebo and received Lumizyme in LOTS extension. There were 176 late-onset patients enrolled in MTAP,

including 52 patients who were previously enrolled in either LOTS or LOTS extension. The remainder of patients reported in this submission (b) (4) includes patients who the Applicant reports as having received only Lumizyme, and no other production scales of alglucosidase alfa.

Deaths
A total of 24 deaths were reported in the Complete Response as of the March 16, 2009 cutoff. The majority of deaths (21) were reported from the postmarketing setting. Of these 21 patient deaths, 14 patients were infantile-onset patients, 5 were late-onset patients, and 2 were of unknown phenotype. The cause of death in these cases was cardiac or respiratory failure in the majority of cases. Three deaths were reported from MTAP as part of the original BLA submission, but were not included in the original clinical review. One patient died due to respiratory arrest, one patient died after a hemorrhagic stroke, and one patient died of cardiac arrest. None of these deaths were assessed as related to treatment with Lumizyme. There were no deaths reported during LOTS extension.

There were a total of 27 serious adverse events (SAEs) previously reported in 19 patients in LOTS. An additional 5 SAEs in 3 new patients (16705, 65713, and 18702), were reported in the LOTS extension safety data submitted in the Complete Response. The SAEs reported in these new patients included cervical carcinoma stage II, nephrolithiasis, renal cyst, and gastric ulcer. A new SAE (spinal compression fracture) was reported in patient 47705 who had previously developed an SAE in LOTS (intervertebral disc protrusion). These SAEs were all assessed as not related to treatment with Lumizyme, and this Reviewer agrees with the Applicant's assessment of relationship to treatment.

Serious adverse events
There were a total of 38 SAEs previously reported in 15 patients in MTAP. During the safety update period, an additional 28 SAEs in 8 patients were reported. The most frequent SAEs reported overall were respiratory failure (4 events in 4 patients), pneumonia (5 events in 4 patients), aspiration pneumonia (3 events in 3 patients), and muscular weakness (3 events in 3 patients). One patient was reported to have developed an SAE of black skin discoloration, which may be immune-mediated. Detailed information regarding this patient was not available for this review. Although there were no SAEs reported in MTAP during the safety update period, at least 3 new patients appear to have developed anaphylaxis (see below).

There were a total of 54 SAEs in 17 late-onset patients reported in the post-marketing setting between March 29, 2008 and December 28, 2009. The types of SAEs reported during this period were consistent with those reported previously in the original review. The majority of SAEs were characterized by the Applicant as infusion reactions and include urticaria, facial edema, fever, irritability, decreased oxygen saturation, and tachypnea. Anaphylaxis, pneumonia, respiratory and cardiac failure were also noted.

Significant adverse events
Anaphylaxis
Anaphylaxis, allergic adverse reactions, and infusion reactions remain the major safety concerns with Lumizyme. As noted by the clinical reviewer, the definition of anaphylaxis

used for the clinical review was based on the Second Symposium on the Definition and Management of Anaphylaxis, which uses clinical criteria to define anaphylaxis, rather than reliance on laboratory criteria. The incidence of anaphylaxis noted in the original clinical review by Dr. Yao was 6.7% (4/60 patients). There appears to be a similar incidence of anaphylaxis in LOTS extension based on review of the updated safety information. Based on a review of the adverse events from LOTS extension, two additional patients (29705 and 18708) appear to have developed anaphylaxis during LOTS extension. One patient (29705) was previously treated with Lumizyme and was suspected of having anaphylaxis in LOTS. Another patient (18708) was previously treated with placebo and developed anaphylaxis after treatment with Lumizyme in LOTS extension. Therefore, if these two patients are included in the total, the incidence of anaphylaxis is 6.7% (6/90), and remains the same when compared with LOTS data. The Applicant has also reported 3 patients (50018, 50091, and 10523) in MTAP with signs and symptoms consistent with anaphylaxis during the safety update period.

Infusion reactions

Infusion reactions remain the most common adverse event with Lumizyme. Infusion reactions, defined by the reviewer as adverse events occurring during or up to two hours after completion of the infusion occurred in 45/90 patients (50%) overall. The most common adverse events occurring during infusion are shown in Table 4. Other noteworthy infusion reactions that were reported in at least one patient include angioneurotic edema, hypertension, hypertension, lip or tongue swelling, wheezing, oral pruritis, tachycardia, and photophobia. The Applicant also reports that there were an additional 256 adverse events in 68 patients (76%) that occurred on the day of the infusion, but the time of these events was not clearly established by the investigator. Many of these adverse events were also noted in the original review and include falls (17%), hypoacusis (9%), fatigue (8%), dizziness (6%), peripheral edema (8%), musculoskeletal pain or weakness (6%), arthralgia (4%), areflexia (3%), and hyporeflexia (2%). It should be noted that the Applicant did not separate data from LOTS extension that had been previously submitted for review. Thus, an update of the incidence of adverse events compared to the previous review is difficult. Nevertheless, the types of infusion reactions and incidence of infusion reactions appears to be consistent between the LOTS and combined LOTS and LOTS extension data, suggesting that these adverse events are more likely during or immediately after infusion with Lumizyme.

Table 4: Most common infusion reactions overall

Preferred Term	Number of patients (%)
Headache	10 (11)
Dizziness	8 (9)
Nausea	8 (9)
Infusion site reaction	7 (8)
Hypersensitivity	6 (7)
Urticaria	6 (7)
Rash	5 (6)
Chest discomfort	4 (4)
Flushing	4 (4)
Pruritus	4 (4)
Vomiting	4 (4)
Blood pressure increased	3 (3)
Hyperhidrosis	3 (3)
Pyrexia	3 (3)
Chills	2 (2)
Ear discomfort	2 (2)
Erythema	2 (2)
Fall	2 (2)
Feeling hot	2 (2)
Local swelling	2 (2)
Edema peripheral	2 (2)
Paraesthesia	2 (2)
Throat tightness	2 (2)

Potential chronic, immune mediated adverse reactions
Other significant adverse events that were uncovered during the original review include the possibility of chronic, immune-mediated skin and kidney adverse reactions. The clinical reviewer notes that additional potential immune-mediated skin and kidney adverse reactions appear in both LOTS extension data, and MTAP. Long-term follow up for potential chronic immune-mediated adverse events was agreed upon with the Applicant as a post-marketing requirement.

Common adverse events
As stated previously, the Applicant did not separate data from LOTS extension that had been previously submitted for review. Thus, an update of the incidence of adverse events compared to the previous review is difficult. Overall, however, the common adverse events from LOTS appear to be similar to common adverse events reported in combined LOTS/LOTS extension data. Falls, musculoskeletal pain/myalgia/muscle spasms, nasopharyngitis, headache, dizziness, diarrhea, arthralgia, hypoacusis, nausea, vomiting, fatigue, back pain, peripheral edema, and fever were all seen in at least 20% of patients.

Conclusions
The safety data included by the Applicant appears adequate to determine the overall safety profile of Lumizyme. The safety update provided by the Applicant in this submission provides additional data confirms the important risks as uncovered in the first cycle review. Anaphylaxis and infusion reactions continue to be important safety concerns, as well as the potential for chronic immune-mediated (e.g., skin and kidney) adverse reactions. These safety findings warrant the placement of a boxed warning in the product labeling (see section XII,

labeling), implementation of a Risk Evaluation and Mitigation (REMS) program (see section XIII.C.) to ensure the benefits of Lumizyme outweigh the risks, and the initiation of post-marketing requirement and commitment studies (see section XIII.D.) to evaluate the long-term safety and effectiveness of Lumizyme in patients with late-onset Pompe disease.

IX. Advisory Committee Meeting

Initial Submission
The reader is referred to the Clinical Review of the original BLA 125291 submission by L. Yao for details of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) meeting held on October 21, 2008.

The EMDAC was convened to obtain advice regarding statistical and clinical review issues as described above. The committee voted 16 to 1 to approve Lumizyme based on the clinical data presented. However, the majority of the committee recommended approval under Accelerated Approval (21 CFR 601 Subpart E), based on improvement in % predicted FVC. Under Accelerated Approval regulations, the Applicant would be required to perform a post-marketing verification study to confirm the clinical effectiveness of Lumizyme. The committee also voted 17 to 0 to require post-marketing safety studies to address the concerns of anaphylaxis, immunogenicity, and potential chronic immune-mediated reactions. The committee members also recommended that a REMS be required to ensure that the benefits of Lumizyme outweigh the risk.

Current Submission
There was no advisory committee meeting convened during this review cycle.

X. Pediatrics

Aglucosidase alfa (Myozyme/Lumizyme) received orphan designation in August, 1997. Therefore, the regulations that pertain to the Pediatric Equity in Research Act (PREA) do not apply to Lumizyme. Additionally, there were no pediatric consults obtained either during the first review cycle or during the present review cycle.

XI. Other Relevant Regulatory Issues

A. DSI audits

Initial Submission
The Division of Scientific Investigations (DSI) performed clinical site inspections at 3 sites (Site #26 Erasmus Medical Center, the Netherlands; Site #4 Sophia's Children Hospital, the Netherlands; Site #29 Tower Hematology Oncology Medical Group, US). The DSI inspector found that the data from the three sites inspected are reliable and can be used in support of the BLA.

Financial disclosures were submitted by the Applicant during the first review cycle and include two notable findings for the LOTS and LOTS extension studies: One site investigator

(b) (6), received grants, equipment payments, consultation payments and retainers totaling over €1,139,000 from (b) (6), and an additional $940,246.00 in royalties and payments upon FDA and EMEA approval of Myozyme between (b) (6)7. Another investigator for a US transfer site (b) (6) (b) (6) received royalties and payments upon FDA approval of Myzoyme of $7,914,895 and an additional $468,715 in grants, retainers, honoraria, and retainers from (b) (6) Despite the significant financial relationships between these two investigators and the Applicant, the conduct of the studies does not appear to have been affected by these financial arrangements.

Current Submission

There were no issues cited in the Complete Response letter by the Division of Scientific Investigations. Thus, there were no clinical site inspections performed for this submission.

B. Clinical Consults

There were no clinical consults obtained in the original review or for the current review.

C. Drug Shortage

There has been a persistent drug shortage of alglucosidase alfa (Myozyme and Lumizyme) since the first quarter of 2007. The cause of this drug shortage is multifactoral, and includes issues such as manufacturing constraints with Myozyme, management decisions against increasing Myozyme production in favor of pursuing unapproved larger scale production (i.e., Lumizyme), comparability concerns between Lumizyme and Myozyme, viral contamination of two of the Applicant's manufacturing facilities, and management decisions to cease production of Lumizyme despite continued pursuit of a marketing application for this product. The Agency is aware of many patients with Pompe disease in the US who are still unable to receive treatment. Currently, patients with Pompe disease under the age of 18 years are being treated with the commercially available Myozyme product, and an additional approximately 180 adult patients with Pompe disease are receiving the unapproved product, Lumizyme through the Alglucosidase Alfa Temporary Access Program (ATAP, formerly the Myozyme Temporary Access Program or MTAP). However, the Agency is aware of approximately 50 to 150 patients with late-onset (non-infantile) Pompe disease in the US who have no access to alglucosidase alfa treatment, although given the estimated prevalence of Pompe disease, the number of patients who are unable to receive treatment is likely higher than this estimate. In August, 2009, an amendment to ATAP was received by the Agency, to allow use of 4000 L alglucosidase alfa in patients currently enrolled in this treatment protocol. This amended treatment protocol was intended to conserve the supply of Lumizyme for patients awaiting treatment after anticipated US approval of Lumizyme in November, 2009. However, ATAP continues to be closed to new enrollment, and does not address the current and persistent drug shortage for adult Pompe patients. Genzyme reiterated at a meeting with FDA on July 2, 2009, that expanding ATAP would not be feasible at this time unless there is a known timeframe for approval of the 4000 L product.

Alglucosidase alfa received orphan designation under the Orphan Drug Act in August, 1997. The Orphan Drug Act was passed by Congress to foster the development and marketing of sufficient supplies of drugs for rare diseases. Thus, the Agency may grant a seven-year

marketing exclusivity to the orphan product developer without price restriction, provided that the developer can provide sufficient quantities of that drug to patients in need. It is the opinion of this Reviewer that the Applicant has not provided sufficient quantities of alglucosidase alfa to Pompe patients in need. At the time of this review, the Agency is requesting high-level discussions with the Applicant to address this drug shortage and to provide access for all Pompe patients who require treatment.

XII. Labeling

A. Proprietary Name

Initial Review

During the initial review cycle, the originally proposed trade name of "Myozyme" was submitted for the 2000 L product. A review of the trade name was performed by Z. Oleszczuk in the Division of Medication Errors Prevention and Analysis (DMEPA). DMEPA expressed concern over a potential name confusion that could lead to medication errors given that the trade name "Myozyme" has been in use since 2006 for the 160 L product. The Applicant withdrew the proposed trade name of "Myozyme" and proposed other trade names including "Lumizyme." Lumizyme was found to be acceptable by DMEPA.

Current Submission

In the current review cycle, a re-review of the trade name was performed by Z. Oleszczuk in the Division of Medication Errors Prevention and Analysis (DMEPA). The trade name "Lumizyme" was found to be acceptable by DMEPA.

B. Physician Labeling / Carton and Container Labeling

Final labeling for Lumizyme was also satisfactorily negotiated during the current review cycle. The final labeling conforms to the Physician Labeling Rule (PLR) format. The reader is referred to final labeling for Lumizyme for complete details. Highlights of final labeling for Lumizyme are presented below.

Boxed Warning

A boxed warning was included in the labeling to inform prescribers about the risk of life-threatening anaphylactic and severe allergic and immune-mediated reactions during Lumizyme infusions. Additionally, the boxed warning also informs prescribers about the potential risk of rapid disease progression in Pompe patients less than 8 years of age, and the restricted distribution program called the Lumizyme ACE Program (see section XII.C.).

Indication

The indication for Lumizme is restricted to patients 8 years of age and older with late (non-infantile) onset Pompe disease who do not have evidence of cardiac hypertrophy. The safety and efficacy of LUMIZYME have not been evaluated in controlled clinical trials in infantile-onset patients, or in late (non-infantile) onset patients less than 8 years of age.

Warnings and Precautions

The Warnings and Precautions section includes information regarding the most serious adverse reactions associated with Lumizyme and information regarding the restricted distribution

program. These warnings include the risk of anaphylaxis, severe allergic and immune-mediated reactions, (b) (4)

Use in Specific Populations: Pediatric Use
The labeling informs prescribers that Lumizyme is not indicated for patients 8 years of age and younger due to lack of efficacy data in patients 8 years of age and younger and because of the risk of rapid disease progression in younger patients. However, the labeling does not explicitly state that Myozyme is available for use in infantile-onset Pompe patients or in late-onset Pompe patients 8 years of age and younger.

Description
This section discusses the structure and biochemical properties of Lumizyme. The section also states that Myozyme and Lumizyme are produced using different manufacturing processes. However, the section does not describe the differences critical product attributes including (b) (4) that may affect differences in potency between the two products.

Clinical studies
The clinical studies section includes data from both controlled studies (i.e., LOTS) and uncontrolled studies (i.e., the Pompe Registry) used to support the clinical effectiveness of Lumizyme. This section does not include information regarding potential differences in clinical effectiveness between Lumizyme and Myozyme.

Patient Counseling Information
This section includes information to prescribers regarding the Lumizyme ACE Program, the Pompe Registry, and the most common adverse reactions associated with Lumizyme (i.e., infusion reactions).

Medication Guide
A medication guide was not included in the REMS because patients treated with Lumizyme would be expected to receive treatment only at specialized infusion centers under the supervision of trained personnel.

XIII. Recommendations/Risk Benefit Assessment

A. Recommended Regulatory Action

The Applicant has provided satisfactory responses to all of the clinical and CMC deficiencies cited in the Complete Response Letter. However, persistent manufacturing deficiencies at the Allston Landing, MA facility noted by the New England District Office have resulted in an update the facility's GMP profile to "further action indicated." The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of the Therapeutic Biologic-Establishment Evaluation Report (TB-EER) and states that the Allston Landing, MA facility is currently classified as OAI, an unacceptable compliance status. Thus, the Office of Compliance has issued a recommendation to withhold approval of Lumizyme. Therefore, I recommend that a Complete Response action be taken for Lumizyme.

B. Risk Benefit Assessment

Lumizyme is recommended for a Complete Response action based on the current manufacturing classification of Office Action Indicated (OAI) at the Allston Landing, MA facility, an unacceptable compliance status. Therefore, the risk benefit assessment does not support approval of the product until the manufacturing deficiencies have been adequately addressed.

C. Recommendation for Postmarketing Risk Evaluation and Management Strategies

Initial Submission

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Food Drug and Cosmetic Act (FDCA) to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). This provision took effect on March 25, 2008.

A REMS was required by the Applicant to mitigate the potential risk of rapid disease progression in infantile-onset Pompe disease patients and patients with late (non-infantile) onset disease less than 8 years of age for whom the safety and effectiveness of Lumizyme have not been evaluated, and to ensure that the known risks of anaphylaxis and severe allergic reactions, and the potential risks of severe cutaneous and systemic immune-mediated reactions to Lumizyme are communicated to patients and prescribers. However, a complete REMS was not agreed upon during the first cycle. The Applicant was required to submit a revised REMS with the Complete Response that included a communication plan, elements to assure safe use (ETASU), an implementation system, and a timetable for assessments.

Current Submission

The Applicant submitted a revised, proposed REMS with the Complete Response. During the current review cycle, a satisfactory REMS was negotiated with the Applicant. The Applicant's REMS program, entitled, "The Lumizyme Access, Control, and Education (ACE) Program" includes all components of a REMS to ensure that the benefits of Lumizyme outweigh the risk. A medication guide was not included in the REMS because patients treated with Lumizyme would be expected to receive treatment only at specialized infusion centers under the supervision of trained personnel. Therefore, the Lumizyme REMS includes the following elements:

1. Goals
   - To mitigate the potential risk of rapid disease progression in infantile-onset Pompe patients and patients with late (non-infantile) onset disease less than 8 years of age for whom the safety and effectiveness of Lumizyme have not been evaluated
   - To ensure that the known risks of anaphylaxis and severe allergic reactions associated with the use of Lumizyme are communicated to patients and prescribers, and to ensure that the potential risks of severe cutaneous and systemic immune mediated reactions to Lumizyme are communicated to patients and prescribers

2. Communication plan
   - Communication plan will include introductory letters that will be provided to anyone who will receive, prescribe, administer, or dispense Lumizyme. The communication plan will also provide information regarding the Lumizyme ACE Program.

3. Elements To Assure Safe Use
   - Requirement for patients, healthcare facilities, and prescribers to enroll in the program
   - A training module for healthcare facilities and prescribers
   - A restricted distribution system to ensure that only patients enrolled in the program receive Lumizyme, and that only prescribers and healthcare facilities enrolled in the program are able to prescribe and administer Lumizyme

4. Implementation System
   - Requirement for Genzyme to maintain a validated and secure database of certified physicians, healthcare facilities, and patients enrolled in the Lumizyme ACE Program
   - Requirement for Genzyme to monitor re-enrollment of certified participants
   - Requirement for Genzyme to monitor healthcare facilities and providers to ensure only enrolled patients receive Lumizyme

5. System of Assessments
   - Genzyme will submit REMS assessments to FDA 6 months and 1 year after the date of approval of the Lumizyme ACE Program, and then annually thereafter.

D. Recommendation for other Postmarketing Requirements and Commitments

Initial Submission

Title IX, Subtitle A, Section 901 of the FDAAA amends the FDCA to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)). This provision took effect on March 25, 2008.

Based on the review of the safety data provided by the Applicant, serious adverse reactions, including anaphylaxis and immunologically mediated reactions have been noted. In order to more fully characterize these safety findings, two clinical postmarketing requirements (PMRs) were agreed upon during the first review cycle and are listed below:

1. A retrospective immunogenicity study based on the pattern of antibody responses in patients enrolled in the LOTS and LOTS Extension Studies. The objective of this study is to determine which immunogenicity profiles may predict the development of the known serious risks of treatment with Lumizyme, including anaphylaxis, severe allergic reactions, and signals of severe cutaneous and systemic immune complex-mediated reactions. The study will include GAA protein quantitation ELISA, CRIM by Western Blost (using monoclonal antibody) and HLA analyses (Class I and II; A, B, C and DR genotypes) on individual patients to evaluate whether there is GAA protein levels and/or HLA genotype profiles associated with these three diverse

outcomes in LOTS: 1) patients who developed anaphylaxis; 2) patients who had continually rising (i.e., sustained or non-tolerizing) antibody titers at study's end; and 3) patients who developed an antibody response that diminished over time in the course of the study. Data collection and analyses will also include antibody titer, neutralizing titer, epitope mapping (in a subset of patients with sustained IgG titer and neutralizing antibody at specific timepoints), and time course of generation and disappearance of antibody titer for all patients in the LOTS and LOTS Extension Studies. HLA analysis will be performed per standard methods.

2. A prospective safety study conducted within the ongoing Pompe Registry to assess the known serious risks of treatment with Lumizyme, including anaphylaxis, severe allergic reactions, and signals of severe cutaneous and systemic immune complex-mediated reactions. This sub-study will assess the occurrence of these adverse events and the effect of antibody responses (both timing and pattern of responses) and CRIM status (only on infantile-onset patients) on the occurrence of these events.

Additionally, two clinical postmarketing commitments were agreed upon during the first review cycle, and were included in the resubmission.

Current Submission
Both clinical PMRs that were agreed upon during the first cycle review were included in the Complete Response and are listed below. However, the content of these PMRs was shortened during this review cycle to conform with the preferred PMR content. The reviewer notes that information that was removed from the original clinical PMRs should be incorporated into the final protocol for each PMR. Therefore, the original language used during the first cycle review is included above.

1. A retrospective immunogenicity study based on the pattern of antibody responses in patients enrolled in the Late Onset Treatment Study (LOTS) and LOTS Extension Studies. The objective of this study is to determine which immunogenicity profiles may predict the development of the known serious risks of anaphylaxis and severe allergic reactions, and signals of severe cutaneous and systemic immune complex-mediated reactions with Lumizyme (alglucosidase alfa) treatment.

2. A prospective safety study conducted within the ongoing Pompe Registry to assess the known serious risks of anaphylaxis and severe allergic reactions, and signals of severe cutaneous and systemic immune complex-mediated reactions with Lumizyme (alglucosidase alfa) treatment.

Three clinical post-marketing commitments (PMCs) that were agreed upon with the Applicant during the first review cycle were included in the Complete Response. Additionally, four CMC PMCs and one clinical pharmacology PMC were negotiated during the current review cycle. The clinical and clinical pharmacology PMCs were negotiated as post-approval studies because of the current drug shortage and the current urgent need for available treatments for

Pompe disease. All of the clinical studies require long-term evaluation that cannot be completed in a timely manner, but will likely provide additional clinical efficacy and information when completed. The clinical pharmacology CMC will provide pharmacokinetic information to support labeling of Lumizyme in pediatric patients age 8-18 years, for which there are only limited data available from LOTS. The CMC PMCs were also negotiated as post-approval studies because of the current drug shortage. These studies will promote improved product quality, but were not assessed as critical to the approval of Lumizyme. The seven PMCs are listed below:

(b) (4)

4. Genzyme commits to evaluate the use of the (b) (4) method as a release test for glycan profiling of the drug substance.

5. Genzyme commits to develop an analytical method to monitor (b) (4) and evaluate its use in the release and stability specifications.

(b) (4)

7. Genzyme commits to establish in process control limits for cell viability during the (b) (4) period using the data collected from four upcoming (b) (4) cell culture runs.

(b) (4)

CLINICAL REVIEW

Application Type	BLA 125291
Application Number(s)	125291/0/72
Priority or Standard	Complete Response Resubmission
Submit Date(s)	15 May 2009
Received Date(s)	15 May 2009
PDUFA Goal Date	13 November 2009
Division / Office	Division of Gastroenterology Products
Reviewer Name(s)	Christine Mueller, DO 11/10/09
Acting Clinical Team Leader	Lynne Yao, MD 11/10/09
Review Completion Date	9 November 2009
Established Name	Alglucosidase alfa
(Proposed) Trade Name	Lumizyme
Therapeutic Class	Enzyme Replacement Therapy
Applicant	Genzyme
Formulation(s)	Intravenous Injection
Dosing Regimen	20mg/kg every other week
Indication(s)	Treatment of Pompe Disease (glycogen storage disease type II, acid maltase deficiency)
Intended Population(s)	Late-onset Pompe Disease

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Recommend regular approval of this application after agreement with the Applicant to revise proposed labeling, to perform post-marketing commitments (PMCs) and post-marketing requirements (PMRs), and to implement a Risk Evaluation and Mitigation Strategy (REMS). It is recommended that Lumizyme (alglucosidase alfa, 2000 L production scale) treatment be restricted to patients with late onset (non-infantile) Pompe disease 8 years of age and older, who do not have evidence of cardiac hypertrophy.

This is a review of the submission of items requested of the Applicant based on a Complete Response (CR) letter issued by the Agency on February 29, 2009, after review of the initial BLA submission for Lumizyme. The clinical review for this initial BLA submission supported approval of Lumizyme under Subpart E Accelerated approval regulations for the agreed upon labeled indication, "patients 8 years and older with late-onset (non-infantile) Pompe disease (GAA deficiency) who do not have evidence of cardiac hypertrophy." However, the effectiveness of Lumizyme was based on stabilization of % predicted forced vital capacity in 60 non-infantile-onset Pompe disease patients (8-70 years) compared with 30 non-infantile-onset Pompe disease patients randomized to placebo in the Late-Onset Treatment Study (LOTS). Improvements in survival or ventilator-free survival have not been evaluated in clinical trials. Therefore, the product could not be approved under Subpart E without agreement from the Applicant to conduct an appropriate verification study to confirm that treatment with Lumizyme is associated with clinical benefit.

The Applicant and FDA discussed options for the approval of Lumizyme after the Complete Response Letter was issued. These discussions included the option for the Applicant to include additional information in the Complete Response submission that could potentially support regular approval of the product. After these discussions, the Applicant provided additional clinical information from the Pompe Registry in the Complete Response submission to support full clinical approval of Lumizyme in patients 8 years and older with late-onset (non-infantile) Pompe disease (GAA deficiency) who do not have evidence of cardiac hypertrophy. The Pompe Registry data suggests that there is improvement in survival (33%) in infantile-onset patients treated with Lumizyme compared to an untreated infantile-onset historical control cohort (2%). Thus, the totality of the clinical data supports the clinical effectiveness of Lumizyme. However, because of the limitations of the Pompe Registry data, the insufficient numbers of patients age 8 years and younger treated with Lumizyme in clinical trials, and the availability of Myozyme for these younger patients, this Reviewer recommends that Lumizyme (alglucosidase alfa, 2000L production scale) treatment be restricted to patients with late onset (non-infantile) Pompe disease 8 years of age and older, who do not have evidence of cardiac hypertrophy.

1.2 Risk Benefit Assessment

The Agency approved Myozyme, alglucosidase alfa manufactured at the 160 L production scale in 2006, and is currently the only approved treatment for Pompe disease. In April, 2008, given the inability to establish product comparability based on chemistry, manufacturing and controls (CMC), pharmacokinetic, or clinical data, the 160 L (Myozyme) and 2000 L (Lumizyme) alglucosidase alfa products were determined to be different products by the Agency. The Agency required the Applicant to submit efficacy and safety data to support separate licensure of Lumizyme.

During the first cycle review, the review team recommended that Lumizyme be approved under Subpart E, accelerated approval, based on stabilization in % predicted FVC in Lumizyme-treated patients. Therefore, a verification study would be required to confirm the clinical benefit of Lumizyme. However, a verification study that would be likely to evaluate a clinically meaningful effect of Lumizyme in late-onset Pompe patients would be difficult to complete in a reasonable timeframe because disease progression occurs over years to decades. Thus, the Agency agreed to review data from the Pompe Registry, a disease registry maintained by the Applicant, to determine whether these data were sufficient to evaluate a clinical benefit for Lumizyme. The Pompe Registry includes data in infantile-onset patients treated with Lumizyme who match the baseline characteristics of the Phase 3 clinical trial that lead to the approval of Myozyme (AGLU1602, reviewed by Anne Pariser, M.D., BLA 129141). The Pompe Registry data suggests that there is improvement in survival (33%) in infantile-onset patients treated with Lumizyme compared to an untreated infantile-onset historical control cohort (2%). However, the Registry includes small numbers of age and disease-matched patients, the comparator group was not concurrent (i.e., historical control group), and some data from the registry were collected retrospectively. Thus, review of the registry data are limited to descriptive analyses and limited analyses of specific subgroups (e.g., age, gender, CRIM status).

A safety update was submitted by the Applicant and includes data from the completed Late-Onset Treatment Study (LOTS) and the LOTS extension studies, the Myozyme temporary access program (MTAP), and postmarketing information. The incidence anaphylaxis and allergic reactions remains similar to the safety findings of the original BLA 125291 submission reviewed by Dr. Yao. Skin and renal adverse events that may be related to chronic immunologic-mediated events continue to appear. These risks appear to be similar in incidence to the currently approved product, Myozyme.

Thus, the overall risk benefit assessment for Lumizyme appears acceptable for patients with Pompe disease 8 years of age and older.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

- Under Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Food, Drug, and Cosmetic Act (FDCA) the Agency is authorized to require the submission of a REMS (Risk Evaluation and Mitigation Strategy) by the Applicant if it has determined that such a strategy is necessary to ensure that

the benefits of the drug outweigh the risks (section 505 1(a)(l)). Based on the potential for serious allergic reactions, including anaphylaxis, and to ensure that the administration of Lumizyme is limited to the intended population, the Agency recommends that a REMS is necessary for Lumizyme. The REMS has been successfully negotiated. The Lumizyme Access, Control, and Education (ACE) Program includes all components of a REMS to ensure that the benefits of Lumizyme outweigh the risk. The goals of the REMS are to mitigate the potential risk of rapid disease progression in infantile-onset Pompe disease patients and patients with late (non-infantile) onset disease less than 8 years of age for whom the safety and effectiveness of Lumizyme have not been evaluated, and to ensure that the known risks of anaphylaxis and severe allergic reactions associated with the use of Lumizyme are communicated to patients and prescribers, and to ensure that the potential risks of severe cutaneous and systemic immune complex-mediated reactions to Lumizyme are communicated to patients and prescribers.

The elements of the REMS include the following:

1. A communication plan
2. Elements to Assure Safe Use (ETASU)
3. Implementation System
4. Plan for Assessments

Please see the final REMS proposal and supporting document for details of the requirements.

1.4 Recommendations for Postmarket Requirements and Commitments

On February 24, 2009, the Applicant formally agreed to all clinical post-marketing requirements (PMRs) and post-marketing commitments (PMCs) proposed by the Agency. There are no new clinical PMR/PMCs included in this submission.

Based on the review of the safety data provided by the Applicant, serious adverse reactions, including anaphylaxis and immunologically mediated reactions have been noted. In order to more fully characterize these safety findings, there are two postmarketing studies *required* of the Applicant under section 505(0)(3) of the Food Drug and Cosmetics Act are the following:

1) A retrospective immunogenicity study based on the pattern of antibody responses in patients enrolled in the Late Onset Treatment Study (LOTS) and LOTS Extension Studies. (b) (4)

(b) (4)

(b) (4)

A final protocol for this study will be submitted to CDER by May 15, 2010, for concurrence. The study will be completed by January 14, 2011, and the final study report will be submitted to CDER by May 16, 2011.

2) A prospective safety study conducted within the ongoing Pompe Registry to assess the known serious risks of anaphylaxis and severe allergic reactions, and signals of severe cutaneous and systemic immune complex-mediated reactions with Lumizyme (alglucosidase alfa) treatment. (b) (4)

Registry data will be analyzed at yearly intervals and the results will be submitted in annual reports for IND 10,780. The sub-study protocol will be submitted to CDER by May 14, 2010. The final study report, including the sub-studies, will be submitted to CDER by September 30, 2022.

There are 3 clinical PMCs agreed to by the Applicant and are listed as follows:

(b) (4)

(b) (4)

2) A long-term follow-up study of patients in LOTS and LOTS Extension Studies whose response to Lumizyme (alglucosidase alfa) is associated with substantial improvement over baseline in the 6MWT results. This study will be conducted as a sub-study within the ongoing Pompe Registry. (b) (4)

3) As part of the ongoing Pompe Registry, prospective outcome data will be collected in patients enrolled in the Registry to assess the long-term efficacy of Lumizyme (alglucosidase alfa). (b) (4) (b) (4)

Four CMC post-marketing commitments were agreed to by the Applicant during this review cycle.

1. Genzyme commits to evaluate the use of the (b) (4) method as a release test for glycan profiling of the drug substance.

2. (b) (4)

3. (b) (4)

4. Genzyme commits to establish in process control limits for cell viability during the (b) (4) period using the data collected from four upcoming 4000 L cell culture runs.

One clinical pharmacology post-marketing commitment is still being negotiated with the Applicant.

(b) (4)

Pharmacokinetic assessments will be conducted using a validated assay and will be calculated both with and without correcting for endogenous levels of rhGAA.

2 Introduction and Regulatory Background

2.1 Product Information

Lumizyme (alglucosidase alfa) is a recombinant human form of the enzyme acid a-glucosidase (rhGAA) that is produced by recombinant DNA technology in a Chinese hamster ovary cell line at a 2000 L bioreactor scale. Lumizyme is intended for use as an enzyme replacement therapy to treat patients with severe deficiency of α-1,4 glucosidase (GAA), or Pompe disease (also known as acid maltase deficiency, or glycogen storage disease type II).[1]

Pompe disease is an inherited disorder of glycogen metabolism caused by the absence or marked deficiency of GAA. Alglucosidase alfa provides an exogenous source of GAA and is taken up into cells and transported into lysosomes where the enzyme acts to hydrolyze glycogen. Pompe disease patients have variable activity of the enzyme with infantile-onset patients having undetectable enzyme activity in muscle tissue and in late-onset patients activity is reduced to a lesser extent. However, 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. The infantile onset form leads to severe cardiomyopathy, muscle weakness and death in almost all patients by 18 months of age. 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. However, the classification of juvenile and adult-onset forms is a continuum, and therefore a specific age cut-off between the juvenile and adult-onset forms is difficult to 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. Glycogen accumulation in various tissues leads to the development of progressive muscle weakness, including impairment of respiratory function in all patients, as well as hypertrophic cardiomyopathy in patients with infantile-onset Pompe disease.[1]

Prior to 2006, the only treatment available for patients with Pompe disease was palliative. Myozyme, another member of the class of alglucosidase alfa biologic products, is the only approved treatment for Pompe disease. It is produced at a 160 L bioreactor scale, and was approved for the treatment of all patients with Pompe disease on April 28, 2006 based on a single clinical trial (n=18) that demonstrated improved ventilator-free survival in patients with infantile-onset Pompe disease (age less than 7 months at the time of first infusion) as compared to an age-matched, untreated historical control cohort. Approval of Myozyme in the US for all forms of Pompe disease was on this infantile-onset trial and there have been no controlled studies that have evaluated efficacy in late-onset Pompe disease.

However, because the drug supply of the 160 L scale product is limited, its use in the United States has been reserved for children less than 18 years of age. U.S. Pompe disease patients over

18 years of age have only been able to access rhGAA treatment through a treatment IND for the 2000 L scale product, the product for which the Applicant seeks marketing approval in this BLA. The 2000 L product is approved for use outside the US in approximately 40 other countries including EU and Canada. The access program for adult patients, called the Myozyme Temporary Access Program (MTAP), was closed to new patients by the Applicant during the course of the Agency's review of this BLA, in April, 2008.

2.2 Tables of Currently Available Treatments for Proposed Indications

Alglucosidase alfa 160 L (Myozyme) is the only approved, marketed drug in the United States (US) for the treatment of Pompe disease (see Table 1).

Table 1: Currently Available Treatments for the Proposed Indications

Drug (trade name)	Indication	Manufacturer
Alglucosidase alfa 160 L product (Myozyme)	Treatment of Pompe disease	Genzyme

2.3 Availability of Proposed Active Ingredient in the United States

The proposed active ingredient, alglucosidase alfa, produced at the 2000 L scale, has not been approved for use in the US. It is available under Investigation New Drug (IND) 10,780. Alglucosidase alfa 2000 L has been approved for use in at least 40 other countries outside the US, including Canada.

2.4 Important Safety Issues With Consideration to Related Drugs

The development of enzyme replacement therapy for lysosomal storage disease began in the early 1960s, and in 1974 the use of purified glucocerbrosidase for the treatment of Gaucher disease was first published.[2,3] There are now several enzyme replacement therapies available in the US for lysosomal storage diseases including Gaucher (Cerezyme and Ceredase), Mucopolysaccharidosis (MPS) I (Aldurazyme), MPS II (Elaprase), and VI (Naglazyme), Fabry (Fabrazyme), and Pompe (Myozyme). All of these therapies are associated with immunogenicity, which may lead to important safety concerns including the development of allergic reactions and anaphlaxis.[4] Boxed warnings for the risk of anaphylaxis were required in the labeling for Aldurazyme and Elaprase. A boxed warning for the risk of anaphylaxis was placed on the label for Myozyme based on a 5% incidence of anaphylaxis, and is part of the proposed labeling for Lumizyme. Delayed-onset infusion reactions have also been seen with Myozyme and chronic immune-mediated skin reactions and glomerulonephritis have also been reported.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Applicant, Genzyme, submitted the original Biologics Licensing Agreement (BLA) for alglucosidase alfa (STN 125141/0) on July 29, 2005. At the time, the Applicant 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 the BLA were treated with 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. The Applicant withdrew the 2000 L scale manufacturing process from BLA 125141 on December 12, 2005. The Agency approved 160 L scale of this product on April 28, 2006, under the trade name Myozyme™. The primary efficacy endpoint that was measured in the supporting trial for the approval of Myozyme was the effect on ventilator-free survival on 18 infantile-onset disease patients only. There was a statistically significant difference in the ventilator-free survival at 18 months when compared to an historical control. Juvenile and adult-onset patients were not enrolled in the clinical trial. However, the Agency noted that no other commercially available products were approved for use in Pompe disease in the US; therefore, Myozyme was approved for use in all Pompe disease patients.

The Applicant then submitted this BLA on October 31, 2007, as a BLA supplement to the original BLA for the Myozyme 160 L product. The Office of Biotechnology Products reviewers noted significant differences in the biochemical attributes of the 2000 L product relative to the 160 L product. The differences were believed to result from the process utilized to increase the cell production in the 2000 L scale; (b) (4) There was also concern that 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. Because there was insufficient information available to establish the biochemical, nonclinical, or clinical comparability of the two products, the reviewers concluded that the 2000 L product could not be considered the same product as the Myozyme 160 L product. These differences were presented in a briefing to the CDER Center Director, Janet Woodcock, M.D., and the BLA supplement was recoded as a new BLA. The submission of the new BLA occurred on May 30, 2008. It was designated a priority review. The PDUFA clock was extended in response to a November 21, 2008 major amendment to the BLA.

The BLA 125291 submission included one clinical study to support the efficacy of the 2000 L product, which will be referred to as Lumizyme throughout the remainder of this document. The clinical study submitted was a randomized, double-blind, placebo-controlled trial that evaluated the efficacy and safety of Lumizyme in 90 patients with late-onset Pompe disease, Late Onset Treatment Study or LOTS. The clinical and biostatistical reviewers raised concerns regarding the strength of evidence of effectiveness of Lumizyme provided by the study submitted for review. Issues included the patient population enrolled, the primary efficacy endpoints, the randomization procedure, and study design changes made during the conduct of the study. The efficacy data for the submission was reviewed by the Clinical Reviewer, Lynne Yao, M.D. The major study objectives of LOTS were to evaluate the effect of Lumizyme on functional endurance as measured by the six minute walk test (6MWT) and to evaluate the effect of Lumizyme of respiratory muscle weakness as measured by percent predicted forced vital capacity (% predicted FVC).

Treatment with Lumizyme demonstrated a benefit of 3.4% (p=0.004) in % predicted FVC at 78 weeks. A benefit of 28.1 meters in the 6MWT was demonstrated at 78 weeks (p=0.06). There

were were no patients enrolled in LOTS less than 8 years of age, and therefore, efficacy in this age group could not be established. 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. However, the subgroup sizes were too small to make clear conclusions regarding the effect of Lumizyme. Important clinical safety issues were noted including acute and chronic allergic and immunologically-mediated reactions and anaphylaxis. Chronic exposure to Lumizyme as not adequately studied, but both skin reactions and urinary abnormalities reported in LOTS suggested that, as with Myozyme, immune mediated reactions may occur with chronic exposure. These risks were similar to those found with Myozyme. Thus, the the overall safety profile appears to be acceptable for patients with Pompe disease 8 years of age and older. The safety and effectiveness of Lumizyme have not been evaluated in patients with infantile-onset or late (non-infantile) onset Pompe disease less than 8 years of age. Due to the potential risk of rapid disease progression in these populations, Lumizyme should not be used in these patients. In addition, anaphylaxis and severe acute and chronic allergic reactions have been reported with Lumizyme. It was determined that a REMS is necessary for Lumizyme to mitigate the potential risk of rapid disease progression in infantile-onset Pompe disease patients and patients with late (non-infantile) onset disease less than 8 years of age for whom the safety and effectiveness of Lumizyme have not been evaluated. In addition, it was determined that a REMS is necessary to ensure that the known risks of anaphylaxis and severe allergic reactions associated with the use of Lumizyme and the potential risks of severe cutaneous and systemic immune complex-mediated reactions to Lumizyme are communicated to patients and prescribers. However, the Agency was not able to come to an agreement with the Applicant regarding the components of the REMS for Lumizyme prior to the action date.

There were no deficiencies noted by the Nonclinical Pharmacology/Toxicology reviewer, Niraj Mehta, PhD, the Clinical Pharmacology reviewer J.I. Kim, PhD, or the Biopharmaceutics reviewer, J. Earp, PhD.

Several quality deficiencies were noted by the primary reviewer, Fred Mills, PhD, Division of Therapeutic Proteins, and included the following:

1) Cell viability is a critical parameter for controlling product quality during (b) (4) The Applicant was requested to provide adequate justification for not using cell viability as an in process control for bioreactor monitoring.

2) An established reference standard for use in testing control strategy that is representative of the 2000 L process was not submitted to this BLA. The Applicant was requested to provide data to support the qualification of a reference standard.

3) The acceptance criteria for drug substance and drug product specifications were not consistent with manufacturing process capability and considerations regarding potential impact on safety and efficacy. The Applicant was requested to provide an evaluation on the following analytical tests: (b) (4); assay; SDS-PAGE gel assays; HPLC for measurement of (b) (4) HPAEC-PAD for measurement of (b) (4); and size exclusion chromatography.

(b) (4)

The application was discussed before the Endocrinologic and Metabolic Drug Products Advisory Committee on October 21, 2008. In closed session, the Advisory Committee was briefed on the biochemical differences between Lumizyme and Myozyme, and their potential impact on the relative efficacy and safety of Lumizyme. In open session, discussions centered on the demonstration of efficacy based on the effects of Lumizyme on the 6-minute walk test (6MWT) in the single placebo-controlled trial (LOTS). The majority of Committee members recommended approval of the Lumizyme under Subpart E, accelerated approval, based on its effects on a surrogate endpoint, % predicted forced vital capacity (11 votes for Subpart E approval, 4 votes for regular approval and 1 vote for nonapproval). Fifteen members voted to "require" Genzyme to perform post-marketing studies to assess efficacy. Recommendations included that the study should include a clinically relevant endpoint and should be designed to measure a robust effect. The committee also understood that a placebo-controlled study would not likely be feasible and stated that a dose-ranging study may be considered. However, the Agency was not able to come to agreement with the Applicant regarding the study design of the verification study, including the proposed sample size and primary endpoint, the statistical analysis plan, and the timeframe for enrollment and completion of the study prior to the action date. Sixteen members voted against restricting the indication to adult-onset patients only. Several committee members agreed that a REMS should be required to ensure the safe use of Lumizyme. It was suggested by some members that the inclusion criterion of LOTS could be used as age of cut-off for Lumizyme to treat late (non-infantile onset) patients ages 8 years or older. Seventeen members voted to require Genzyme to conduct post marketing studies to assess safety. Recommendations included an emphasis on the immunopathologies associated with chronic administration, long-term use in children, and immunogenicity and anaphylaxis with long-term use.

The FDA New England District Office issued an FDA 483 form on October 10, 2008, identifying numerous cGMP deficiencies and manufacturing problems with the Applicant's Allston Landing, MA, manufacturing facility for this application. The lack of controls at this plant was deemed to potentially affect sterility, purity, and availability of the finished product and bulk drug substance. The Applicant's written response to the FDA 483 form did not adequately address these concerns and the New England District Office recommended issuance of a Warning Letter. On February 2, 2009 the Office of Compliance approved the issuance of the Warning Letter, which was issued on February 27, 2009. The Warning Letter cited (b) (4)

(b) (4)

(b) (4) The Office of Compliance recommended that a withhold approval action be taken. A re-inspection of the facility in May 2009 found that there was not satisfactory resolution of these deficiencies. An ongoing inspection at the time of this review has found that the cGMP deficiencies have not been resolved.

Access to Lumizyme has been further limited by a report of rapid cell death in a bioreactor used to produce Lumizyme at the Allston Landing, MA, facility in November, 2008, due to viral contamination with Vesivirus 2117. There have been two additional bioreactor crashes involving Vesivirus 2117, including a bioreactor crash at the Applicant's Geel, Belgium, facility during a production run for 4000 L alglucosidase alfa. Based on the pattern of these viral contaminations, the Applicant believes that raw materials used in the production process may have been contaminated with the virus. However, the root cause of the viral contamination remains unresolved at the time of this review.

It was determined that the Agency could not approve the application based on the following deficiencies:

1. Manufacturing deficiencies identified on inspection of the Allston Landing, MA, facility, leading to the issuance of a Warning Letter
2. CMC deficiencies
3. Design of a post-approval study conducted under the accelerated approval regulations to verify the clinical benefit of Lumizyme, and
4. Submission of a completed Risk Evaluation and Mitigation Strategy (REMS).

On February 27, 2009, a complete response letter was signed by Julie Beitz, MD, Director of ODE III, and describes the deficiencies as outlined above. Other items required for resubmission requested in the letter were postmarketing studies, labeling revisions, and a safety update.

2.6 Other Relevant Background Information

Update on events since CR letter issued:
During a teleconference on April 17, 2009, the Agency communicated to the Applicant that data to support full approval of Lumizyme may be feasible based on clinical data from the Pompe Registry. Therefore, approval under subpart E would not be required. This decision was based on the Agency's preliminary analysis of survival and ventilator-free survival data provided by the Applicant from 25 infantile-onset patients from the Pompe Registry who matched the pivotal study patients in terms of baseline disease characteristics. In accordance with an Information Request (IR) from the Agency on April 27, 2009, the Applicant has submitted further datasets from the Pompe Registry Protocol as part of the Complete Response.

During a teleconference on March 27, 2009, the Applicant agreed to submit a revised REMS to incorporate the Agency's comments which was submitted on April 6, 2009.

Genzyme included revised labeling in accordance with a discussion held with the Agency on March 20, 2009 in their resubmission package (see section 9.2 and final product labeling for details).

A safety update including data from all nonclinical and clinical studies of the drug under consideration, regardless of indication, dosage form, or dose level was requested upon response to the action letter to the Applicant. Safety data was included in the Applicant's resubmission package (see section 7, Review of Safety, for details).

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall quality of the data submitted by the Applicant was adequate for comprehensive review of the data, and the integrity of the investigators and the conduct of the trial were found to be acceptable by the Division of Scientific Investigation during the first cycle review.

3.2 Compliance with Good Clinical Practices

The Applicant stated that LOTS was conducted, recorded, and reported incompliance with the principles of Good Clinical Practice (GCP) regulations and clinical research guidelines established by the principles defined in the U.S. 21 CFR Part 312, and ICH E6 "Guideline for Good Clinical Practice, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use".

3.3 Financial Disclosures

Financial disclosures were not required as part of the Applicant's Complete Response (see original BLA review by L. Yao, M.D., for review of financial disclosure information).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please see full review by Dr. Fred Mills, PhD, DTP for his review of the Applicant's responses to CMC issues outlined in section 2.5 above in the Complete Response letter. In brief, the CMC review team has received adequate responses to all the clinical deficiencies noted below:

FDA Question 1

Modification of their procedures for monitoring cell viability during 2000 L bioreactor culture.

FDA Question 2
Qualification of a reference standard for the 2000 L process

FDA Question 3
Lot release specifications for [redacted] (b) (4) assay, SDS-PAGE gel assays, HPLC for measurement of total [redacted] (b) (4) HPAEC-PAD for measurement of [redacted] (b) (4) ; and size exclusion chromatography

FDA Question 4
Revision of the system suitability criterion for the [redacted] (b) (4) analytical test

Four CMC postmarketing commitments agreed to by the Applicant (see section 1.4, Recommendations for Postmarket Requirements and Commitments) are:

1) To evaluate the use of the [redacted] (b) (4) method as a release test for glycan profiling of the drug substance.
2) To develop an analytical method to monitor [redacted] (b) (4) and evaluate its use in the release and stability specification
3) [redacted] (b) (4)
4) To establish in process control limits for cell viability during the [redacted] (b) (4) period using the data collected from four upcoming 4000 L cell culture runs.

4.2 Clinical Microbiology

Clinical microbiology considerations do not apply to this application because Lumizyme is not an antimicrobial agent.

4.3 Preclinical Pharmacology/Toxicology

There are no Preclinical Pharmacology/Toxicology issues with this submission to the Complete Response.

4.4 Clinical Pharmacology

There are no Clinical Pharmacology issues with this submission to the Complete Response. However, during the first cycle review, the clinical pharmacology reviewers, J.I. Kim and J. Earp, recommended that additional post-marketing studies be performed to evaluate the pharmacokinetics of Lumizyme in pediatric patients because this age group had not been adequately studied in the clinical studies submitted for review. One post-marketing commitment

was successfully negotiated during the current review cycle to address this concern (see section 1.4, Recommendations for Postmarket Requirements and Commitments).

4.4.1 Mechanism of Action

Acid alpha-glucosidase is a hydrolase that degrades lysosomal glycogen to glucose. During trafficking to the lysosome, acid alpha-glucosidase is proteolytically processed, which results in the formation of an enzymatically active multi-subunit complex. Acid alpha-glucosidase degrades glycogen by catalyzing the hydrolysis of α-1,4- and α-1,6 glycosidic linkages of lysosomal glycogen. Pompe disease is due to the deficiency of acid alpha-glucosidase results in the accumulation of glycogen in the lysosomes of a variety of cells, predominantly in skeletal muscle. This accumulation in skeletal muscle lysosomes results in progressive muscle weakness, affecting motor and respiratory function. Death in all forms of the disease is usually a result of cardiorespiratory failure.

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. 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. The rationale for therapy is that exogenous administration of the enzyme should theoretically replace the deficiency in Pompe disease patients. After intravenous administration, alglucosidase alfa is internalized by cells via cellular membrane manose-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.

4.4.2 Pharmacodynamics

There were no pharmacodynamic studies conducted for this submission.

4.4.3 Pharmacokinetics

There were no pharmacokinetic studies conducted for this submission.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The following table (see Table 2) lists the clinical studies submitted by the Applicant for review in support of the Complete Response to Lumizyme.

Table 2: Table of Clinical Studies

Study	Trial Design	Comments
AGLU02074	LOTS: Randomized, double-blind, placebo-controlled study of late-onset Pompe patients ages 8-70 years; 2000L 20mg/kg/qow, n=90	Submitted to BLA 125291, only safety data
AGLU03206	LOTS extension: open label extension of 86 patients who participated in LOTS; 2000L 20mg/kg/qow	Only safety data
AGLU3907	MTAP: open label, expanded access protocol to treat US patients over age 18, n=176	Only safety data
Pompe Registry	Voluntary, observational study of patients with Pompe disease	Efficacy data on 25 patients

qow=every other week

5.2 Review Strategy

For an overview of the clinical development program, the reader is directed to see Dr. Yao's review of the original BLA submission. This reviewer's efficacy and safety review strategies are outlined in sections 6 and 7 below.

5.3 Discussion of Individual Studies/Clinical Trials

See Sections 6 and 7 for a detailed outline of the studies used for efficacy and safety review in this submission.

6 Review of Efficacy

Efficacy Summary

Pompe Registry data suggests that there is improvement in survival in infantile-onset patients treated with Lumizyme compared to an untreated infantile-onset historical control cohort. Overall survival (2%) is extremely poor for the untreated infantile-onset patients. Treatment with either Myozyme or Lumizyme leads to improvement of overall survival, 80% and 33%, respectively. When cross-reactive immunologic material (CRIM) negative patients are excluded, overall survival in the Lumizyme group increases to 40% and overall survival for Myozyme decreases to 78%. Thus, it appears that some of the difference in survival between the Lumizyme and Myozyme groups may be due to differences in CRIM status. However, the sample sizes were too small to make definite conclusions regarding the relationship of CRIM to overall survival by treatment group. Gender and immunogenicity do not appear to affect overall survival. Additionally, the Reviewer notes that there appears to be a difference in survival between the Lumizyme and Myozyme treatment groups. As has been previously noted, there are

important differences in critical product quality attributes that may contribute to differences in potency between the two products. However, the sample sizes for these subgroup analyses are too small to make definite conclusion regarding any differences in survival or treatment effect between Lumizyme and Myozyme.

The Reviewer also notes that the Pompe Registry includes small numbers of age and disease-matched patients, the comparator group was not concurrent (i.e., historical control group), and some data from the registry was collected retrospectively. Thus, review of the registry data is limited to descriptive analyses and limited analyses of specific subgroups (e.g., age, gender, CRIM status).

6.1 Indication

The indication that is currently being proposed for Lumizyme is the following:

"LUMIZYME (alglucosidase alfa) is a lysosomal glycogen-specific enzyme indicated for patients 8 years and older with late (non-infantile) onset Pompe disease (GAA deficiency) who do not have evidence of cardiac hypertrophy. The safety and efficacy of LUMIZYME have not been evaluated in controlled clinical trials in infantile-onset patients, or in late (non-infantile) onset patients less than 8 years of age."

For a final version of the indication for Lumizyme, please see final product labeling.

6.1.1 Methods

The efficacy information available for the medical review includes clinical efficacy or outcomes measures from the Pompe Registry. As discussed earlier, the Agency and the Applicant agreed to review data from the Pompe Registry, a disease registry that includes data in infantile-onset patients treated with Lumizyme who match the baseline characteristics of the Phase 3 clinical trial that lead to the approval of Myozyme (AGLU1602, reviewed by Anne Pariser, M.D., BLA 129141).

Pompe Registry Study Design
The Pompe Registry was initiated in September 2006, as part of a post-marketing commitment negotiated with the Applicant prior to the approval of Myozyme. The Registry is a multi-center, multi-national, voluntary, observational clinical data program that tracks the natural history and outcomes of patients with Pompe disease. It primarily relies on standard of care assessments to collect longitudinal data on patients. Demographic, baseline genetic, and relevant clinical information is collected at the time of enrollment and standard-of-care assessments are used to collect longitudinal data.

Study objectives
The primary objectives of the Registry are:

1. To enhance the understanding of the variability, progression, identification, and natural history of the manifestations of Pompe disease

2. To assist the Pompe medical community with the development of recommendations for monitoring patients and reports on patient outcomes to help optimize patient care
3. To characterize and describe the Pompe disease population as a whole
4. To evaluate the long-term effectiveness and safety of available treatment options and support measures including ERT.

The objectives of the current review of the Pompe Registry Data are:

1. To evaluate the survival of infantile-onset patients, matched to patients enrolled in Study 1602, treated with Lumizyme compared to an age and diseased match historical control group
2. To evaluate ventilator-free survival of infantile-onset patients, matched to patients enrolled in Study 1602, treated with Lumizyme compared to an age and diseased match historical control group
3. To evaluate the overall safety profile of infantile-onset patients, matched to patients enrolled in Study 1602, treated with Lumizyme

Inclusion and exclusion criteria

All patients with a confirmed diagnosis of Pompe disease are eligible for inclusion. Confirmation of diagnosis is defined as documented GAA enzyme deficiency from any tissue source and/or documentation of 2 GAA gene mutations. There are no exclusion criteria for the Registry. However, patients enrolled in Genzyme sponsored clinical trials are requested to suspend active participation in the Pompe Registry.

Schedule of assessments

Physicians determine the frequency of necessary assessments according to a patient's individualized needs for medical care and routine follow-up. However, a Recommended Schedule of Assessments is encouraged (Table 3).

Table 3: Recommended Schedule of Assessments

	All Patients	Age < 5 Years			Age ≥ 5 Years		
	Upon Enrollment	Every 3 Months	Every 6 Months	Every 12 Months	Every 3 Months	Every 6 Months	Every 12 Months
Initial Enrollment							
Demographics	X						
Diagnosis (Enzyme Assay, DNA Analysis)	X						
Medical History	X						
General Patient Monitoring[B]							
Clinical Follow-up			X			X	
Pregnancy Status (females of childbearing potential only)	X					X	
ERT[C]	X		X			X	
Physical Examination							
Height/Weight/Head Circumference[D]	X	X	X[D]				X
Vital Signs (Blood Pressure/Temperature)	X	X					X
Laboratory Tests[E,K]							
Blood Tests	X		X				X
Urine Tests	X		X				X
Clinical Events							
X-rays[F]	X		X				X
ECG	X		X				X
ECHO	X		X				X
Auditory Examination	X			X			X
Ophthalmologic Examination[G]	X			X			
Pulmonary Function Tests	X		X				X
Cognitive and Developmental Assessments (as age appropriate)							
DDST-II Test[H]	X[H]		X[H]			X[H]	
Bayley III Test			X				
Leiter-R Scale				X			X
Neuroimaging							
MRI, CT scan, or ultrasound				X			X
Motor Assessments (as age appropriate)							
GGFM-66 and Pompe PEDI	X		X				X
Motor Milestones Checklist	X		X				
Motor Functional Activities							X
Walton & Gardner-Medwin Scale							X
Arm and Leg Functional Tests							X
Hand Held Dynamometry	X						X
6-Minute Walk Test							X
Manual Muscle Testing (MRC Scale)	X						X
Quality of Life/Health Outcomes							
SF-36v2[I]	X						X
RHI[J]	X					X	
FSS[J]	X					X	
Patients Receiving ERT							
Upon ERT Initiation	In addition to completing the initial assessments upon Pompe Registry enrollment, there should also be documentation of these assessments as a baseline at the time of first ERT infusion						
Ongoing ERT Administration	At a minimum ERT information including dose and frequency should be collected at first infusion and every 6 months thereafter and/or when a change in the ERT regimen has occurred						
Antibody Testing	Antibody testing is recommended for all patients receiving ERT in the following sequence • Submit Baseline (1st ERT infusion) Serum sample • Submit Serum sample every 3 months						
Adverse Event Reporting	For patients receiving Myozyme, there must be ongoing/continuous monitoring with reporting through the Genzyme Pharmacovigilance Department. See safety section (12) of the Pompe Registry Protocol for specific reporting guidelines and instructions						

Registry Assessments

Demographics and Medical History

Demographics, medical history, pregnancy status, and Pompe disease diagnosis, are collected for all patients upon enrollment into the Pompe Registry. Clinical follow-up involving the development/neurological, EENT (ears, eyes, nose, and throat), respiratory, cardiovascular, gastrointestinal/hepatic/renal, and musculoskeletal/motor systems are requested to be conducted

in all patients every 6 months thereafter. Specific information pertaining to ventilator use at the time of enrollment and at the time of each follow-up assessment are to be collected.

Enzyme Replacement Therapy Status
ERT status (if the patient is receiving ERT or not) and initial ERT information (for patients receiving ERT) is collected for each patient upon enrollment into the Pompe Registry. If a patient is receiving ongoing ERT, the ERT regimen since first infusion is to be collected every 6 months and/or when a change in the ERT regimen occurs. Dose change, infusion frequency change, infusion time change, temporary interruption in ER, restart of ERT following a temporary interruption, or permanent discontinuation of ERT is also followed.

Physical Examinations
Height, weight, head circumference, and vital signs (blood pressure and temperature) are to be measured for all patients upon enrollment and every 3 months thereafter for patients < 5 years of age, and every 12 months thereafter for patients ≥ 5 years of age.

Laboratory Testing
Laboratory testing is to be conducted for all patients upon enrollment and every 6 months thereafter for patients < 5 years of age, and every 12 months thereafter for patients ≥ 5 years of age. Blood and urine laboratory tests should include liver function studies, coagulation factors, renal functions, CK-MB fraction, and urinary oligosaccharides.

X-Rays
Chest X-rays (a posterior to anterior [PA] view) and an X-ray of the spine (cervical, thoracic, and lumbosacral regions) are to be performed for all patients upon enrollment and every 6 months thereafter for patients < 5 years of age, and every 12 months thereafter for patients ≥ 5 years of age.

Electrocardiograms (ECGs)
A standard 12-lead ECG is to be performed on all patients upon enrollment and every 6 months thereafter for patients < 5 years of age, and every 12 months thereafter for patients ≥ 5 years of age. The following are to be assessed: Sinus rhythm, conduction, PR interval, QRS interval, QTc interval, evidence of left/right ventricular hypertrophy, and evidence of left/right atrial enlargement.

Echocardiograms (ECHOs)
ECHOs are to be performed on all patients upon enrollment and every 6 months thereafter for patients < 5 years of age, and every 12 months thereafter for patients ≥ 5 years of age. The following are to be assessed: left ventricular mass (LVM), left ventricular ejection fraction (LVEF), left ventricular shortening fraction (LVSF), left ventricular outflow tract obstruction (LVOTO), left ventricular function (LVF), and evidence of cardiomyopathy.

Auditory and Ophthalmologic Assessments
Auditory examinations are to be performed on all patients upon enrollment and every 12 months thereafter, regardless of their treatment with ERT. One or more of the following methods may be

used for the assessment: Pure tone audiometry, otoacoustic emissions (OAE), and the brain stem auditory response (BAER). Ophthalmologic examinations are to be performed on all patients upon and every 12 months thereafter for patients < 5 years of age. The following assessments are recommended: External examination (patients ≤ 2 years of age), ocular motility (patients ≤ 2 years of age), Red Reflex examination (patients ≤ 2 years of age), visual acuity (patients ≥ 3 years of age), and fundoscopy (patients ≥ 4 years of age).

Pulmonary Function Tests
Pulmonary function tests are to be conducted in all patients upon enrollment and every 6 months thereafter for patients < 5 years of age, and every 12 months thereafter for patients ≥ 5 years of age and should include at a minimum the assessment of forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1), as well as the percent predicted values.

Cognitive and Developmental Assessments
Cognitive and developmental assessments are to be conducted for all patients < 6 years of age upon enrollment and are to include The Denver Developmental Screening Test II (DDST-II), The Cognitive and Language Scales of The Bayley Scales of Infant and Toddler Development III (Bayley III), and the Modified Leiter International Performance Scale-Revised (Leiter-R) tests.

Neuroimaging
A magnetic resonance imaging (MRI), computed tomography (CT) scan, or ultrasound of the brain according to institutional procedures is recommended for patients every 12 months in order to evaluate possible changes in brain structures over time.

Motor and Functional Assessments
The Gross Motor Function Measure (GMFM-66) and the Pompe Pediatric Disability Index (PEDI) are to be conducted in all patients upon enrollment and every 6 months thereafter for patients < 5 years of age (until the patient reaches 5 years of age), and every 12 months thereafter for patients ≥ 5 years of age (for the duration of their participation in the Pompe Registry).

Quality of Life/Health Outcomes
Patients ≥ 14 years of age (and/or their legal guardians if the patient is physically unable to complete the form) are to complete the SF-36® Health Survey prior to the first ERT infusion (to obtain baseline results) and every 12 months thereafter. Patients ≥ 18 years of age are to complete the Fatigue Severity Scale (FSS) and the Rotterdam 9-item Handicap Scale (RHI) upon enrollment and/or prior to the first ERT infusion (to obtain baseline results) and every 6 months thereafter.

Safety Information
Investigators were advised to report all AEs promptly to the Applicant's Pharmacovigilance Department.

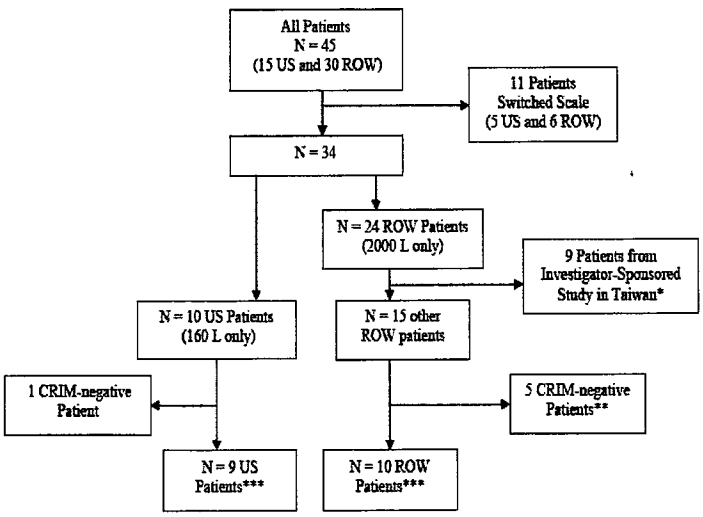
Patient Population

The Applicant reviewed the Pompe Registry for infantile-onset patients that met the inclusion criteria for AGLU1602, the Phase 3 trial that led to the approval of Myozyme. These criteria included:

1. Onset of symptoms of Pompe disease on or before 6 months of age
2. Confirmed diagnosis based on GAA activity
3. Evidence of hypertrophic cardiomyopathy
4. Initiation of treatment prior to 6 months of age

There were 48 patients in the Registry who matched the AGLU1602 population, however, 3 patients were excluded from the Applicant's summary because they received other sources of rhGAA (e.g. (b) (4) or transgenic rhGAA), resulting in a total of 45 evaluable patients (see Figure 1). Eleven patients received both 160 L and 2000 L scale products (switched scale) and were excluded from the final analysis due to the possible confounding influence of receiving both scales. The 10 patients who were treated in the US received Myozyme (160 L scale) and the 24 patients who were treated outside the US (Rest of the World, ROW) received Lumizyme (2000 L scale). Nine of the 24 patients treated outside the US were part of an Investigator-sponsored study in Taiwan. The Taiwan patient outcomes were reported during the original BLA submission for Lumizyme. This analysis included a total of 11 patients with one patient who began treatment at 14 months of age and one patient who was not in the Pompe Registry. All patients were alive and free of ventilator support at the time of their last follow-up visit (median age at last follow-up was 23.7 months, range 5.5-31.1 months). The Taiwanese patients were diagnosed earlier because of a state-sponsored prenatal screening program and began treatment earlier than other infantile-onset patients. Therefore, subset analyses of the registry data were performed excluding the Taiwan patients.

Figure 1: Derivation of Analysis Populations



US = United States, ROW = rest-of-world

* 11 patients included in submission during the first cycle review

** 2 CRIM negative ROW patients are presumed CRIM negative based on genetic mutation analysis

*** Includes CRIM positive and CRIM status unknown

Efficacy and Endpoint measures

There were no pre-specified primary efficacy endpoints selected because the data from the Pompe Registry were reviewed retrospectively. However, the endpoints chosen were similar to the endpoints pre-specified for Study 1602 and were:

1. Survival in infantile-onset patients overall and at 18 months of age
2. Ventilator-free survival in infantile-onset patients overall and at 18 months of age

6.1.2 Demographics

Table 4 summarizes the demographic characteristics of the 25 infantile-onset patients in the Pompe Registry who met inclusion criteria for the 1602 study. The demographics of patients receiving Myozyme and Lumizyme are similar. Patients in all groups were followed for approximately 20 months. There was a slight difference in the median duration of treatment for Lumizyme-treated patients, 15 months, and for Myozyme-treated patients, 18 months. The median age of 1st infusion was also similar between groups. More males were treated with Myozyme than females.

Table 4: Demographics and Baseline Characteristics of All Patients

Parameter	Registry US Myozyme	Registry ROW Lumizyme
Total number	10	15
Median Age of Death or Last follow-up (months)	20.7 (2.1-45.6)	19.0 (4.9-51.4)
Median Duration of Treatment (months)	18.4 (0.5-40.2)	14.6 (3.4-48.4)
Median Age at 1st Infusion (months)	4.6 (0.4-6.0)	3.6 (0.6-6.0)
Gender N (%)		
Male	7 (70)	6 (40)
Female	3 (30)	9 (60)
Ethnicity N (%)		
Caucasian	4 (40)	8 (53)
Black	2 (20)	3 (20)
Hispanic	2 (20)	0 (0)
Asian	1 (10)	0 (0)
Other	1 (10)	3 (20)
Unknown	0 (0)	1 (7)

6.1.3 Subject Disposition

As discussed earlier, the efficacy information available for this medical review includes clinical efficacy or outcomes measures from the ongoing Pompe Registry. Since these data were

collected as part of a disease registry, no specific screening failures were noted. The Sponsor did not provide information on discontinuations or patients lost to follow-up from the Registry. The Sponsor reviewed the Pompe Registry for infantile-onset patients that met the inclusion criteria for AGLU1602, the Phase 3 trial that led to the approval of Myozyme. There were 25 patients chosen for data analysis as described in Section 6.1.1, Patient Population.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint in the AGLU01602 pivotal clinical study was the proportion of patients treated with Myozyme (n=18) who were alive and free of invasive ventilator support at 18 months of age, compared to the survival of a matched historical control group. Data regarding ventilator status could not be reliably verified in the historical control group and, therefore, survival alone was used for these analyses. Myozyme was approved based on a ventilator-free survival of 89% compared to a 2% overall survival in the historical control group. In the Registry cohort, either death or the use of invasive-ventilation could be evaluated as a clinical endpoint, whereas in the natural history cohort, only death was evaluated as a clinical endpoint because invasive-ventilation was a pre-morbid condition in the natural history of Pompe disease. Thus, including both invasive-ventilation and death as clinical endpoints in the natural history cohort would likely overestimate the incidence of patients reaching the primary endpoint in this group. The primary efficacy endpoint used in the Registry data analysis was overall survival and invasive-ventilator free survival at 18 months.

Overall survival
Table 5 summarizes the overall survival of all 25 evaluable infantile-onset Pompe registry patients compared with the historical control cohort. Overall survival is extremely poor (2%) for the untreated infantile-onset patients. Treatment with either Myozyme or Lumizyme leads to improvement of overall survival, 80% and 33%, respectively. Overall survival appears to be higher in the Myozyme group compared to the Lumizyme-treated group in this Pompe Registry population, however, the small sample sizes for these subgroups prevents the ability for the Reviewer to draw clear conclusion regarding the relative treatment effect between Lumizyme and Myozyme.

Table 5: Overall Survival

Survival	Lumizyme (%)	Myozyme (%)	Historical control (%)
Alive	5 (33)	8 (80)	1 (2)
Deceased	10 (67)	2 (20)	60 (98)
Total	15	10	61

Invasive Ventilation
Two patients were started on invasive-ventilation prior to receiving Myozyme. Patient 10620 was placed on invasive ventilation the same day of his first infusion at 1.6 months of age and was still alive at 30.4 months. Patient 10575 was placed in invasive ventilation 2 days prior to her first infusion at 5.3 months of age and was alive at 45.6 months. Therefore, time to invasive ventilation cannot be measured. If these two patients are excluded, the overall survival of the

Myozyme-treated group decreases to 60% (6/10). Only one patient (Patient 10310) began invasive-ventilation after starting treatment. This patient was treated with Lumizyme beginning at 4.2 months of age and was placed on invasive ventilation at 9.3 months and died at 27.3 months. Therefore, most patients who died did not receive invasive ventilation prior to death (11/12), and analysis of patients who required invasive-ventilation does not appear to provide meaningful information regarding the efficacy of Lumizyme. In summary, invasive ventilator use in this Pompe Registry group overall is minimal, and does not provide meaningful efficacy information for Lumizyme.

Survival at 18 months

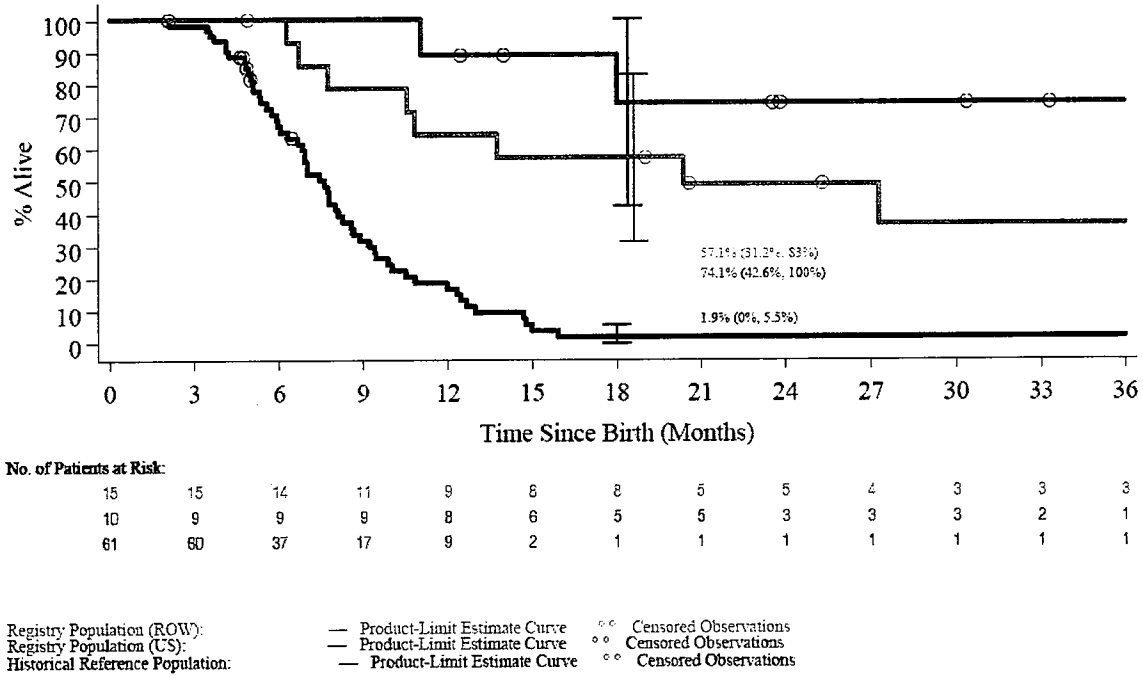
Survival at 18 months of age was also analyzed because this endpoint was also used in the Myozyme pivotal trial. Table 6 shows the survival at 18 months of age for the 25 evaluable infantile-onset Pompe registry patients. It should be noted that only 8/15 (53%) Lumizyme-treated patients and only 5/10 (50%) Myozyme-treated patients had reached the age of 18 months. Of the 8 patients in the Lumizyme group who had not reached 18 months of age, only 1 patient was alive, but had not reached 18 months of age at the time of the analysis. However, in the Myozyme group, 3 patients who had not reached 18 months of age were alive, but had not yet reached 18 months of age at the time of the analysis. Four of the 8 Lumizyme-treated patients who survived to 18 months ultimately died. Therefore, survival for Lumizyme, 57% (8/14), is improved compared to historical control (2%). However, survival at 18 months may not adequately reflect survival given the small number of patients that had actually reached the age of 18 months in order to evaluate this endpoint.

Table 6: Survival Status at 18 months

Alive at 18 months	Lumizyme	Myozyme
no	6	2
no* (not reached 18 months)	1	3
yes	4	5
yes** (died after 18 months of age)	4	0
Total	15	10

* Have not reached 18 months of age but were alive at the time of the analysis
** Alive at 18 months of age, but died subsequently

Figure 2: Kaplan-Meier Estimate of Time to Death from Date of Birth Comparison of Historical Control Patients with Registry Patient Population



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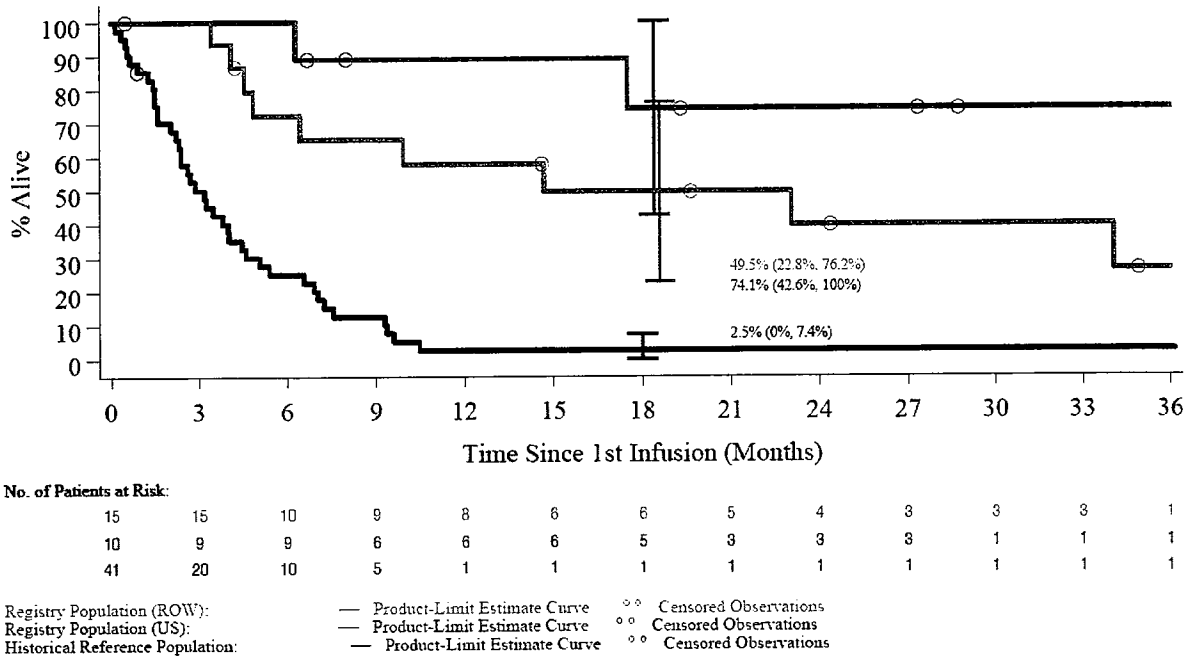
Time to Death from Initiation of Treatment

An estimate of the survival of the 25 evaluable patients from the Registry includes only patients that initiated treatment prior to 6 months of age. Some studies suggest that early initiation of ERT may improve survival thus time from initiation of treatment to death may be a more appropriate measurement of the effectiveness of ERT on survival. Figure 4 shows that similar to overall survival from birth, the Lumizyme-treated group had improved survival (42%) 18 months after 1st infusion compared to historical controls (2.5%), and the Myozyme-treated group showed improved survival (64%) compared to the Lumizyme-treated group

Figure 3: Kaplan-Meier Estimate of Time to Death from Date of 1st Infusion Comparison of Historical Control Patients with Registry Patient Population



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6.1.5 Analysis of Secondary Endpoints(s)

There were no secondary efficacy endpoints submitted by the Applicant for review.

6.1.6 Other Endpoints

There were no other endpoints selected submitted by the Applicant for review.

6.1.7 Subpopulations

Immunogenicity

The development of immune responses to the infused enzyme is an important safety consideration with all enzyme replacement therapies. These immune responses can lead to the development of allergic/hypersensitivity reactions as well as alter the effectiveness of treatment. Lumizyme, as with all of the currently studied enzyme replacement therapies, is associated with development of immunogenicity. In the LOTS study, anti-rhGAA IgG antibodies were measured throughout the course of the study at specific time points, and by week 20 of the study all of the Lumizyme-treated patients developed anti-rhGAA IgG antibodies. Only 8/25 patients from the Pompe registry had antibody data reported, and the majority of these patients (6/8) were treated with Myozyme in the US. It is difficult to evaluate the effect of immunogenicity on safety or efficacy in these patients since this information was collected in a minority of patients evaluated. However, in the 8 patients with antibody data, 3 of 4 patients with antibody titer >

100,000 (range 102,400-409,600) died, while all patients (4/4) with antibody titers < 100,000 (range 100-51,200) survived. These data suggest that patients with higher antibody responses to alglucosidase alfa had worse outcome, however, the numbers of patients is too small to make clear conclusions regarding immunogenicity and outcome.

CRIM status

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.[5] Infantile-onset patients are more likely to be CRIM negative. Therefore, a review of the effect of CRIM status in the 25 evaluable infantile-onset Pompe registry patients was performed.

Table 7: CRIM status by treatment group

CRIM status	Lumizyme	Myozyme
NEGATIVE	5 (33%)	1 (10%)
NOT DONE	6 (40%)	3 (30%)
POSITIVE	4 (27%)	6 (60%)
Total	15	10

Table 7 shows that more patients in the Lumizyme-treated group were CRIM negative (5/15, 33%) than in the Myozyme-treated group (1/10, 10%), and there were more CRIM positive patients in the Myozyme group (60%) compared with the Lumizyme group (27%). However, 6/15 (40%) patients in Lumizyme treated group and 3/10 (30%) patients in Myozyme treated group had unknown CRIM status.

The Applicant evaluated overall survival excluding the six CRIM negative patients. Overall survival in the Lumizyme group increases from 33% to 40% (Table 8). Overall survival for Myozyme decreases slightly from 80% to 78%. The reviewer also notes that the two Myzoyme-treated patients who were invasively ventilated prior to treatment were CRIM positive, and overall survival decreases to 71% if the two patients who are invasively ventilated prior to treatment are excluded. However, this reviewer believes that these two patients should be included in the analysis since these two patients were both alive at the time of the analysis.

Table 8: Overall survival, excluding CRIM negative patients

Survival	Lumizyme (%)	Myozyme (%)
Alive	4 (40)	7 (78)
Deceased	6 (60)	2 (22)
Total	10	9

Thus, it appears that CRIM status may contribute to the lower survival seen in Lumizyme-treated patients. However, the sample size for this subgroup analysis is too small to make definite conclusions regarding the effect of CRIM status on overall survival.

Gender

In LOTS, gender differences may have associated with differences in clinical effect of Lumizyme. Subgroup analysis suggested that female patients had less improvement in the 6MWT compared with male patients. However, the subgroups were too small to make clear conclusions regarding the effect of gender on Lumizyme treatment. In the Pompe Registry patients, there were 6 males and 9 females in the Lumizyme group, and 7 males and 3 females in the Myozyme group (see table 4). Table 9 shows overall survival by gender, the overall survival of males and females is better with Myozyme, which is similar when the prior to treatment invasively-ventilated patients are excluded. However, only 2 females were treated with Myozyme. Since these are descriptive analyses including a small number of patients, it is difficult to make conclusions about the affect of therapy based on gender.

Table 9: Overall Survival of All Patients by Gender

Gender	Survival	Lumizyme (%)	Myozyme (%)	Total
Male	Alive	2 (13)	5 (50)	6
Male	Deceased	4 (27)	2 (20)	6
Female	Alive	3 (20)	3 (30)	7
Female	Deceased	6 (40)	0	6
Total		15	10	

In summary, the Registry data suggests that there is improvement in survival in infantile-onset patients treated with Lumizyme compared to an untreated infantile-onset historical control cohort. Differences in invasive ventilator-free survival could not be performed because these numbers were too small, and limited by patients who were receiving invasive ventilation prior to starting treatment. These data also suggest a difference in overall survival between Lumizyme and Myozyme treatment. These differences may be related to differences in critical product quality attributes between the two products that may affect potency. Gender and immunogenicity do not appear to affect overall survival. However, clear conclusions regarding differences between Lumizyme and Myozyme treatment cannot be made due to the small sample sizes reviewed, and the retrospective nature of the analyses.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The approved commercial dose of Myozyme is 20mg/kg every other week, and the same dose has been selected for the use of Lumizyme outside the US.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No analyses were done to evaluate persistence of efficacy and/or tolerance effects.

6.1.10 Additional Efficacy Issues/Analyses

No additional efficacy analyses were performed.

7 Review of Safety

Safety Summary

Important clinical safety issues that were seen in this review are consistent with those seen in the initial review of Lumizyme and include safety issues related to the immunogenicity of Lumizyme. The known risks of anaphylaxis and infusion reactions were seen in patients in this safety update. Additionally, potential immunologically-mediated reactions including chronic skin and kidney reactions were noted in the initial review. Both skin reactions and urinary abnormalities have occurred in patients in this safety update. However, no new safety issues were observed in the analyses of the additional safety data reviewed.

7.1 Methods

A safety update submitted as part of the Complete Response includes the following data:

1) Cumulative final data from AGLU03026, the open label extension study of patients with late-onset Pompe disease (LOTS Extension) who completed 78 weeks in the randomized, double-blind, placebo-controlled multi-center study AGLU02704 (LOTS);
2) Cumulative interim safety data from the ongoing clinical study AGLU03907, the Myozyme Temporary Access Program (MTAP);
3) World-wide postmarketing experience as available through the Genzyme Pharmacovigilance Database.

The most comprehensive safety data submitted to the application were the safety data collected as part of the GCP-compliant LOTS and LOTS extension studies. Safety data in these studies were collected in a rigorous and comprehensive manner, including regular AE assessment and documentation at scheduled study visits, clinical laboratory evaluations, physical examinations, site monitoring and Data and Safety Monitoring Board (DSMB) and Allergic Reaction Review Board (ARRB) oversight. Patients in MTAP had prior commercial exposure and the types and quality of safety data collected were variable. The post-marketing safety data were collected predominantly through spontaneous report of Serious Adverse Events (SAEs) outside of the US. Therefore, the primary analyses were performed using LOTS/LOTS extension data.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

A summary of the three studies used to evaluate safety is provided in Table 10.

Table 10: Overview of Reporting Intervals for Safety Update

Source of Safety Data	Data Analysis Start Date	Data Analysis Cut-off Date	Late-Breaking Information Cut-off Date	Cumulative / Final
AGLU02704/ AGLU03206 (LOTS/LOTS Extension)	Start of study (September 06, 2005)	End of study[a]	Not applicable	Yes / Yes
AGLU03907 (MTAP)	Start of study (May 24, 2007)	IND annual reporting interval for BB-IND 10780 (October 15, 2008)	March 16, 2009	Yes / No
Spontaneous Post-Marketing Serious Case Reports	1 day after data cut-off for Summary of Clinical Safety (March 29, 2008)	Data lock for 11th Periodic AE Report (December 28, 2008)	March 16, 2009	No / Not applicable

[a]-The last patient completed treatment on October 10, 2008 and AE follow-up data were reported through October 24, 2008.

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7.1.2 Categorization of Adverse Events

The Applicant coded adverse events (AEs) by System Organ Class (SOC) and AE preferred terms using the Medical Dictionary for Regulatory Activities 9.1 (MedDRA). The MedDRA coding system contains greater than 15,000 AE preferred terms that can result in substantial granularity, fragmentation, and dilution of AE terms. AE preferred terms and SOC terms were revised by this Reviewer so that related AE terms were combined to allow for a more meaningful description of the AE profile. For example, abdominal discomfort, abdominal pain, abdominal pain lower and upper, were all classified as abdominal pain by this Reviewer.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Data from the LOTS/LOTS extension and MTAP have not been pooled by this Reviewer because the majority of patients in MTAP had prior commercial exposure to Myozyme and the types and quality of safety data collected were variable. The post-marketing safety data were collected predominantly through spontaneous report of Serious Adverse Events (SAEs) outside of the US. Since these data were not collected as part of a GCP study, post-marketing safety data were also not pooled.

7.2 Adequacy of Safety Assessments

Safety assessments occurred in LOTS at specified intervals and included laboratory, physical examination, echocardiography, and immunologic measurements. These assessments appear to be adequate to evaluate the safety profile of the drug.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Table 11 shows the exposure length in weeks in each study. Sixty patients received Lumizyme in LOTS and 55 of these completed the 78 weeks of treatment and continued to receive Lumizyme in the open-label LOTS extension study. Patients received a dose of 20 mg/kg/qow IV. The median time from the first infusion until study completion/discontinuation was 113 weeks (range 1.7-139 weeks). Twenty six patients received placebo in LOTS and subsequently received Lumizyme in the open-label LOTS extension study. The median time from first infusion for this group until study completion was 44 weeks (range 25-53 weeks). One hundred seventy six patients were treated under MTAP with a mean duration of exposure of 36.8 weeks (range 0.7-72.7 weeks). The planned dose was 20mg/kg/qow. Fifteen patients received a dose other than this at one or more infusions, however the Applicant did not provide further detail on the reason for dose adjustment.

Table 11: Exposure length (weeks) by treatment group LOTS/LOTS extension and MTAP

	LOTS/LOTS Extension		MTAP[a]	
Weeks in Study	Placebo/ Alglucosidase Alfa Patients (N=26) n (%)	Alglucosidase Alfa /Alglucosidase Alfa Patients (N=60) n (%)	Naïve Patients (N=31)	Patients Already Receiving Alglucosidase Alfa (N=145)
< 4 weeks	0	1 (1.7)[b]	0	3 (2.1)
>= 4 weeks to < 12 weeks	0	1 (1.7)[b]	0	14 (9.7)
>= 12 weeks to < 26 weeks	4 (15.4)	1 (1.7)[b]	4 (12.9)	27 (18.6)
>= 26 weeks to < 38 weeks	9 (34.6)	0	6 (19.4)	35 (24.1)
>= 38 weeks to < 52 weeks	3 (11.5)	1 (1.7)[b]	14 (45.2)	35 (24.1)
>= 52 weeks to < 64 weeks	10 (38.5)	0	6 (19.4)	25 (17.2)
>= 64 weeks to < 78 weeks	0	1 (1.7)[b]	1 (3.2)	6 (4.1)
>= 78 weeks to < 104 weeks	0	0	0	0
>= 104 weeks to < 116 weeks	0	26 (43.3)	0	0
>= 116 weeks to < 130 weeks	0	3 (5.0)	0	0
>= 130 weeks	0	26 (43.3)	0	0

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7.2.2 Explorations for Dose Response

There was only one standard dose of Lumizyme (20mg/kg/dose, every other week) for the pivotal study. Therefore, no explorations of dose response were included in this submission.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or *in vitro* testing was conducted.

7.2.4 Routine Clinical Testing

Routine safety laboratory studies were performed as part of LOTS/LOTS extension. These results are discussed in section 7.4.7

7.2.5 Metabolic, Clearance, and Interaction Workup

Studies evaluating metabolic, clearance, and interaction were not conducted.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Enzyme replacement therapy is approved for use in several metabolic diseases including Mucopolysaccharidoses I, II, VI, Gaucher disease, and Fabry disease. These therapies all have significant potential to produce anaphylaxis and other severe hypersensitivity reactions and have lead to a boxed warning for each of these therapies. Myozyme, which was approved in April, 2006, for treatment of Pompe disease, also carries a boxed warning for anaphylaxis. Infusion reactions (IRs) are also commonly found in these treatments. The labeling for Myozyme also includes a warning of the risk of cardiac failure and immune-mediated skin reactions and kidney disease. However, in the pivotal clinical trial leading the approval Myozyme, only infantile-onset patients were studied, a form of Pompe disease that is associated with the development of hypertrophic cardiomyopathy. Patients studied in LOTS, LOTS extension, and MTAP all had late-onset Pompe disease and do not have this same underlying risk for hypertrophic cardiomyopathy. However late-onset patients would be expected to have the potential for development of immune-mediated skin reactions and kidney disease.

7.3 Major Safety Results

AGLU03206 (LOTS Extension) was an open-label, extension study in patients with late-onset Pompe disease who completed 78 weeks in the randomized, double-blind, placebo-controlled, multi-center study AGLU02704 (LOTS). All patients received intravenous (IV) infusions of Lumizyme at a dose of 20 mg/kg every other week for up to 52 weeks in the open-label LOTS Extension study. Because total exposure to Lumizyme varied in these studies, safety analyses were performed for 2 treatment groups: (1) patients who received only Lumizyme during participation in the LOTS and LOTS extension studies, denoted as the Lumizyme/Lumizyme group and (2) patients who received placebo during LOTS and Lumizyme during the LOTS extension, denoted as the placebo/Lumizyme group. Since the Lumizyme/Lumizyme group had a longer exposure than the placebo/Lumizyme group, cumulative final safety data for all patients who received at least 1 infusion of Lumizyme in LOTS and LOTS Extension (N=60) was performed to provide additional safety information regarding total length of exposure for Lumizyme. However, analyses of the placebo/Lumizyme group were also performed to compare the incidence of adverse events with the original LOTS adverse event data.

For the Lumizyme/Lumizyme-treatment group, the median time of exposure was 113 weeks (range 1.7 to 139 weeks). Thirty patients received placebo in LOTS, and 26 of these patients subsequently received Lumizyme in LOTS Extension. In the Placebo/Lumizyme group, the

median time from the first infusion of Lumizyme until study completion was 44 weeks (range 25 to 53 weeks).

Overview of Adverse Events in LOTS/LOTS extension
Overall, 2072 adverse events were collected in the Lumizyme/Lumizyme-treated group compared to a previously reported 1479 adverse events in this same group during LOTS. All 60 Lumizyme/Lumizyme treated patients reported at least 1 adverse event.

There were 271 adverse events collected in 25 of the 26 patients in the Placebo/Lumizyme-treated group during their Lumizyme treatment. The numbers of patients reporting serious adverse events, infusion-associated adverse events, discontinuations, and deaths is summarized in Table 12 and is discussed in detail below.

Table 12: Overall Summary of Treatment-emergent Adverse Events in combined LOTS/LOTS Extension compared to LOTS only

	Lumizyme/Lumizyme (median exposure 113 weeks) N (%)		Placebo/Lumizyme (median exposure 44 weeks) N (%)		Lumizyme (LOTS only)	
	Number of patients (N=60)	Number of AEs (N=2072)	Number of patients (N=26)	Number of AEs (N=271)	Number of patients (N=60)	Number of AEs (N=1445)
Any AEs	60 (100)	2072 (100)	25 (96.2)	271 (100)	60 (100)	1445 (100)
Infusion-Associated Reactions	21 (35.0)	278 (13.4)	2 (7.7)	35 (12.9)	17 (28.3)	236 (16.3)
Serious AEs (SAEs)	15 (25.0)	25 (1.2)	2 (7.7)	2 (0.7)	13 (21.7)	20 (1.4)
Discontinuations due to AEs	3 (5.0)	N/A	0	N/A	3 (5.0)	N/A
Deaths	1 (1.7)	N/A	0	N/A	1(1.7)	N/A

7.3.1 Deaths

There were no deaths during the LOTS extension study in either the Lumizyme/Lumizyme group or the Placebo/Lumizyme group. One death occurred during LOTS in a Lumizyme treated patient, and was previously described in the original BLA review by Dr. Yao.

7.3.2 Nonfatal Serious Adverse Events

Serious Adverse Events (SAEs) were defined by the Applicant in the study protocol as any AE that results in death, life-threatening experience, prolonged or significant hospitalization,

persistent or significant disability, congenital anomaly, new ventilator use, or an important medical event, based on medical judgment, that may jeopardize the patient or lead to medical or surgical intervention to prevent one of the outcomes listed above. This definition is consistent with the regulatory definition of SAEs as noted in the International Conference on Harmonization (ICH E2A). The medical reviewer agrees with the classification of SAEs by the Applicant.

A total of 25 SAEs were reported in 15 Lumizyme/Lumizyme-treated patients during LOTS/LOTS extension. Of these 25 SAEs, five SAEs in two patients were reported during the LOTS Extension portion of the study. The following SAEs were reported during LOTS in this group: anaphylaxis, brain stem ischemia, coronary artery disease, angioneurotic edema, throat tightness, intervertebral disc protrusion, cerebral aneurysm, supraventricular tachycardia, gastroenteritis, gastric ulcers, chest pain/discomfort, pneumonia, dehydration, abdominal pain, falls, and fractures. The SAEs reported during the LOTS Extension portion of the study in this group were fall, renal stones/cysts, spinal cord compression fracture, and gastric ulcer.

Two SAEs were reported in 2 Placebo/Lumizyme-treated patients during LOTS extension. One patient had hydronephrosis and the other cervical carcinoma stage II in a 42 year old female. Both were considered unrelated to treatment with Lumizyme and this Reviewer agrees. This is compared to 7 SAEs in 6 of these patients while receiving placebo during the LOTS portion of the study, which included diverticulitis, falls, fractures, headache, and septal paniculitis.

7.3.3 Dropouts and/or Discontinuations

No Lumizyme/Lumizyme or Placebo/Lumizyme-treated patients discontinued treatment during LOTS extension. Three Lumizyme/Lumizyme-treated patients discontinued treatment due to adverse events during the LOTS portion of the study, and were previously described in the original BLA review by Dr. Yao.

7.3.4 Significant Adverse Events

Anaphylaxis

Anaphylaxis as seen in other enzyme replacement therapies is the primary safety concern with Lumizyme treatment. A boxed warning for the risk of anaphylaxis was placed in the label for Myozyme based on a 5% incidence of anaphylaxis in the clinical trial of 18 infantile-onset patients who received Myozyme. 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 (Table 13). The participants of this Symposium agreed that the definition should be made based on clinical criteria, and that laboratory test results such as IgE antibody presence or skin testing do not play a role in making the diagnosis of anaphylaxis.[6]

Table 13: Second Symposium on the Definition and Management of Anaphylaxis-Clinical Definition of Anaphylaxis

Anaphylaxis is highly likely when any one 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 likely allergen for that patient* (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 *known allergen for that patient* (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.

The Applicant, however, has 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).

The Applicant previously described three Lumizyme-treated patients with anaphylaxis in LOTS. Based on the Symposium definition, Dr. Yao described an additional Lumizyme-treated patient, thus the overall incidence of anaphylaxis was 6.7% (4/60 patients) compared to 0% incidence in the placebo treated group during LOTS.

This Reviewer considers one Lumizyme/Lumizyme-treated patient in LOTS/LOTS extension (29705) to have symptoms consistent with anaphylaxis, with the onset of dizziness and urticaria occurring during his week 96 infusion. If these five patients are included in the analysis of anaphylaxis, then the cumulative incidence of anaphylaxis in the Lumizyme/Lumizyme-treated patients during LOT/LOTS extension is 5/60 patients or 8.3%, slightly higher than the incidence in LOTS. One patient (18708) in the Placebo/Lumizyme group experienced two episodes of anaphylaxis once during infusion and once 2 hours after infusion during LOTS extension. If these six patients are included in the analysis of anaphylaxis, then the incidence of anaphylaxis in all Lumizyme-treated patients is 6.9% (6/86).

Infusion Reactions

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). However, elevated IgE antibody titers are not necessary to diagnose anaphylaxis. The pathogenesis of acute infusion reactions developing at or shortly after an infusion that do not meet the clinical criteria for anaphylaxis is less clear.[7]

The National Cancer Institute has developed terminology, published as Common Terminology Criteria for Adverse Events v3.0 (CTCAE), to distinguish between hypersensitivity reactions and

acute infusion reactions (Table 14).[8] There is clear overlap between the clinical definitions of anaphylaxis (Table 15) and infusion associated reactions. 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 "hypersensivity/allergic" and reactions that may involve other mechanisms but do not clearly fulfill the clinical definition of anaphylaxis. Table 17 lists some of the signs and symptoms of infusion associated reactions.

Infusion reactions were defined by the Applicant as any AE that occurred during either the infusion or the 2 hour observation period following the infusion which were assessed by the Investigator as treatment-related (i.e., possibly, probably, or definitely related). The Applicant also submitted data on the timing of the AE in relationship to the infusion. The relationship of the AE to the study drug was re-evaluated independently by this 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, hyperhydrosis, diarrhea, somnolence, Raynaud's syndrome, hematuria, and proteinuria.

Table 14: Grading Reactions according to the NCI CTCAE

	Grade				
	1	2	3	4	5
Hypersensitivity (allergic reaction)	Transient flushing or rash; drug fever <38°C (<100.4°F)	Rash; flushing; urticaria; dyspnea; drug fever ≥38°C (≥100.4°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.

Based on the Applicant's classification of infusion reactions found in the electronic dataset, there were a total of 278 IRs in the Lumizyme/Lumizyme treatment group during LOTS/LOTS extension, occurring in 21 patients. However, there were a total of 435 AEs in a total of 50 Lumizyme/Lumizyme treated patients that occurred during or within 2 hours of completion of the infusion without regard for investigator assignment of relationship to study medication. This is compared to a total of 358 AEs in 50 patients in this group during the LOTS portion of the study. There were 35 IRs in the Placebo/Lumizyme group in 2 patients during LOTS/LOTS extension compared to 47 events in 5 patients reported in this group during the placebo phase in LOTS. Similar to the initial LOTS safety analysis, the reactions reported during LOTS/LOTS extension in both groups while on treatment differed from that of placebo and included hypersensitivity reactions, such as urticaria, chest discomfort, nausea, vomiting, stomach discomfort, chills, flushing, hyperhydrosis, and throat tightness. Other adverse events that occurred during this observation period included hypoacusis, ear discomfort, neck pain, tendonitis, hyporeflexia, areflexia, musculoskeletal tightness and pain, skin nodule, hematoma, and hematuria. There is no clear explanation for the increased incidence of these infusion associated reactions.

Skin Reactions and other Potential Immune-mediated AEs

Other significant adverse events that were uncovered during the original review include the possibility of chronic immune-mediated skin and kidney adverse reactions. Skin reactions have also been noted in postmarketing safety data collected for Myozyme, and the Myozyme labeling has been updated to reflect this safety finding. In the initial safety evaluation of Lumizyme by Dr. Yao skin reactions were found to be more common in the Lumizyme group (50%) compared with the placebo group (10%). These included angioneurotic edema, rash (and subcategories of rash including erythema and pruritus), urticaria, and septal panniculitis. In this safety update a total of 36 Lumizyme/Lumizyme-treated patients had skin reactions (60%, 36/60), likely due to

the extended time of follow-up. Four patients (26%) in the Placebo/Lumizyme-treated group had skin reactions during LOTS Extension.

In the previous safety review, Dr. Yao noted evidence of possible glomerular injury as manifested by hematuria and/or proteinuria in patients treated with Lumizyme. Seven patients in the Lumizyme treatment group developed hematuria and/or proteinuria, and only two patients in the placebo group. Two patients in the Lumizyme treatment group and one patient in the placebo group developed both hematuria and proteinuria. Two of the patients in the Lumizyme treated group also developed anaphylaxis. The combined LOTS and LOTS extension data were reviewed for potential kidney related adverse events and 6 patients with a potential kidney injury were noted by the reviewer. These six patients had at least two findings consistent with a possible glomerular injury including hypertension, hematuria, proteinuria, and edema (see Table 16). Long-term follow up for potential chronic immune-mediated adverse events was agreed upon with the Applicant as a post-marketing requirement.

Table 16: Kidney-related adverse events in LOTS/LOTS extension

Patient	Potential renal adverse events
18713	Hypertension, edema, hematuria, proteinuria
26710	Hypertension, edema
29708	Hypertension, edema
47708	Hypertension, edema
65713	Hematuria, proteinuria

Common Adverse Events

A review of the overall common adverse events in patients treated with Lumizyme in LOTS compared to their overall common adverse events in LOTS extension shows that there was a 10% increase in reporting of myalgia, headache, arthralgia, upper respiratory tract infection, rash, and fatigue, however their incidence is similar to that reported in the LOTS placebo group. It is possible that these adverse events are related to chronic exposure to Lumizyme, however, these symptoms are also known to occur with Pompe disease, and therefore any determination of relationship to treatment is difficult.

In order to evaluate overall common adverse events in a larger number of treated patients, the data for both Lumizyme/Lumizyme and Placebo/Lumizyme were combined. The overall common adverse events occurring in at least 20% of patients (as was used by Dr. Yao in the first cycle clinical review) in LOTS/LOTS extension is similar to that reported in LOTS (Table 17).

Table 17: Overall common adverse events occurring in at least 20% of patients treated in LOT/LOTS extension compared to patients treated in LOTS

Preferred Term	LOTS/LOTS Extension (N=86) Number of episodes	LOTS (N=60)
Musculoskeletal pain	83 (96)	39 (65)
Fall	60 (67)	39 (65)
Nasopharyngitis	48 (53)	27 (45)
Headache	46 (51)	25 (42)
Arthralgia	38 (42)	18 (30)
Diarrhea	33 (37)	17 (28)
Hypoacusis	33 (37)	20 (33)
Upper respiratory tract infection	29 (32)	11 (18)
Rash	28 (31)	12 (20)
Muscle spasms	26 (29)	14 (23)
Nausea	26 (29)	11 (18)
Dizziness	25 (28)	16 (27)
Myalgia	23 (26)	12 (20)
Pharyngolaryngeal pain	21 (23)	12 (20)
Pyrexia	21 (23)	8 (13)
Fatigue	20 (22)	7(12)
Vomiting	19 (21)	13 (22)
Cough	18 (20)	11 (18)
Peripheral edema	18 (20)	10 (17)

Based on this review of the most comprehensive safety data submitted to the application as part of the GCP-compliant LOTS and LOTS extension studies, the main safety concerns that were seen in this review are consistent with those seen in the initial review of Lumizyme and include safety issues related to the immunogenicity of Lumizyme. Anaphylaxis and infusion reactions were seen with a similar incidence in patients in this safety update. Additionally, potential immunologically-mediated reactions including chronic skin and kidney reactions were again noted. Common adverse events appear similar to those reported in the initial LOTS review. No new safety issues were observed in the analyses of the additional safety data.

7.4 Supportive Safety Results

MTAP

This study, AGLU2907, included 176 patients enrolled in a temporary access program to allow patients 18 years of and older to be treated with Lumizyme due to a drug shortage of the approved product, Myozyme. The safety information provided by the Applicant reflects interim data from the start of the study on 25 May 2007 to the data cut-off date of 15 October 2008. As of 16 March 2009, the data cut-off agreed upon with the Agency for the complete response submission, 184 patients have been treated via MTAP. The planned dose for all patients treated

in this program is 20 mg/kg qow. A small number of patients received a dose other than 20 mg/kg at one or more infusions in MTAP; 11 patients received a dose less than 20 mg/kg (range 10 to 19 mg/kg), 3 patients received a dose greater than 20 mg/kg (range 21.4 to 59.45 mg/kg), and the dose was not reported for 1 patient. The total time of exposure to Lumizyme ranged from 4 weeks to 72 weeks with a median time of exposure of 45.9 weeks.

Adverse events continue to be collected and monitored in this ongoing study, therefore, these data are based on interim reporting. All SAEs, regardless of relationship to treatment, were reported to the Applicant within 24 hours of the Investigator's knowledge of the event. A summary of adverse event data is included in Table 18 below. A total of 520 adverse events were noted in 78 patients. There were 155 adverse events that did not include a reported term, preferred term, or system organ class assignment. Therefore, these AEs were not able to be included in the analysis of safety for this study. Thus, the total number of adverse events reported in this study was 365. A total of 181 (34.8%) of these events were assessed as related to treatment, 86 occurred on the day of infusion and 95 occurred on a day other than the day of infusion or unknown date. Of these, 127 were considered IRs by the Applicant. However, the safety data from MTAP did not include the timing of the adverse event in relationship to the last infusion, and therefore, the Reviewer was unable to verify whether many AEs were infusion reactions. Thus, a separate analysis of IRs based on MTAP data was not included by this Reviewer.

Table 18: Overall Summary of Treatment-emergent Adverse Events in MTAP

	Number of patients (N=176) N (%)	**Number of AEs (N=520) N (%)**
Any AEs	**78 (44.3)**	**520 (100)**
Treatment-related AEs	**31 (17.6)**	**181 (34.8)**
Anaphylaxis	**2 (1.1)**	**N/A**
SAEs	**23 (13.1)**	**66 (12.7)**
Discontinuation Due to AEs	**6 (3.4)**	**N/A**
Deaths	**3 (1.7)**	**N/A**

Discontinuations

Six patients discontinued treatment due to AEs. Patient 3907-50091 experienced a significant hypersensitivity reaction with chest discomfort, dyspnea, and flushing. Patient 3907-50036 experienced hypotension and dizziness and nausea. One patient (3907-50018) was reported in late-breaking information to have experienced angioedema as well as recurrent dyspepsia, pruritus, tremor, and urticaria which resulted in discontinuation of treatment. Three deaths also occurred which are described below.

Deaths

Three patients have died during treatment in MTAP (3907-10272, 3907-10401, 3907-50094). None of these deaths were assessed as related to treatment with Lumizyme. Patient 3907-50094 died at week (b) (6) with a cause of death believed to be due to respiratory arrest secondary to mucous plug from tracheostomy. Patient 3907-10401 died (b) (6) after the (b) (6) infusion due to anoxic encephalopathy secondary to cardiac arrest. Patient 3907-10272 had a hemorrhagic stroke and died at week (b) (6) of respiratory failure, which was possibly due to intracranial bleed.

Nonfatal Serious Adverse Events

There were 66 SAEs reported in 23 patients, with 62 of these assessed by the treating physician as unrelated to treatment. However, anaphylaxis and skin reactions were seen as described below.

Anaphylaxis

Dr. Yao described two patients in her initial review with the possibility of anaphylaxis. In this update, the Applicant has reported one more patient described above, 3907-50018. This Reviewer considers the hypersensitivity reactions described in patients 3902-50091 3907-50037 above as developing anaphylaxis as well.

Skin Reactions and other Potential Immune-mediated AEs

Two patients in MTAP had decubitus ulcer and two experienced skin discoloration. The skin discoloration in one patient (3907-50017) was reportedly at the port site. Another patient (3907-50001) experienced black discoloration on his hands during his 22nd infusion , which resolved approximately one month later. After 3 months of treatment interruption, he experienced skin discoloration with another infusion. This SAE is concerning for the possibility of an immune-mediated skin reaction. Skin biopsy at this time was normal. No patients in MTAP developed glomerulonephritis, hematuria, or proteinuria.

Common adverse events

Common adverse events, defined by the Reviewer as occurring in at least 5 patients, are listed in Table 19. However, MTAP was designed as a treatment protocol, to provide access to patients due to a drug shortage of Myozyme. Therefore, adverse event data were not collected with the same frequency as other clinical trials for Lumizyme. This may explain the substantially lower percentage of patients reporting adverse events, as well as a substantially lower incidence of adverse events in this study compared with other clinical studies evaluating the safety of Lumizyme. These adverse events are similar to the most common adverse events reported from LOTS/LOTS extension and from the previous MTAP safety report reviewed by Dr. Yao. However, the number of patients reporting nasopharyngitis, fall, nausea, headache, pyrexia, respiratory tract infection, respiratory failure, arthralgia, muscle weakness, fatigue, chest discomfort, and pruritus has increased since the last review, possibly due to increased patient enrollment since the initial review. Again, it is not possible to determine whether these adverse events are related to the patient's underlying disease or to chronic exposure to Lumizyme.

Table 19: Adverse events occurring in at least 5 patients in MTAP

Preferred term	Number of patients, N=176
Fall	14
Nausea	14
Nasopharyngitis	14
Respiratory tract infection	12
Headache	9
Muscle weakness	9
Diarrhea	8
Pyrexia	8
Rash	9
Arthralgia	7
Fatigue	7
Urticaria	6
Arrhythmia	6
Chest discomfort	5
Influenza	5
Muscle spasms	5
Pneumonia	5
Pruritus	5
Respiratory failure	5
Sinusitis	5

There appears to be a substantially lower percentage of patients reporting adverse events, as well as a substantially lower incidence of adverse events in this study compared with other clinical studies evaluating the safety of Lumizyme. This finding may be related to potential underreporting of AEs in the MTAP, since MTAP is a treatment protocol, and intended only to obtain "standard of care" assessments. Nevertheless, specific adverse events of interest include reports of skin discoloration and may indicate that this type of reaction may be a potential long-term safety issue.

7.4.1 Common Adverse Events

See the above sections for a description of common adverse events for individual studies. Calculation of an overall incidence of common adverse events across studies was not performed, as MTAP was a treatment protocol, and as such, did not collect adverse event data as regularly as LOTS extension. Therefore, pooling of these data could lead to an underestimation of the true incidence of common adverse events found in clinical trials.

7.4.2 Laboratory Findings

Laboratory testing, including chemistry and hematology panels, and urinalysis testing were performed according to the study schedules outlined in the study visits and procedures section of

the initial clinical review. Clinically significant worsening in any laboratory parameter was documented as an AE and these AEs have been considered in the overall review of AEs.

7.4.3 Vital Signs

Vital signs were performed according to the study schedules outlined in the study visits and procedures sections of the protocol for AGLU02704. Clinical significant worsening in vital signs were documented as AEs, and have been considered in the overall review of AEs. Notable vital sign changes that were reported as AEs tended to be associated with product infusion (e.g. tachycardia, hypotension, hypertension, tachypnea). No other notable, relevant or remarkable findings for changes in vital signs were seen; however, there was insufficient time available in the review period to thoroughly review these data.

7.4.4 Electrocardiograms (ECGs)

Changes in ECGs were evaluated as part of the safety evaluation of LOTS/LOTS extension above. One event of supraventricular tachycardia and one event each of right bundle and left bundle branch block was reported in the original BLA review. There were no additional episodes of arrhythmias reported in the safety update.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were conducted.

7.4.6 Immunogenicity

See section 7.3.4 (anaphylaxis and infusion reactions)

7.5 Other Safety Explorations

No other safety explorations were performed.

7.5.1 Dose Dependency for Adverse Events

Only one dose of drug (20mg/kg/dose) was administered in LOTS extension. There were some patients in MTAP that did not receive this standard dose, however, there were too few patients to assess dose dependency for AEs.

7.5.2 Time Dependency for Adverse Events

There was not specific time dependence for the development of adverse events. Many adverse events documented occurred with the initial infusion and adverse events occurred throughout the course of the study.

7.5.3 Drug-Demographic Interactions

No drug-demographic interaction studies were conducted by the Applicant.

7.5.4 Drug-Disease Interactions

No drug-disease interaction studies were conducted by the Applicant.

7.5.5 Drug-Drug Interactions

No drug-drug interaction studies were conducted by the Applicant.

7.6 Additional Safety Evaluations

No additional safety evaluations were performed with this submission.

7.6.1 Human Carcinogenicity

No animal or human studies were conducted to assess the carcinogenic or mutagenic potential of Lumizyme.

7.6.2 Human Reproduction and Pregnancy Data

No formal studies with Lumizyme have been conducted in pregnant women, and there are no reports of pregnancy in any patients treated to date.

7.6.3 Pediatrics and Assessment of Effects on Growth

Growth was not assessed as a primary efficacy endpoint in any of the studies submitted thus far by the Applicant for Lumizyme. Only two patients under the age of 18 received treatment with Lumizyme in LOTS/LOTS extension, therefore, no conclusions can be made regarding pediatric patients.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no withdrawal/rebound phenomena or abuse potential issues identified with Lumizyme. There have been no reports of overdose with Lumizyme.

7.7 Additional Submissions / Safety Issues

There were no additional submissions reviewed for this application.

8 Postmarketing Experience

Postmarketing experience is limited to the use of Lumizyme outside the US, collected in the EU and Canada. A safety data update was provided by the Applicant to a cutoff of 16 March 2009. The Applicant estimated that the total worldwide exposure to Lumizyme was 885 patients, with 808 of those patients being treated outside the US as of 29 March 2008. According to the Applicant, these 808 patients include some who were enrolled in clinical trials or treated via the International Expanded Access Program (EAP) at various product scales (i.e., (b) (4) development scale; 160 L scale (Myozyme), or a combination) prior to transitioning to treatment with Lumizyme. Therefore, the Applicant estimates that approximately 618 patients received Lumizyme exclusively based on their date of first infusion. AE data were analyzed from March 29, 2008, the data cut-off for the Summary of Clinical Safety submitted on August 29, 2008, through December 28, 2008, and includes late-breaking information as of March 16, 2009. For this safety update reporting period, 54 patients for whom spontaneous postmarketing SAEs were reported and analyzed by the Applicant. The Applicant states that the exact incidence for these AEs cannot be determined because the total number of patients evaluated is based on an estimate. Datasets for postmarketing adverse events were not provided, therefore, a complete review of these data was not possible. A summary of the safety update from the postmarketing setting is provided below.

Deaths

The Applicant reported twenty-one patient deaths in their safety update, 14 patients with infantile-onset Pompe disease, 5 patients with late-onset Pompe disease and 2 patients with Pompe disease of unknown phenotype. Although late-onset Pompe disease is more prevalent than the infantile-onset form, more deaths were reported in the infantile-onset patients. This finding was expected given the more severe phenotype of infantile-onset disease. Eleven of the 14 infantile-onset reports of fatal outcome were reported as cardiac and/or respiratory in nature, two were unknown, and one was reported as 'disease progression'. The cause of death for three of the late-onset patients were reported as cardiac and/or respiratory failure, one patient had pulmonary embolism, and one hepatic cirrhosis. One patient with unknown phenotype had respiratory failure and the other intracranial aneurysm. The majority were assessed as being related to the underlying Pompe disease in both patient populations and consequently assessed as unrelated to Lumizyme.

Serious Adverse Events

Spontaneous AEs are provided to the Applicant on a voluntary basis. Thus, it is difficult to accurately assess incidence rates for adverse events reported in the post-marketing setting. Additionally, the relationship to treatment is not always included in case reports. For this safety update, a total of 187 SAEs and 54 non-serious AEs were reported in 54 patients. One hundred and fifteen SAEs were reported in 28 infantile-onset Pompe patients, 54 SAEs were reported in 17 late-onset Pompe patients, and 18 SAEs were reported in 9 patients with Pompe disease of unknown phenotype. Overall, the post-marketing SAEs reported were consistent with those previously reported in clinical trials. In the patients with infantile-onset Pompe disease, SAEs reported in more than one patient included pneumonia, pyrexia, respiratory failure, respiratory tract infection, cardiac failure, diarrhea, irritability, no therapeutic response, oxygen saturation

decreased, and wheezing. In patients with late-onset Pompe disease, SAEs reported in more than one patient included respiratory failure, cough, and respiratory disorder. In both infantile-onset and late-onset patients, approximately 1/3 of SAEs were assessed as related (possible, probable or definite) to administration of Lumizyme (29.6% and 25.9%, respectively) and a majority of these treatment related SAEs were reported as IRs (88.2% and 92.9% of related SAEs, respectively). There were four patients who the Sponsor reported as having appeared to experience anaphylaxis based on their presentation of SAEs. The reviewer is unable to confirm the Applicant's assessment of relationship to treatment as there were no case report forms or datasets for review.

Common Adverse Events
The Applicant did not submit any data regarding the common adverse events from the postmarketing setting.

Submission Specific Primary Safety Concerns
Important clinical safety issues were seen in this review of the most comprehensive safety data of the GCP-compliant LOTS and LOTS extension studies, MTAP, and postmarketing experience. The main safety concerns with Lumizyme continue to be those related to immunogenicity, anaphylaxis and infusion reactions. Potentially immune-mediated skin and kidney reactions continue to be reported and should be considered potential long-term safety issues. The common adverse events reported appear similar to those reported in the initial LOTS review. No new safety issues were observed in the analyses of the additional safety data reviewed.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

Most sections of the labeling have not changed substantially from what was outlined in the initial review by Dr. Yao. The final labeling contains all of the revisions negotiated with the Applicant. Labeling will require a boxed warning for the REMS and the risk for anaphylaxis.

9.3 Advisory Committee Meeting

There was no Advisory Committee Meeting with this submission.

Division Director Summary Review

Date	February 27, 2009
From	Donna J. Griebel, MD 2/27/09
Subject	Division Director Summary Review
BLA # **Supplement #**	BLA STN 125291 N000 Cross Reference STN 125141/75
Applicant Name	Genzyme Corporation
Date of Submission	May 30, 2008
PDUFA Goal Date	February 27, 2009
Proprietary Name / **Established (USAN) Name**	Lumizyme Recombinant human acid alpha-alglucosidase
Dosage Forms / Strength	Lyophilized cake or powder for reconstitution with sterile water for injection (5.0 mg/mL) 50 mg/vial
Proposed Indication(s)	Long-term use in Late Onset Pompe Disease
Recommended Action for NME:	Complete Response

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Lynne Yao, MD/Joanna Ku, MD
Statistical Review	Lisa Kammerman, PhD/Mike Welch, PhD
Pharmacology Toxicology Review	Niraj Mehta, Ph.D./David Joseph, Ph.D.
OBP Review	Fred Mills, PhD/Barry Cherney, PhD/Amy Rosenberg, Ph.D.
DMPQ/OC	Kalavati Surava, Ph.D./Patricia Hughes, Ph.D.
Clinical Pharmacology Review	Jang-Ik Lee, Pharm.D., Ph.D./Sue-Chih Lee, Ph.D./Justin Earp, PhD/Yaning Wang, Ph.D.
DDMAC	Sam Skariah, Pharm.D.
DSI	Khairy Malek, MD/Constance Lewin, MD, MPH
CDTL Review	Joanna Ku, MD
OSE/DMEPA	Zachary Oleszczuk, Pharm.D./Todd Bridges, R. Ph.
OSE/DRISK	Yasmine Choudhry, MD/Claudia Karwoski, Pharm.D.
DPAP	Susan Limb, MD/Sally Seymour, MD/Badrul Chowdhury, MD, Ph.D.

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DMPQ = Division of Manufacturing and Product Quality
DPAP = Division of Pulmonary and Allergy Products
DRISK = Division of Risk Management
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader
OBP = Office of Biotechnology Products
OC = Office of Compliance

Division Director Summary Review

1. Introduction

Recombinant human acid alpha-glucosidase (rhGAA) is produced by recombinant DNA technology using Chinese hamster ovary cells. Genzyme's 160 liter scale rhGAA product, Myozyme, was approved for treatment of Pompe disease on April 28, 2006, based on a study conducted in children with infantile-onset Pompe disease. The labeled indication does not restrict use to patients with the infantile-onset form of Pompe disease:

INDICATIONS AND USAGE
MYOZYME (alglucosidase alfa) 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 (see CLINICAL STUDIES).

However, because the drug supply of the 160 L scale product is limited, its use in the United States has been reserved for children less than 18 years of age. U.S. Pompe disease patients over 18 years of age have only been able to access rhGAA treatment through a treatment IND for the 2000 liter scale product, the product for which the Applicant seeks marketing approval in this BLA. That access program, called the Myozyme Temporary Access Program (MTAP), was closed to new patients by the Applicant during the course of the FDA's review of this BLA, in April, 2008. Access to the rhGAA 2000 L has been further limited by a report of rapid cell death in a bioreactor used to product the 2000 L product at the Allston Landing, MA, facility in November, 2008. The Applicant continues to investigate the cause of the rapid cell death in the bioreactor, including the possibility of viral contamination, but has not determined the root cause of this event. In January, 2009, due to the world-wide shortage of 2000 L product, patients receiving the 2000 L product were asked to reduce their infusions of the 2000 L rhGAA from two per month to one per month.

The Applicant initially submitted this BLA on October 31, 2007 as a BLA supplement to the original BLA for the Myozyme 160 L product. The Office of Biotechnology Products reviewers, however, noted significant differences in the biochemical attributes of the 2000 L product relative to the 160 L product. The differences were believed to result from the process utilized to increase the cell production in the 2000 L scale. (b) (4) Furthermore, there was concern that 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. Because there was insufficient information available to establish the biochemical, nonclinical, or clinical comparability of the two products, the reviewers concluded that the 2000 L product could not be considered the same product as the Myozyme 160 L product. These differences were presented in a Center briefing of the CDER Center Director, Janet Woodcock, MD. Ultimately, the BLA supplement was recoded as a new BLA. The submission of the new BLA occurred on May

30, 2008. It was designated a priority review. The PDUFA clock was extended in response to a November 21, 2008 major amendment to the BLA.

The clinical study submitted in this BLA is a randomized, controlled trial that evaluates the efficacy and safety of the 2000 L product in patients with late-onset Pompe disease. The clinical and biostatistical reviewers raised concerns regarding the strength of evidence of effectiveness of the 2000 L product provided by the study submitted for review. Issues included the patient population enrolled, the primary efficacy endpoints, the randomization procedure, and study design changes made during the conduct of the study. These concerns were taken to an Advisory Committee meeting on October 21, 3008 (Endocrinologic and Metabolic Drug Products Advisory Committee). The meeting included a closed session in which the Committee members discussed proprietary manufacturing information and the differences between the 160 L and 2000 L products, and an open session. Although the Committee members expressed concerns regarding the robustness of the evidence provided by the study in Late Onset Pompe Disease, the Committee recommended approval of the 2000 L product under Subpart E, accelerated approval based on the surrogate endpoint percent predicted forced vital capacity, FVC (12 votes for Subpart E approval, 4 votes for regular approval and 1 vote for nonapproval). Subpart E approval requires that the Applicant conduct a verification study.

My review will summarize the salient findings and recommendations of each review team. Because the 160 L product was approved based on a clear survival benefit in patients with infantile-onset disease, and because the safety and efficacy of 2000 L product has not been studied in patients less than 8 years of age, a group of patients with generally more severe disease, the reviewers concluded that it was critical to assure that the most severely effected patients with Pompe Disease, those with infantile-onset disease, and children with late (non-infantile onset) onset disease, receive the 160 L product when both products are marketed in the U.S. In order to avoid errors in administration, i.e. administration of the 2000 L product to patients with infantile-onset disease, or patients with late (non-infantile onset) onset disease less than 8 years of age, the clinical reviewers: 1) worked with reviewers from the Office of Safety and Epidemiology (OSE) to develop a REMS and 2) requested that the Applicant provide a new name for the 2000 L product (instead of Myozyme, which is the proprietary name of the U.S marketed 160 L product). Information regarding the development of the REMS for this product can be found in Section 8 Safety of this review.

Unfortunately, at the PDUFA goal date the Applicant and FDA had not reached agreement on an appropriate verification study for a Subpart E Accelerated Approval or on the REMS. In addition, issues identified by the manufacturing site by the inspectors who conducted the inspection of the Allston Landing, MA manufacturing facility resulted in issuance of an FDA 483. Upon review of the Applicant's response to the FDA 483, the Office of Compliance approved issuance of a Warning Letter and a recommended that the Division not approve a new product from the site until there had been adequate resolution of the identified issues. For these reasons, a Complete Response letter will be issued.

2. Background

Acid alpha-glucosidase is a hydrolase that degrades lysosomal glycogen to glucose. Pompe disease is a rare inherited disorder caused by deficiency of acid alpha-glucosidase. It is characterized by organelle bound (lysosomal) and extra-lysosomal accumulation of glycogen in body tissues. There are more than 300 defective alleles for the α-glucosidase gene. Some result in reduced or absent levels of enzyme and others yield amino acid substitutions that result in GAA protein with reduced enzymatic activity. Pompe Disease is divided into two major phenotypes, infantile onset disease and late onset disease. Patients with infantile onset Pompe's, a severe form of the disease, have essentially complete deficiency of α-glucosidase. They experience progressive lethal degeneration of both cardiac and skeletal muscle in the first months of life. Late-onset Pompe's disease varies in severity and age of onset. Patients with Late-onset disease have low levels of GAA, which results in slowly progressive skeletal muscle weakness and degeneration, including respiratory muscle involvement. They don't have cardiac effects from the disease.

(b) (4)

(b) (4) (See Section 3 of this review.) The important potential impact of these differences between the 160 L and 2000 L products on efficacy and safety resulted in a decision that this BLA should be classified a new BLA, not a supplemental BLA, and prompted the reviewers to seek measures to assure that, once the 2000 L product is approved, it will not be used to treat U.S. patients with infantile onset disease until it has been shown to be effective in that population. This is because patients with infantile onset disease have severe and rapidly progressive disease, and the 160 L product has been shown to be a safe and effective therapy for these patients based on mortality and ventilator support endpoints.

3. Office of Biotechnology Products/CMC

Alglucosidase alfa (recombinant human acid alpha-glucosidase (rhGAA)) is produced by recombinant DNA technology from Chinese hamster ovary cells. RhGAA is a large glycosylated

protein, with N-glycosyl groups at seven positions on the molecule. Its amino acid sequence is identical to human GAA.

Myozyme, the previously approved 160 L rhGAA product, is manufactured at Genzyme's Framingham, MA facility. The 2000 L rhGAA product is produced at the Applicant's Allston Landing, MA plant. The production processes for both products involve cell culture in bioreactors. One major difference between the 160 L and 2000 L cell culture processes pointed out by Dr. Mills, the OBP primary reviewer, involves the growth phase of the cell culture. (b) (4) The OBP reviewers noted that this higher productivity may be the cause of significant differences in rhGAA glycoforms they observed between the 2000 L and 160 L process products.

(b) (4)

In his review of the Applicant's proposed drug substance specifications for the 2000 L product, Dr. Mills noted differences in the specifications between the 2000 L and the previously approved product, as well as specifications that he recommended should be revised. (b) (4) Dr. Mills noted that the specification was very low and acceptable. He expressed concern that the applicant proposed SDS-PAGE testing specifications for product species that (b) (4) than the (b) (4) size of rhGAA that did not reflect the Applicant's demonstrated manufacturing capability, as demonstrated in the clinical lots used in the LOTS study. He recommended that the specifications should be set to better reflect the characteristics of the lots used in that study.

(b) (4)

(b) (4)

Dr. Mills agreed with the Applicant that data support a 4 week expiry at 6-10°C for the Drug Substance.

The OBP reviewers stated that the following issues must be addressed before the product is approved and these will be included as deficiencies in the CR letter:

1. Cell viability is a critical parameter for controlling product quality during (b) (4). The Applicant needs to provide adequate justification for not using cell viability as an in-process control for bioreactor monitoring.

2. An established reference standard for use in the Applicant's testing control strategy that is representative of the 2000 L process has not been submitted to this BLA. The Applicant needs to provide data to support the qualification of a reference standard.

3. The acceptance criteria for drug substance and drug product specifications are not consistent with manufacturing process capability and considerations regarding potential impact on safety and efficacy. The Applicant needs to provide an evaluation on the following analytical tests: (b) (4); assay; SDS-PAGE gel assays; HPLC for measurement of (b) (4); HPAEC-PAD for measurement of (b) (4); and SEC.

4. (b) (4)

Please also refer to Section 6 Microbiology regarding additional manufacturing issues.

4. Nonclinical Pharmacology/Toxicology

In a meeting with the Applicant on April 28, 2008, the Division of Gastroenterology Products agreed that the nonclinical studies for this BLA 125,291 for the 2000 L product could be cross

referenced from the BLA for the 160 L product, BLA 125,141 (Myozyme®), dated March 20, 2006). The nonclinical section of this BLA contained a summary of the previously submitted studies. The sponsor also submitted new preclinical studies in amendments to this BLA 125,141. The FDA reviewers reviewed the studies listed below under the current submission for Lumizyme, which were conducted as post-marketing commitments (PMC) for the 160 L Myozyme® product (PMCs listed in the approval letter dated April 28, 2006). The studies that fulfilled PMCs are listed below.

a) Study No. FFA00067: Six-month intravenous repeated-dose toxicity study of Recombinant Human Acid-α-Glucosidase (rhGAA) in juvenile mice (PMC 8)
b) Study No. FFA00051: Intravenous injection study of Recombinant Human Acid-α-Glucosidase (rhGAA) on fertility and early embryonic development in mice (PMC 12)
c) Study No. 6354-155: Intravenous injection study of Recombinant Human Acid-α-Glucosidase (rhGAA) on fertility and early embryonic development to implantation in mice (Study Phase: Qualitative spermatogenesis evaluation and testicular pathology) (PMC 11)
d) Study No. FFA00053: Intravenous developmental toxicity study of Recombinant Human Acid-α-Glucosidase (rhGAA) in rabbits (PMC 10)
e) Study No. FFA00058: Intravenous developmental and perinatal/postnatal reproduction toxicity of Recombinant Human Acid-α-Glucosidase (rhGAA) in mice, including postnatal behavioral/functional evaluation (PMC 13)
f) Study No. 6354-163: Intravenous Injection Study of Recombinant Human Acid-α-Glucosidase (rhGAA) on Female Fertility and Early Embryonic Development to Implantation in Mice (PMC 9)

The Pharmacology reviewers recommended that from a preclinical viewpoint, the application should be approved, with the provision that their recommended changes in the label are incorporated by the Applicant.

5. Clinical Pharmacology

The clinical pharmacology reviewers recommended approval under Subpart E, but noted that the pharmacokinetics of rhGAA have not been characterized in patients with late onset Pompe disease in patients younger than 21 years of age. The clinical pharmacology review team recommended collection of adequate pharmacokinetic data from pediatric patients with late-onset Pompe disease from the Subpart E verification study.

The multiple dose pharmacokinetic parameter values of the 2000 L product of rhGAA (2000 L scale product) were estimated in a subgroup of 32 patients with late onset Pompe disease who received rhGAA in the LOTS trial. The reviewers found that the parameters appeared comparable at Weeks 0, 12 and 52. In the group studied, age and sex had no significant impact on pharmacokinetics. The reviewers noted that the estimated effective half life seemed to be more reflective of distribution half-life than elimination half-life due to relatively short pharmacokinetic sampling (up to 16 hours post dose).

The clinical pharmacology reviewers also evaluated the immunogenicity data from the LOTS trial. Serum samples for immunogenicity testing were obtained pre-infusion every four weeks in the study. They noted that all patients in the rhGAA treatment group who were tested for post-exposure immunogenicity had evidence of anti-rhGAA IgG antibodies (binding antibodies) as assessed by enzyme-linked immunosorbent assay (ELISA) and confirmed by radioimmunoprecipitation assay (RIP). The median time to seroconversion was 4 weeks (range, 4 to 12 weeks) after first dose. None of those patients (n=60) tested positive for inhibition of enzyme activity in an rhGAA inhibition assay. However, assessment for inhibition of rhGAA uptake in human fibroblast cells revealed that 10 patients were positive for inhibition and 8 were borderline positive,

High anti-rhGAA IgG antibody titers and positive inhibitory antibody status based on uptake appeared to impact rhGAA pharmacokinetics. The reviewers noted that the 5 patients with the highest binding antibody titer also had evidence of inhibition of uptake, and those 5 patients had higher clearance and a lower C_{max} and AUC than the patients who were negative. However, the clinical significance of these findings was questioned because the pharmacometrics review team found that patients with higher binding antibody titers seemed to experience a greater response to therapy, as measured by 6-minute walk test. There also did not appear to be an association between higher antibody titers and the risk of developing an infusion associated reaction (IAR). .

The clinical pharmacology reviewers' comments on labeling have been conveyed to the Applicant during the course of labeling negotiations and they have reached agreement with the Applicant regarding those issues.

The verification study design remains under negotiation. The clinical pharmacology reviewers have recommended that the verification study incorporate a pharmacokinetic sub-study that includes the following features to assure that pharmacokinetic information for the pediatric population with non-infantile onset Pompe disease is obtained:

a. A sufficient number of patients (e.g., N = 20) representing the entire range of the population studied.
b. Sufficient time points of sampling to fully characterize the pharmacokinetics (at least an entire dosing interval at steady state and adequately selected trough concentrations)
c. Determination of exposure-response relationships
d. Determination of the impact of immunogenicity of pharmacokinetics
e. Use of an accurate, precise, and validated analytical method.

6. Clinical Microbiology

The DMPQ reviewer from Office of Compliance, Dr. Kalavati Suvana, PhD, recommended the BLA, as amended, for approval from a microbial control, sterility assurance, and microbiology product quality perspective. Her review included the following findings:

a. Bioburden of the purification intermediates is not routinely monitored at the end of hold time. The Applicant, in correspondence dated 9/26/08, agreed to initiate a bioburden monitoring program in October 2008 for [redacted] (b) (4)

b. There was no drug substance release specification for bioburden. The applicant agreed to an FDA recommendation to perform bioburden testing on drug substance at release and proposed [redacted] (b) (4) action level. They agreed to

establish this bioburden release specification [redacted] (b) (4) and implement it by the end of the year 2008.

c. The reviewer noted that the Applicant's endotoxic specification, based on the recommended dose of rhGAA, provides a two-fold safety margin.

d. [redacted] (b) (4)

Dr. Suvana's review notes, however, that "The approvability based on establishment acceptability will be made by the Case Management Team in the Office of Compliance." In fact, an FDA 483 was issued after inspection of the Allston Landing, MA manufacturing facility and, after review of the Applicant's response to the 483, the Office of Compliance recommended issuance of a Warning Letter on February 6, 2009. They also recommended that the approval action of this BLA should be withheld based on the issues identified in the Warning Letter. Manufacturing facility issues that prompted the FDA 483 include [redacted] (b) (4)

In addition, the Division was notified that on November 14, 2008 (subsequent to the inspection), rapid cell death was observed in a bioreactor at the Allston Landing, MA facility. This bioreactor had to be taken out of production during an investigation to determine the cause of the rapid cell death. Viral contamination was suspected, but has not been confirmed. The investigation is ongoing and the root cause has still not been identified. A world-wide shortage of the 2000 L product has developed and the Applicant has responded by asking all adult patients using the 2000 L product to decrease the number of infusions per month, from 2 to 1. The 2000 L product is not approved in the U.S. and access of new patients to the 2000 L product in the U.S, through MTAP ended in April 2008. Hence, adult Pompe patients in the U.S. who have had to increase the interval between treatments during this shortage are those already enrolled and treated under MTAP.

7. Clinical/Statistical-Efficacy

The single major study, or "pivotal trial", that the Applicant submitted to support this BLA was a randomized, double-blind, placebo controlled study, called the LOTS. Ninety patients with late-onset (non-infantile onset) Pompe Disease entered the study. Eligibility criteria extended down to the age of 8, however there were only 4 patients under the age 18 who participated in this study, 2 on each study arm. The youngest patient on the Lumizyme arm was age 16 and the youngest on placebo was 10 years of age. Patients were randomized, 2:1, between treatment with Lumizyme 20 mg/kg every other week or placebo. The original planned study duration was 52 weeks. Eligible patients had to be able to ambulate at least 40 meters in a 6-minute walk test (6MWT) and have a percent predicted forced vital capacity (%

predicted FVC) between 30% and 80%. The original co-primary endpoints were 1) change in distance walked during the 6MWT and 2) change in upright % predicted FVC. If the change in 6MWT was found to be statistically significant, then the % predicted FVC could be evaluated.

Major statistical concerns regarding the LOTS study design and analysis were identified. Rather than utilizing a block randomization, the study employed a minimization algorithm to maintain treatment balance between study arms in the prespecified baseline strata: 6MWT distance (≤300 meter vs. > 300 meter) and % predicted FVC (≤55% predicted vs. >55% predicted). In addition, the study design was changed during the conduct of the study to an "adaptive design", reportedly in an effort to determine the optimal study duration and to "compare the two treatments over the entire course of the study, rather than focusing only on the difference at 52 weeks." The amendment that changed the study to an adaptive design was submitted concurrently with the meeting of the Data Safety Monitoring Board (DSMB) who implemented the analysis that assessed the adequacy of study duration. The amendment stated that the evaluation would be conducted with the last enrolled patient had completed 38 weeks on study, and at the time of the DSMB meeting the last enrolled patient had completed 38 weeks on study. Based on their evaluation of the data, the Data Safety Monitoring Board extended the study duration from 52 to 78 weeks.

The analysis plan for the primary endpoints was also changed during the conduct of the study to an evaluation of linear rate of change, i.e. slope, in the 6MWT and % predicted FVC, to be analyzed utilizing a linear mixed effects (LME) model. The statistical analysis plan was amended to include a supportive analysis of the primary endpoints with an analysis of covariance model (ANCOVA).

The Applicant's modified comparison, the monthly rate of change in the 6MWT between the two treatment arms, however, was not found to be statistically significantly different. The difference was 1.24 meters/month, $p = 0.09$. The Applicant then argued that the most appropriate analysis method for the comparison was a sandwich estimator of the variance-covariance matrix, because the 6MWT data were not linear and violated the assumption of normality, although this was not the prespecified analysis. Analysis with the latter technique yielded a lower p value, 0.046. Dr. Kammerman, the biostatistical reviewer, stated in her review that she believed the results of the ANCOVA should be emphasized because of the violations of the assumptions underlying the linear mixed effects model and because the changes to the model occurred after the data were unblinded. By ANCOVA analysis, the difference between treatment arms was 28 meters, favoring Lumizyme. The p value for this analysis, however shifted from 0.035 to 0.06 when the re-randomization test was applied, which is the appropriate in light of the Applicant's use of a minimization algorithm to allocate patients to treatment arms. Dr. Kammerman noted in her review that re-randomization tests are the "appropriate approach for assessing statistical significance when a minimization algorithm is used."

The % predicted FVC results were statistically significant between the treatment arms, favoring Lumizyme, no matter what analysis was utilized. The difference in change from baseline between the two arms was small: an absolute 3.4% difference ($p = 0.004$, ANCOVA

after re-randomization). The reviewers questioned whether this small, but statistically significant, difference between Lumizyme and placebo was clinically relevant. They noted that a consensus statement from the American Thoracic Society states that in COPD patients a % change in % predicted FVC from year to year considered clinically meaningful is at least 15%[1]. The reviewers performed an exploratory responder analysis based on varying interval increases in % predicted FVC. The proportion of patients on the Lumizyme arm who experienced a 15% improvement in % predicted FVC was 12% compared to 0% on the placebo arm.

In summary, with regard to efficacy, Lumizyme was found to be statistically significantly superior to placebo for only one of the co-primary endpoints, % predicted FVC. The clinical relevance of the small mean difference observed between study arms, however, was questionable, and change in % predicted FVC has not been established as a clinical benefit endpoint. The difference in change for the 6MWT, which has been utilized as a clinical benefit endpoint, was not statistically significant (p=0.06) when the re-randomization test was appropriately applied to the ANCOVA. The clinical reviewers recommended approval under Subpart E Accelerated Approval, utilizing the statistically significant observation in the change in % predicted FVC, which they considered a surrogate endpoint reasonably likely to predict clinical benefit. Approval under sub-part E necessitates conduct of a verification study to demonstrate that treatment with Lumizyme is in fact associated with clinical benefit.

The reviewers recommended, in light of the age of the patients with Late Onset Disease that were studied in LOTS (primarily 18 years of age and older) and the limited evidence of efficacy based on a surrogate endpoint, that Lumizyme's indication should be restricted at this time to patients with late-onset disease who are 8 years of age and older and who do not have cardiac hypertrophy. They recommended this restriction because LOTS did not include any patients less than 8 years of age for study, and because there is already an approved product in the US, the 160 L Myozyme product, that has been demonstrated to improve ventilator-free survival in patients with the most severe form of Pompe disease. In addition, the differences between the two products might result in a higher risk of serious allergic/hypersensitivity reactions in this population. To address this, the product will be approved with a REMS. See Section 8 below and Office Director Julie Beitz's review for further details regarding the REMS.

8. Safety

Please see the reviews of Clinical Reviewer Lynne Yao and the CDTL Review from Dr. Joanna Ku for detailed summaries of the safety data submitted in this BLA. The safety dataset included safety data from the LOTS trial, 80 patients from the LOTS Extension Study, data from the Myozyme Temporary Access Program (MTAP) in which patients were treated with the 2000 L product and the world-wide post marketing safety reporting through April 15, 2008.

[1] American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. Am Reg Respir Disease 1991, 144: 1202-1218.

The clinical reviewer, Dr. Yao, reviewed the safety data for evidence of anaphylaxis utilizing the clinical definition set by the Second Symposium on the Definition and Management of Anaphylaxis. She identified 4 cases of anaphylaxis, which yielded an overall incidence of 4/60 (7%) on the Lumizyme arm of the study. There were no such cases on the placebo arm.

Review of post-marketing adverse events uncovered a patient treated with 2000 L product who developed severe cutaneous necrosis and died as a result of this. Additionally, immune mediated skin adverse events have been reported with the 160 L product. Therefore, Dr. Yao carefully evaluated the Lumizyme safety dataset from the clinical trials for similar events. She did note a higher incidence of skin-related adverse events in the Lumizyme treated patients, but no other definitive cutaneous necrosis events. Also, because there has been a published report of membranous glomerulonephritis associated with an earlier form of alglucosidase alfa, Dr. Yao further examined the dataset for evidence of treatment induced chronic immune-mediated reactions. There were slightly more patients on the Lumizyme arm (n=7) who develop hematuria and/or proteinuria than in the placebo arm (n=2). These findings were not adequate to establish a diagnosis of an immune-mediated nephrotoxic events related to Lumizyme.

The reviewers concluded that Lumizyme appears to have an acceptable safety profile for patients with late-onset Pompe disease patients. They raised concern that this product might be more immunogenic than the 160 L product, but there has been no direct comparison of the products, so this cannot be definitively established. The clinical reviewers recommended that the product should carry a boxed warning for the risk of anaphylaxis, given the observed 7% event rate in LOTS. They believe it is particularly important to communicate this risk and the potential risk of other allergic and severe immune mediated reactions to health care providers,. In addition, the reviewers were concerned that health care providers might be confused by the availability of two alglucosidase alfa products, and mistakenly consider them interchangeable. The currently marketed 160 L product has been shown to increase ventilator-free survival in patients with infantile-onset Pompe disease, a rapidly progressive form of the disease. The reviewers wanted to ensure that health care providers are aware that the 2000 L product has not been studied in this more seriously affected infantile onset disease population, or in patients less than 8 years of age with late (non-infantile) onset Pompe disease. Therefore, the reviewers recommend that 2000 L product should be restricted to patients with late (non-infantile) onset Pompe disease, 8 years of age and older who do not have evidence of cardiac hypertrophy.

To address these concerns, the reviewers worked with reviewers from OSE to delineate the safety concerns and how a REMS could appropriately address those concerns. The text of the REMS memo, written by the Office Director Julie Beitz, is reproduced below:

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

The safety and effectiveness of LUMIZYME have not been evaluated in patients with infantile-onset or late (non-infantile) onset Pompe disease less than 8 years of age. Due to the potential risk of rapid disease progression in these populations, Lumizyme (alglucosidase) should not be used in these patients.

In addition, anaphylaxis and severe allergic reactions have been reported during and up to 3 hours after Lumizyme (alglucosidase alfa) infusion. One case of severe cutaneous necrosis and clinical signs suggestive of systemic immune complex-mediated reactions in Lumizyme (alglucosidase)-treated patients have also been observed.

In addition, anaphylaxis and severe allergic reactions have been reported during and up to 3 hours after Lumizyme (alglucosidase alfa) infusion. One case of severe cutaneous necrosis and signals of systemic immune complex-mediated reactions in Lumizyme (alglucosidase)-treated patients have also been observed.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for Lumizyme (alglucosidase alfa) to ensure that the benefits of the drug outweigh the potential risk of rapid disease progression in infantile-onset Pompe disease patients and patients with late-onset disease less than 8 years of age for whom the safety and effectiveness of Lumizyme (alglucosidase alfa) have not been evaluated. In addition, we have determined that a REMS is necessary to ensure that the known risks of anaphylaxis and severe allergic reactions, and the potential risks of severe cutaneous and systemic immune complex-mediated reactions to Lumizyme (alglucosidase alfa) are communicated to patients and prescribers.

In reaching this determination, we considered the following:

A. The estimated size of the population likely to use the drug involved:

An estimate of the size of the population is challenging because Pompe disease affects an ultra-orphan population, and patients who are afflicted with the late (non-infantile) onset form of the disease may not be diagnosed until later in life. The frequency of infantile-onset disease appears to be highest in African-American (1/14,000) and Chinese (1/40-50,000) populations. The frequency of late (non-infantile) onset disease is approximately 1/60,000 in Caucasian populations. It is currently estimated that the product is intended for the treatment, at a maximum, of approximately 2,000 patients in the United States.

B. The seriousness of the disease or condition that is to be treated with the drug:

Pompe disease is a serious, progressive, and life-threatening inherited disorder. The infantile-onset form is rapidly progressive and death usually occurs before 2 years of age, if untreated. The late (non-infantile) onset form of the disease is less severe than the infantile-onset form. Patients with the late (non-infantile) onset form may live for decades, though eventually patients will require wheelchair use and invasive ventilation support.

C. The expected benefit of the drug with respect to such disease or condition:

Data from the single placebo-controlled trial of Lumizyme (alglucosidase alfa) suggest that treatment with the drug resulted in a stabilization of pulmonary function. Improvements in survival or ventilator-free survival were not evaluated in this trial. The expected long term benefit of the drug is unknown.

D. The expected or actual duration of treatment with the drug:

The drug is intended for life-long therapy.

E. The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug:

Anaphylaxis and severe allergic reactions have been reported in 7% of Lumizyme (alglucosidase alfa)-treated patents during and up to 3 hours after Lumizyme (alglucosidase alfa) infusion. Additionally, delayed onset infusion reactions occurring up to 48 hours after treatment with Lumizyme (alglucosidase alfa) have been reported. These events have been highlighted in a Boxed Warning and in the WARNINGS AND PRECAUTIONS section of the product label which advise that appropriate medical support measures be readily available when Lumizyme (alglucosidase alfa) is administered.

In addition, a single (non-US) case of severe cutaneous necrosis has been reported with Lumizyme (alglucosidase alfa) use in the postmarketing setting. Clinical signs suggestive of systemic immune complex-mediated reactions have also been observed. These reactions are highlighted in the WARNINGS AND PRECAUTIONS section of the label for Lumizyme (alglucosidase alfa).

F. Whether the drug is a new molecular entity:

The term new molecular entity (NME) is generally not used with respect to biologics. Lumizyme (alglucosidase alfa) is a member of the class of alglucosidase alfa biologic products, but has not yet been approved.

The elements of the REMS will be a communication plan, elements to assure safe (including that prescribers and healthcare facilities will be specially certified prior to prescribing and dispensing and that patients will have documentation of safe use conditions), an implementation system, and a timetable for submission of assessments of the REMS.

9. Advisory Committee Meeting

This BLA was presented at an Advisory Committee meeting that included both a closed and open session. The votes on the questions posed to the committee are summarized below:

a. 16/17 voted that LOTS established the effectiveness of Lumizyme. There was a single "no" vote.
b. 14/17 voted that Lumizyme should be approved under Subpart E Accelerated Approval, using % predicted FVC as a surrogate endpoint reasonably likely to predict clinical benefit and requiring a verification study to demonstrate clinical benefit. 3/17 voted for regular approval. In their discussion of the verification study, the members stated that it should include clinically meaningful endpoints and should enroll younger children whose disease progresses more rapidly (and who were not studied in LOTS).
c. 16/17 voted that the indication should not be restricted to the adult-onset population (patients over the age of 18, reflecting the population who actually participated in the study). 1/17 abstained. In the discussion the members of the committee stated that the inclusion criterion for the study, ≥8 years of age could be used as the age cut-off for the indication.
d. 17/17 voted that additional studies should be required as post-marketing requirements to assess safety. Members were interested in more information on the risk of anaphylaxis and the possible risk of chronic immunopathologies such as glomerulonephritis and vasculitis.

10. Other Relevant Regulatory Issues

Lumizyme is an orphan product. PREA does not apply. There were no pediatric consults. Consistent with the recommendations of the members of the Advisory Committee, as discussed in the section above, the clinical reviewers recommended that the product be approved for patients with non-infantile onset Pompe disease who are ≥8 years of age. The reviewers recommended that the population be further restricted to patients who have no evidence of cardiac hypertrophy, a manifestation of Pompe Disease that is limited to the infantile onset form of the disease.

DSI inspected 3 clinical sites, two in the Netherlands and one in the U.S. They recommended that the data from all 3 sites could be considered reliable and could be used to support the BLA.

Dr. Yao evaluated the financial disclosures in detail in her Clinical Review. She noted that two primary site investigators received substantial financial support from the Applicant, (b) (4) but that both sites were investigated by DSI and the data from both sites were found acceptable for inclusion in the FDA review. (b) (4), and her site organization, (b) (4) also received substantial funds from the Applicant. However, this site was a "transfer investigational site" in the LOTS study. Twenty-two transfer investigational sites were used to allow patients to receive infusions closer to home after 6 months of treatment in LOTS. Patients continued to return to their primary investigational site every 3 months for assessment and data collection. Thus, transfer investigational sites were involved primarily in the administration of study infusions and in the collection of adverse event data relating to infusions.

11. Labeling

The Division of Medication Error Prevention and Analysis (DMEPA) concluded that the proprietary name of Lumizyme was acceptable.

All major labeling issues had been resolved by the time of completion of this review. Some of the major issues that required negotiations with the Applicant included:

1) Inclusion of a boxed warning to inform of the risk of life-threatening anaphylactic reactions.

2) Indication statement language – The description of the population for whom the product is indicated was revised to state that the product is indicated for "patients 8 years and older with late-onset (non-infantile) Pompe disease (GAA deficiency) who do not have evidence of cardiac hypertrophy." In addition the Indication Section was modified to include information that the product was approved based on a surrogate endpoint, i.e. (b) (4)

3) Inclusion of information that the 2000 L product should not be substituted for the 160 L product in patients with infantile onset Pompe Disease in the label Highlights under the Use in Specific Populations section as (b) (4)

A Medication Guide was not considered necessary because the product is delivered by infusion at physicians' offices or in infusion centers. A component of the REMS will be an attestation by the patient that he/she was provided information about the benefits and risks of Lumizyme treatment by the physician and that he/she was counseled on the safety information in the product labeling by his/her physician. The patient attests that he/she understands the risk (e.g. life threatening or severe allergic reactions, problems with breathing, skin rashes, diarrhea and vomiting) associated with the use of Lumizyme. The product label will include information on the REMS in the boxed warning.

12. Decision/Action/Risk Benefit Assessment

- **Regulatory Action** – Complete Response. Because the product will be approved under the Subpart E Accelerated Approval regulations, the BLA cannot be approved until the Applicant has agreed to conduct an adequately designed verification study that will establish the clinical benefit of Lumizyme.

(b) (4)

- **Risk Benefit Assessment**

Although the reviewers all agree that the benefit/risk assessment supports approval of Lumizyme under Subpart E Accelerated approval regulations for the agreed upon labeled indication, "patients 8 years and older with late-onset (non-infantile) Pompe disease (GAA deficiency) who do not have evidence of cardiac hypertrophy. The effectiveness of Lumizyme is based on stabilization of % predicted forced vital capacity. Improvements in survival or ventilator-free survival have not been evaluated in trials," the product cannot be approved under Subpart E without agreement from the Applicant to conduct an appropriate verification study that will confirm that treatment with Lumizyme is associated with clinical benefit.

At the time of the CR action, the Applicant and FDA have not reached agreement on the design of that study. The reviewers all agreed that this BLA could not be approved without a REMS, and the Applicant and FDA have not, at the time of the CR action, reached agreement on a finalized version of the REMS. There were outstanding CMC deficiencies that had not yet been addressed at the time of the CR action. In addition, the Office of Compliance has approved issuance of a Warning Letter and recommended that an approval action be withheld due to serious manufacturing issues identified during the inspection of the manufacturing facility in Allston Landing, MA.

Given these unresolved issues, the BLA cannot be approved at this time.

- **Recommendation for Postmarketing Risk Management Activities**

A REMS has been recommended (See Section 8 of this review for details) with the following goals:

1) To mitigate the potential risk of rapid disease progression in infantile-onset Pompe disease patients and patients with late (non-infantile) onset

disease less than 8 years of age for whom the safety and effectiveness of LUMIZYME have not been evaluated.

2) To ensure that the known risks of anaphylaxis and severe allergic reactions associated with the use of LUMIZYME are communicated to patients and prescribers, and to ensure that the potential risks of severe cutaneous and systemic immune complex-mediated reactions to LUMIZYME are communicated to patients and prescribers.

The proposed REMS will incorporate:

1. A communication plan
2. Elements to assure safe use
3. Implementation system
4. Timetable for submission of assessments of the REMS

The FDA and the Applicant have not reached agreement on the REMS at the time the PDUFA goal date was reached. The REMS, in its current state of development at the time of the CR action, will be included in the CR letter.

- **Recommendation for other Postmarketing Study Commitments**

A verification study must be conducted as a condition of Subpart E Accelerated approval. The design must be adequate to demonstrate that treatment with Lumizyme is associated with clinical benefit. At the time of this CR action the FDA and the Applicant had not reached agreement on the design of that study.

In addition, pursuant to section 505(o)(3) of the FDCA, the applicant will conduct the following required post-marketing studies (PMRs):

1. A retrospective immunogenicity study based on the pattern of antibody responses in patients enrolled in the Late Onset Treatment Study (LOTS) and LOTS Extension Studies. (b) (4)
(b) (4)

2. A prospective safety study conducted within the ongoing Pompe Registry to assess the known serious risks of anaphylaxis and severe allergic reactions, and signals of severe cutaneous and systemic immune complex-mediated reactions, with Lumizyme (alglucosidase alfa) treatment.

Cross-Discipline Team Leader Review

Date	February 26, 2009
From	Joanna W. Ku, M.D., Acting Clinical Team Leader, DGP
Through	Donna J. Griebel, M.D., Division Director, DGP
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	BLA STN 125291 N000 Cross reference STN 125141/75
Applicant	Genzyme Corporation
Date of Submission	May 30, 2008
PDUFA Goal Date	With major amendment February 27, 2009
Proprietary Name / **Established (USAN) names**	LUMIZYME Alglucosidase alfa
Dosage forms / Strength	Intravenous solution/50 mg per vial
Proposed Indication	Patients with late (non-infantile) onset Pompe disease
Recommended:	Complete Response (CR)

2/26/09

1. Introduction

This Biologic License Application (BLA) is for a new biologic product, Lumizyme (USAN: alglucosidase alfa), which is recombinant human acid alpha-glucosidase (rhGAA), an exogenous source of enzyme replacement intended to treat deficiency of α-1, 4-glucosidase, the defect causing Pompe disease (also known as acid maltase deficiency, glycogen storage disease type II, or glycogenosis type II). The enzyme, produced by recombinant DNA technology, is one of the normal variants of the human enzyme. Lumizyme is alglucosidase alfa produced at a 2000 L bioreactor scale. The product is to be administered every 2 weeks (QOW) at a dose of 20 mg/kg of body weight as an intravenous infusion over approximately 4 hours. (b) (4)

The BLA relies upon a single placebo-controlled clinical study. Issues surrounding the study design and procedures, and interpretation of the results will be discussed. This memo documents my concurrence with the review team's recommendation for a complete response (CR) action.

The review disciplines have all written review documents. The document relied upon are the following:

Clinical Review by L. Yao, dated February 25, 2009
Clinical Review by J. Ku, dated February 26, 2009.
Statistical Review by L. Kammerman, dated February 9, 2009.

Office of Clinical Pharmacology Reviews: Clinical Pharmacology Reviews by T. Chen dated August 26, 2008; Clinical Pharmacology Review by J. I. Kim, dated January 7, 2009, and Pharmacometrics Review by J. Earp, dated January 7, 2009.
Pharmacology/Toxicology Review by N. Mehta, dated January 30, 2009.
Pharmacology/Toxicology Team Leader Memo by D. Joseph, dated February 12, 2009
Chemistry Review (Division of Therapeutic Proteins) by F. Mills, dated February 9, 2009.
Chemistry Memo (Division of Therapeutic Proteins) by F. Mills, dated February 27, 2009.
Product Review (Division of Manufacturing and Product Quality) by K. Suvarna, dated January 9, 2009.
Clinical Inspection Summary by K. Malek, dated November 13, 2008.
Division of Medication Error Prevention and Analysis (DMEPA) Proprietary Name, Label and Labeling Review by Z. Oleszczuk, dated November 14, 2008.
Division of Drug Marketing, Advertising, and Communications (DDMAC) Review by S. Skariah, dated January 14, 2009.
Division of Risk Management Review by Y. Choudhry, dated February 25, 2009.
Division of Pulmonary and Allergy Products Consultation by S. Lim, dated September 18, 2008.
Project Manager's Review by W. Ishihara, dated December 30, 2008
Memo to Division of Gastroenterology Product re: Recommendation to Withhold Approval, CDER Office of Compliance, dated February 6, 2009.
Advisory Committee Meeting Transcript, dated October 21, 2009

This memorandum summarizes selected information from these documents, and they should be consulted for more specific details of the application.

2. Background

Clinical Background

Pompe disease is a lysosomal storage disorder, a category of diseases characterized by a genetic deficiency in production or function of one or more of the lysosomal enzymes. Deficiency in the enzyme acid α-alglucosidase (GAA) results in accumulation of glycogen in lysosomes in various tissues. The disorder is autosomal recessive, and numerous mutations have been identified. The estimated incidence is between 1:300,000 to 40,000. Various forms of the disease are described; all involve myopathy, but with a wide range in severity. In the most severely affected phenotype, the classic infantile-onset form, symptoms are identified usually in the first few months of life. The features are hypotonia, progressive weakness, and cardiomegaly and cardiohypertrophy. Pulmonary function becomes progressively impaired and patients usually die of cardio-respiratory failure by 2 years of age. A muscular variant of the infantile-onset form also presents with symptoms early in life, but does not include cardiomegaly or cardiohypertrophy; these patients also have progressive weakness but it may progress more slowly, and the patients can have longer survival.

Non-infantile onset populations can be further categorized as juvenile- and adult-onset populations, sometimes referred to as "late-onset" Pompe disease. These forms usually do

not involve cardiomegaly, and have longer survival. Symptoms may begin in childhood, but especially mild cases may not come to medical attention until well into adulthood. Symptoms are proximal muscle weakness, greater in the lower extremities, which become more extensive and progresses. Respiratory functions deteriorate, and death is usually secondary to respiratory failure.[1]

The only approved disease-specific therapy for Pompe disease in the US is Myozyme (alglucosidase alfa produced at a 160 L bioreactor scale). Myozyme was approved on April, 28 2006 based on clinical data in 18 classic infantile-onset patients in whom ventilator-free survival advantage was demonstrated as compared to a historical control. Although the study had been conducted in the infantile onset population only, indication for Myozyme was extended to all Pompe population because there was no alternative treatment. The labeling states: "Myozyme® (alglucosidase alfa) 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 other forms of Pompe disease has not been adequately studied to assure safety and efficacy."

Pre-submission Communications between FDA and the Applicant

In early 2007 the Applicant announced that Myozyme was in a drug shortage due to unexpected demand. The Applicant sought approval for alglucosidase alfa produced at a scaled up process, the 2000 L bioreactor scale, as a post-licensing manufacturing supplement (STN 126141/75) to the Myozyme BLA (125291). After reviewing the data in the sBLA, FDA concluded that there was sufficient CMC evidence to demonstrate that the two products were different, and there was insufficient evidence to demonstrate pharmacokinetics (PK) or clinical comparability between the two products. Therefore, the Agency considers alglucosidase alfa produced at the 160 L and 2000 L scales to be 2 different products. These differences were presented at a CDER Regulatory Briefing and in a briefing of the CDER Center Director, Janet Woodcock, M.D. FDA stated that approval of the 2000 L product would require submission of a new BLA, containing clinical data to demonstrate safety and efficacy of the 2000 L product. In May 2008, the Applicant submitted a separate BLA (STN 125291) for the 2000 L product, seeking indication for treatment of late-onset (non-infantile onset) Pompe disease based on the Late-Onset Treatment Study (LOTS). Information submitted in the sBLA (STN 126141/75) was rolled over to the new BLA (STN 125291).

Submission and Review

Lumizyme was granted Orphan Drug Designation, Fast Track Designation, and Priority Review Status.

The Applicant initially proposed the trade name of "Myozyme" for the 2000 L product. DMEPA expressed concern over a potential name confusion that could lead to medication errors given that the trade name "Myozyme" has been in use since 2006 for the 160 L

[1] This section of the Clinical Background is modified from the Team Leader Review (J. Hyde) of BLA 12512.

product. The Applicant withdrew the proposed trade name of "Myozyme" and proposed [redacted] (b) (4) and "Lumizyme." The latter was found to be acceptable by DMEPA and DDMAC.

An Advisory Committee was convened on October 21, 2008 to discuss the Lumizyme application. A major amendment was received on November 7, 2008 containing the Applicant's proposal for the Risk Evaluation and Mitigation Strategy (REMS), and the PDUFA review clock was extended 3 months to permit time for the additional review.

The 2000 L product has been approved in over 40 countries outside of the US.
At the time of this writing, the Applicant projects that the 2000 L product is in short global supply including in the US and that that the company intends to seek FDA approval for alglucosidase alfa produced at a 4000 L bioreactor scale in the near future.

3. CMC

General product quality considerations
RhGAA formulation is lyophilized powder for solution for injection. The product is provided in a 20 ml vial containing 52.2 mg rhGAA, along excipients. Each vial contains 50 mg of rhGAA. The drug substance and the drug product are manufacture by Genzyme Corporation (the Applicant) at the Allston Landing, MA facilities.

Product-specific issues
See the Chemistry Review by F. Mills dated February 9, 2009 for complete information. The CMC Review contains 1) a comparability exercise between Myozyme and Lumizyme, and 2) a discussion on product quality issues pertaining to Lumizyme.

(b) (4)

The Chemistry Reviewer recommended the BLA for approval for Lumizyme as a different product from Myozyme. However, before the Lumizyme can be approved, the following CMC deficiencies must be resolved:

1. Cell viability is a critical parameter for controlling product quality during (b) (4) The Applicant will need to provide adequate justification for not using cell viability as an in-process control for bioreactor monitoring.

2. An established reference standard for use in the Applicant's testing control strategy that is representative of the 2000 L process has not been submitted to this BLA. The Applicant will need to provide data to support the qualification of a reference standard.

3. The acceptance criteria for drug substance and drug product specifications are not consistent with manufacturing process capability and considerations regarding potential impact on safety and efficacy. The Applicant will need to provide an evaluation on the following analytical tests: (b) (4) assay; SDS-PAGE gel assays; HPLC for measurement of (b) (4); HPAEC-PAD for measurement of (b) (4); and size exclusion chromatography.

(b) (4)

Product quality from a microbiology perspective
See the Product Review (Division of Manufacturing and Product Quality, Office of Compliance), by K. Suvarna, dated January 9, 2009 for compete information. The Reviewer concluded that from the microbial control, sterility assurance, and microbiology product quality perspective, the BLA is acceptable for approval (see Section 12 Other Relevant Regulatory Issues, Bioreactor crash).

Facilities review/inspection
FDA's New England District Office issued an FDA483 form on October 10, 2008, identifying numerous CGMP deficiencies and manufacturing problems with Genzyme's Allston Landing, MA Facility. The lack of controls at this plant potentially affects sterility, purity and availability of the finished product and bulk drug substance. Genzyme's written response to the FDA483 did not adequately address the systemic concerns, and the District Office recommended issuance of a Warning Letter. On February 2, 2009 the Office of Compliance approved the issuance of the Warning Letter. At the time of this writing, the Warning Letter is pending. Based on the significance of the deficiencies found in the pre-approval inspection, and that the Agency is currently pursuing regulatory action (issuance of the Warning Letter), on February 6, 2009 the Office of Compliance recommended withholding approval of Lumizyme.

5. Nonclinical Pharmacology/Toxicology

See the Pharmacology/Toxicology Review and Evaluation by N. Mehta dated January 30, 2009 for complete information.

With agreement with FDA, as per meeting with the Applicant on April 25, 2008, all non-clinical pharmacology/toxicology studies submitted for Myozyme BLA were cross-referenced to support the non-clinical requirements in this BLA. The Reviewer included a summary of the non-clinical information presented in the review of the original Myozyme approval, as well as new studies that have been submitted since Myozyme approval. The new studies are summarized as follows.

Two pharmacology studies showed that 2000 L alglucosidase alfa produced similar glycogen clearance as compared to the 160 L product but these studies did not use a method of testing sensitive enough to establish comparability. Two other pharmacology studies showed that glycogen clearing activity appeared to be directly correlated with mannose-6-phosphate receptor binding affinity.

Toxicology studies showed no treatment-related effects on developmental parameters. Based on the results of a 6-month repeat-dose toxicity study of rhGAA in juvenile mice, the NOAEL of rhGAA was 20 mg/kg/every other week. The kidney and the thymus were the target organs of toxicity. Five reproductive toxicity studies showed no treatment-related effects on fertility or early embryonic development in mice, or on fetal development in rabbits. A special toxicology study showed that methotrexate induced a long-lived reduction in alglucosidase alfa directed antibody responses.

The Reviewer recommended approval provided agreement could be reached regarding recommended labeling changes. No phase 4 commitments were recommended.

6. Clinical Pharmacology/Biopharmaceutics

See the Clinical Pharmacology Reviews by J. I. Kim and the Pharmacometrics Review by J. Earp, both dated January 7, 2009 for complete information.

General clinical pharmacology and intrinsic factors potentially affecting elimination
Lumizyme is a therapeutic protein product that is disintegrated to amino acid and it is not expected to be excreted.

The table below shows the multiple-dose pharmacokinetic (PK) parameters of Lumizyme, estimated in 32 patients with late (non-infantile) onset Pompe disease patients who received Lumizyme dosed at 20 mg/kg body weight every-other-weekly, using a 2-compartment linear PK model with a zero-order input in LOTS. The parameters appear to be comparable at Weeks 0, 12, and 52. Patient's age and sex had no significant impact on the PK parameters, but body weight did affect Cmax, Clearance (CL), and the central volume of distribution (V1). However, body weight did not affect the effective half-life of Lumizyme, which is approximately 2-3 hours.

Table 1: Pharmacokinetic parameters of rhGAA (2000L scale) estimated in 32 patients with late onset Pompe disease who received rhGAA 20 mg/kg every other week using a 2-compartment linear pharmacokinetic model (Study AGLU02704)

Parameter	*Week 0*	*Week 12*	*Week 52*
Cmax (mcg/mL)	385 ± 106	349 ± 79	370 ± 88
AUCinf (mcg*hr/mL)	2672 ± 1140	2387 ± 555	2700 ± 1000
Clearance (mL/hr)	633 ± 175	700 ± 244	645 ± 198
Vss (L)	69 ± 92	70 ± 91	70 ± 92
Effective half-life(hr)	2.4 ± 0.4	2.4 ± 0.3	2.5 ± 0.4

Vss, volume of distribution at steady state

Drug-drug interactions
No studies were conducted to evaluate drug-drug interactions.

Through QT Study or other QT assessment
Lumizyme is a biologic product. No TQT study or other QT assessment was performed.

Demographic interactions/special populations
No studies were done to evaluate the effects of demographic or special populations on the PK of Lumizyme.

Immunogenicity
All patients in the Lumizyme-treated group tested positive for anti-rhGAA IgG antibodies as assessed by ELLISA and confirmed by RIP. The median time to seroconversion was 4 weeks after exposure. Approximately 61% of the patients trended toward decreasing titers from peak to last observation with continued treatment. However, 9 of 59 (15%) of patients who developed positive IgG titers during the study had a persistently elevated IgG titer at the end of the study. The median peak titer was 6,400 (range 200 to 819,000), and the median last titer was 1,600.

None of the 60 IgG positive patients tested positive for inhibition of enzyme activity. However, 10 patients (17%) tested positive, 8 (14%) borderline positive, and 41 (68%) negative for inhibition of cellular uptake into fibroblast cells. Both high anti-rhGAA IgG antibody titers and positive inhibitory antibody status appeared to impact on PK: five patients with the highest binding IgG titer also tested positive for inhibitory antibody, and these 5 patients had higher mean CL, lower Cmax, and lower AUC than the 29 patients with negative status. There is insufficient data, however, to indicate whether inhibitory or high IgG antibodies are responsible for the increased clearance.

The Pharmacometrics Reviewer noted that although the data suggested a trend towards higher improvement in the 6 minute walk test (6MWT) with higher IgG titers and possibly also with positive inhibitory antibody status, he felt that the clinical significance of high antibody titers or positive uptake inhibition status remains unclear. When considering the percent predicted forced vital capacity (% FVC), no effects of immunogenicity on that was seen. There also did not appear to be apparent association between higher anti-rhGAA IgG titers and occurrence of infusion reactions.

Other issues
The Reviewers thought that there were there were insufficient patients ages 16 and younger (only 2 patients were treated with Lumizyme) to determine whether pediatric patients responded differently from adult patients in PK parameters.

Conclusions
The Clinical Pharmacology review team recommended approval, provided agreement could be reached regarding the recommended labeling changes. However, because the PK of Lumizyme has not been characterized in patients with late-onset Pompe disease who are younger than 21 years old, the team recommended collecting PK data from pediatric patients with late (non-infantile) onset Pompe disease in the Subpart E verification study.

7. Clinical Microbiology

Clinical Microbiology considerations do not apply to this application because Lumizyme is not an antimicrobial agent.

8. Clinical/Statistical- Efficacy

The reader is referred to the Clinical Reviews by J. Ku, dated February 26, 2009 for the sBLA and by L. Yao dated February 25, 2009 for the Lumizyme BLA, and the Statistical Review by L. Kammerman, dated February 9, 2009 for complete information.

In the clinical review conducted for the sBLA, the Reviewer found that based on the infantile-onset Pompe patient data that were submitted in the attempt to establish Myozyme and Lumizyme comparability, there were insufficient clinical data to establish that Lumizyme was clinically comparable to Myozyme. The results showed that the 18-month invasive ventilator free survival rate (i.e., alive and not dependent on invasive ventilator support) was 83% (N=15/18) in patients treated with Myozyme in the Myozyme Pivotal Study-Extension Study (AGLU01602-AGLU02403), compared to 71 % (N= 2/7 patients) for patients treated with Lumizyme in an expanded access program (AGLU02203), favoring Myozyme treatment. Median ventilator survival time (age at which half of the patient population became ventilator dependent or died) was longer in the Myozyme than the Lumizyme-treated patients: 32 months for the Myozyme-treated patients in the Pivotal-Extension Study compared to 20 to 25 months for the Lumizyme-treated patients in the EAP, favoring Myozyme treatment. Thus, it appears that based on the 18-month invasive ventilator free survival and median ventilator survival data, which came from an exceedingly small number of matched patients available for comparison (N=7 in the EAP and N=18 in the Pivotal Study), clinical comparability could not be established. The results were limited by these analyses being conducted in a retrospective fashion, and the studies were not performed as head-to-head comparisons. Also, because the data were derived from an exceedingly small number of patients studied, with chance alone being able to explain the results, no definitive conclusions could be reached. Nonetheless, Lumizyme appears to show a trend towards inferior efficacy, which, in the opinion of the Reviewer, was a concerning finding

given that Lumizyme contains (b) (4) than Myozyme, which could render Lumizyme (b) (4) and therefore, be less potent. This Reviewer believes that concerns should be raised that there may be an increased risk to the infantile-onset patients due to the potential risk for rapid disease progression if they were to be treated with Lumizyme. Since the safety and efficacy of Lumizyme have not been established in the infantile-onset population, but the safety and efficacy have been established with Myozyme, the Reviewer recommended that infantile-onset patients continue to be treated with Myozyme, and that Lumizyme be restricted for use only in the population in whom an acceptable risk/benefit profile has been established.

The substantial evidence for efficacy for Lumizyme in this BLA application came from the Applicant's single pivotal study, the Late-Onset Treatment Study (LOTS). This study was conducted in accordance with PMC 1 for STN 125141. This data was reviewed by Dr. Yao, and Dr. Kammerman, as follows.

Phase 3 Study — LOTS (AGLU02704)

LOTS (AGLU02704) was a multi-national, randomized, double-blind, placebo-controlled, 78-week study in 90 patients late-onset (non-infantile onset) Pompe disease. Patients age 8 to 70 years were eligible for enrollment. The sites were in the US and the EU. Patients who completed LOTS could be entered into the long-term, open-label study, 26-week LOTS Extension Study (AGLU03206).

Eligibility, treatment, and assessments

To be eligible, patients must have had a confirmed diagnosis of Pompe disease and must be ≥ 8 years old. They must also have been able to ambulate at least 40 meters during a 6-minute walk test (6MWT), and a percent predicted forced vital capacity (% FVC) in the upright position of between 30 to 80%. Patients were excluded if they required invasive ventilator support.

Patients were randomized at treatment allocation of 2:1, to be treated with IV dosing of either Lumizyme 20 mg/kg QOW or placebo. Instead of a blocked randomization, which is typically used, the study used a minimization algorithm to maintain a 2:1 (Lumizyme: placebo) treatment balance within study site (n=8), within 6MWT baseline strata (≤ 300, > 300 meters), and within % FVC baseline strata (≤ 55% predicted, > 55% predicted). Study drug was to be administered for 52 weeks. Enzyme replacement therapy with another GAA was not allowed.

In-office study visits were conducted at the infusion visits of the study drug. Adverse event (AE) assessment and concomitant medication use information were collected throughout the study period. Pulmonary function testing and 6MWT (along with secondary and exploratory assessments including Quantitative Muscle Testing, Manual Muscle Testing, Functional Activities Assessment , SF-36 Health Survey, Fatigue Severity Scale, and Rotterdam 9-Item Handicap Scale) were performed at Week 12, 26, 38, 52, 64, and 78. Physical exam, laboratory testing, antibody testing were performed at more frequent intervals. See the Clinical Review for details.

Endpoints

The study was initially planned to be 52-weeks with no plans for an interim analysis. The original co-primary endpoints were 1) change in distance walked during the 6MWT from baseline to completion of treatment, and 2) change in upright % FVC. The 6MWT was to be examined first. If the treatment effect for the 6MWT was statistically significant at 0.05, then % FVC would be evaluated.

During the study, the study was changed from a fixed design to an adaptive design. The rationale for these changes was to determine the optimal duration of the study and to "compare the two treatments over the course of the study, rather than focusing on comparisons at 52 weeks." An external Independent Statistical Center performed an interim analysis of the 6MWT data when all patients had enrolled and a significant number had completed parts of the study, and recommended extension of the study period. With the approval of the Data Safety Monitoring Board (DSMB), the study was extended the study from 52 weeks to 78 weeks. To accommodate the adaptive design changes made, the primary endpoints became the linear rate of change (i.e., slope, or average monthly increase) in distance walked in the 6MWT and % FVC. The plan was to analyze these using a linear mixed effects (LME) model. The statistical plan was also amended to include supportive analyses to include 1) a re-randomization analysis, which was to consist of running the minimization algorithm used for the treatment assignments 10,000 times, and 2) an analysis of covariance (ANCOVA) model for the primary endpoints.

When the study was completed and after the final data were unblinded and analyzed, the Applicant discovered that after fitting the pre-specified LME to the data, the assumptions of the pre-specified statistical model had been violated, and again changed the statistical analysis plan to correct for these violations. See the Statistical Review for details.

Results

The study enrolled 90 subjects (Lumizyme n=60; placebo, n=30). There were 2 patients in the Lumizyme group and 2 patients in the placebo group who were under 18 years of age at the time of the first infusion: the youngest patients enrolled in the Lumizyme treatment arm was 16 years of age, compared with 10 years of age for the placebo treatment arm. These minimum enrollment ages is important (b) (4) The oldest subject in either group was around 70 years of age. The median age was around 45 years in both groups. The distribution of gender was different between the groups: among patients randomized to Lumizyme, 57% were male, compared with 37% of patients randomized to placebo. Over 90% of patients were Caucasian, and the average duration of disease was about 9 years. Nine patients discontinued the study early (Lumizyme n=5; placebo, n=4). A total of 81 patients completed LOTS and 80 enrolled into the LOTS Extension Study.

Examination of the monthly of rate of change in 6MWT after blinding showed a difference of 1.24 meters/month, with a p-value of 0.09. The Applicant argued that the 6MWT data departed from linearity and violated the assumption of normality, and thus a sandwich estimator of the variance-covariance matrix should be used. The results from the LME with a sandwich estimator (i.e. robust variance estimation) showed a difference of 1.24

meters/month, with a p-value of 0.046, which improved the p value, but still borderlines the traditional alpha level of 0.05.

The Clinical Reviewer felt that the monthly rate of change in distance walked was not a clinically meaningful analysis, as it is conceptually difficult to interpret a rate of change. Rather, she argued (and the AC members concurred) that the ANCOVA would be a more meaningful analysis because it would examine whether the change from baseline to the last observation between the Lumizyme and placebo-treated patients differed. The results showed that for the ANCOVA of the 6MWT, the treatment effect was a difference of about 28 meters improvement, favoring Lumizyme treatment. However, when re-randomization test was used to address the minimization algorithm that was used to allocate patients in a 2:1 ratio, the p-value of the ANCOVA for the 6MWT changes from 0.035 to 0.06, which is a non-statistically significant result at the traditional alpha level of 0.05. When re-randomization test was used for the LME model with the sandwich estimator, the p-value changes from 0.46 to 0.15, which is also a non-statistically significant result at the traditional alpha level of 0.05.

The results for % FVC are statistically significant regardless of the test used, and showed a treatment effect of about 3 point in the % FVC difference between treatment groups, favoring Lumizyme treatment.

The following tables summarize the efficacy results (copied electronically from the Statistical Review):

Table 2 Change in distance walked in six-minute walk test

	Myozyme N = 60	Placebo N = 30	Difference	P value
Estimates/Tests of Monthly Change in Distance Walked (Repeated Measures Analysis)				
GEE, meters/month (95% CI)	1.37 (0.42, 2.33)	-0.13 (-1.12, 0.85)	1.51 (0.12, 2.89)	0.0326
LME with model-based variance estimation, meters/month (95% CI)	1.18 (0.34, 2.03)	-0.06 (-1.26, 1.14)	1.24 (-0.21, 2.70)	0.0931
LME with robust variance estimation, meters/month (95% CI)	1.18 (0.26, 2.11)	-0.06 (-0.90, 0.78)	1.24 (0.02, 2.47)	0.0464
Wei-Lachin test	--	--	--	0.0133
Estimates/Tests of Change in Distance Walked From Baseline to Last Observation				
ANCOVA, meters (95% CI)	25.13 (10.07, 40.19)	-2.99 (-24.16, 18.18)	28.12 (2.07, 54.17)	0.0347
Wilcoxon-Mann-Whitney test				0.0283

Reference: 14.2.1.1.1, 14.2.1.2.A, 14.2.1.3.1

Source: Table 11-3, Clinical Study Report

Table 4 Re-randomization p-values for the 6MWT

Model	Re-randomization p-value
LME with robust variance estimation, meters/month	.15
ANCOVA	.06

Source: Table 1. Errata 2. Clinical Study Report; e-mail communication

Table 5 Change in 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)		
Wilcox-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)		

Reference: 14.2.1.1.1, 14.2.1.2.A, 14.2.1.18

Source: Table 11-7, Clinical Study Report

Table 6 Re-randomization p-values for FVC

Model	Re-randomization p-value
LME with robust variance estimation, meters/month	.004
ANCOVA	.004

Source: Table 1, Errata 2, Clinical Study Report; e-mail communication

Setting aside the statistical issues, the Clinical Reviewer questioned whether such magnitude of difference (28 meters improvement in the 6MWT and 3 point percentage improvement in the % FVC after 78 weeks of treatment) was clinically meaningful.

Normal ranges for healthy adults in 6MWT range from 500-580 meters, with men walking slightly longer than women. Healthy adolescents may walk up to 700 meters. The results for the LOTS population are shown in the following table (copied from the Clinical Review):

Change from baseline in distance walked in 6MWT in meters

	2000 L N=60	Placebo N=30	Difference
Summary statistics:			
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
Results of ANCOVA:*			
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

Although the 6MWT has been used as an efficacy endpoint for the approval enzyme replacement therapies (including for Aldurayzme and Elaprase), 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 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.[2] The 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 starting rating themselves as "a little better" and the mean 6MWT differences was -70 meters for patients to stop rating themselves as "about the same" and start rating themselves as a "little worse."

Similarly, the clinical meaningfulness in a treatment effect of +3 points on the % FVC is uncertain. Measurements of pulmonary function such as the % FVC were designed to objectively assess clinical response in COPD. One consensus statement presented by the American Thoracic Society states that a year-to-year difference in the % FVC in COPD

[2] Redelmeier DA, Bayoumi AM, Goldstein RS, Guyatt GH. Interpretating small differences in functional status: the Six Minute Walk Test in chronic lung disease patients. Am J Respir Crit Care Med. 1997, 155:1278-1282.

patients should be at least 15% to be considered clinically meaningful.[3] The results for the LOTS population are shown in the following table (copied from the Clinical Review):

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)		
Wilcox-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 actually refers to LUMIZYME
Copied electronically from the CSR page 111/1841

The Clinical Reviewer notes that there are no data correlating the change in % FVC or 6MWT and clinical response in Pompe disease. Therefore, the magnitude of change that could be considered clinically meaningful for Pompe disease patients is unknown.

However, a sensitivity analysis examined the % of responders who met certain improvement criteria based on the 6MWT and % FVC. The results demonstrated that there were more responders in the Lumizyme treated group reaching specific efficacy thresholds, compared with the placebo treated group, suggesting a trend toward some beneficial effects; see table below.

[3] The American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. Am Reg Respir Disease. 1991, 144:1202-1218.

Table 7 Proportions of subjects improving and declining, using a range of threshold values

Change Threshold	Patients Improving		Patients Declining		Myozyme versus Placebo Treatment Effect[1]
	Myozyme N = 60	Placebo N = 30	Myozyme N = 60	Placebo N = 30	
6MWT					
54m	23.7%	13.3%	5.1%	13.3%	16.2%
37m	28.8%	16.7%	8.5%	20.0%	19.3%
30m	30.5%	20.0%	11.9%	20.0%	14.9%
FVC					
15%	11.9%	0.0%	6.8%	6.7%	11.0%
10%	20.3%	6.7%	8.5%	26.7%	27.0%
5%	40.7%	20.0%	20.3%	46.7%	32.1%

[1] Calculated using the methods of Guyatt et al (1998).

Source: Table 11-10, Clinical Study Report

Finally, the Clinical Reviewer conducted several retrospective, subgroup analyses, examining the relationship between immunogenicity and endogenous GAA levels, and efficacy outcomes in the 6MWT. The Reviewer cautions against arriving at definite conclusions about these observations given that the number of patients was small and the analyses were conducted retrospectively; but, the Reviewer believes that these trends are worthwhile for exploring in the phase 4 setting because it could help to delineate which patient populations are likely (or unlikely) derive benefits from Lumizyme treatment. Moreover if certain patients could be predicted to have poor outcome based on their immunogenicity profile, they could be considered for immune tolerance regimen.

1. In 9 patients who had persistent anti-GAA IgG antibodies, the mean improvement in the 6MWT appeared less than that of the entire Lumizyme population, suggesting that patients with persistent high antibody titers may have an attenuated response to Lumizyme.
2. Four patients performed significantly better than the rest of the Lumizyme group: these "high performers" improved over 100 meters in 6MWT walked from baseline. Three of the four patients had inhibitory antibody titers, were male, and none had rising IgG antibodies at the end of the study. In other words, positive neutralizing antibody status in the setting of tolerizing IgG antibody response seemed to actually enhance efficacy. The Clinical Reviewer postulated that neutralizing or inhibitory antibody in some cases may have a paradoxical effect of enhancing enzyme effect, referencing the case in the literature where when neutralizing antibody to the cytokine IL-4 was injected into the animal, the *in vivo* activity of IL 4 was enhanced in mice, possibly by mechanism of the neutralizing antibody acting as a carrier protein and thus increasing the half-life of the cytokine.[4]
3. In the 10 patients who had endogenous GAA level of <1 %, both the 6MWT and %FVC improvement were less than the overall Lumizyme treated group.

[4] Finkleman FD, madden KB, Morris SC, et al. Anti-cytokine antibodies as carrier proteins. J Immun. 1993. 151: 1235-1244.

Conclusions and Recommendations

The Statistical Reviewer outlined her concerns about the statistical design changes, analyses, and conclusions. Usually, the result from using re-randomizations tests is similar to the result from using classical tests. This was not the case in LOTS. For example, for the ANCOVA of the 6MWT, the p-value changed from 0.035 to 0.06 with re-randomization. The results for the % FVC were statistically significant regardless of the test used. Although the p-value of 0.06 for the randomization test (which the Statistical Reviewer believes is the appropriate test) was not statistically significant at the traditional alpha level of 0.05, the Statistical Reviewer believes that the orphan status of the indication needs to be entertained when deciding on the efficacy of this product.

The Clinical Reviewer felt that although the Applicant was not able to demonstrate a statistically significant difference between Lumizyme and placebo in the pre-specified primary endpoint (6MWT), there was a trend toward improvement in the Lumizyme group, and there was a statistically significant difference in the % predicted FVC, albeit the clinical significance of a treatment effect of 3% in the predicted FVC is not clear. Given the lack of either a clearly clinically meaningful or statistically significant difference between Lumizyme and placebo, she could not recommend full approval. However, given the totality of the evidence, and also in the context of the drug shortage of Myozyme in the US, she thought there is sufficient cause for approval of Lumizyme under Subpart E accelerated approval based on the % FVC findings. The change in % FVC represents a surrogate endpoint that is reasonably likely to predict clinical benefit.

Under Subpart E, adequate and well-controlled studies must be carried out with due diligence to verify and describe clinical benefits. The Reviewer (and the AC members) stated that the verification study should include juvenile-onset patients who have not been adequately studied in LOTS.

The Reviewer recommended that indication for Lumizyme should be restricted to late (non infantile-onset) patients older than 8 years of age and without cardiohypertrophy, to reflect the inclusion criteria of LOTS. Postmarketing requirement (PMR) studies and postmarketing (PMC) studies were recommended to further study the relationship between immunogenicity, efficacy, and safety. This Reviewer concurs with the Clinical Reviewer's conclusions and recommendations.

9. Safety

The primary safety information included data from LOTS, the only placebo-controlled study of Lumizyme. Additional safety data as supportive evidence included interim safety data from the LOTS Extension Study (n=80) through April 15, 2008; data from 3 small open label studies of late (non-infantile) onset patients; data from the Myozyme Temporary Access Program (MTAP)[5] (n=135); and data from world-wide post marketing safety reporting through April 15, 2008.

[5] In the Myozyme Temporary Access Program (the MATP), Lumizyme (the 2000 L product), not Myozyme is the administered product. The name "MTAP" was designated for the program when the two products were being evaluated for comparability, and the trade name Myozyme was temporarily used interchangeably for the

The LOTS treatment duration was 78 weeks. Monitoring included vital signs, routine laboratory testing, physical exam, AE reporting, infusion associated reactions, and immunogenicity testing (including IgG antibody and neutralizing antibody testing).

One death occurred, reported in a 33 year old woman who died of brain stem ischemia secondary to basilar artery thrombosis, a known complication of Pompe disease. The Reviewer concurred with the Applicant's assessment that the death was unrelated to the study drug.

Nine patients dropped out of the study (n=4 in the placebo group, and n=5 in the Lumizyme treated group). In the placebo group, one patient was discontinued due to persistent headache, and three patients dropped out "wishing to receive commercial product." In the Lumizyme group, one patient died from brain stem ischemia; two patients were discontinued due to infusion reactions that were serious adverse events (anaphylaxis); one dropped out for personal reasons; and, one dropped out to receive commercial product. In the two patients who withdrew due to anaphylaxis as infusion reactions, one patient had anaphylaxis with laboratory confirmation of IgE mediated anaphylaxis, and the other developed severe angioneurotic edema after the third Lumizyme dose, and based on the risk/benefit profile, the Investigator withdrew the patient from the study.

There was a total of 27 serious adverse events (SAEs), occurring in 19 patients. The SAEs that occurred at a higher incidence in the Lumizyme group than placebo included anaphylaxis, brain stem ischemia, coronary artery disease, angioneurotic edema, throat tightness, intervertebral disc protrusion, cerebral aneurysm, supraventricular tachycardia, gastroenteritis, chest pain/discomfort, pneumonia, and dehydration.

Anaphylaxis, allergic adverse reactions, and infusion reactions are the major safety concerns for Lumizyme. Using the clinical definition set by the Second Symposium on the Definition and Management of Anaphylaxis,[6] which uses clinical criteria to define anaphylaxis, rather than relying on laboratory profiles to confirm an IgE-mediated anaphylactic response, the Reviewer identified 4 cases of anaphylaxis for an overall incidence anaphylaxis of Lumizyme treated patients of 4/60, or 6.7 %, compared with no case in the placebo group. Anaphylaxis and severe allergic reactions have been observed in patients during and up to 3 hours after LUMIZYME infusion.

The incidence of infusion reaction was examined independently by the Reviewer. Adverse events (regardless of relatedness as determined by the Investigator) that occurred during the infusion and up to 48 hours afterwards were reviewed. Notable infusion reactions that occurred in an incidence of at least 5% greater in the Lumizyme treatment group compared with placebo include anaphylaxis, urticaria, diarrhea, vomiting, dyspnea, rash, hematuria, and chest discomfort. Additionally, delayed infusion reactions, occurring up to 48 hours after the infusion include urticaria, dizziness, musculoskeletal weakness and pain. As some reactions

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two products. After FDA deemed the two products not comparable, the 2000 L product was given a new trade name, Lumizyme.

[6] 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.

occurred up to 48 hours after the infusion, they highlight the need for longer monitoring for delayed onset reactions.

The Reviewer found one case of death due to skin necrosis in a patient treated with Lumizyme in the post marketing experience outside of the US. There was also a higher incidence of skin-related AEs occurred in the Lumizyme treated group in LOTS. There were slightly more patients who developed hematuria and/or proteinuria in the Lumizyme group (n=7) than in the placebo (n=2), suggesting a signal for chronic immune mediated kidney reactions. There has been at least one report in the literature of the development of membranous glomerulonephritis associated with Myozyme treatment. The Reviewer felt that though the number of cases seen during LOTS and the characterization of these complications do not suffice to assess whether this drug may cause chronic immune-mediated reactions, phase 4 studies should be required to explore these issues by following the long term safety profile of the drug.

Conclusions

The Clinical Reviewer concluded that Lumizyme appears to have an acceptable risk/benefit profile for the late (non-infantile) onset Pompe disease patients. The Reviewer provided recommendations for the safety section of the labeling and recommended that a (b) (4) Long term safety is to be evaluated in the verification study, as well as in post marketing requirement studies. A Risk Evaluation and Mitigation (REMS) program should be instituted to communicate risks to ensure that the benefits of Lumizyme outweigh the risks. See Review for details.

10. Advisory Committee Meeting

This application was presented to the Endocrinologic and Metabolic Advisory Committee on October 21, 2008. The 17 voting members of the Committee voted as follows:

- 16 votes: LOTS has established the effectiveness of Lumizyme. 1 vote: LOTS has not.

- 11 votes: Lumizyme should be approved under Accelerated Approval (Subpart E), whereby Lumizyme can be approved using the % FVC as a surrogate endpoint reasonably likely to predict clinical benefit, and a verification study to demonstrate clinical benefit Lumizyme would be required of the Applicant during the post-marketing period. 4 votes: Lumizyme should be approved under regular approval based on the 6MWT in LOTS. 1 vote: Lumizyme should not be approved. 1 vote: abstain.

- 16 votes: The indication for Lumizyme should not be restricted to the adult-onset population only (i.e., patients who were diagnosed and had symptom onset over 18 years of age). 1 vote: abstain. The general feeling was that such a restriction based on age would be an arbitrary cutoff because the disease exists on a continuum, and that restriction in indication could potentially limit access. It was suggested by some members that the inclusion

criterion of LOTS (≥8 years) could be used as age of cut-off for Lumizyme to treat late (non-infantile onset) patients ages 8 years or older.

- 16 votes: Additional studies should be required as a post marketing commitment to assess efficacy. 1 vote: no.

- Regarding the design of the verification study, the committee members expressed various opinions and concerns. The general sense was that such a study should be prospectively defined and rigorously conducted, using clinically meaningful endpoints and the study should include younger children whose disease progression is more rapid and who have not been adequate studied in LOTS.

- 17 votes: Additional studies should be required as post-marketing requirements to assess safety. The majority pointed out the need for monitoring risks of acute reactions such as anaphylaxis, and chronic immunopathologies such as vasculitis and glomerulonephritis.

For complete content of the AC meeting, see transcript.

11. Pediatrics

Lumizyme is an orphan product so the Pediatric Research Equity Act does not apply. There was no formal pediatric consult.

The safety and efficacy of Lumizyme was assessed in a randomized, double-blind, placebo-controlled study of 90 patients with late (non-infantile) onset Pompe disease. Patients who are 8 to 70 years of age were eligible for enrollment. The study included 2 patients 16 years of age or younger (n=1, age 16 years, Lumizyme treatment group, n=1, age 10 years, placebo group). The Clinical Reviewer recommended that the age cut-off for the indication of Lumizyme to include only late (non-infantile) onset patients who are ≥ 8 years, based on the inclusion criteria of LOTS.

The clinical team recommends that patients with infantile-onset Pompe disease (i.e., onset before 12 months and with presence of cardiac hypertrophy), and also patients who have the late-onset form of the disease but who are < 8 years be treated with Myozyme.

12. Other Relevant Regulatory Issues

Division of Scientific Investigation (DSI) audits

Clinical site inspections were conducted at 3 sites (Site #26 Erasmus Medical Center, the Netherlands; Site #4 Sophia's Children Hospital, the Netherlands; Site #29 Tower Hematology Oncology Medical Group, US). The Inspector found that the data from the three sites inspected are reliable and can be used in support of the BLA.

Bioreactor crash
On November 14, 2008, evidence of rapid cell death was observed in Bioreactor 7B (run 11013526) at the Allston Landing, MA facility, where the drug substance and drug product of Lumizyme is manufactured. The root cause of the rapid cell death has not been identified as of this writing. Although there was no conclusive evidence of viral contamination, the event has been treated as a possible viral contamination with respect to the implementation of isolation and decontamination procedures. This event contributed to a global shortage of Lumizyme, prompting Genzyme to announce that adult patients using Lumizyme would need to forego 1 treatment per month beginning in January 2009. Investigation of the root cause is ongoing.

13. Labeling

The Lumizyme labeling is to conform to the Physician Labeling Rule (PLR) format. Labeling negotiation is ongoing at the issuance of the CR Letter. Some of the major issues include: 1) a black box warning about the risk of anaphylaxis, 2) the indication population to reflect the inclusion criteria of LOTS, i.e., late (non infantile) onset patients with Pompe disease 8 years and older who do not have evidence of cardiac hypertrophy, 3) efficacy is based on the stabilization of % FVC, and that improvements in survival or ventilator free survival have not been evaluated in trials; 4) inclusion of the REMS program, 4) distinction between Myozyme and Lumizyme, 5) risks of anaphylaxis and other severe allergic reactions, delayed onset infusion reactions, and chronic immune mediated reactions that include skin and kidney manifestations, 6) the Pompe Registry (note: the Registry has been ongoing since around the time of the Myozyme approval).

14. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action
The recommended action is a Complete Response (CR). Before this application can be approved, the Applicant must 1) address the CGMP deficiencies identified on FDA's inspection of the Allston Landing, MA, facility, 2) address the CMC deficiencies, 3) reach agreement with FDA on the design of the post-approval study that will be conducted under accelerated approval regulations to verify the clinical benefit of Lumizyme, and 4) submit a revised proposed Risk Evaluation and Mitigation Strategy (REMS).

Recommendation for Postmarketing Risk Evaluation and Management Strategy (REMS)
Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Food Drug and Cosmetic Act (FDCA) to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). This provision took effect on March 25, 2008.

A REMS program for Lumizyme is recommended. Its goal should include: 1) to mitigate the potential risk of rapid disease progression in infantile-onset Pompe disease patients and patients with late (non-infantile) onset disease less than 8 years of age for whom the safety

and effectiveness of Lumizyme have not been evaluated; and 2) to ensure that the known risks of anaphylaxis and severe allergic reactions associated with the use of Lumizyme are communicated to patients and prescribers, and to ensure that the potential risks of severe cutaneous and systemic immune complex-mediated reactions to Lumizyme are communicated to patients and prescribers.

The REMS does not need to include a Medication Guide or PPI. However, a Communication Plan to health care providers, Elements to Ensure Safe Use, an Implementation System, and an Assessment of the REMS should be required.

Recommendation for Postmarketing Requirement (PMR) Studies:
Title IX, Subtitle A, Section 901 of the FDAAA amends the FDCA to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)). This provision took effect on March 25, 2008.

Two PMR studies are recommended:

1. A retrospective immunogenicity study based on the pattern of antibody responses in patients enrolled in the Late Onset Treatment Study (LOTS) and LOTS Extension Studies. The objective of this study is to determine which immunogenicity profiles may predict the development of the known serious risks of anaphylaxis and severe allergic reactions, and signals of severe cutaneous and systemic immune complex-mediated reactions with Lumizyme (alglucosidase alfa) treatment.

2. A prospective safety study conducted within the ongoing Pompe Registry to assess the known serious risks of anaphylaxis and severe allergic reactions, and signals of severe cutaneous and systemic immune complex-mediated reactions, with Lumizyme (alglucosidase alfa) treatment.

Recommendation for other Postmarketing Commitment (PMC) Studies:
PMC studies will be included upon final approval.

Recommended Comments to Applicant
The MTAP has been closed to new patients since Q2 of 2008. While the deficiencies in the BLA are being addressed, it would be important to optimize patient access by re-opening the MTAP to allow late-onset patients to receive Lumizyme treatment.

CLINICAL REVIEW

Application Type	Manufacturing sBLA
Submission Number	125291
Submission Code	000
Letter Date	30 October 2007
Stamp Date	1 November 2007
PDUFA Goal Date	27 February 2009 (with Major Amendment)
Reviewer	Joanna W. Ku, MD 2/26/09
Clinical Team Leader	Anne R. Pariser, MD 2/26/09
Review Completion Date	26 February 2009
Established Name	Alglucosidase alfa
(Proposed) Trade Name	Lumizyme
Therapeutic Class	Enzyme Replacement Therapy
Applicant	Genzyme Corporation
Priority Designation	Priority
Formulation	IV Injection
Dosing Regimen	20 mg/kg every other week
Indication	Treatment of Pompe disease (glycogen storage disease type II, acid maltase deficiency)
Intended Population	Patients with Pompe disease

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Based on the infantile-onset Pompe patient data that were submitted in this supplemental Biologic License Application (sBLA), there are insufficient clinical data to establish that Lumizyme (alglucosidase alfa produced at the 2000 L manufacturing scale) is clinically comparable to Myozyme (alglucosidase alfa produced at the 160 L scale). Therefore, this Reviewer recommends that Lumizyme not be approved in this sBLA with the same indication as that for Myozyme, which is for use in all patients with Pompe disease.

Genzyme (the Applicant) states that the Late-Onset Treatment Study (LOTS, Study AGLU02704) could address the issue of safety and efficacy in a distinct population, the late (non-infantile) onset patients, and proposes to submit a new BLA for Lumizyme for use in that population. The Applicant's proposal is acceptable. Information submitted and reviewed in this sBLA could be rolled over to a new BLA for Lumizyme. The Reviewer recommends that given the complexity of the issues, an Advisory Committee (AC) meeting be convened to discuss the final approval decision regarding Lumizyme.

1.2 Summary of Clinical Findings

Since comparability of Lumizyme and Myozyme could not be established based on non-clinical data (chemistry, manufacturing, and control [CMC] and animal pharmacology-toxicology) and clinical pharmacology data, the focus of this review was to examine comparability of the two products based on clinical data. The original Myozyme approval was based on improved invasive ventilator-free survival in infantile-onset Pompe patients compared to a historical-control study. In this submission, the Applicant attempted to establish comparability of Lumizyme based on clinical data in infantile-onset patients who were treated with Lumizyme and Myozyme. However, there was insufficient evidence to support the comparability of the two products, as described below.

1.3 Brief Overview of Clinical Program

Myozyme (USAN: alglucosidase alfa) is recombinant human acid alpha-glucosidase [rhGAA] produced at the 160 L scale process. It is labeled for use in the United States (US) as an enzyme replacement therapy (ERT) for patients with Pompe disease. Marketing approval was granted on 28 April 2006 by the US Food and Drug Administration (FDA). In this sBLA, the Applicant is seeking marketing approval for alglucosidase alfa produced at the 2000 L scale manufacturing process (proposed trade name: Lumizyme).

A total of 27 infantile-onset patients' experience was analyzed in this clinical review. These patients were chosen for analysis because their disease characteristics, baseline clinical status, and alglucosidase alfa treatment history matched that of the original 18-patient cohort who were studied in the pivotal trial that supported the approval of Myozyme, thus making it possible to compare their experience with the 18-patient cohort. Specifically,

1. The approval for the original BLA was based on the experience of 18 infantile-onset patients who were studied in Study AGLU01602 (the Pivotal Study), during which patients were treated with Myozyme, with length of treatment ranging from 52 to 106 weeks. Of the 18 patients enrolled and treated in the Pivotal Study, 16 continued on treatment in Study AGLU02403 (the Extension Study), during which patients were switched to and treated with Lumizyme, with length of treatment ranging from 60 to 150 weeks. In this combined AGLU01602/02403 experience (the Pivotal-Extension Study), 16 patients (N=16) were followed until they were about 3 years of age. In this review, comparisons were made between the patients' clinical outcomes (ventilator-free survival and motor function) during the Myozyme vs. Lumizyme treatment periods.

2. Two patients (N=2) in Study AGLU01702 (the 1702 Study) were found matching with the infantile-onset patients in the Pivotal Study. Study AGLU01702 was an open-label study of the safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of Myozyme in 21 patients with infantile-onset Pompe disease aged 4 to 43 months at first infusion, with the length of treatment ranging from 52 to 104 weeks. These two patients were initially treated with Myozyme then Lumizyme. Comparisons were made between the patients' clinical outcomes (ventilator-free survival and motor function) on Myozyme vs. Lumizyme.

3. Seven patients (N=7) in Study AGLU02203, an Expanded Access Program (the EAP Study) in the US, were found matching with the infantile-onset patients in the Pivotal Study. During the EAP study period, alglucosidase alfa treatment-naïve patients received Lumizyme as their initial ERT. After the EAP ended, patients continued treatment, but switched to Myozyme, which by then had become commercially available in the US. Comparisons were made between the experiences of these 7 patients who received Lumizyme as initial ERT treatment, and the experience of the 18 patients in the Pivotal Study who received Myozyme as initial ERT treatment. A comparison between these populations was possible because they were matched in terms of disease characteristics and prognosis, and timing of initiation of therapy. This comparison between these two treatment-naïve infantile-onset populations formed the most important analysis of this review for the purpose of establishing clinical comparability between the two products.

The Applicant did not identify any other patients in the alglucosidase alfa clinical development program who matched the characteristics of the infantile-onset patients in the Pivotal Study. Hence, these matched 27 patients' data were the only clinical data

available for comparison, on which a decision regarding clinical comparability had to be made in this sBLA review.

1.4 Efficacy

A comparison was made in the efficacy outcome (ventilator free survival) for the patients who received Lumizyme in the EAP Study as their first ERT (the EAP) and the patients who received Myozyme in the Pivotal Study as their first ERT (the Pivotal-Extension Study). A comparison was also made in the efficacy outcomes (motor function) after the switch was made from Myozyme to Lumizyme in patients in the Pivotal-Extension Study and the 1702 Study.

The results showed that the 18-month invasive ventilator free survival rate (i.e., alive and not dependent on invasive ventilator support) was 83% (N=15/18) in patients treated with Myozyme in the Pivotal Study, compared to 71 % (N= 2/7 patients) for patients treated with Lumizyme in the EAP, favoring Myozyme treatment. Median ventilator survival time (age at which half of the patient population became ventilator dependent or died) was longer in the Myozyme than the Lumizyme-treated patients: 32 months for the Myozyme-treated patients in the Pivotal-Extension Study compared to 20 to 25 months for the Lumizyme-treated patients in the EAP, favoring Myozyme treatment. Thus, it appears that based on the 18-month invasive ventilator free survival and median ventilator survival data, which came from an exceedingly small number of matched patients available for comparison (N=7 in the EAP and N=18 in the Pivotal Study), clinical comparability could not be established. The results were limited by these analyses being conducted in a retrospective fashion, and the studies were not performed as head-to-head comparisons. Also, because the data were derived from an exceedingly small number of patients studied, with chance alone being able to explain the results, no definitive conclusions could be reached. Nonetheless, Lumizyme appears to show a trend towards inferior efficacy, which, in the opinion of this Reviewer, is a concerning finding given that Lumizyme (b) (4) be less potent. This Reviewer believes that concerns should be raised that there may be an increased risk to the infantile-onset patients due to the potential risk for rapid disease progression if they were to be treated with Lumizyme. Since the safety and effectiveness of Lumizyme have not been established in the infantile-onset population, but the safety and effectiveness have been established with Myozyme, this Reviewer recommends that infantile-onset patients continue to be treated with Myozyme, and that Lumizyme be restricted for use only in the population in whom an acceptable risk/benefit profile has been established.

Motor data (as supportive data for clinical efficacy) and left ventricular myocardial index (LVMI) data (as supportive pharmacodynamics [PD] data) could not be used as additional information because patients were treated with Lumizyme for only a relatively short period of time (approximately 7 to 8 months), and there were only 1 or 2 data points per patient collected for most patients during the Lumizyme treatment experience.

(b) (4)

About 50% of the original cohort of the 18 patients in the Pivotal Study had either become ventilator dependent or died by 3 years of age. There was also a plateau reached in motor development in even the most treatment responsive patients. It appears that motor improvement could only reach a maximum level, which still lagged behind age-matched healthy children. The data demonstrate that alglucosidase alfa is not a cure and there is still an unmet medical need for the treatment of Pompe disease. The limitations of the drug effects should be updated in the Myozyme labeling to allow patients and physicians to re-evaluate the over all risk-benefit profile of Myozyme treatment now that data for longer follow up have become available since its original approval in 2006.

1.5 Safety

Deaths reported were predominantly due to underlying disease, including respiratory and cardiac failure, cardiac arrest, and infections. Serious Adverse Events (SAEs) also tended to be consistent with underlying disease, except for one case of hyperparathyroidism in a patient who was treated with Lumizyme. The case was considered "possibly" related to the study drug because hyperparathyroidism is rare in infants and in Pompe disease patients, and there was no other plausible etiology for the event. Common adverse events (AEs) tended to reflect underlying disease or were AEs commonly seen with ERT infusions.

This Reviewer was unable to perform a meaningful analysis on product comparability with regard to safety or immunogenicity because of the small number of patients studied, the short duration of the Lumizyme experience, the underlying disease related morbidity, the open-label design of the study, and the lack of a head-to-head comparison of the two products. Further identification/characterization of adverse reactions under such circumstance was difficult.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Myozyme (USAN: alglucosidase alfa) is recombinant human acid alpha-glucosidase (rhGAA) produced at the 160 L scale. Myozyme marketing approval was granted on April 28, 2006 by the US Food and Drug Administration (FDA), and is labeled for use in US as an ERT for patients with Pompe disease. The Applicant is seeking marketing approval for Lumizyme (USAN: alglucosidase alfa), which is alglucosidase alfa produced at the 2000 L scale. The Applicant is seeking approval for Lumizyme through submission of an sBLA to the Myozyme BLA. If comparability could be demonstrated, Lumizyme could be approved under the Myozyme BLA as the same product.

Alglucosidase alfa is a recombinant human acid α-glucosidase (alglucosidase alfa, rhGAA). Endogenous acid α-glucosidase (GAA) is a lysosomal protein that catalyses the hydrolysis of α-1, 4- and α-1, 6-glucosidic linkages in lysosomal glycogen, leading to the complete hydrolysis of glycogen to glucose. Deficiency in the activity of acid α-glucosidase results in intra-lysosomal accumulation of glycogen, and is thought to be the cause of Pompe disease.

Alglucosidase alfa is produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells, and is one of the normal variants of the human enzyme. The rhGAA in alglucosidase alfa is an extremely complex biologic product with possible molecular diversity of up to approximately 1.5 million variants for a protein with seven glycosylation sites with up to approximately ten observed glycan variants per location.

The product is to be administered every two weeks (QOW) at a dose of 20 mg/kg of body weight, as an intravenous (IV) infusion over approximately 4 hours.

2.2 Currently Available Treatment for Indications

Myozyme is the only targeted therapy for Pompe disease approved by FDA and marketed for use in the US. Even though the Pivotal Study studied infantile-onset patients only, Myozyme was approved for use in all Pompe disease patients because there is no alternative therapy. Supportive care, such as ventilatory support and the use of mobility assistive devices (e.g., wheelchair use), remain necessary in the overall disease management of Pompe disease as the disease progresses.

The Applicant states that Lumizyme has been approved and is commercially available in more than 40 other countries, including the European Union (EU), Japan, and Canada. The European Medicines Agency (EMEA) approved the Lumizyme on April 3, 2005 with the acknowledgement that the two products are not comparable.

Myozyme has been under a drug shortage in the US since 2007. The Applicant states that demand has exceeded supply. At the time of the sBLA review, the Applicant estimated that there are 460 patients in the US with a confirmed diagnosis of Pompe disease. Of these, the minority, 20 (4%) patients are < 1 year old; 90 (20%) patients are 1-17 years old; and the majority, 350 (76%) patients are >17 years old. The Applicant is treating [redacted] (b) (4) of the 460 patients in the US with either Myozyme as commercial product, or Lumizyme under an experimental treatment protocol known as the Myozyme Temporary Access Program (the MTAP).[1] Of the [redacted] (b) (4) patients receiving alglucosidase alfa in the US, only [redacted] (b) (4) patients are receiving 160 L commercial Myozyme, [redacted] (b) (4) are receiving Lumizyme via the following ongoing clinical trials:

- Study AGLU03206 (N=39), the extension study of Late-Onset Treatment Study [LOTS Extension Study].
- Study AGLU03306 (N=4), Postmarketing Commitment PMC #7, a dose increase exploration study in patients with poor responses to treatment, including infantile-onset, juvenile-onset, and adult-onset patient populations.
- Myozyme Temporary Access Program (MTAP) (N=133), a treatment IND study, created specifically to address drug shortage of Myozyme, in which adult patients who meet specific clinical criteria can receive Lumizyme as experimental therapy.
- Emergency INDs for individual patients (N=3) to receive Lumizyme intended to treat seriously ill patients with advanced disease in whom it is felt by the treating physician that given the fragility of the patients' health they could not be without drug treatment.

Of the remaining estimated untreated [redacted] (b) (4) patients, the Applicant is aware of 73 confirmed untreated patients (3 patients are 1-17 years old; 59 patients are >17 years old; and, 11 are of unknown ages), and estimates that there are 141 patients who have a diagnosis of Pompe disease but have not come forth for treatment. Additionally, the Applicant estimates using a prevalence model that there are likely as many as 1,464 symptomatic patients in the US who may not yet be diagnosed with Pompe disease given the complexity of the differential diagnosis, and the long time that lapses between symptom onset and diagnosis.

2.3 Availability of Proposed Active Ingredient in the United States

Since only Myozyme has received an FDA approval, it is the only marketed alglucosidase alfa drug product and active ingredient in the US. Myozyme is under a drug shortage, and is under restricted distribution by the Applicant (refer to Section 2.2 Currently Available Treatment for Indication for details). At this time, Lumizyme is

1 In the Myozyme Temporary Access Program (the MTAP), Lumizyme (the 2000 L product), not Myozyme is being administered. The name "MTAP" was designated when the two products were being evaluated for comparability and the trade name Myozyme was temporarily used interchangeably for the two products. After FDA deemed the two products not comparable, the Applicant proposed a new trade name for the 2000 L product: Lumizyme.

available under Investigational New Drug (IND) 10780, and is considered an experimental therapy.

2.4 Important Issues with Pharmacologically Related Products

Acid α-glucosidase has been clinically investigated in two other formulations: (b) (4) (b) (4) These products are no longer being investigated, and patients previously treated with these formulations have been transitioned to treatment with alglucosidase alfa. The (b) (4) formulations were administered to small numbers of Pompe disease patients, so the clinical experience with these products was limited, but preliminary data from these studies suggested that ERT with rhGAA was efficacious, though both products appeared to be highly immunogenic,[2] as is the case with alglucosidase alfa.

2.5 Pre-submission Regulatory Activity

The original Biologics Licensing Application (BLA) for alglucosidase alfa was submitted under STN 125141/0, in which the Applicant described three manufacturing scales for alglucosidase alfa, defined by the bioreactor working volume at each scale (b) (4), 160 L, and 2000 L). Myozyme (alglucosidase alfa 160 L scale) was approved on 28 April 2006 based on clinical data that demonstrated a superior benefit/risk profile in 18 infantile-onset Pompe disease patients who received Myozyme, as compared to a historical control in 61 patients who received no disease-specific treatment such as enzyme replacement therapy. Marketing approval for Myozyme was granted with orphan exclusivity. Although efficacy and safety were shown in the infantile-onset patient population only, Myozyme was approved for use in all patients with Pompe disease because there was no other treatment available for the late (non-infantile) onset Pompe disease population. All clinical studies submitted to the initial BLA were performed using Myozyme.

The Applicant initially sought approval for both the 160 L and 2000 L product in the Myozyme BLA but during the review FDA noted differences in critical CMC product attributes and in animal pharmacokinetic (PK) profiles between the two products. (b) (4) At that time, animal PK biodistribution data in a GAA knock-out mice model also showed that Lumizyme had a lower activity level in the quadriceps muscle as compared with Myozyme, raising further concern about the ability of the drug to reach the target sites. With these concerns, FDA requested additional information. In response to FDA's

2 See Clinical Review for BLA 125141/0 by FDA clinical reviewer, Anne Pariser, M.D.

Information Request Letter dated November 18, 2005, the Applicant voluntarily withdrew the request for the approval of Lumizyme.

The required Myozyme dose is extremely high relative to the other lysosomal enzyme replacement therapies (to illustrate: Myozyme: 20 mg/kg IV QOW, vs. Naglazyme: 1 mg/kg IV QW and Elaprase 0.5 mg/kg IV QW). About 8 months after the original approval of Myozyme, in early 2007 the Applicant projected a drug shortage for the juvenile- and adult-onset (collectively known as the late-onset) Pompe disease patients, because the 160 L manufacturing process could not provide sufficient Myozyme to supply US patients due to unexpected demand. The Applicant submitted a manufacturing sBLA for the scaled up 2000 L manufacturing process (Lumizyme) under the Myozyme BLA on June 15 2007. Because the submission lacked critical clinical data necessary for review, including motor function response to treatment, the Applicant voluntarily withdrew the application. The Applicant resubmitted the sBLA on October 31 2007, under BLA STN 125141/75, which is the subject of this review.

2.6 Other Relevant Background Information

The disease is autosomal recessive in genetic transmission, and numerous mutations have been identified. It is an ultra rare disease that affects a world-wide orphan population including patients in the US. The estimated global incidence of Pompe disease is 1:40,000, with variations in incidence reported between different ethnic groups. Pompe disease encompasses a wide range of phenotypes, all of which include varying degrees of myopathy, but differ in the age of onset, presence of cardiohypertrophy and cardiomyopathy, extent of organ involvement, and rate of progression to death. Deficiency in the activity of acid α-glucosidase results in intra-lysosomal accumulation of glycogen, and is thought to be the cause of Pompe disease. Theoretically, replacement of the missing/defective enzyme should correct the underlying metabolic deficiency and ameliorate the disease.

Different phenotypic subtypes of Pompe patients have different natural histories. Thus, in clinical trials of Pompe disease, a well-defined study population is critical for determining the therapy's true effects. The Pivotal Study of the original BLA was conducted in classic infantile-onset Pompe disease. Classic infantile-onset Pompe disease is the most severe phenotype, with severe cardiohypertrophy and cardiomyopathy, hypotonia, hepatomegaly, and early death before the age of 2 years. The cause of death is usually cardiopulmonary failure.

Not all infantile-onset patients have as severe a course. There is *muscular variant* of the infantile-onset form of Pompe disease, which also presents with symptoms early in life, but does not include cardiomyopathy and/or cardiohypertrophy, usually progresses more slowly, and can have longer survival. So in a clinical trial, if one of the endpoints of therapy is survival, it will be necessary to differentiate these muscular variant, atypical (non-classic) infantile-onset Pompe disease infants from the classic infantile-onset patients, because the muscular variant infantile patients may have a natural potential to

survive beyond a certain age than is typical for the classic infantile-onset patients.[3] In the muscular variant infantile-onset patients, cardiomegaly does not manifest, ventricular hypertrophy is less severe, and LV outflow obstruction does not develop, all of which allow cardiac function to remain normal. Hence, the presence of cardiohypertrophy and cardiomyopathy is an important disease defining prognostic indicator. For the reminder of this review, the term "infantile-onset patients" will refer to the classic-infantile onset Pompe disease patients (i.e., it will exclude the muscular variant, atypical or "non-classic" infantile-onset patients).

In the Pivotal Study, the patients studied were infantile-onset patients who had 1) disease onset and diagnosis ≤6 months of age and 2) left ventricular cardiohypertrophy[4] defined as LVMI ≥ 65 g/m^2 or LVM-Z ≥ 2 for this age group. The other important characteristics of this study population were 1) Myozyme treatment began at ≤ 6 months of age adjusted for gestational age, and 2) because the primary endpoint analysis was ventilator-free survival, enrolled patients were not to have been dependent on invasive ventilation at baseline.

In contrast to the infantile-onset subtypes, the adult-onset subtype of Pompe disease is at the other extreme of the disease spectrum, and is typically a slowly progressive, proximal myopathy with onset as late as the second to sixth decade of life, and involves mostly skeletal muscle; patients may live for decades. Between the two extremes of the infantile-onset and the adult-onset patients is a heterogeneous group of presentations, juvenile-onset Pompe disease, which is usually without cardiac involvement, and with an intermediate progressive course of myopathy, including impairment of respiratory function. Survival is intermediate between the two other extremes but as with all other subtypes death is usually due to cardiopulmonary failure.

Prior to available treatment with alglucosidase alfa, classic infantile-onset Pompe disease was a uniformly and rapidly fatal disease, for which there were no treatments known to impact survival or disease progression. Death occurred before 1 or 2 years of age. Conducting a large scale study was impossible in this orphan population. The natural history of Pompe disease was not known due to the rarity of the disease and multiple disease subtypes. Using a placebo control was considered unethical because earlier studies using GAA preparations made by [redacted] (b) (4) had shown promising clinical results, and because the disease was rapidly and universally fatal prior to 1 to 2 years of age. These study design challenges required extensive discussions between the

3 Slonim AE, Bulone L, Ritz S, Goldberg, T, Chen, A, and Martiniuk F. Identification of two subtypes of infantile acid maltase deficiency. J Pediatr 2000: 283-5.

4 The Applicant referred to left ventricular cardiohypertrophy as "cardiomyopathy" throughout the submissions. Left ventricular cardiohypertrophy was measured by left ventricular mass index adjusted for body surface area, i.e., left ventricular myocardial index [LVMI]. The Applicant also defined left ventricular cardiac hypertrophy as LVMI >2 SDs from the normal mean in patients less than 1 year old. Clinically speaking, however, left ventricular cardiohypertrophy does not always associate with cardiomyopathy, or vice versa. Hence for the remainder of this review document, this Reviewer will use the term "cardiohypertrophy" to more accurately reflect what was measured: LVMI and LVM-Z scores.

Applicant and the Agency, which took place over a number of years during drug development, and it was ultimately agreed that a historical control could be used for the Pivotal Study, but the historical control study population had to be matched to the Pivotal Study population to ensure that the two populations were comparable in baseline status, disease characteristics and prognosis to allow for a meaningful comparison in clinical response to drug treatment.

The primary efficacy endpoint for the Pivotal Study was the proportion of patients alive and not dependent on invasive ventilator support (ventilator-free survival)[5] at 18 months of age, as compared to a matched historical control study cohort. This endpoint was chosen because survival was a clinically meaningful outcome that was easily observed, unequivocal, and well documented—all of these being important characteristics in a retrospective, chart analysis, historical study, which served as the control. In the historical control study (AGLU-004-00), it was found that only 1 out of the 61 matched patients studied survived until at least age 18 months (2% 18-month survival rate) without treatment. In comparison, in the Pivotal Study with Myozyme treatment, 15 out of the 18 treated patients survived and were independent of invasive ventilator support at age 18 months (83% ventilator-free survival rate at 18 months). In actuality, the survival benefit was probably less robust than this dramatic difference observed and stated (2% untreated vs. 83% treated) for methodological and statistical reasons (for details see Statistical Review by Lisa Kammerman, Ph.D., and Clinical Team Leader's Review by John Hyde, M.D., Ph.D.) but it was still felt that the data strongly suggested an improved outcome seen among patients treated with Myozyme compared with patients not treated in the historical control study.

Allergic (or hypersensitivity reactions) and immunogenicity have been the main focus in the alglucosidase alfa safety review. The current Myozyme labeling contains a boxed warning about the risk of life-threatening anaphylactic reactions, including anaphylactic shock associated with its use. Anaphylaxis is a multi-organ phenomenon. In clinical trials and expanded access programs with Myozyme, approximately 14% of patients treated developed infusion reactions that involved at least two of three body systems (cutaneous, respiratory, or cardiovascular), suggestive of anaphylactic reactions. The labeling also states that serious/severe infusion related hypersensitivity reactions require that patients be monitored closely during administration of Myozyme, especially in patients with advanced Pompe disease who usually have compromised cardiac and respiratory function, which may predispose them to a higher risk of severe complications from infusion reactions.[6] Less severe infusion-related hypersensitivity reactions occurred

5 "Ventilator-free survival" (as opposed to survival) was chosen for the endpoint for study AGLU01602 because in the historical setting, parents/caretakers might have been reluctant to place their infants on ventilator support since there was no treatment available at the time, other than supportive care, whereas in Study AGLU1602, parents might have been more likely to place their infants on ventilatory support now that there was a potential treatment for Pompe disease. Since ventilator support placement could have added additional survival benefits not attributable to Myozyme treatment--giving the Myozyme treated group an "advantage" in survival--it was decided that "invasive ventilator free survival" was to be used for the Study AGLU01602 cohort.

6 The product labeling also contains warning about risk of acute cardio-respiratory failure that required

in about half (51%) of patients treated with Myozyme in clinical studies. The primary clinical reviewer (A. Pariser) for the original BLA concluded that Myozyme appeared to be highly immunogenic. The majority of patients (89%) in the 2 main clinical trials tested positive for IgG antibodies to alglucosidase alfa, using an enzyme-linked immunosorbent assay (ELISA) and radioimmunoprecipitation (RIP) assay for alglucosidase alfa-specific IgG antibodies. Titers were high. Half of the patients had antibody titers > 10,000 (an arbitrary cut off); the highest titer peaked at 409,600. Table 1 shows, by individual patient listing, peak titers measured based on available data at the time of the original BLA review of the Pivotal Study. These data show that patients in the higher dose group (40 mg/kg IV QOW) had higher IgG titers compared with the lower dose group (20 mg/kg IV QOW).

Table 1 IgG titers in the Pivotal Study patients at the time of the original BLA review writing (copied electronically from Myozyme BLA FDA clinical review by A. Pariser, MD)

(b) (4)

[redacted]

intubation and inotropic support that was observed in one infantile-onset patient with underlying cardiac hypertrophy, possibly associated with fluid overload with intravenous administration of Myozyme.

In the original clinical review, it was also found that patients with high-risk mutations and high antibody titers appeared to more likely to have poor clinical outcomes than patients with low-risk mutations and lower antibody titers. Particularly worrisome was that in two patients who initially achieved gains in motor scores, they lost those motor milestones coinciding with rising and markedly elevated antibody titers (and both these two patients later died), suggesting that high antibody titers might have inhibited or neutralized the enzyme's activity/efficacy. Patients who developed sustained titers ≥ 12,800 of anti-alglucosidase alfa antibodies appeared to have a poorer clinical response to treatment, or may have lost motor function as antibody titers increased. The Myozyme product labeling recommends that patients on treatment who experience a decrease in motor function be tested for neutralization of enzyme uptake or activity. Though not explicitly stated, the intention for testing is so that the etiology of loss of efficacy could be delineated, such as due to the development of inhibitory antibody, and that immune tolerance regimens may be considered, though the data on the efficacy and safety of immune tolerance regimen are still in the development stage.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

CMC data have been reviewed by FDA Product Reviewer, Frederick Mills, Ph.D. Dr. Mills notes differences in a number of the critical product attributes for Myozyme that are in the direction of greater clinical potency/efficacy relative to Lumizyme. (b) (4) [redacted] For details, please see the final CMC review.

3.2 Animal Pharmacology/Toxicology

Nonclinical data have been reviewed by FDA Animal Pharmacology Reviewer, Ke Zhang, Ph.D., who stated the following conclusions:

- In the current manufacturing sBLA submission, the Applicant submitted the following non-clinical studies: 1) Pharmacology studies (#05-0823Pga and #06-0276), and 2) Pharmacokinetic studies (#05-0858Pga, #05-0859Pga, #06-0273, and #06-0274). The animal model used in these studies was a GAA knockout mouse model, which more closely resembles non-infantile onset Pompe disease in humans rather than infantile-onset Pompe disease.
- There is no valid animal model for infantile-onset Pompe disease.
- The pharmacokinetic equivalence between the Myozyme and the Lumizyme were not consistently demonstrated in the pharmacokinetic and biodistribution studies.
- Therefore, due to a lack of adequate information, an approval of Lumizyme cannot be recommended from a nonclinical standpoint. The final approval of Lumizyme should be based on clinical outcomes.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

In addition to Study AGLU-004-00, a retrospective, chart-review, observational, natural-history study of historical cohort used as control in the original BLA (the Historical Control Study), the Applicant submitted data from four clinical studies, and one expanded-access program (EAP).

Of the five studies submitted, four are relevant to the review of Lumizyme, including the following:

- AGLU01602 (Pivotal Study)
- AGLU02403 (Extension Study of the Pivotal Study)
- AGLU01702 (Study 1702)
- AGLU02203 (EAP)

The fifth study submitted (Study AGLU02804) is a study of late (non-infantile) onset Pompe disease patients, which is not pertinent to this review on infantile-onset patients. The four studies reviewed are summarized in Table 2, in Section 4.2 Table of Clinical Studies. Only patients whose data are relevant to this clinical review are referenced in the table. The reader is referred to Table 2 in conjunctions with Section 4.3 Review Strategy for the justification of how patients were selected for the analysis of this review.

4.2 Table of Clinical Studies

Table 2 Table of clinical studies

Study	Number of patients to be analyzed (N=27)	Median Age ± SD at first infusion [d]	Study design	Dosage	Start date-end date	Duration of study
AGLU01602 (Pivotal Study)	N=18	First 160 L at 5 ± 2 months	A randomized, open-label, multi-national, dose-ranging study of the safety, efficacy, PK, and PD of Myozyme treatment in patients ≤ 6 months of age with infantile-onset Pompe disease	1:1 Randomized to 20 mg/kg QOW, or 40 mg/kg QOW	26 May 2003-15 Jun 2005	52 weeks
AGLU02403	16 of the 18 patients from Study AGLU01602 [a]	First 2000 L at 28 ± 5 months	Open-label extension study of AGLU01602	Same as dose assigned in Study AGLU01602	20 Jun 2005-15 Jun 2006	52 weeks
AGLU02203 (EAP)	N=7 [b]	First 2000 L at 4 ± 2 months First 160 L at 13 ± 5 months	Multi-center US Expanded Access use of Myozyme in patients with infantile-onset Pompe disease	20 mg/kg QOW	16 Dec 2003-31 Jul 2006	52 weeks
AGLU01702	N=2 [c]	First 160 L at 5 ± 2 months First 2000 L at 31 ± 15 months	Open label, multi-national study of the safety, efficacy, PK, and PD of Myozyme treatment in patients > 6 and ≤ 36 months of age with infantile-onset Pompe disease	20 mg/kg QOW (eligible patients could receive 40 mg/kg QOW after 6 months) [e]	19 Feb 2003- 14 Jul 2006	52 weeks

[a] Of the original 18 patients in the pivotal study (AGLU01602), 16 patients switched to Lumizyme during the extension study (AGLU02403).

[b] Seven patients in Study AGLU02203 matched the study population of the Pivotal Study (see Figure 1). Patient 2203-001792 received a single infusion of Myozyme followed by 34 weeks of Lumizyme, but for simplicity, he will be considered a Myozyme naïve patient who received only Lumizyme during the study.

[c] Two patients in Study AGLU01702 matched the study population of the Pivotal Study (see Figure 1), and were switched from Myozyme to Lumizyme during the study.

[d] Median age at first infusion was calculated by this reviewer for only those patients who were matched to the Pivotal Study population

[e] Both patients had an increase from 20 to 40 mg/kg IV QOW during the 160 L treatment experience. One of the two patients was only on the 40 mg/kg IV QOW regimen during the 2000 L experience.

4.3 Review Strategy

Thus far the only population in whom safety and efficacy have been established for alglucosidase alfa is the classic infantile-onset Pompe disease patients who received Myozyme in the Pivotal Study. Thus, the experience of the Pivotal Study patients who received Myozyme could be used as the comparator against whom the experience of patients who received Lumizyme was compared. In that respect, to qualify as a comparable population with the Pivotal Study population, a study population must match the Pivotal Study population in baseline characteristics, disease prognosis, and treatment experience. In other words, Patients must meet the following criteria (Figure 1), which were the inclusion criteria for the Pivotal Study population:

Figure 1 Criteria used by this Reviewer to establish a "matched" population with the Pivotal Study population

Patient must:

1. Have infantile-onset Pompe disease (i.e., be diagnosed before 6 months of age).
2. Have left ventricular cardiohypertrophy, defined as LVMI $\geq$ 65 g/m^2, or LVM-Z score $\geq$ 2 for this age group.
3. Receive first infusion before 7 months of age.
4. Not be on invasive ventilator support at baseline.

The following describes the patient selection in the relevant studies:

1. Pivotal Study and its Extension Study: Eighteen patients were enrolled in the Pivotal Study reviewed in the original BLA. All 18 patients received Myozyme during the Pivotal Study. Of the original 18 patients, 2 did not enroll in the open-label extension study (Patient 1602/2403-5202305 died at age 20 months; Patient 1602/2403-6002303[7] was enrolled in an expanded access protocol [EAP] and died at 32 months). The remaining 16 patients enrolled in the Extension Study, in which they switched from Myozyme to Lumizyme. Because Study AGLU02403 was the Extension Study for the Pivotal Study AGLU01602, data from the 2 protocols were combined and treated as one continuous set of data for the purpose of this supplement, and will at times be referred to as Study AGLU01602/02403 (or the Pivotal-Extension Study). This review evaluated the patients' clinical

7 Patient 1602/2403-6002303 completed Study AGLU01602 after treatment with Myozyme. The patient then transitioned into the International EAP and is believed to have received treatment with Lumizyme based on shipping records maintained by the Applicant. Because the International EAP did not require collection of data, efficacy and exposure data during treatment with Lumizyme are not available for this patient. Survival data, however, became available for the patient after his death was reported to the Applicant's Pharmacovigilance Department via a Serious Adverse Event (SAE) report 3 months after entering the EAP. The patient was included in the survival analysis of "switched" patients, but was excluded in other efficacy analyses since data on other outcomes were not collected.

response after they were switched to Lumizyme as compared to their previous response on Myozyme.

2. EAP, or Study AGLU02203, was a US expanded access program in which patients received Lumizyme. This Reviewer identified 7 patients who matched the study population of the Pivotal Study (see Figure 1). Of note, the EAP was instituted to allow patients who did not qualify for any other Genzyme-sponsored clinical studies to receive Lumizyme while Myozyme was under review. After Myozyme was approved and became commercially available, patients ended their participation in EAP and transitioned to the commercial product Myozyme. There was no formal data collection after the study ended, but at the request of the Division for the purpose of this review, the Applicant obtained additional clinical data on these patients by conducting queries of the company's Pharmacovigilance (PV) database, and making retrospective inquiries via email/telephone calls to the treating physicians. Since these patients received Lumizyme only during the study, their experience on Lumizyme could be compared to that of the experience on Myozyme in the Pivotal Study population. This comparison formed the most important analysis between the two products in this clinical review, i.e., it allowed for comparison between alglucosidase-alfa treatment naïve patients who were initially treated with Lumizyme vs. Myozyme.

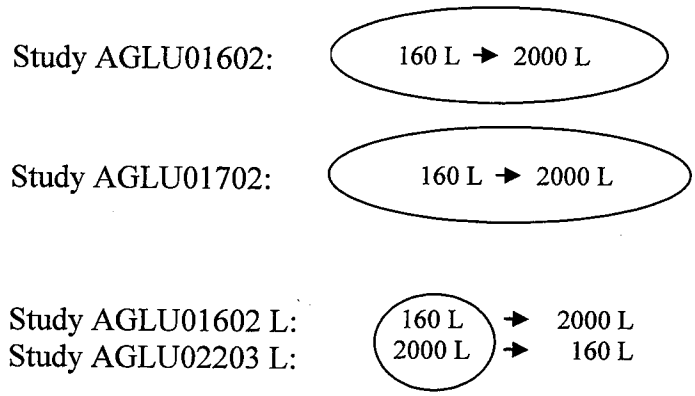
3. Study 1702 was a study in which of the 21 patients studied, 15 patients received Myozyme initially, and switched to Lumizyme for various treatment durations in the study. This Reviewer identified 2 patients who matched the study population of the Pivotal Study (see Figure 1). This review analyzed the data from these 2 patients and compared their clinical response while on Myozyme and after switching to Lumizyme.

The following table summarizes the sample size of the studies and the treatment experience.

Table 3 Number of "matched" patients analyzed in this sBLA review, and their treatment experience

Study	Number of patients to be analyzed	Experience on alglucosidase alfa
AGLU01602/02403 (Pivotal Study and Extension Study)	18 patients	Myozyme → Lumizyme
AGLU01702 (Study 1702)	2 patients	Myozyme → Lumizyme
AGLU02203 (EAP)	7 patients	Lumizyme (during the study) → Myozyme commercial product (after the study ended)
Total number of patients available for analysis in this sBLA clinical review	27 patients	

Figure 1 Schematic of comparisons of Myozyme vs. Lumizyme (comparisons are circled)



In sum, 27 patients' data were analyzed in this sBLA clinical review in the effort to establish clinical comparability. The major limitations of the data included the small sample size available for making the comparison, relatively short duration on Lumizyme treatment compared with Myozyme treatment, and the fact that none of the studies were designed to demonstrate head-to-head comparisons between the two products.

4.4 Data Quality and Integrity

Multiple clinical information requests were sent to the Applicant to obtain additional information to allow for completion of the review. For example, on 27 December 2007 the Division requested information regarding the data from EAP, including the following: 1) date of first patient enrollment and last patient completion; 2) complete study protocol, including enrollment criteria, and study duration; 3) baseline patient characteristics of all 33 patients, including cardiomyopathy (cardiac hypertrophy) status, age of onset of clinical symptoms of Pompe disease, deficiency in GAA activity, age of first infusion, and cross-reactive immunologic material (CRIM) status; 4) duration of treatment, total number of infusions received, date of first and last infusion, and whether the study treatment was completed or discontinued (and if discontinued, include reason for discontinuation) for all 33 patients; and, 5) most recent clinical status on selected (matched) patients such as survival, ventilator status, continuation on therapy, duration of treatment, time of last follow up, and any other relevant clinical information such as motor status. FDA's CMC reviewers also made multiple requests for important information for review, e.g., which manufacturing lots of the alglucosidase alfa products were used for which patients for what periods of time during the clinical studies. The Applicant submitted the requested information accordingly.

The overall data quality and integrity appeared acceptable. There was no Division of Scientific Investigations (DSI) inspection conducted for the purpose of this sBLA, as inspections had been conducted and found to be satisfactory (University of Florida and Duke University) for the original BLA review. Moreover, given that the results are inconclusive, approval will not be based on the studies that have been submitted.

4.5 Compliance with Good Clinical Practices

The Pivotal Study and its Extension Study, and Study AGLU01702 were conducted under Good Clinical Practices (GCP) standards. The EAP was not a GCP study.

4.6 Financial Disclosures

Financial disclosures were included in the original BLA submission. For the Pivotal Study and Study AGLU01702, notable findings were the following:

- (b) (6) had a financial interest in the outcome of the study. A $200,000 payment was due to (b) (6) upon approval of the Myozyme BLA, and (b) (6) has received over $1.5 million from the Applicant, including a payment upon filing of the Myozyme BLA, research grants and fellowship funding. These payments do not reflect monies paid directly to the Principal Investigator (PI) (b) (6), who accepted payments (honoraria) from the Applicant totaling $5,000.

- The Principle Investigator at [redacted] (b) (6). [redacted] (b) (6) reported acceptance of honoraria and laboratory support grants of more than $40,000 from the Applicant.

For this submission, FDA has obtained additional financial disclosure information, listed by investigators and institutions in Figure 2:

Figure 2 Additional financial disclosures relevant to this sBLA

(b) (6)

[redacted]

(b) (6)

(b) (6)

[redacted]

The Reviewer cannot conclude whether these financial disclosures impacted study integrity, but notes that the primary comparison was ventilator-free survival, which is an easily measured outcome measure not thought to be subject to bias. Moreover, approval will not be based on these inconclusive results, and approval for Lumizyme will be based on the LOTS data.

5 CLINICAL PHARMACOLOGY

See Clinical Pharmacology Review by FDA Clinical Pharmacology Reviewer, Tien-Mien Chen Ph.D. for details. The Reviewer concluded that based on the clinical PK data provided for the Extension Study, the Applicant did not demonstrate that Lumizyme is bioequivalent to Myozyme. Also, it is not clear how the immunogenicity profile for Lumizyme compares to that for Myozyme since the immunogenicity data for Lumizyme are lacking.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The current product label for Myozyme states:

"MYOZYME (alglucosidase alfa) 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 in other forms of Pompe disease has not been adequately studied to assure safety and efficacy."

The Applicant has not sought changes to the indication statement of the product labeling based on the results submitted in this sBLA.

6.1.1 Methods

The clinical study reports for the Pivotal-Extension Study, Study 1702, and the EAP, and their corresponding electronic datasets were analyzed. The goal was to determine 1) how patients responded after they switched to Lumizyme from Myozyme (in the Pivotal-Extension Study, and Study 1702), and 2) how the clinical outcomes compared between patients who initially received Lumizyme in the EAP and those who received Myozyme in the Pivotal Study (see Figure 2, Section 4.3 Review Strategy).

Analysis of data was severely limited by the amount and type of data available, due to the fact that these clinical studies were not designed to provide head-to-head comparisons of the two manufacturing scales. Specifically, the data had the following limitations:

- The exposure on Lumizyme was short (approximately 7-8 months).
- The number of patients available for comparison was small (N=7 in the EAP; N=18 in the Pivotal Study; N=2 in Study 1702).
- The EAP was not a Good Clinical Practice (GCP) study, and data regarding ventilator free survival status were not prospectively collected. They were collected by querying of the Applicant's postmarketing Pharmacovigilance (PV) database, and inquiries via phone calls/emails to physicians by the Applicant more than a year after the study had ended.
- Attempt to correlate clinical outcomes with product specification was impossible due to the fact that different patients received different manufacturing lots of Drug Substance (DS) and Drug Product (DP), and that patients were treated with different lots for different amounts of time, and in various random orders.

6.1.2 General Discussion of Endpoints

The most important efficacy endpoint was ventilator-free survival. Data on motor development were used as a supportive clinical endpoint, and data on left ventricular size were used as a supportive and PD endpoint.

6.1.3 Study Design

Study AGLU01602 (the Pivotal Study) was an international, randomized, historical cohort controlled, dose-ranging, open-label, 52-week study of the safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of Myozyme in 18 patients with classic infantile onset Pompe Disease who were less than 7 months of age at enrollment. Patients were randomized 1:1 to either 20 mg/kg IV every other week (QOW) or 40 mg/kg IV QOW treatment. Patients had symptom onset and definitive diagnosis of Pompe disease by age $\leq$ 6 months, and received the first dose of Myozyme by age $\leq$ 6 months (adjusted for gestational age). Patients also had left ventricular cardiohypertrophy adjusted for body surface area (defined as left ventricular myocardial index [LVMI] $\geq$ 65 g/m^2 or LVMI-Z[8] $\geq$ 2 for this age population), and were not dependent on invasive ventilation at baseline. The primary efficacy endpoint for the study was the proportion of patients alive and free of invasive ventilator support[9] at 18 months of age, as compared to a historical control group of matched patients of similar age and disease severity in Study AGLU-004-00. All 18 patients' data were analyzed.

Study AGLU02403 (the Extension Study) was an open-label, 52-week, extension study of patients with infantile-onset Pompe disease who were previously enrolled in and completed the Pivotal Study. Sixteen of the 18 patients enrolled in the Pivotal Study were treated with Lumizyme in the Extension Study, and continued to receive the same dose that they were assigned to in the Pivotal Study. The Extension Study provided longer term data on alglucosidase alfa treatment, up to approximately 3 years of age in these 16 patients. There was no comparator treatment given the almost universal fatal outcome of untreated classic infantile-onset patients and the lack of any other approved treatment. The follow up data from the Extension Study provided important insights into Myozyme's longer term effects.

Study AGLU01702 (Study 1702) was an international, open-label, non-randomized, uncontrolled, 52-week study of the safety, efficacy, PK, and PD of Myozyme treatment in 22 patients with infantile-onset Pompe disease. Patients initially received a dose of 20 mg/kg QOW, and after at least 26 weeks of treatment with alglucosidase alfa, patients were evaluated to determine whether they met at least one of the criteria for augmentation to a maximum dose of 40 mg/kg QOW. Eight patients qualified for dose augmentation and received the 40 mg/kg QOW (from a minimum of 20 doses to a maximum of 52 doses). Fifteen patients in the study were "switched" patients: they were initially treated with Myozyme and then switched to Lumizyme. Of these 15, this Reviewer identified 2 patients who matched the Pivotal Study population (see Figure 1). The data on these two matched patients were analyzed.

Study AGLU02203 (the EAP) was a US open-label, 52-week expanded access program (EAP) of Lumizyme used to treat infantile-onset Pompe disease patients for whom there was no alternative treatment because they did not qualify for any other Genzyme-sponsored studies.

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8 The interpretation of LVMI Z-score is similar to the interpretation to LVM Z-score. An LVMI Z-score of 4 means that the patient's LVMI is 4 standard (SDs) above the mean LVMI score of a body surface-matched normal cohort. For the rest of this review, LVMI Z-score will be referred to as LVM Z-score. Please refer to Section 6.1.4.3.3 Left Ventricular Myocardial Index for additional discussion on the interpretation of the LVM Z-score.

9 The term "ventilator dependence" does not include brief periods of ventilator support in association with medical procedures or for management of a temporary acute illness.

Patients received Lumizyme at a dose of 20 mg/kg QOW. Patients were asked to provide samples, on a voluntary basis, for laboratory evidence of Pompe disease diagnosis and CRIM status. Of the 33 patients in the study, 7 patients matched the study population of the Pivotal Study (see Figure 1), and their data were analyzed. After their participation in the EAP, patients switched to the commercial Myozyme product once Myozyme was approved in April 2006.

Study AGLU-004-00 (Historical Control Study) was "an international historical cohort study designed to characterize the natural history of disease progression in untreated patients with infantile-Pompe disease. Historical data were derived from retrospective review of the patients' medical records. The study sites searched for cases of Pompe disease, living or dead, who had not been treated with enzyme replacement therapy. To be enrolled in the study, patients were required to have a clinical diagnosis of infantile-onset Pompe disease and onset of symptoms by 12 months of age (corrected for gestation age). A total of 300 cases were screened, 172 patients met eligibility criteria, and 168 of these patients were known not to have received exogenous enzyme replacement. For comparison to the Pivotal Study population, a subset of 62 patients was selected from within the 168 patients in the Historical Control Study cohort based on screening criteria adapted from Pivotal Study. This subgroup is known as the historical control subgroup, and was designed to select a control population that most closely matched the study population of the Pivotal Study. Inclusion criteria for the historical control subgroup included age at first symptoms and confirmed diagnosis at ≤ 6 months of age and presence of cardiohypertrophy by 26 weeks of age (LVMI ≥ 65 g/m^2). Exclusion criteria included any known ventilator use between 0 and 6 months of age. Most of the cases were born within the past 20 years, although 17 of the 168 were born before 1985 (and the Applicant found that patients from earlier years had worse prognosis, probably due to availability of less modern medical support). The survival experience for the entire historical cohort was poor with a median age of death at 8.7 months, but it was noteworthy that nearly one quarter survived to one year, and a small percentage also lived past two years.

In the historical control study, of the 61 patients with a known date of death in the historical control subgroup, one patient survived beyond age 18 months (2% survival, 95% CI [0%, 9%]), and median survival was 7.5 months (range 0.3 to 43.9 months). Although no historical comparison could provide the certainty of comparison as, for example, a placebo-control group, it appeared that survival in the historical control at 18 months provided a reasonable comparator for ventilator-free survival in Study AGLU01602 treatment group."[10]

10 This summary of the historical control study was taken from the FDA Clinical Team Leader's Review by John Hyde, M.D., Ph.D. of the original BLA review

6.1.4 Efficacy Findings

6.1.4.1 Patient Selection and Baseline Demographics

Study AGLU01602/02403 (Pivotal Study and Extension Study)

Eighteen patients were studied, and they had symptom onset and diagnosis before the age of 6 months. All patients received their first Myozyme infusion ≤ 6 months of age, adjusted for gestational age.

The age at symptom onset, diagnosis, and first infusion are summarized in Table 4. Individual patient data can be found in the Appendix.

Table 4 Pivotal-Extension Study patient age at symptom onset, diagnosis and first Myozyme infusion

Age at symptom onset, unadjusted for gestational age	Range of age at symptom onset: 0→5.4 months Median age at symptom onset: 1.0 month (±1.8 SD)
Age at diagnosis, unadjusted for gestational age	Range of age at diagnosis: 0.2→6.8 months (unadjusted for gestational age). If adjusted for gestational age, all ages of diagnosis would have been ≤ 6 months of age. Median age at diagnosis: 4.4 months (± 2.2 SD)
Age at first Myozyme infusion, adjusted for gestational age	Range of age: 1.2 → 6.1 months Median age at first infusion: 5.3 (± 1.7 SD)

All but three patients had baseline echocardiograms. For the three patients who did not (Patients 1602/2403-6001302, 1602/2403-6002303, 1602/2403-0203318) their first echocardiogram measurements were recorded after initiation of treatment, at Weeks 4, 8, and 4, respectively. At baseline, all 18 patients had left ventricular hypertrophy, indicated by their initial LVM-Z scores of > 2 (rounded to whole numbers). All except Patient 1602/2403-6003315* had LVMI ≥ 65 g/m^2. See Appendix for individual patient data.

Majority of the patients (78%) were CRIM positives; 4 patients (22%) were CRIM negatives. See Appendix for individual patient data.

Patients were randomized in a 1:1 ratio to receive IV infusion of Myozyme at a dose of either 20 mg/kg QOW or 40 mg/kg QOW. There was no dose increase from 20 mg/kg QOW to 40 mg/kg QOW in patients who were randomized to the 20 mg/kg QOW group.

Study 1702

Of the 22 patients studied, the Applicant selected 15 patients for consideration for this sBLA because they were patients who switched from Myozyme to Lumizyme. Of these 15 patients, this Reviewer identified 2 patients were identified as matched patients to the Pivotal Study population based on the criteria listed in Figure 1; the remaining 13 patients did not qualify as a comparable study population based on the fact that they received their first dose of Myozyme later than the cutoff age of 6 months, and therefore were not analyzed in this review.

The two selected patients were not dependent on invasive ventilator support at baseline. One patient was CRIM positive, and the other was CRIM negative. Both patients had left ventricular cardiac hypertrophy at the start of the study. Their demographic data by individual patients can be found in the Appendix.

Table 5 Study 1702 patient age at symptom onset, diagnosis and first Myozyme infusion

Age at symptom onset, unadjusted for gestational age	Range of age at symptom onset: 1.5→ 3 months Median age at symptom onset: 2.3 months (±1.1 SD)
Age at diagnosis, unadjusted for gestational age	Range of age at diagnosis: 1.5→6.6 months (unadjusted for gestational age). If adjusted for gestational age, all ages of diagnosis would have been ≤ 6 months of age. Median age at diagnosis: 4.1 months (± 3.6 SD)
Age at first Myozyme infusion, adjusted for gestational age	Range of age: 3.7 → 6.1 months Median age at first infusion: 4.9 months (± 1.7 SD)

EAP

There were 33 patients enrolled in the EAP study. Of the 12 patients that the Applicant selected for consideration (based on the age at the time of first Lumizyme infusion being between 1 month to 3.5 years, and they were infantile-onset patients), this Reviewer selected 7 patients for analysis based on the matching criteria listed in Figure 1. Reasons for the Reviewer's excluding the remaining 5 of the 12 patients that were selected by the Applicant are summarized in the table below:

Table 6: Reasons for excluding 5 of the 12 of the Applicant's selected patients for analysis

Patient ID	Reason(s) for exclusion
2203-001512	1st infusion was later than 6 months of age
2203-226526	Patient was invasive ventilator dependent at baseline
2203-173513	There were no echocardiogram recordings at any time during the study
2203-001794	1st infusion was later than 6 months of age
2203-193795	1st infusion was later than 6 months of age

The range of age at first infusion was between 0.5 to 6 month of age (calendar age; gestational age was unavailable), and the median age was 4 (± 2.2) months of age. Though the age at disease onset and diagnosis were unknown, it would be reasonable to assume that both were before first dose of Lumizyme treatment, i.e., ≤ 6 months of age. Four patients' CRIM status was not known, one patient was CRIM positive, and two were CRIM negative. All patients had cardiohypertrophy at baseline. No patient was dependent on invasive ventilator support at baseline. All patients were on the 20 mg/kg IV QOW dose of Lumizyme until the study end. After the study, the patients switched to commercial Myozyme treatment.

Table 7 EAP: demographics of the 7 matched patients

Patient ID	Age at first infusion (months), calendar age	CRIM Status
2203-001521	0.5	POSITIVE
2203-013511	0.5	NEGATIVE
2203-030759	2.3	NEGATIVE
2203-190510	4	Not known
2203-001792	4.6	Not known
2203-021783	5.3	Not known
2203-001776	6	Not known
	Range of age at first infusion: 0.5→6 Median age of first infusion ± SD: 4 ± 2.2	

All seven patients in the EAP were ERT naïve prior to starting Lumizyme. As a group, they were younger at first Myozyme infusion than patients in the other two studies: the median age at first infusion was 4 months for the EAP patients as compared to 5.5 months for the Pivotal-Extension Study, and 6 months for Study 1702. Baseline/Screening LVMI and LVM-Z scores for the 7 matched patients in the EAP are shown in the following table.

Table 8 EAP: Baseline LVMI and LVM-Z for the seven matched patients selected for analysis

Patient ID	LVMI	LVM-Z
2203-013511	88.0	2.8
2203-030759	141.0	5.1
2203-190510	187.9	6.3
2203-021783	226.8	8.0
2203-001521	305.7	8.4
2203-001776	823.1	12.1
2203-001792	1048.4	13.0
Range Median ± SD	88.0→1048.4 226.8 ± 375.9	2.8→13.0 8.0 ± 3.7

Reviewer's comment: The Applicant suggested that the EAP population had a worse disease prognosis as compared to the Pivotal Study population because the EAP population baseline cardiac hypertrophy was worse. The Reviewer cautions against this interpretation given that there were significant differences in the collection methods of echocardiogram readings between the studies. In the Pivotal Study, there was one central reader and one protocol; the central reader was blinded until Week 52, and LVMI was calculated via 2D mode measurements. In the EAP, readings were not done in a standardized manner; results were measured and interpreted by different readers at different sites using local site protocols, and LVMI was calculated via either the 2D mode or the M-mode. These methodological differences in echocardiogram readings preclude the ability to make such a direct comparison of the LVMI scores between the two study populations.

In sum, based on the analysis of patient demographics above, a total of 27 infantile-onset patients matched for age and baseline characteristics were selected for analysis for this review, and they are listed in Table 9.

Table 9 Listing of the 27 "matching" patients analyzed in this clinical review

Pivotal-Extension Study
1602/2403-6003315
1602/2403-8103319
1602/2403-8101313
1602/2403-8304314
1602/2403-0202308
1602/2403-0201301
1602/2403-0102309
1602/2403-5202305
1602/2403-8305312
1602/2403-0203318
1602/2403-2101316
1602/2403-8102317
1602/2403-6001302
1602/2403-5204310
1602/2403-5203306
1602/2403-0101307
1602/2403-6002303
1602/2403-0103311
Study 1702
1702-0107420
1702-8102404
EAP
2203-001521
2203-013511
2203-030759
2203-190510
2203-001792
2203-021783
2203-001776

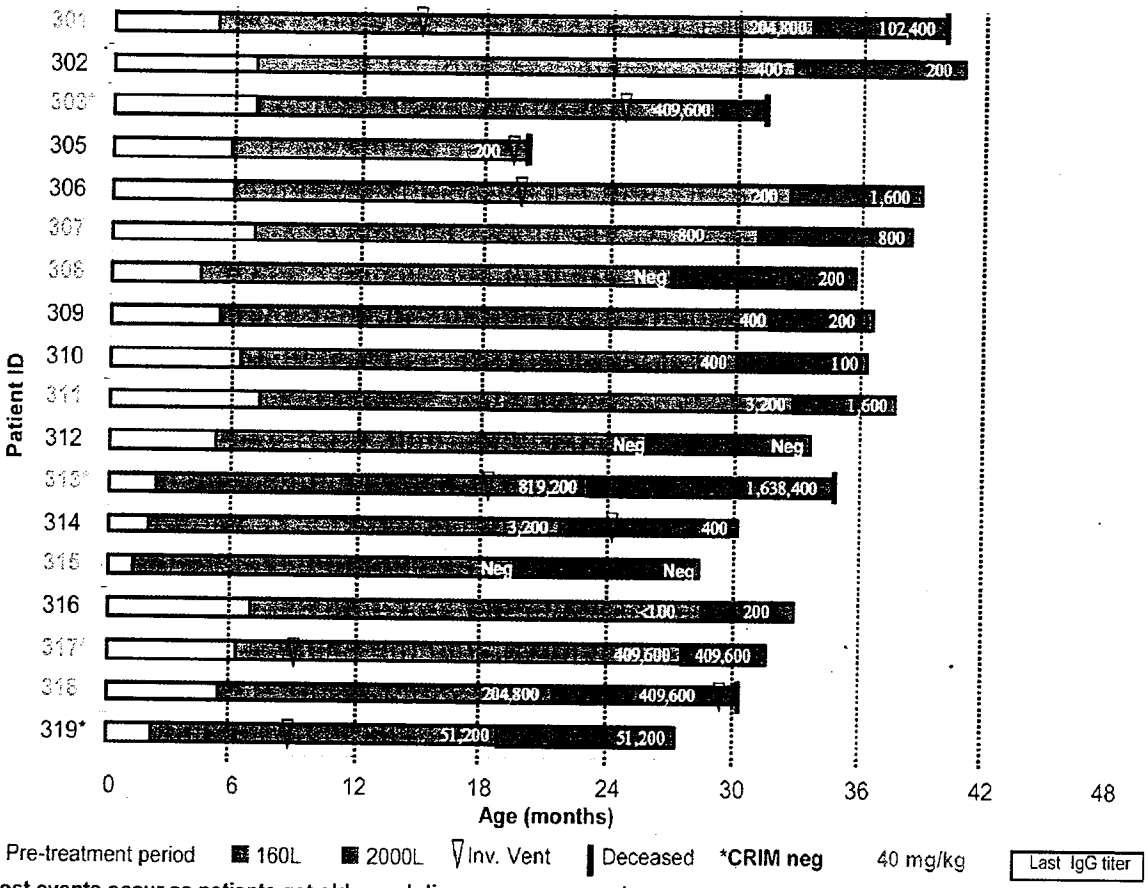
6.1.4.2 Treatment Exposure

The following figures summarize the patient's treatment exposures and ventilator free survival outcomes on treatment with the 2 scaled products (in the following Figure). In these figures it appears that for the Pivotal Study and Study 1702, the patients' calendar age rather than their gestational adjusted age was used to demarcate the time of first study drug infusion. So while it may appear that some of the patients started treatment later than 6 months of age, in fact all patients began their first treatment before 6 months of age when adjusted for gestational age. For the EAP, since patients' gestational age information was not available, their calendar age was

used. This Reviewer was able to independently verify the Applicant's summary of the treatment experience by examining the data from the electronic datasets in the clinical study reports.

Figure 3 Patient exposures to Myozyme (160 L) and Lumizyme (2000 L), and timing of events of ventilator-free survival (copied electronically from the Applicant's submission)

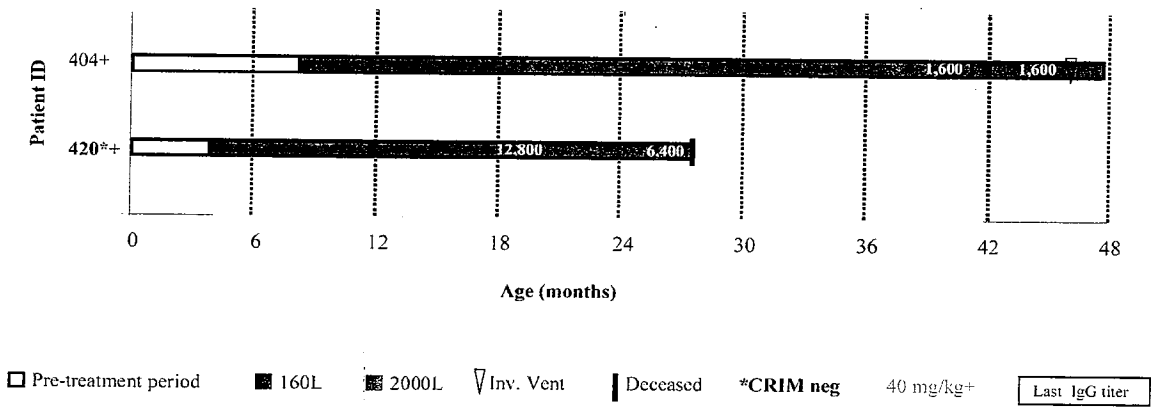
AGLU01602/02403 Patient Exposure and Timing of Events



Most events occur as patients get older and disease progresses:[1]
3 events before age 16.6 months vs. 11 events after age 16.6 months (mid point of average age at study end)

[1] Last titer available during the study at the end of each exposure scale is shown

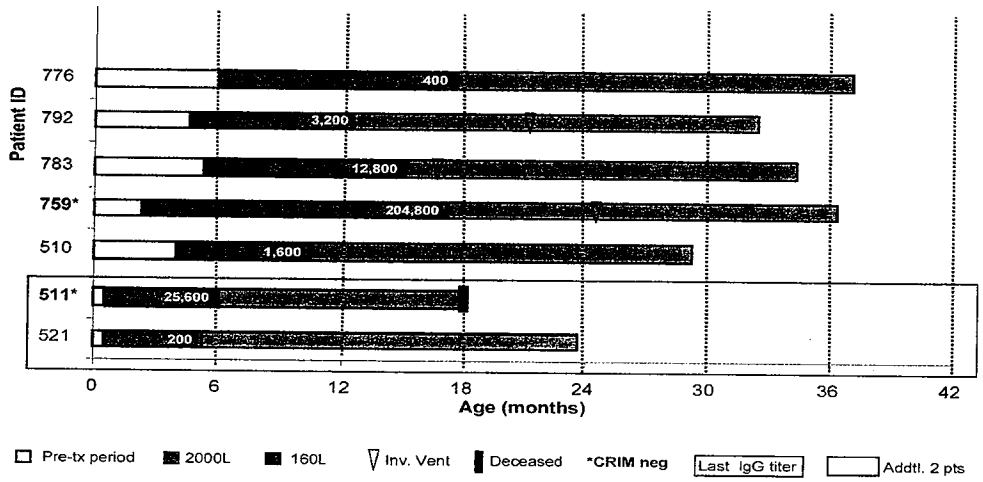
AGLU01702 Patient Exposure and Timing of Events[1]



[1]Last titer available during the study at the end of each exposure scale is shown

+Patients initiated Myozyme at a dose of 20 mg/kg on the 160 L scale and then increased dose to 40 mg/kg on 160 L scale after 71 weeks for Patient 404 and 60 weeks for Patient 420. Dose increase was maintained for both patients after switching to the 2000 L scale.

AGLU02203 Patient Exposure and Timing of Events[1]



Last titer available during study at end of 2000 L exposure is shown

As graphically demonstrated above, in all three studies treatment duration on Lumizyme was shorter than on Myozyme.

The treatment exposures of the 27 patients are summarized in the following table.

Table 10 All 27 patients' treatment exposures

Study	Age at first Myozyme infusion* (months)	Age at first Lumizyme infusion (months)	Age at product switch (months)	Age at last follow up (months)	Duration on Myozyme (months)	Duration on Lumizyme (months)	Ratio of Myozyme treatment duration to Lumizyme
Pivotal-Extension Study (N=18)	5.3 ± 1.7	28.4 ± 4.9	28.4 ± 4.9	33.5 ± 5.7	22 ± 4	8 ±2	Ratio: 3:1
Study 1702 (N=2)	4.9 ± 1.7	30.6 ± 14.8	30.6 ± 14.8	37.5 ± 14.7	25 ± 11	7± 0	Ratio: 4:1
EAP (N=7)	12.6 ± 5.2	4 ± 2.2	12.6 ± 5.2	31.8 ± 7.0	8 ± 4	7 ± 3.4	Ratio: 2:1

* Numbers are median ± SD

Sixteen of the 18 Pivotal Study patients enrolled in the Extension Study, during which they were treated with Lumizyme. Patients were treated with Myozyme longer than Lumizyme, and the ratio of treatment duration was approximately 3:1 (Myozyme: Lumizyme). Patients were on Lumizyme for about 8 months, which was a limited amount of time from which to derive clinical data. In addition, any outcome that occurred in that time period could also have been due to any "residual" effects of Myozyme with which patients had been treated for a much longer period of time, for approximately 22 months just immediately prior to treatment with Lumizyme. Moreover, because the Extension Study experience was uncontrolled, it is impossible to determine whether the outcomes during this period were due to Lumizyme treatment, or due to natural progression of the disease. In sum these issues limited the interpretation of clinical comparability between Myozyme and Lumizyme.

Similarly, the 2 matched patients in Study 1702 were treated with Myozyme for a longer period than Lumizyme in ratio of about 4:1. Patients were on Lumizyme for about 7 months. Patient 1702-0107420 had a dose increase (from 20 mg/kg QOW to 40 mg/kg QOW) during both treatment periods. Patient 1702-8102404 had a dose increase in the Myozyme phase, and received only the 40 mg/kg dose in the Lumizyme phase. Patients started treatment with Myozyme at about 5 months of age, and switched to Lumizyme at about 31 months, with study follow-up ending at about 38 months, or approximately 3 years of age. Similar issues regarding the limitations due to the study design as described above for the Pivotal-Extension Study applies here.

In the EAP, patients were treated with Lumizyme for approximately 8 months, which was a limited amount of time to derive clinical data from. Patients were treated on Myozyme for a longer period of time (19 months), and the ratio of duration of treatment was 2:1 (Myozyme: Lumizyme). Note that the duration of treatment experience was derived from the PTINFO3.XPT dataset (from Efficacy Amendment submitted on 14 March 2008). This Reviewer assumed that

once the EAP ended, the patients transitioned to treatment with commercial Myozyme and continued that until the last follow up.

In conclusion, the age of initial alglucosidase alfa treatment was similar among all three studies, about 5 months of age. Patients were treated with Myozyme for a longer period than with Lumizyme. Age at last follow up was about 3 years of age. The duration of treatment of Lumizyme was about 7 to 8 months for all 3 populations.

6.1.4.3 Clinical Outcomes

6.1.4.3.1 Ventilator-free Survival

The Pivotal-Extension Study

In the Pivotal-Extension Study by 18 months of age, 3 of the 18 patients of the pivotal trial cohort had become ventilator dependent: the 18 months ventilator free survival (defined by % of patients alive and not on invasive ventilator support) was N=3/18 or 83%. By the end of the study follow up at approximately 3 years of age (32 months), 9 patients of the original 18 patient cohort (9/18 or 50%) in the Pivotal Study had either become ventilator dependent or died. In other words, the median ventilator-free survival for the Pivotal Study cohort (who first received Myozyme then Lumizyme) was at about 3 years of age (32 months). Table 11 summarizes the events relating to invasive-ventilator free survival in patients in the Pivotal-Extension Study.

Table 11 Events of death or invasive ventilator dependence by individual patient listing in the Pivotal-Extension Study

Patient ID	Age at invasive ventilator dependence (months)	Age at death (months)
1602/2403-0201301	15 (160 L)	41 (2000 L)
1602/2403-6001302	.	.
1602/2403-6002303*	24 (160 L)	32 (160L)
1602/2403-5202305	19 (160 L)	20 (160 L)
1602/2403-5203306	20 (160L)	.
1602/2403-0101307	.	.
1602/2403-0202308	.	.
1602/2403-0102309	.	.
1602/2403-5204310	.	.
1602/2403-0103311	.	.
1602/2403-8305312	.	.
1602/2403-8101313*	18 (160 L)	34 (2000 L)
1602/2403-8304314	24 (2000 L)	.
1602/2403-6003315	.	.
1602/2403-2101316	. .	.
1602/2403-8102317*	9 (160 L)	.

Patient ID	Age at invasive ventilator dependence (months)	Age at death (months)
1602/2403-0203318	30 (2000 L)	30 (2000 L)
1602/2403-8103319*	9 (160 L)	.

*CRIM negative patients 160 L = Myozyme; 2000 L =Lumizyme

Of the nine patients who became ventilator dependent, four were CRIM negative patients, and five were CRIM positives. All four CRIM negative patients became ventilator dependent and two subsequently died. The reader is cautioned against making a simple and direct comparison between the CRIM positive and CRIM negative patients in this study because there were approximately 3.5 times more CRIM positive patients than CRIM negative patients in the study. It is generally recognized, however, that a CRIM negative status likely portends a worse prognosis both for ventilator dependence and for death (which is supported by data shown in Table 12).

Table 12 Pivotal-Extension Study CRIM status and clinical outcomes

	Ventilator dependence (number of patients with the event/total number of patients of the CRIM status)	**Death** (number of patients with the event/total number of patients of the CRIM status)
CRIM positive	5/14 (35%)	3/14 (21%)
CRIM negative	4/4 (100%)	2/4 (50%)

Study 1702

For the two matched patients in Study 1702, the CRIM negative patient died at 27 months; the CRIM positive patient was alive at last follow up (about 4 years of age), but had become ventilator dependent shortly before. Ventilator-free survival in the two matched patients in Study 1702 is summarized in Table 13.

Table 13 Events of death or invasive ventilator dependence by individual patient's listing in Study 1702

Patient ID	Age at invasive ventilator dependence (months)	Age at death (months)
1702-0107420 (CRIM -)	.	27.1 (2000 L)
1702-8102404 (CRIM +)	46.5 (160 L)	

The EAP

Two patients had became ventilator-dependent or died by the 18-month milestone; so the 18-month ventilator free survival was 5/7 patients, or 71% for the EAP population--lower than that for the Pivotal-Extension Study population, which was 15/18 patients, or 83%. Additionally, by age 20 to 25 months, half of the patients had either become ventilator dependent or died; so the median ventilator survival for this cohort was 20 to 25 months--lower than that for the Pivotal-Extension study, which was approximately 32 months. These data do not support that the two products are clinically comparable.

Ventilator-free survival in the seven matched patients in the EAP is summarized in Table 14.

Table 14 Events of death or invasive ventilator dependence by individual patient's listing in the EAP

Patient ID *Known CRIM negative patient	Age at invasive ventilator dependence (months)	Age at death (months)	CRIM Status
2203-001521	.	.	Positive
2203-001776	.	.	Not known
2203-001792	20.8	.	Not known
2203-013511*	.	18.0	Negative
2203-021783	16.6	.	Not known
2203-030759*	25.0	.	Negative
2203-190510	.	.	Not known

Given the small number of patients available for comparison and other limitations in the study design, no definitive conclusions could be drawn about inferiority. But it is the opinion of this Reviewer that both of these findings are worrisome, suggesting that the Lumizyme may be an inferior product, especially given that the CMC data have shown (b) (4) and that it may contribute to a lower potency/efficacy with Lumizyme.

The data additionally demonstrate that alglucosidase alfa (either Myozyme or Lumizyme) is not a cure. Even under the best circumstance where treatment was initiated by 6 months of age and compliance was carried out with full medical support under the stringent conditions of a clinical trial, a significant number of patients succumb to disease progression by 3 years of age. The longer term efficacy of Myozyme for these survivors is unknown. This Reviewer believes that this data on the original 18 patients in the Pivotal Trial at approximately 3 years of age should be reflected in an updated Myozyme product labeling.

6.1.4.3.2 Motor development

It was concluded in the original BLA clinical review that Myozyme-treated patients generally exhibited some progressive development of motor function, whereas it was shown in the historical control and from the medical literature that untreated patients achieved only a few motor milestones, and that the few milestones achieved were lost with disease progression. Though showing an improvement over no-treatment, a majority of Myozyme-treated patients still lagged significantly behind normal children by the end of the study.[11]

Motor development is an important supportive endpoint for this sBLA review. Since the amount of time on the Lumizyme was short (approximately 7-8 months), one might not expect to see progressive end-stage clinical events such as respiratory failure or death to occur (if they were to occur) within a relatively short amount of time after transition to Lumizyme treatment. In this regard, motor development could be seen as a harbinger for the patients' eventual clinical response. A decrease in motor ability could be interpreted as a poor prognostic indicator for impending respiratory failure/death. This rationale is based on the findings that in the Pivotal Study a decline in motor ability correlated with and was predictive of poor clinical outcomes (see original BLA clinical review by A. Pariser).

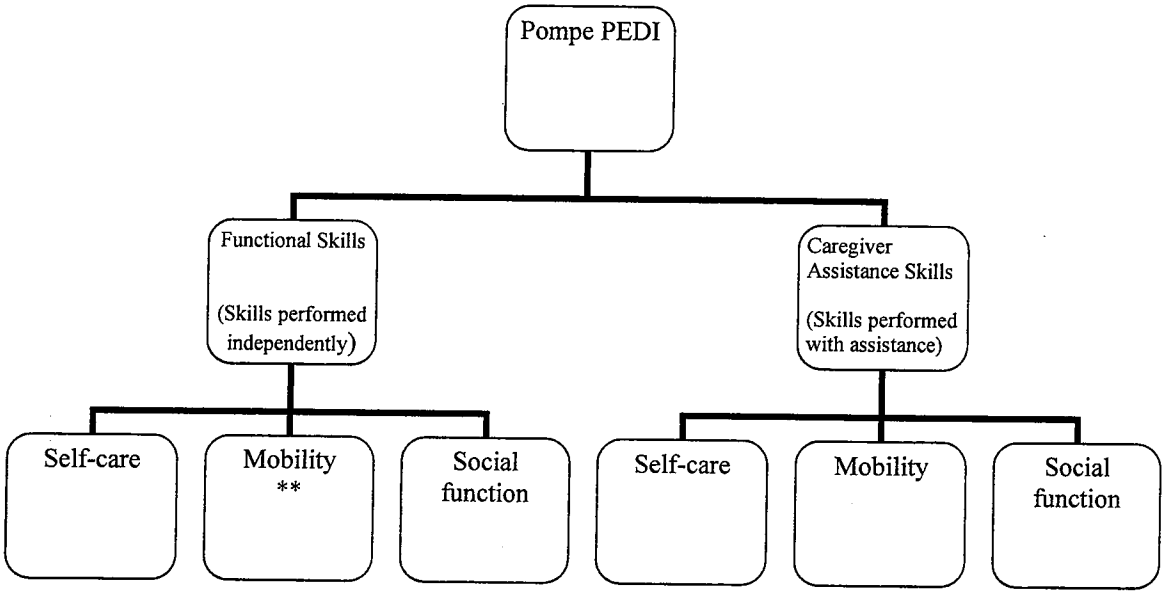
In the Pivotal Study of the original BLA, results for motor development were assessed using the Alberta Infant Motor Score (AIMS) and Pompe Pediatric Evaluation of Disability Inventory (Pompe PEDI) assessment tools. The AIMS is a widely used observational measure of infant motor performance that assesses motor maturation of the infant through the age of independent walking (approximately 18 months of age). Since for this sBLA patients had to be followed beyond 18 months of age, AIMS was not used for analysis. This review used the Pompe PEDI score.

The PEDI is a standardized instrument developed to assess the functional capabilities of children 6 months to 7½ years of age. Functional skills (skills that are performed independently) and caregiver assistance skills (skills that are preformed with assistance) are assessed in the following three content domains: 1) self-care (e.g., feeding, grooming, bathing, and dressing), 2) mobility (e.g., chair or bed transfer, locomotion), and 3) social function (e.g., comprehension, expression). Higher scores indicate better performance and increased independence.

The Pompe PEDI is a standardized, modified version of the PEDI specifically designed for evaluating patients with Pompe disease. Since Pompe disease primarily impacts motor function, the PEDI mobility and self-care functional skill scales are modified for the Pompe PEDI by adding items that reflect the types of functional skills and deficits noted in children with Pompe disease. Also, new items are added to the original PEDI to increase the ceiling level, decrease the basal level, create smaller skill increments between items to improve scoring precision and potential sensitivity to change, and to include assistive technology items (e.g., use of wheelchair). Pompe PEDI is intended to examine changes in functional performance by a particular patient; hence, it is suited for intra-patient evaluation. The Pompe PEDI has the following organizational hierarchy (see the Figure below, this Reviewer's construction).

11 See Clinical Review for BLA 125141/0 by FDA clinical reviewer, Anne Pariser, M.D.

Figure 4 Structure of the Pompe PEDI



** Functional mobility score is the score analyzed in this review

For the purpose of this review, the functional mobility score was evaluated because this domain reflects the patient's independent motor abilities. In Pompe PEDI, raw scores are transformed to scaled and normative scores. According to the developers of the PEDI and Pompe PEDI, an increase in raw score of one point indicates the acquisition of one new skill for each domain. Scaled scores evaluate intra-patient functional change, without reference to chronological age or same-age peers, on a scale from 0 to 100 (the higher the score, the more skills the child can perform). Normative scores are available for children up to 7 years of age to describe how a child is performing compared to same-aged peers without a disability. The Applicant states that Pompe patients exhibiting normative scores within ± 1 SD (i.e., ± 10) of the mean score (50) are considered to be acquiring functional skills at pace consistent with normally developing peers, while normative scores <40 or >60 indicate delayed or accelerated acquisition of functional skills, respectively.

In this review, the Pompe PEDI functional scaled and normative scores were analyzed. The mobility scaled scores has four levels:

1. Limited movement (0-30) for patients who are not yet mobile.
2. Incipient mobility (30-50) for patients who use powered wheelchairs or have floor mobility/weight bearing.
3. Basic self mobility (50-70) for patients who are able to manually driving a wheelchair or walking with crutches.
4. Advanced skill movement (70-100) for patients who are self-mobile and can participate in sports.

It was found in the original BLA review that higher motor scaled scores were associated with a better overall clinical outcome. Of the 6 patients requiring ventilation (invasive or noninvasive), 5 had scaled scores less than 20 at Week 52, suggesting that a score of 20 or below predicted poor clinical prognosis. There were no obvious differences in the results by treatment dosing groups.

The following Tables summarize the results for the Pivotal-Extension Study, and Study 1702 of Pompe PEDI functional skills motor scores (both normative and scaled scores) over time, spanning both Myozyme and Lumizyme treatment periods. The following tables are included here to illustrate that for patients in the Pivotal-Extension Study, and the two selected patients in Study 1702, the experience on the Lumizyme was very limited (in gray): there were at most two data points for the motor scores during the Lumizyme treatment period.

Given such limited data, no meaningful conclusion could be drawn about whether patients' motor abilities improved, declined, or remained the same on treatment with Lumizyme as compared to Myozyme.

Table 15 Pivotal-Extension Study motor score on Myozyme and Lumizyme treatment (Lumizyme treatment in shaded gray)

Patient ID 1602/2403-	VISIT (18 months=78 weeks)	On treatment	Functional skilled mobility normative score	Functional skilled mobility scaled score
0101307	BASELINE		53.73	21.01
	WEEK 4	160L	20.7	23.23
	WEEK 8	160L	26.24	25.93
	WEEK 12	160L	34.73	30.07
	WEEK 26	160L	36.13	40.49
	WEEK 38	160L	52.19	48.66
	WEEK 52	160L	41.37	50.7
	WEEK 64	160L	50.26	54.48
	WEEK 78	160L	41.78	57.27
	WEEK 90	160L	45.33	58.59
	WEEK 116	2000L	44.79	59.61
	WEEK 130	2000L	39.68	61.39
0102309	BASELINE		53.73	21.01
	WEEK 4	160L	20.7	23.23
	WEEK 8	160L	27.84	26.71
	WEEK 12	160L	32.15	28.81
	WEEK 26	160L	42.86	34.04
	WEEK 38	160L	39.97	42.44
	WEEK 52	160L	51.6	48.36
	WEEK 64	160L	42	50.97
	WEEK 78	160L	51.68	55.08
	WEEK 104	160L	29.72	54.48
	WEEK 130	2000L	43.73	59.25
0103311	BASELINE		41.67	13.08
	WEEK 4	160L	10	15.06
	WEEK 8	160L	10	16.81
	WEEK 12	160L	16.15	21.01
	WEEK 26	160L	10	18.37

Patient ID 1602/2403-	VISIT (18 months=78 weeks)	On treatment	Functional skilled mobility normative score	Functional skilled mobility scaled score
	WEEK 38	160L	10	26.71
	WEEK 52	160L	10	28.81
	WEEK 64	160L	10	31.85
	WEEK 78	160L	10	31.85
	WEEK 104	160L	10	37.01
	WEEK 130	2000L	10	41.69
0201301	BASELINE		34.04	8.07
	WEEK 4	160L	49.71	18.37
	WEEK 8	160L	10.73	.
	WEEK 12	160L	18.55	22.18
	WEEK 26	160L	26.24	25.93
	WEEK 38	160L	10	21.01
	WEEK 52	160L	10	4.53
	WEEK 64	160L	10	19.75
	WEEK 78	160L	10	13.08
	WEEK 90	160L	10	13.08
	WEEK 104	160L	10	0
	WEEK 130	2000L	10	0
0202308	BASELINE		38.2	10.8
	WEEK 4	160L	47.33	16.81
	WEEK 8	160L	55.51	22.18
	WEEK 12	160L	20.7	23.23
	WEEK 26	160L	37.2	31.28
	WEEK 38	160L	39.97	42.44
	WEEK 52	160L	44.81	44.9
	WEEK 64	160L	10	33.5
	WEEK 90	160L	35.89	55.08
	WEEK 104	2000L	40.08	56.64
	WEEK 130	2000L	35.1	56.31
0203318	BASELINE		38.2	10.8
	WEEK 4	160L	10	15.06
	WEEK 8	160L	20.7	23.23
	WEEK 12	160L	26.24	25.93
	WEEK 26	160L	32.15	28.81
	WEEK 38	160L	19.13	31.85
	WEEK 52	160L	25.45	35.06
	WEEK 78	2000L	10	36.56
	WEEK 104	2000L	10	37.01
2101316	BASELINE		51.81	19.75
	WEEK 4	160L	18.55	22.18
	WEEK 8	160L	24.58	25.12
	WEEK 12	160L	29.38	27.46
	WEEK 26	160L	41.75	33.5
	WEEK 38	160L	39.97	42.44
	WEEK 52	160L	46.8	53.01
	WEEK 64	160L	49.56	54.18
	WEEK 90	160L	36.69	55.38
	WEEK 116	2000L	38.88	57.6
5202305	BASELINE		47.33	16.81
	WEEK 26	160L	10.73	18.37

Patient ID 1602/2403-	VISIT (18 months=78 weeks)	On treatment	Functional skilled mobility normative score	Functional skilled mobility scaled score
	WEEK 38	160L	10	10.8
	WEEK 52	160L	10	16.81
5203306	BASELINE		53.73	21.01
	WEEK 12	160L	18.55	22.18
	WEEK 26	160L	10	16.81
	WEEK 38	160L	10	8.07
	WEEK 52	160L	10	10.8
	WEEK 64	160L	10	10.8
	WEEK 78	160L	10	8.07
	WEEK 90	160L	10	0
	WEEK 116	2000L	10	4.53
	WEEK 142	2000L	10	0
5204310	BASELINE		22.73	24.23
	WEEK 4	160L	20.7	23.23
	WEEK 8	160L	29.38	27.46
	WEEK 12	160L	29.38	27.46
	WEEK 26	160L	23.44	34.04
	WEEK 38	160L	38.49	41.69
	WEEK 52	160L	26.19	44.24
	WEEK 64	160L	39.32	49.83
	WEEK 78	160L	44.76	52.14
		160L	27.98	52.14
	WEEK 104	2000L	29.72	54.48
	WEEK 130	2000L	37.91	57.27
6001302	BASELINE		62.41	26.71
	WEEK 4	160L	30.8	28.15
	WEEK 8	160L	22.73	24.22
	WEEK 12	160L	38.37	31.85
	WEEK 26	160L	36.13	40.49
	WEEK 38	160L	53.9	49.53
	WEEK 52	160L	50.97	54.78
	WEEK 64	160L	44.76	52.14
	WEEK 78	160L	26.44	51.57
	WEEK 90	160L	36.69	55.38
	WEEK 104	160L	32.66	53.88
	WEEK 116	2000L	44.79	59.61
	WEEK 142	2000L	38.9	61.02
6002303	BASELINE		16.15	21.01
	WEEK 4	160L	22.73	24.22
	WEEK 8	160L	18.55	22.18
	WEEK 12	160L	26.24	25.93
	WEEK 26	160L	20.25	32.42
	WEEK 38	160L	31.12	37.94
	WEEK 52	160L	36.57	48.66
	WEEK 64	160L	29.29	45.56
	WEEK 90	160L	10	10.8
6003315	BASELINE		21.75	0
	WEEK 4	160L	28.65	4.53
	WEEK 8	160L	44.68	15.06
	WEEK 12	160L	38.2	10.8

Patient ID 1602/2403-	VISIT (18 months=78 weeks)	On treatment	Functional skilled mobility normative score	Functional skilled mobility scaled score
	WEEK 26	160L	24.58	25.12
	WEEK 38	160L	48.95	37.01
	WEEK 52	160L	49.24	47.16
	WEEK 64	160L	60.16	52.71
	WEEK 90	2000L	48.15	53.58
	WEEK 116	2000L	53.81	61.75
8101313	BASELINE	160L	34.04	8.07
	WEEK 4	160L	51.81	19.75
	WEEK 8	160L	53.73	21.01
	WEEK 12	160L	53.73	21.01
	WEEK 26	160L	33.5	29.47
	WEEK 38	160L	39.54	32.42
	WEEK 52	160L	36.96	40.91
	WEEK 64	160L	13.17	28.81
	WEEK 78	160L	10	21.01
	WEEK 104	2000L	10	15.06
8102317	BASELINE		10	8.07
	WEEK 4	160L	10	4.53
	WEEK 8	160L	10	10.8
	WEEK 12	160L	10	8.07
	WEEK 26	160L	10	10.8
	WEEK 38	160L	10	4.53
	WEEK 52	160L	10	10.8
	WEEK 78	160L	10	4.53
	WEEK 104	2000L	10	10.8
8103319	BASELINE		21.75	0
	WEEK 4	160L	41.67	13.08
	WEEK 8	160L	49.71	18.37
	WEEK 12	160L	44.68	15.06
	WEEK 26	160L	10.73	18.37
	WEEK 38	160L	13.56	19.75
	WEEK 52	160L	10	16.81
	WEEK 78	2000L	10	13.08
	WEEK 104	2000L	10	13.08
8304314	BASELINE		28.65	4.53
	WEEK 4	160L	47.33	16.81
	WEEK 8	160L	47.33	16.81
	WEEK 12	160L	57.11	23.23
	WEEK 26	160L	26.24	25.93
	WEEK 38	160L	30.8	28.15
	WEEK 52	160L	24.44	34.55
	WEEK 64	160L	29.29	37.01
	WEEK 78	160L	25.34	43.88
	WEEK 116	2000L	.	.
		2000L	10	30.67
8305312	BASELINE		47.33	16.81
	WEEK 4	160L	16.15	21.01
	WEEK 8	160L	16.15	21.01
	WEEK 12	160L	18.55	22.18
	WEEK 26	160L	24.58	25.12

Patient ID 1602/2403-	VISIT (18 months=78 weeks)	On treatment	Functional skilled mobility normative score	Functional skilled mobility scaled score
	WEEK 38	160L	13.17	28.81
	WEEK 52	160L	23.44	34.04
	WEEK 64	160L	10	37.01
	WEEK 78	160L	14.47	39.26
	WEEK 104	2000L	10	42.44
	WEEK 116	2000L	10	40.91

Table 16 Study 1702 Motor score on Myozyme and Lumizyme treatment (Lumizyme treatment in shaded rows)

Patient ID 1702-	VISIT (18 months=78 weeks)	On treatment	Functional skilled mobility normative score	Functional skilled mobility scaled score
0107420	BASELINE	160L	21.75	0
0107420	WEEK 4	160L	44.68	15.06
0107420	WEEK 8	160L	47.33	16.81
0107420	WEEK 12	160L	18.55	22.18
0107420	WEEK 26	160L	22.73	24.22
0107420	WEEK 38	160L	13.17	28.81
0107420	WEEK 52	160L	11.87	28.15
0107420	WEEK 64	160L	10	30.67
0107420	WEEK 78	2000L	10	34.55
0107420	WEEK 90	2000L	10	35.06
8102404	BASELINE	160L	10	13.08
8102404	WEEK 4	160L	10	13.08
8102404	WEEK 8	160L	10	8.07
8102404	WEEK 12	160L	10	16.81
8102404	WEEK 26	160L	10	18.37
8102404	WEEK 38	160L	10	22.18
8102404	WEEK 52	160L	10	19.75
8102404	WEEK 64	160L	10	21.01
8102404	WEEK 78	160L	10	22.18
8102404	WEEK 90	160L	10	24.22
8102404	WEEK 104	160L	10	25.93
8102404	WEEK 116	160L	10	31.85
8102404	WEEK 130	160L	10	28.15
8102404	WEEK 142	2000L	10	28.15
8102404	WEEK 168	2000L	10	27.46

Motor development information is also plotted graphically, shown in the following Figures (see Appendix for a larger version). The arrow denotes time of the product switch (160 L→2000 L). The most important conclusion derived from these motor data is there is insufficient data during the short Lumizyme experience to establish clinical comparability in motor development. The graphs also visually illustrate that patients generally fell into one of the three categories: 1) patients who performed poorly (scores of < 20) and never developed any meaningful motor development; 2) patients who initially improved but declined abruptly (which might have been attributed to rising IgG antibody titers that interfered with product efficacy); and 3) patients who

performed progressively but started to plateau or decline at about 20-30 months of age, reaching a scaled score of approximately 40-70 as of last follow up at about 3 years of age. This last group constituted the largest population, and the maximum responders but even they obtained only basic self mobility (e.g., manually driving a wheelchair or walking with crutches) at about three years of age. Whether this plateau occurred because there was a switch made to possibly an "inferior" product (Lumizyme), or it occurred as a function of the downward progression of Pompe disease despite treatment cannot be determined. This Reviewer believes that it seems more likely it was due to disease progression given that the decline generally started before the product switch. If that is true, then the data demonstrate that Myozyme (which might be superior to Lumizyme) is not a cure and is ineffective in stopping the motor devastation of the disease in a significant number of infantile onset patients. Although Myozyme is an improvement over no treatment, and is presently the only viable strategy for treating Pompe disease, the long-term efficacy of alglucosidase alfa as a therapeutic drug is uncertain, and there is still room for improvement to meet an unmet need.

Figure 5 Pompe PEDI mobility functional skills scaled scores in the Pivotal-Extension Study (electronically copied from the Applicant's submission)

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS
AGLU01602/02403

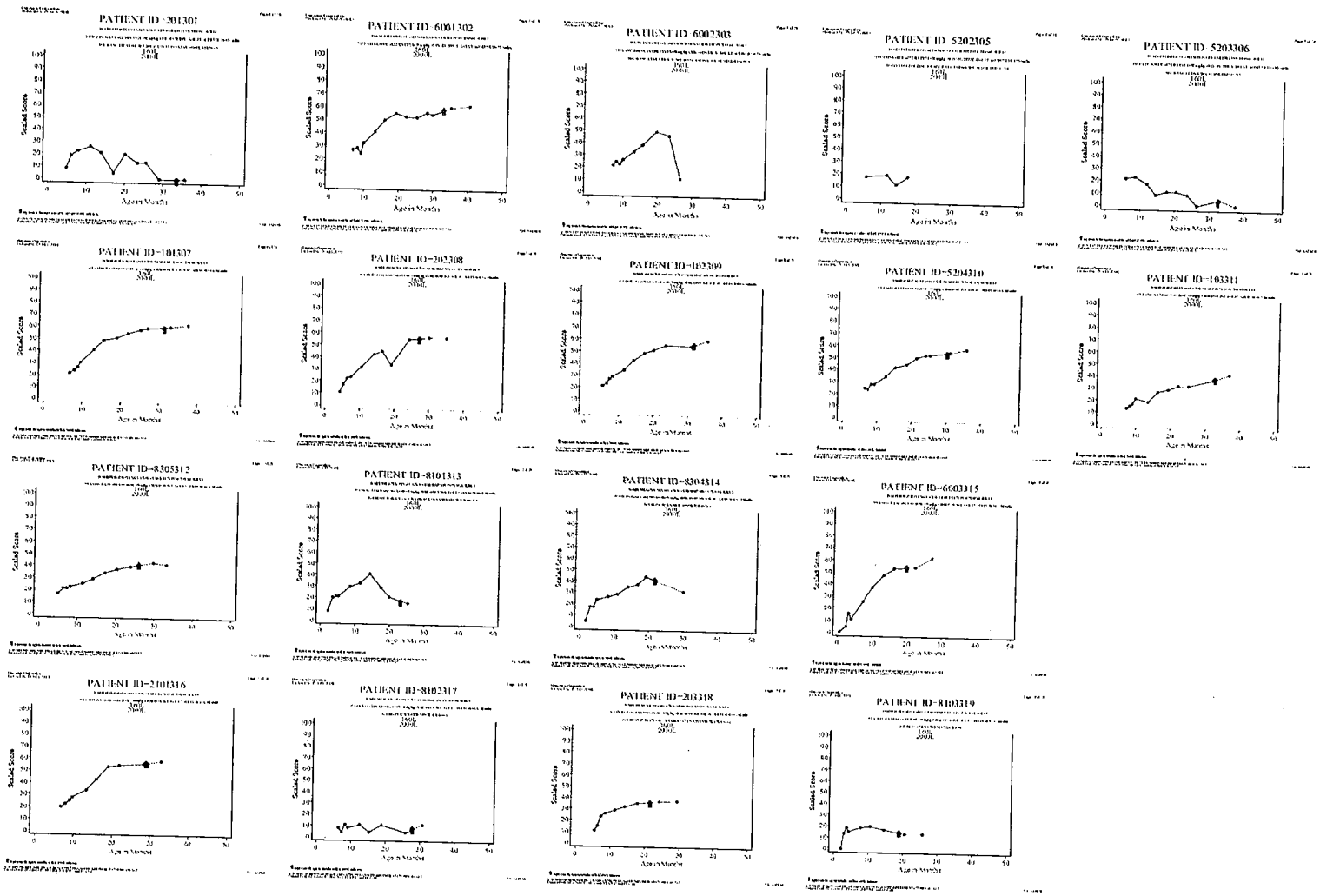


Figure 6 Pompe PEDI mobility functional skills scaled scores in Study 1702 (electronically copied from the Applicant's submission)

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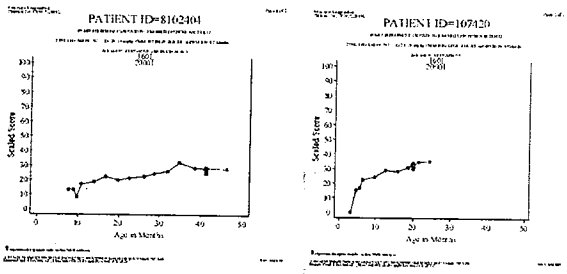
POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS
AGLU01702



The Table below contains the Pompe PEDI functional mobility scores for the seven selected patients in EAP. Only one patient had results at Week 52, but most had some gain in the mobility scaled score. However, it cannot be concluded from this limited data whether these patients' motor performance was comparable to that of patients in the Pivotal Study.

Table 17 Motor scores during treatment on Lumizyme in the EAP population

Patient ID	VISIT (18 months=78 weeks)	Functional skilled mobility normative score	Functional skilled mobility scaled score
1521	Baseline	.	15.06
1521	Week 12	59.99	25.12
1776	Baseline	55.51	22.18
1776	Week 12	27.84	26.71
1776	Week 26	35.97	30.67
1776	Week 38	26.45	35.57
1792	Baseline	44.68	15.06
1792	Week 12	10	16.81
1792	Week 26	24.58	25.12
13511	Baseline	.	8.07
13511	Week 12	47.33	16.81
21783	Week 12	16.15	21.01
21783	Week 26	20.7	23.23
21783	Week 38	10	22.18
30759	Baseline	38.2	10.8
30759	Week 12	57.11	23.23
30759	Week 26	32.15	28.81
30759	Week 38	35.97	30.67
30759	Week 52	23.44	34.04
190510	Baseline	28.65	4.53
190510	Week 12	10	16.81

In summary there was insufficient information based on motor development data to provide supportive evidence for clinical efficacy comparability between the two products.

6.1.4.3.3 Left Ventricular Myocardium Index (LVMI)

In classic infantile-onset Pompe disease patients, cardiac enlargement and myocardial failure are prominent and defining features. Death usually occurs within 1 to 2 years of birth due to cardio-respiratory failure.

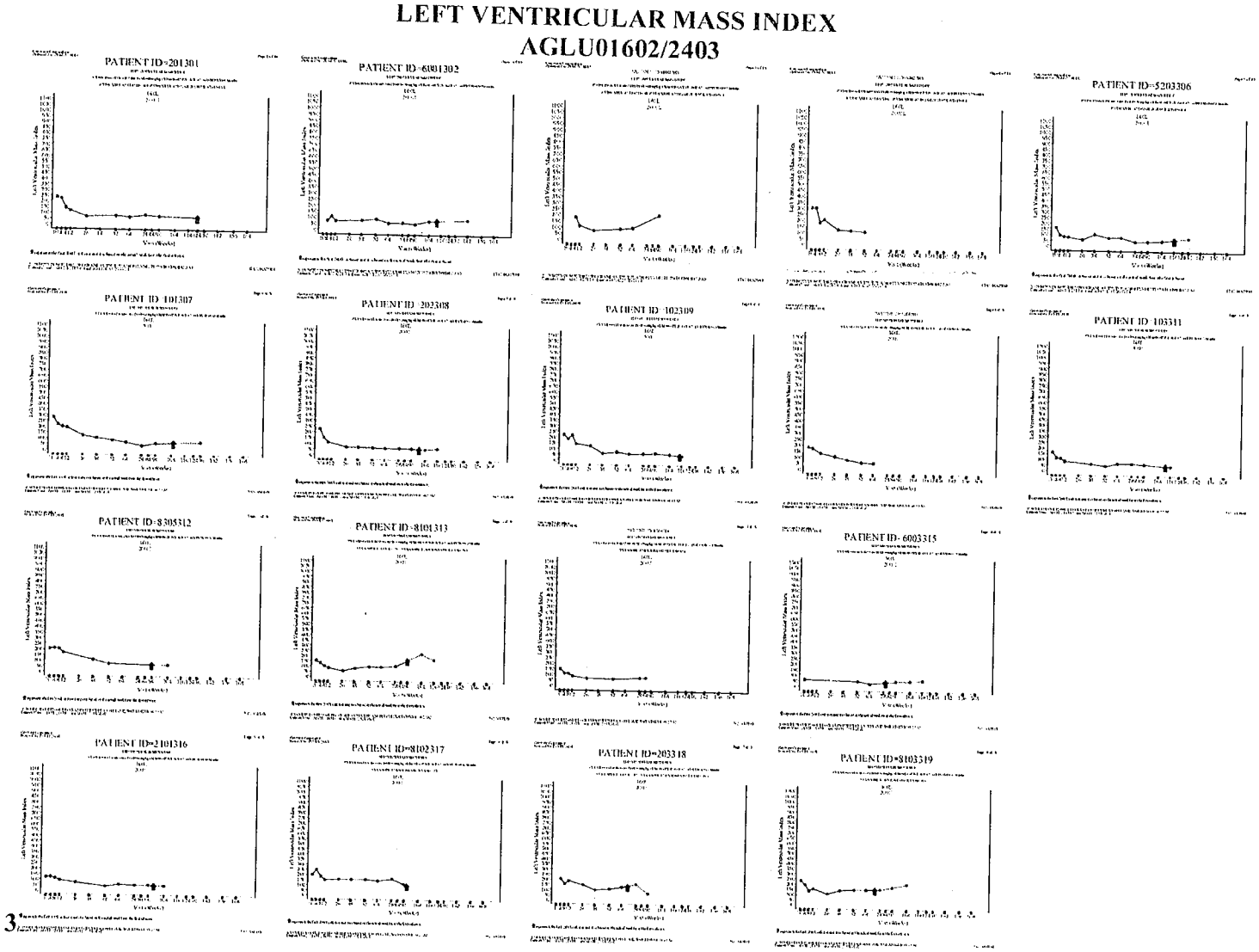
Data from the Pivotal Study demonstrated that there was a decrease in left ventricular myocardial index (LVMI) and left ventricular mass Z (LVM-Z) scores in all patients through Week 52 with Myozyme treatment (see original BLA Clinical Review by A. Pariser). Although Myozyme exerted pharmacodynamic (PD) effect on cardiac muscle, this PD effect did not correlate with overall cardiac function or clinical outcomes during the study. The clinical relevance of the decrease in LVMI remains unknown, and so decrease in LVMI should not be considered as a true clinical efficacy outcome such as motor improvement or ventilator free survival.

The Applicant submitted data on both LVMI and LVM-Z scores for this review, but this Reviewer did not review the LVM-Z scores for the following reason. An "improvement" in the LVM-Z score is misleading and not clinically meaningful. An LVM-Z of *x* denotes a patient's LVMI score as *x* SDs above the mean LVMI score (of a body-surface area matched normal cohort)—not as *x* times greater than the mean from the matched cohort. Because the z-score comes from a normal distribution with a mean of zero and a standard deviation of one, an LVM-Z score of 2 means that the patient's LVMI score corresponds to the 97.7th percentile of the distribution of the LVMI scores from the body-surface-area matched cohort. A decrease in the LVM-Z score from 8 to 6 to 4 provides no meaningful clinical information because it simply means that the LVMI decreased from the 99.9999999999999th percentile to the 99.9999999013412th percentile to the 99.9968328758163th percentile of the distribution of LVMI scores. Such a decrease does not represent a clinically significant improvement in LVMI (Thanks to L. Kammerman for providing this interpretation of the LVM-Z scores, based on the Applicant's clarification on the meaning of LVM-Z scores).

Similar to the results for the motor data, there were, at most, three data points collected for LVMI per patient during the short Lumizyme experience in the Pivotal-Extension Study and Study 1702, rendering the data insufficient to establish clinical comparability (data not shown). In addition, LVMI data from the EAP could not be used to be compared to that of the Pivotal Extension Study due to methodological differences used in obtaining the echocardiogram results.

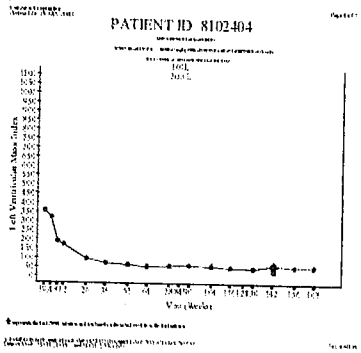
LVMI Results are represented graphically in the following Figure. Although LVMI was measured in all three studies, echocardiogram measurements in the EAP were not obtained using the same standardized procedure that was used in the other two studies. Therefore, caution should be exercised when interpreting the results across the studies. The arrows in the graphs denote the time of product switch. (b) (4) However, it appears that for the majority of the patients in the EAP, the LVMI decreased with Lumizyme treatment, suggesting a pharmacodynamic effect, though caution should be exercised in making this interpretation given that there were only a handful data points per patient, and that the clinical meaningfulness of this PD marker has not been established.

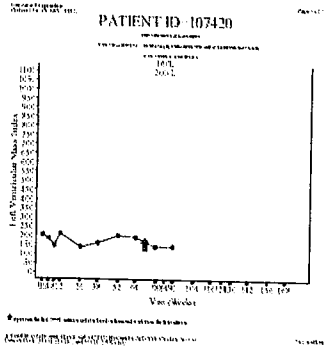
Figure 7 LVMI in the Pivotal-Extension Study, Study 1702, and the EAP (copied electronically from the Applicant's submission)



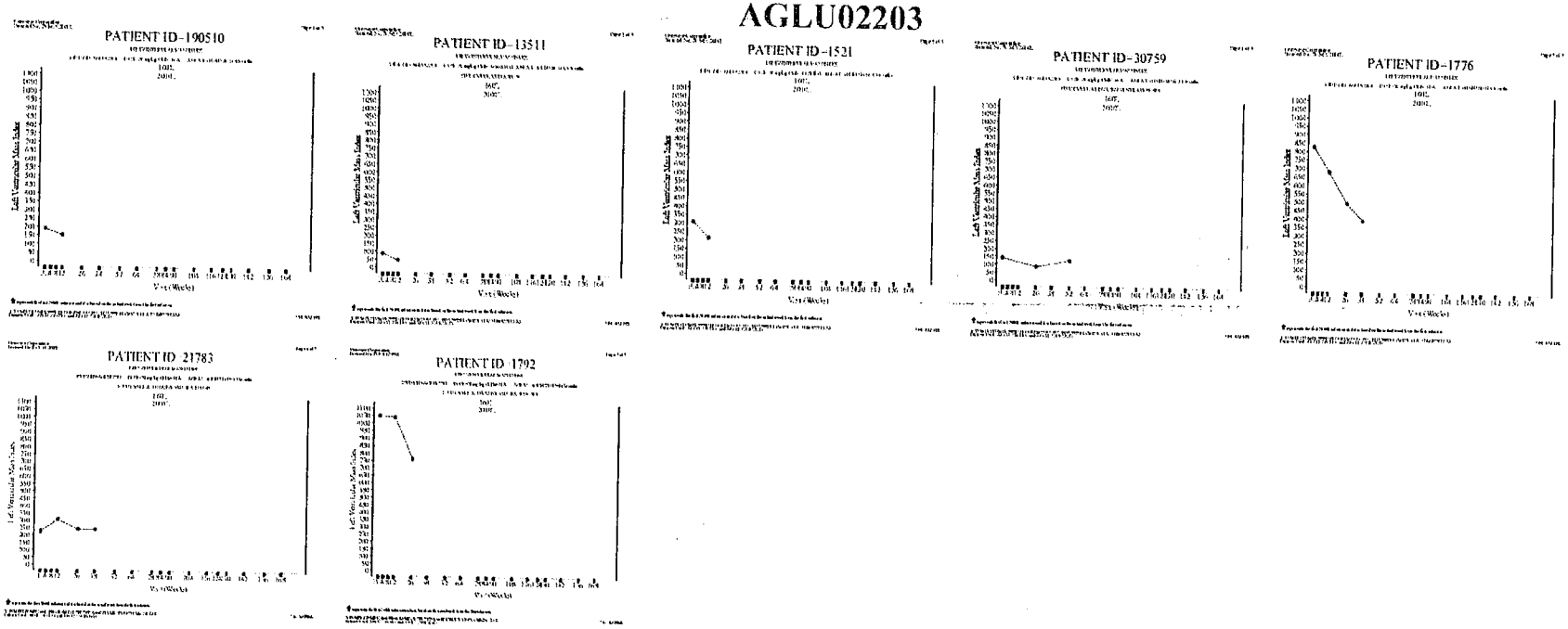
3

LEFT VENTRICULAR MASS INDEX
AGLU01702





LEFT VENTRICULAR MASS INDEX
AGLU02203



6.1.4.3.4 Product attributes and clinical efficacy

For lysosomal enzyme replacement therapy (ERT) to be effective, the enzyme must be delivered to the lysosomes where the storage defect occurs. The goal is for alglucosidase alfa to be targeted to inside the lysosomes where it digests glycogen. Alglucosidase alfa is thought to be delivered to the lysosomes of skeletal and cardiac muscle cells by interaction of the (b) (4) Indeed, as compared to the other lysosomal storage disorder enzyme replacement therapies, alglucosidase alfa needs to be delivered in larger doses (20 mg/kg IV QOW), as compared to Naglazyme (1 mg/kg IV weekly), Aldurazyme (0.58 mg/kg IV weekly), and Elaprase (0.5 mg /kg IV weekly).

Though there may be other physicochemical differences that may affect efficacy (b) (4),), the (b) (4) profile comparability has been highlighted as a critical issue and so an attempt was made by this Reviewer to establish a correlation between the levels of (b) (4) in the product administered and the patients' clinical outcomes.

Unfortunately no clear conclusions could be made because multiple, different product lots were administered to different patients, for different amounts of time, in various random orders. In this Reviewer's examining the by-patient, by-lot alglucosidase alfa administration history for patients in the Pivotal-Extension Study and EAP, the data showed that each patient received different numbers of infusions of different drug product lots in random orders. Few (if any) patients were treated with lots having the same attributes in the same sequence over a similar interval of time during the same period in life to allow making a meaningful comparison.

6.1.5 Efficacy Conclusions

The data available for analysis were extremely limited, and were based on the experience of 27 patients only. There were 7 Lumizyme treatment naïve patients in the EAP available for comparison with 18 Myozyme treatment naïve patients in the Pivotal Study. Treatment duration and follow up on Lumizyme were limited, and were about 7 to 8 months. Five patients in the EAP study had unknown CRIM status, which is a critical factor for predicting natural disease prognosis. It was not possible to determine whether the EAP population had a worse prognosis to begin with as compared to the Pivotal Study population because of their unknown CRIM status. The EAP was also not a GCP study. None of the studies were head-to-head comparisons. These study design issues rendered it impossible establish clinical comparability between the two alglucosidase alfa products.

The results showed that the 18-month invasive ventilator free survival rate was higher for the 18 patients treated with Myozyme in the Pivotal-Extension Study as compared to the 7 matched patients treated with Lumizyme in the EAP (83% vs. 71% ventilator-free survival, respectively). Median ventilator-free survival time (age at which half of the study patient population became

invasive-ventilator dependent or died) was 32 months for the Myozyme-treated group in the Pivotal-Extension Study, which was longer than the 20 to 25 months median ventilator free survival time for the Lumizyme-treated group in the EAP. The results were limited by these analyses being conducted in a retrospective fashion, and the studies were not performed as head-to-head comparisons. Also, because the data were derived from an exceedingly small number of patients studied, with chance alone being able to explain the results, no definitive conclusions could be reached. (b) (4) This Reviewer believes that concerns should be raised that there may be an increased risk to the infantile-onset patients due to the potential risk for rapid disease progression if they were to be treated with Lumizyme. Since the safety and effectiveness of Lumizyme have not been established in the infantile-onset population, and the safety and effectiveness have been established with Myozyme, this Reviewer recommends that infantile-onset patients be treated with Myozyme, and that Lumizyme be restricted for use only in the population in whom an acceptable risk/benefit profile has been established.

Motor data (as supportive clinical efficacy data) and LVMI data (as supportive PD data) could not be used as additional information because there were only a few data points collected during the Lumizyme experience for these parameters.

Furthermore, no conclusions could be reached about which product attributes correlated with efficacy outcome, or how specifications should be set for each product attribute, because the correlation analysis was limited by the fact that the patients were treated with different Drug Substances and Drug Products lots for different treatment durations and in various random orders. In this Reviewer's examining the by-patient, by-lot alglucosidase alfa administration history for patients in the Pivotal-Extension Study and EAP, the data showed that each patient received different numbers of infusions of different drug product lots in random orders. Few (if any) patients were treated with lots having the same attributes in the same sequence over a similar interval of time during the same period in life to allow making a meaningful comparison. In that regard, in the opinion of this clinical Reviewer, it would be difficult to set specifications for this product attribute based on the clinical efficacy results shown in these studies.

This Reviewer recommends that Lumizyme not be approved as a comparable product to Myozyme. This Reviewer further recommends that changes be made to the Myozyme product labeling based on outcomes of the Pivotal-Extension study to reflect that about 50% of the original cohort in the Pivotal Study had either become ventilator dependent or died by 3 years of age, and there was a plateau (reaching a ceiling) seen in motor development in even the most treatment responsive patients. Limitations of Myozyme treatment should be updated in the labeling to allow patients and physicians to re-evaluate the over all risk-benefit of treatment now that data for longer follow up have become available.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The purpose of this sBLA clinical review was to establish clinical comparability between the two products. Based on the efficacy analysis, this Reviewer concludes that there are insufficient data to establish product comparability, thereby reaching the stated goal of this review.

The safety review, therefore, was performed in a more abbreviated manner not only because a decision about approvability could be made based on the efficacy analysis alone, but also because the review has to be completed in a reasonable time to allow the Applicant to make a timely decision about managing the public health issue regarding the drug shortage. This safety review was also limited by the fact that the data came from open label, uncontrolled studies, and the number of patients available for analysis was extremely small. The patients had extensive underlying medical morbidity, and without a control, safety signals would be difficult to detect as being attributable to the study drug. Also, patients were treated with different lots of different products for different amounts of time in random orders, and the duration on Lumizyme treatment was significantly shorter than that on the Myozyme experience. In addition, the EAP was not a GCP study. Safety surveillance for the EAP cohort after the study ended was conducted in a voluntary manner, with spontaneous reporting of Adverse Events. All of these issues limited the ability to draw meaningful conclusions about the safety of Lumizyme, either by itself or in comparison with Myozyme.

For the purpose of this safety review this Reviewer placed some emphasis on review of new safety findings for Myozyme that have not already been captured in the current product labeling (i.e., unexpected or unlabeled adverse events). It needs to be emphasized that safety for Lumizyme will need to be examined in much greater detail when additional data become available (e.g., in the placebo-controlled LOTS).

Patients studied in the Pivotal-Extension Study and Study 1702 using Myozyme were eventually switched to Lumizyme, with which patients were treated for a mean of about 7 to 8 months. Also, the 7 matched patients in the EAP received Lumizyme for approximately 7 months. For this comparative safety analysis of the 2 products, exposure data from 27 patients with classic infantile-onset Pompe disease were analyzed for the combined dose groups (20 and 40 mg/kg IV QOW). Deaths, Serious Adverse Events (SAEs), common Adverse Events (AEs), infusion reactions (IRs), and immunogenicity were analyzed. Issues that typically pertain to small molecules (such as QT interval prolongation) and to large epidemiological studies (e.g., analyses focused on measures of central tendency) were not reviewed.

Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA v6) with each verbatim term coded to the appropriate preferred term (PT). The Applicant's coding appeared appropriate.

Only treatment-emergent AEs that occurred in the 27 selected patients (Table 17) were included and reviewed. All AEs are listed regardless of relatedness based on the Investigator's assessment.

For the Pivotal-Extension Study and Study 1702, this Reviewer analyzed the data from the ae1.xpt dataset (amendment dated 29 February 2008); and, for Study AGLU02203, the aex1.xpt dataset, (amendment dated 15 February on 2008). For the EAP, AEs were collected for the Lumizyme experience during the EAP. There was no systemic collection of AEs for the commercial Myozyme experience after the study had ended.

7.1.1 Deaths

Eight of the 27 patients died during the study period as of last follow up. No death was attributed by the Investigator or the Applicant to alglucosidase alfa treatment. The patients who died are listed in the following table. It appears that all patients died of complication of the underlying disease and most appear to have died of cardiopulmonary failure.

Table 18 Listing of treatment-emergent deaths in the 27 patients analyzed for review

Patient ID	Age at death	Treatment product at the time of death	Immediate cause of death
1602/2403-0201301	41 months	Lumizyme	Cardiopulmonary arrest
1602/2403-6002303	32 months	Lumizyme	Septicemia related multi-organ failure after cardiac arrest
1602/2403-5202305	20 months	Myozyme	Cardiopulmonary arrest while being hospitalized for pneumonia
1602/2403-8101313	34 months	Lumizyme	Cardiac arrest
1602/2403-8102317	44 months	Unknown	Disease progression; Cardiac arrest
1602/2403-0203318	30 months	Lumizyme	Cardiopulmonary arrest
1702-0107420	27 months	Lumizyme	Cardiopulmonary arrest in the setting of a upper respiratory infection
2203-001511	18 months	Myozyme	Disease progression; progressive respiratory deterioration

The following is a synopsis of the cause of death.

Pivotal-Extension Study

- Patient 301 required invasive ventilatory support at age 5 months and died in the Extension Study at the age of 41 months due to cardiopulmonary arrest.
- Patient 303 suffered a cardiac arrest, and remained in a coma, and died 3 days later of septicemia related multi-organ failure. His death occurred after completing the Pivotal Study while he was under an International EAP, and his death report was received via an SAE report to the Applicant's Pharmacovigilance program.
- Patient 305 died during the Pivotal Study at the age of 20 months due to oxygen desaturation and bradycardia while being hospitalized for treatment of respiratory distress and pneumonia.

- Patient 313 died 5 months later after being withdrawal by family from the Extension Study. The patient experienced cardiac arrest followed by hypoxic encephalopathy with neurological devastation resulting in persistent disability. The patient died from a subsequent cardiac arrest 4 months following the initial event of cardiac arrest at the age of 34 months.
- Patient 317 died at the age of 44 months, which was after the Extension Study. The patient suffered a cardiac arrest, and re-arrested due to cardiac arrhythmia and died. The treating physician considered the cause of death disease progression.
- Patient 318 required invasive ventilatory support at 30 months and died in the Extension Study at the age of 30 months due to cardio-respiratory arrest.

Study 1702:

- Patient 420 was a 2 year old female whose medical history included repeated respiratory infections and distress, gastric tube feeding, catheter related infections, and congestive failure due to decompensated hypertrophic cardiomyopathy. Precipitating the fatal event was respiratory failure secondary to viral bronchiolitis. Of note, the investigator confirmed the patient was well prior to Lumizyme infusion on (b) (6), and infusion was administered without incident. Later that evening, the patient experienced fever and cough, but the Investigator confirmed they were "not related to the study treatment." (b) (6); later, the primary care physician diagnosed the patient with otitis media and upper respiratory infection with probable exacerbation of reactive airway disease. From there on the patient's clinical status deteriorated to requiring invasive mechanical ventilation. A decision was made not to pursue aggressive treatment given the overall dismal prognosis. In palliative care the patient died of bradycardia and asystole secondary to respiratory failure.

EAP:

- Patient 511 had progressive weakness and deteriorating respiratory function after transitioning to commercial Myozyme at the end of EAP, including respiratory syncytial virus bronchiolitis and recurrent respiratory distress. The patient discontinued treatment and died at home in comfort care at the age of 1.5 (18 months of age). The reporter indicated the cause of death as disease progression.

The Reviewer agrees that it appears that all deaths were attributable to Pompe disease related cardiopulmonary arrest. However, given that cardiopulmonary arrest is the endpoint for most fatal medical illnesses including other than Pompe disease, the statement "cardiopulmonary arrest" cannot completely rule out that there were no other upstream or initiating events that may have been treatment related. Given that there was no control, it is impossible to determine whether the deaths were due to the disease progression, another unrelated medical event, alglucosidase alfa treatment, or a switch to Lumizyme. And although more deaths occurred during the Lumizyme treatment phase, this could have been coincidental to Lumizyme's treatment period taking place later in life when the disease progression was more advanced.

For the original cohort of 18 patients in the Pivotal Study, 5/18 (28%) patients died by approximately 3 years of age. This demonstrates that alglucosidase alfa is not a cure.

7.1.2 Other Serious Adverse Events

In accordance with the standard regulatory definition, a Serious Adverse Event (SAE) is any AE that results in any of the following outcomes:

- Death
- Life-threatening experience
- Required or prolonged inpatient hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly
- Important medical events that may jeopardize the patient or subject and may require medical or surgical intervention to prevent of the outcomes listed above.

SAE incidence tables for each of the three studies are listed in the following Tables, organized by individual studies and by treatment. Since Pompe disease is commonly associated with compromised cardiopulmonary status, it is not unexpected that patients were frequently hospitalized for recurrent respiratory infections and associated pulmonary complications, as well as cardiovascular abnormalities. No event was considered definitely or probably related to the study drug by the Investigator. However, one SAE event was judged as possibly related to the study drug treatment by the Investigator: hyperparathyroidism in Patient 1602/2403-810313 while on the Lumizyme treatment. This event was "mild hyperparathyroidism" and it was considered possibly related because hyperparathyroidism is considered rare in children and there was no other plausible etiology for the event.

Table 19 SAE incidence in the Pivotal-Extension Study during the Myozyme treatment period (N=18)

Adverse Event (MedDRA Preferred Term)	Number of patients that this event occurred in at least once
Acute tonsillitis	1
Anaemia	1
Arrhythmia	1
Arrhythmia supraventricular	1
Atrial tachycardia	1
Bacteraemia	1
Bronchial obstruction	1
Bronchitis	1
Bronchitis acute	1
Bronchospasm	1
Cardiac arrest	1
Cardio-respiratory arrest	1
Catheter related complication	1
Catheter site discharge	1
Cough	1
Deafness neurosensory	1

Adverse Event (MedDRA Preferred Term)	Number of patients that this event occurred in at least once
Dehydration	1
Dental caries	1
Diarrhoea	1
Dysphagia	1
Dyspnoea	1
Enteritis	1
Femoral neck fracture	1
Femur fracture	1
Gastritis erosive	1
Gastritis viral	1
Gastroenteritis rotavirus	1
Gastrooesophageal reflux disease	1
Hand-foot-and-mouth disease	1
Heart rate decreased	1
Humerus fracture	1
Hypertension	1
Hypertrophic obstructive cardiomyopathy	1
Hypokinesia	1
Influenza	1
Injury asphyxiation	1
Leukodystrophy	1
Localised infection	1
Lymphadenopathy	1
Medical device complication	1
Middle ear effusion	1
Nausea	1
Nodal arrhythmia	1
Oesophageal erosion	1
Otitis media	1
Otitis media acute	1
Pneumothorax	1
Pulmonary oedema	1
Rales	1
Renal failure acute	1
Respiratory acidosis	1
Respiratory tract infection	1
Sepsis	1
Septic shock	1
Sputum retention	1
Superior vena caval occlusion	1
Supraventricular tachycardia	1
Syncope	1
Talipes	1
Thrombocytopenia	1
Tibia fracture	1
Tracheal disorder	1
Tracheitis	1
Upper respiratory tract infection	1
Urinary tract infection	1
Urticaria	1

Adverse Event (MedDRA Preferred Term)	Number of patients that this event occurred in at least once
Ventricular extrasystoles	1
Ventricular fibrillation	1
Ventricular hypertrophy	1
Ventricular tachycardia	1
Viral rash	1
Vocal cord paresis	1
Vomiting	1
Asthma	2
Bradycardia	2
Ear infection	2
Ejection fraction decreased	2
Electrolyte imbalance	2
Hypotension	2
Myopathy	2
Nasopharyngitis	2
Respiratory tract infection viral	2
Upper gastrointestinal haemorrhage	2
Atelectasis	3
Gastroenteritis	3
Oxygen saturation decreased	3
Pyrexia	3
Bronchiolitis	4
Pneumonia aspiration	4
Viral infection	4
Bronchopneumonia	5
Catheter related infection	5
Respiratory distress	5
Pneumonia	6
Respiratory syncytial virus infection	6
Respiratory failure	7

Table 20 SAE incidence in the Pivotal-Extension Study during the Lumizyme treatment period (N=16)

Adverse Event (MedDRA Preferred Term)	Number of patients that this event in occurred at least once
Aspiration	1
Atelectasis	1
Brain death	1
Bronchitis	1
Bronchopneumonia	1
Cardiac arrest	1
Cardiomyopathy	1
Convulsion	1
Cough	1
Dysphagia	1
Eustachian tube dysfunction	1
Femur fracture	1
Gastroenteritis	1

Hyperparathyroidism**	1
Hypoxic encephalopathy	1
Joint swelling	1
Oedema	1
Otitis media	1
Pericardial effusion	1
Rhinorrhoea	1
Sinus tachycardia	1
Sputum retention	1
Tracheitis	1
Upper respiratory tract infection	1
Urinary retention	1
Respiratory tract infection	2
Supraventricular tachycardia	2
Cardio-respiratory arrest	3
Respiratory distress	3
Respiratory failure	3
Pneumonia	4

**** Considered possibly related to Lumizyme treatment by Investigator**

Table 21 SAE incidence in Study 1702 during the Myozyme treatment period (N=2)

Adverse Event (MedDRA Preferred Term)	Number of patients that this event occurred in at least once
Cardiomyopathy	1
Gastroenteritis viral	1
Hypertrophic cardiomyopathy	1
Pneumonia	1
Respiratory distress	1
Upper respiratory tract infection	1
Catheter related infection	2

Table 22 SAE incidence in Study 1702 during Lumizyme treatment period (N=2)

Adverse Event (MedDRA Preferred Term)	Number of patients that this event occurred in at least once
Bronchiolitis	1
Bronchospasm	1
Pneumonia	1
Pneumonia aspiration	1
Respiratory failure	2

Table 23 AE incidence in the EAP during the Lumizyme period (N=7)

Adverse Event (MedDRA Preferred Term)	Number of patients that this event occurred at least once in
Bacteraemia	1
Bronchiolitis	1
Cardiac failure	1
Dehydration	1
Foreign body trauma	1
Pyrexia	1
Respiratory distress	1
Respiratory tract infection	1
Upper respiratory tract infection	1
Respiratory syncytial virus infection	2

In summary, only one SAE event was judged as possibly related to the study drug treatment by the Investigator: hyperparathyroidism in Patient 1602/2403-810313 while on the Lumizyme treatment. This event was "mild hyperparathyroidism" and it was considered possibly related because hyperparathyroidism is considered rare in young children and there was no other plausible etiology for the event. This Reviewer recommends that this SAE be listed in the Lumizyme labeling given that it is an event that is serious and unusual in the absence of drug therapy and it should be included even if there is only one report (per FDA's Guidance on the Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics). Otherwise, it does not appear that Lumizyme had a different SAE profile from Myozyme, and the overall SAE profiles generally reflect the underlying disease.

7.1.3 Other Significant Adverse Events

7.1.3.1 Other significant adverse events: infusion reactions (IRs)

Administering a recombinant human protein to patients with no or little endogenous levels of the protein can incite allergic reactions during and/or shortly after the infusion. These reactions are included as "infusion reactions." Infusion reactions are reactions that occur during the infusion, or up to 24-48 hours after the infusion[12], and have been observed in other protein based therapies. Several mechanisms of actions have been proposed, and numerous laboratory parameters have been attempted to characterize, quantify, and define these reactions. But no lab test has emerged as definitive, and the diagnosis remains a clinical one, and management is based on clinical needs.

Infusion reactions can have symptoms that range from benign to serious to life-threatening, including fever, headache, anxiety, urticaria, and tachycardia, wheezing, agitation, angioedema, respiratory failure, and hypotensive shock that requires intensive care support. Anaphylaxis is possible, and a delayed-hypersensitive (biphasic) reaction has been described for at least one

12 Sampson, H., Munoz-Furlong, A., Campbell, R., 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 February 2006: 391-397.

other lysosomal enzyme replacement product, Elaprase, whereby there are two waves of anaphylaxis, the second episode of anaphylaxis appearing after treatment and resolution of the first episode. Management of infusion reactions includes slowing the rate of infusion, temporary stopping the infusion, and treatment with antipyretics, antihistamines, beta adrenergic agonist bronchodilators, and steroids, and/or pre-medication with these agents with future infusions. The long-term impact on health and quality of life made by these infusion-related reactions, especially when recurrent and frequent, is unknown.

IRs (or in the Applicant's term, "infusion-associated reactions," or IARs) were defined by the Applicant as those AEs that 1) occurred following the initiation of the infusion up to and including 2-hour post infusion observation period, **and** 2) that were assessed by Investigator as related to drug administration (i.e., possibly, probably, or definitely related). In the opinion of this Reviewer, this definition of IR is overly conservative and narrow given that IRs can occur beyond the 2-hours post infusion window and the definition should not have depended on the Investigator's subjective assessment of relatedness. Using their definition, the Applicant stated that there were no concerning trends observed in the incidence rate of IR in ERT-naïve patients treated initially with Myozyme in the Pivotal Study, compared with ERT-naïve patients treated initially with Lumizyme in the EAP, or when patients in the Pivotal-Extension Study and Study 1702 were switched from Myozyme to Lumizyme. This Reviewer cannot independently verify these results using the more inclusive criteria that would have extended the IR qualifying period to 48 hours after infusion, and using the criteria agreed upon by the attendees of the Second Symposium on the Definition and Management of Anaphylaxis (see Reference 11 below) because the AE database did not record the timing of the start of AE for the majority of the AEs that were not flagged as IRs. During this review cycle, there was no time left to have the Applicant submit a revised AE analysis that could then be independently verified by the Reviewer. It will be important to revisit this issue regarding IRs in LOTS.

7.1.4 Common Adverse Events

7.1.4.1 Eliciting adverse events data in the development program

At every infusion visit the patient's legal guardian(s) was asked "Since your last questioning or visit, has the patient experienced any health problems?" Signs and symptoms experienced by the patient from the time of signing of the informed consent through the final study visit were recorded on the electronic case report form. An AE was any undesirable physical, psychological or behavioral effect experienced by a patient or subject during their participation in an investigational study, in conjunction with the use of the drug or biologic, whether or not product-related. This included any untoward signs or symptoms experienced by the patient from the time of signing of the informed consent until completion of the study. AEs may include, but were not limited to:

- Subjective or objective symptoms spontaneously offered by the patient or subject and/or observed by the Investigator or medical staff
- Findings at physical examinations
- Laboratory abnormalities of clinical significance

Disease signs, symptoms, and/or laboratory abnormalities already existing prior to the use of the product were not considered AEs after treatment unless they recurred after the patient had recovered from the preexisting condition or in the opinion of the Investigator they represented a clinically significant exacerbation in intensity or frequency. Clinical significance is defined as any variation in signs, symptoms, or testing that has medical relevance and might result in an alteration in medical care. The Investigator continued to monitor the patient until the assessment returned to baseline or until the Investigator determined that follow-up was no longer medically necessary.

7.1.4.2 Appropriateness of adverse event categorization and preferred terms

Adverse event categorization and verbatim-to-preferred terms coding appeared appropriate.

7.1.4.3 Incidence of common adverse event tables

The following tables tabulate the incidence of AEs that occurred at least once in more than 10% of the matched study populations, by treatment groups. Because study 1702 yielded only two matched patients, it was not included in this common adverse event analysis.

Table 24 Summary of adverse events occurring in at least 10% of patients (≥ 2 patients) treated with Myozyme in the Pivotal-Extension Study

AE (Preferred Term)	Incidence (the number of patient that this AE occurred in at least once)
Abdominal pain	2
Acoustic stimulation tests abnormal	2
Anorectal disorder	2
Arthropod bite	2
Bacteriuria	2
Blister	2
Blood bicarbonate decreased	2
Blood potassium decreased	2
Blood pressure decreased	2
Cardiac failure	2
Croup noninfectious	2
Deafness neurosensory	2
Dermatitis atopic	2
Dermatitis contact	2
Dry skin	2
Ear pain	2
Ejection fraction decreased	2
Exanthem	2
Eye discharge	2
Fungal skin infection	2
Gastroenteritis rotavirus	2
Haematocrit decreased	2
Humerus fracture	2
Hypertrophic obstructive cardiomyopathy	2
Hyperuricaemia	2
Hyponatraemia	2

AE (Preferred Term)	Incidence (the number of patient that this AE occurred in at least once)
Hypothermia	2
Immunisation reaction	2
Influenza	2
Kidney enlargement	2
Localised infection	2
Macroglossia	2
Osteoporosis	2
Pain	2
Pallor	2
Postoperative infection	2
Respiratory tract congestion	2
Respiratory tract infection bacterial	2
Respiratory tract infection viral	2
Restlessness	2
Rhonchi	2
Sepsis	2
Skin infection	2
Skin ulcer	2
Speech disorder developmental	2
Sputum retention	2
Talipes	2
Tremor	2
Tympanic membrane hyperaemia	2
Ventricular extrasystoles	2
Ventricular hypertrophy	2
Viral rash	2
Viral upper respiratory tract infection	2
Vocal cord paresis	2
Abdominal distension	3
Arrhythmia supraventricular	3
Bacteraemia	3
Blood creatine phosphokinase MB increased	3
Bronchial obstruction	3
Bronchitis acute	3
Cyanosis	3
Dehydration	3
Developmental delay	3
Epistaxis	3
Excoriation	3
Eye infection	3
Hyperhidrosis	3
Hypochloraemia	3
Hypokinesia	3
Hypoparathyroidism	3
Hypotonia	3
Loose stools	3
Lower respiratory tract infection	3
Lymphadenopathy	3
Oral candidiasis	3
Osteopenia	3
Pharyngolaryngeal pain	3

AE (Preferred Term)	Incidence (the number of patient that this AE occurred in at least once)
Pyuria	3
Rigors	3
Urine output decreased	3
Wheezing	3
Acute tonsillitis	4
Anxiety	4
Candidiasis	4
Dyspnoea	4
Electrolyte imbalance	4
Femur fracture	4
Flushing	4
Insomnia	4
Irritability	4
Lung disorder	4
Nausea	4
Pruritus	4
Rash erythematous	4
Rash papular	4
Respiratory tract infection	4
Rhinitis	4
Tracheal disorder	4
Agitation	5
Bronchospasm	5
Catheter related complication	5
Conjunctivitis	5
Dental caries	5
Eczema	5
Eosinophilia	5
Feeding disorder	5
Gastroenteritis viral	5
Haematuria	5
Heart rate decreased	5
Hypercalcaemia	5
Hypercalciuria	5
Increased bronchial secretion	5
Inflammation localised	5
Metabolic acidosis	5
Middle ear effusion	5
Oedema peripheral	5
Teething	5
Urinary tract infection	5
Asthma	6
Bradycardia	6
Bronchiolitis	6
Constipation	6
Dysphagia	6
Respiratory syncytial virus infection	6
Sputum culture positive	6
Asthenia	7
Bronchopneumonia	7
Choking	7

AE (Preferred Term)	Incidence (the number of patient that this AE occurred in at least once)
Gastroenteritis	7
Gastrooesophageal reflux disease	7
Hypoacusis	7
Joint contracture	7
Myopathy	7
Otitis media acute	7
Rash maculo-papular	7
Supraventricular tachycardia	7
Erythema	8
Post procedural pain	8
Hypotension	9
Rash macular	9
Catheter related infection	10
Hypertension	10
Retching	10
Viral infection	10
Pharyngitis	11
Upper respiratory tract congestion	11
Respiratory distress	12
Pneumonia aspiration	13
Tachypnoea	13
Medical device complication	14
Rhinorrhoea	14
Tracheitis	14
Ear infection	15
Nasopharyngitis	17
Atelectasis	18
Respiratory failure	18
Upper gastrointestinal haemorrhage	19
Pneumonia	20
Tachycardia	21
Dermatitis diaper	23
Otitis media	23
Anaemia	26
Rash	26
Diarrhoea	29
Urticaria	30
Upper respiratory tract infection	31
Oxygen saturation decreased	37
Vomiting	39
Cough	46
Pyrexia	113

Table 25 Summary of adverse events occurring in at least 10% of patients (>2 patients) treated with Lumizyme in Pivotal-Extension Study

AE (Preferred Term)	Incidence (the number of patient this AE occurred in at least once)
Atelectasis	2
Bronchopneumonia	2
Conductive deafness	2
Conjunctivitis	2
Convulsion	2
Decubitus ulcer	2
Ear infection	2
Impetigo	2
Joint contracture	2
Pharyngitis streptococcal	2
Pulmonary oedema	2
Rash	2
Rhinorrhoea	2
Supraventricular tachycardia	2
Anaemia	3
Bronchitis	3
Cardio-respiratory arrest	3
Respiratory distress	3
Respiratory failure	3
Respiratory tract infection	3
Cough	4
Diarrhoea	4
Gastroenteritis	4
Pneumonia	4
Upper respiratory tract infection	4
Otitis media	5
Pyrexia	5
Vomiting	5

Table 26 Summary of adverse events occurring in at least 10% of patients (> 1 patient) treated with Lumizyme in the EAP

AE (Preferred Term)	Incidence (the number of patient that this AE occurred in at least once)
Apnoea	1
Aspiration	1
Atelectasis	1
Bacteraemia	1
Blood in stool	1
Bronchitis	1
Candidiasis	1
Catheter site discharge	1
Conjunctivitis infective	1
Croup noninfectious	1
Deafness	1
Dehydration	1
Dysphagia	1
Dyspnoea	1
Eczema	1
Foreign body trauma	1
Hyperhidrosis	1
Hypertension	1
Medical device complication	1
Middle ear effusion	1
Nasal congestion	1
Oral candidiasis	1
Oxygen saturation decreased	1
Pneumonia	1
Post procedural nausea	1
Post procedural pain	1
Rash erythematous	1
Rash papular	1
Respiratory distress	1
Respiratory tract congestion	1
Respiratory tract infection	1
Restlessness	1
Rhinorrhoea	1
Tachycardia	1
Teething	1
Weight gain poor	1
Alanine aminotransferase increased	2
Aspartate aminotransferase increased	2
Blood creatine phosphokinase increased	2
Blood creatine phosphokinase MB increased	2
Bronchiolitis	2
Bronchospasm	2
Catheter site oedema	2
Dermatitis contact	2
Iliotibial band syndrome	2
Myopathy	2
Rash	2
Skin irritation	2
Viral infection	2

AE (Preferred Term)	Incidence (the number of patient that this AE occurred in at least once)
Cardiac failure	3
Cough	3
Gastrooesophageal reflux disease	3
Respiratory syncytial virus infection	3
Upper respiratory tract congestion	3
Conjunctivitis	4
Sinusitis	4
Otitis media	6
Urticaria	6
Diarrhoea	7
Vomiting	7
Upper respiratory tract infection	8
Ear infection	10
Pyrexia	16

7.1.4.4 Identifying common and drug-related adverse events

The most common AEs were related to Pompe disease manifestations and infusion-related allergic reactions. One difference that is noteworthy between the two products is that "decreased oxygen saturation" was listed as a common treatment-emergent adverse reaction in the Myozyme labeling. This was not observed as commonly as with Lumizyme during the EAP study. No other trend could be appreciated in distinguishing the common adverse profiles between the two products, but interpretation is limited given the small number of patients studied, the short duration of treatment on the Lumizyme, and the lack of a placebo control.

7.1.5 Immunogenicity

Immunogenicity was predominantly monitored by serum anti-rhGAA IgG antibody titers, and for some patients, inhibitory antibody status. A comparative analysis of inhibition was not specifically performed for the purpose of this supplement. However, as part of PMC #24 in the 28 April 2006 Myozyme approval letter, the Applicant performed a retrospective analysis of all IgG-positive patients to evaluate patients in the Pivotal-Extension Study and Study 1702, as well as for "any other patients who became invasively ventilated up to a certain cutoff date" for the presence of anti-rhGAA antibodies that inhibited enzyme activity or uptake using in vitro assays. Based on this report with limited data, this Reviewer could not draw conclusions about the comparability between the two products with regards to inhibition of enzyme activity or uptake.

Similar to the data availability for the motor and LVMI data, there were too few data points gathered for IgG antibody titers during the Lumizyme experience (data not shown) per each patient to draw conclusions about product comparability with regards to IgG immunogenicity.

7.2 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

In both treatment groups deaths reported appeared predominantly due to underlying disease, and included respiratory and cardiac failure, cardiac arrest, and infections. Serious Adverse Events (SAEs) also tended to be consistent with underlying disease, except for one case of hyperparathyroidism in a patient who was treated with the Lumizyme; the case was considered "possibly" related to the study drug because hyperparathyroidism is rare in infants and in Pompe disease patients, and there was no other plausible etiology for the event. Common AEs tended to reflect underlying disease or were AEs commonly seen with ERT infusions. For Myozyme "decreased oxygen saturation" in the Pivotal study was one of the most common AEs whereas it was not for Lumizyme in the EAP study. The Reviewer was unable to perform a meaningful analysis on product comparability with regards to IR or immunogenicity due to the limited data available.

8 OVERALL ASSESSMENT

8.1 Conclusions

Since comparability of Lumizyme to Myozyme could not be established based on non clinical data, it was necessary to try to establish comparability based on clinical data. The original BLA was approved based on invasive ventilator-free survival advantage that was demonstrated in infantile-onset Pompe disease patients using a historical control. In this submission the Applicant intended to establish comparability of Lumizyme based on clinical data from infantile-onset populations who received Lumizyme and Myozyme.

Results showed that the 18-month invasive ventilator free survival rate was higher for the 18 patients treated with Myozyme in the Pivotal-Extension Study as compared to the 7 matched patients treated with Lumizyme in the EAP (83% vs. 71% ventilator-free survival, respectively). Median ventilator free survival time (age at which half of the study patient population became ventilator dependent or died) was 32 months for the Myozyme treated group in the Pivotal-Extension Study—which was longer than the 20 to 25 months median ventilator-free survival time for the Lumizyme treated group in the EAP.

The results were limited by these analyses being conducted in a retrospective fashion, and the studies were not performed as head-to-head comparisons. Also, because the data were derived from an exceedingly small number of patients studied, with chance alone being able to explain the results, no definitive conclusions could be reached. (b) (4) This Reviewer believes that concerns should be raised that there may be an increased risk to the infantile-onset patients due to the potential risk for rapid disease progression if they were to be treated with Lumizyme. Since the safety and effectiveness of Lumizyme have not been established in the infantile-onset population, and safety and effectiveness have been

established with Myozyme, this Reviewer recommends that infantile-onset patients continued to be treated with Myozyme, and that Lumizyme be restricted for use only in the population in whom an acceptable risk/benefit profile has been established.

Product comparability could not be established based on clinical efficacy outcome measures. Furthermore, no conclusions could be reached about which product attributes correlated with efficacy outcome, or how specifications should be set for each product attribute, because the correlation analysis was limited by the fact that the patients were treated with different Drug Substances and Drug Products lots for different treatment durations and in various random orders.

This Reviewer recommends that Lumizyme not be approved as a comparable product to Myozyme. This Reviewer further recommends that changes be made to the Myozyme product labeling based on outcomes of the Pivotal-Extension study. About 50% of the original cohort in the Pivotal Study had either become ventilator dependent or died by 3 years of age, and there was a plateau (reaching a ceiling) seen in motor development in even the most treatment responsive patients. Limitations of alglucosidase alfa treatment should be updated in the labeling to allow patients and physicians to re-evaluate the over all risk-benefit of treatment now that data for longer follow up has become available.

In both treatment groups, deaths reported were likely due to underlying disease, including respiratory and cardiac failure, cardiac arrest, and infections. Serious Adverse Events (SAEs) also tended to be consistent with underlying disease, except for one case of hyperparathyroidism in a patient who was treated with Lumizyme. The case was considered "possibly" related to the study drug because hyperparathyroidism is rare in infants and in Pompe disease patients, and there was no other plausible etiology for the event. Consideration should be given to include this SAE in the Lumizyme product labeling. Other than that oxygen desaturation was observed as a common adverse reaction with Myozyme but not with Lumizyme, the common adverse events profile were similar between the two products, and tended to reflect underlying disease or were commonly seen with ERT infusions. This Reviewer was unable to perform a meaningful analysis on immunogenicity comparability given limitations of the data.

9 RECOMMENDATION ON REGULATORY ACTION

This Reviewer recommends that this manufacturing supplemental Biologics License Application (sBLA) not be approved for Lumizyme because there is insufficient data to establish clinical comparability between Lumizyme and Myozyme.

Genzyme (the Applicant) stated that the Late-Onset Treatment Study (LOTS, Study AGLU02704) could address the issue of safety and efficacy in a distinct population, the late (non-infantile onset) patients, and proposes to submit a new BLA for Lumizyme for use in that population. Information submitted and reviewed in this sBLA would be rolled over to the new BLA for Lumizyme. The Applicant's proposal is acceptable. The Reviewer recommends that given the complexity of the issues, an Advisory Committee (AC) meeting be convened to discuss final approval decisions regarding Lumizyme.

This Reviewer recommends that consideration be given to updating the Myozyme labeling to include ventilator-free survival data from the original Pivotal Study cohort with longer term data that have become available for patients reaching about 3 years of age.

Although no definitive conclusions could be drawn due to limitations of the data as discussed, based on the results of the 18-month invasive ventilator free survival rate and the median ventilator survival time, the data suggest an inferior trend in potency/efficacy for Lumizyme, especially in the context of known CMC product attributes that are thought to render this a less potent/efficacious product. Considering the totality of the available evidence, this Reviewer believes that concerns should be raised that there may be an increased risk to the infantile-onset patients due to the potential risk for rapid disease progression if they were to be treated with Lumizyme, and recommends that Myozyme, a proven product in this population, be continued to be used to treat the infantile onset patients. Lumizyme should be indicated only in the population in which an acceptable safety and efficacy have been established.

10 APPENDICES

Pivotal-Extension Study: age at symptom onset

Patient ID	Age at symptom onset, unadjusted for gestational age (months)
1602/2403-0201301	0
1602/2403-0202308	0
1602/2403-6001302	0
1602/2403-8103319	0
1602/2403-8304314	0
1602/2403-8102317	0.1
1602/2403-0102309	0.2
1602/2403-6003315	0.2
1602/2403-8101313	0.4
1602/2403-5203306	1.5
1602/2403-0103311	2.2
1602/2403-6002303	2.4
1602/2403-8305312	2.5
1602/2403-5202305	2.6
1602/2403-2101316	3
1602/2403-0101307	4.2
1602/2403-0203318	4.3
1602/2403-5204310	5.4
Range of age at symptom onset: 0→5.4 months Median age at symptom onset: 1.0 (±1.8 SD)	

Pivotal-Extension Study: age at Pompe disease diagnosis

Patient ID	Age at diagnosis, unadjusted for gestational age (months)
1602/2403-6003315	0.2
1602/2403-0201301	0.7
1602/2403-8101313	0.7
1602/2403-8304314	0.7
1602/2403-0202308	1.7
1602/2403-8103319	1.9
1602/2403-8305312	2.9
1602/2403-5202305	4
1602/2403-0101307	4.2
1602/2403-0203318	4.5
1602/2403-6001302	4.7
1602/2403-5203306	4.8
1602/2403-6002303	4.9
1602/2403-0102309	5
1602/2403-2101316	6
1602/2403-8102317	6
1602/2403-5204310	6.2
1602/2403-0103311	6.8
Range of age at diagnosis: 0.2→6.8 months (unadjusted for gestational age. If adjusted for gestational age, all ages of diagnosis would have been ≤ 6 months of age). Median age at diagnosis: 4.4 months (± 2.2 SD)	

Pivotal-Extension Study age at 1st 160 L infusion

Patient ID	Age at 1st infusion, adjusted for gestational age (months)	Age at 1st infusion (months)
1602/2403-6003315	1.2	1.2
1602/2403-8103319	1.8	2.1
1602/2403-8101313	1.8	2.3
1602/2403-8304314	1.9	1.9
1602/2403-0202308	4.3	4.3
1602/2403-0201301	4.8	5
1602/2403-0102309	4.8	5.3
1602/2403-5202305	5	5.7
1602/2403-8305312	5.1	5.1
1602/2403-0203318	5.4	5.4
1602/2403-2101316	5.5	6.9
1602/2403-8102317	5.6	6.2
1602/2403-6001302	5.6	7
1602/2403-5204310	5.7	6.4
1602/2403-5203306	5.8	5.9
1602/2403-0101307	6	6.9
1602/2403-6002303	6.1	7
1602/2403-0103311	6.1	7.3
Range of age at first infusion:	1.2→6.1	1.2→7.3
Median age of first infusion:	5.3 (± 1.7 SD)	5.5 (± 2.0 SD)

Pivotal Study baseline cardiohypertrophy by left ventricular mass index LVMI and LVM-Z scores

Patient ID	Visit during 1st LVMI measurement	LVMI	LVM-Z scores
1602/2403-6003315*	SCREENING	59.3	1.7
1602/2403-6001302	WEEK 4	73.1	2.1
1602/2403-2101316	SCREENING	122.1	4.4
1602/2403-8304314	SCREENING	149.2	5.3
1602/2403-0103311	SCREENING	162.7	5.5
1602/2403-8101313	SCREENING	153.0	5.5
1602/2403-5203306	SCREENING	163.4	5.6
1602/2403-5204310	SCREENING	179.4	5.8
1602/2403-6002303	WEEK 8	180.0	5.8
1602/2403-8102317	SCREENING	202.1	6.4
1602/2403-8305312	SCREENING	207.8	6.5
1602/2403-0102309	SCREENING	220.3	6.7
1602/2403-0202308	SCREENING	225.2	6.8
1602/2403-0201301	SCREENING	237.9	7.1
1602/2403-8103319	SCREENING	233.4	7.1
1602/2403-0203318	WEEK 4	206.1	7.7
1602/2403-0101307	SCREENING	283.2	7.7
1602/2403-5202305	BASELINE	301.8	8.0
Range of LVMI and LVM-Z		59.3→301.8	1.7→8.0
Mean LVMI and LVM-Z (± SD)		186.7 (± 63.3)	5.9 (±1.7)

Pivotal Study CRIM status

Patient ID	CRIM status
1602/2403-6002303	NEGATIVE
1602/2403-8101313	NEGATIVE
1602/2403-8102317	NEGATIVE
1602/2403-8103319	NEGATIVE
1602/2403-0101307	POSITIVE
1602/2403-0102309	POSITIVE
1602/2403-0103311	POSITIVE
1602/2403-0201301	POSITIVE
1602/2403-0202308	POSITIVE
1602/2403-0203318	POSITIVE
1602/2403-2101316	POSITIVE
1602/2403-5202305	POSITIVE
1602/2403-5203306	POSITIVE
1602/2403-5204310	POSITIVE
1602/2403-6001302	POSITIVE
1602/2403-6003315	POSITIVE
1602/2403-8304314	POSITIVE
1602/2403-8305312	POSITIVE
Summary of CRIM Status	4 NEGATIVES (22%) 14 POSITIVES (78%)

Study 1702 demographic data for the two matched patients

Patient ID	Age at 1st infusion, adjusted for gestational age (months)	Age at 1st infusion (months)	Age at symptom onset (months)	Age at diagnosis (months)	CRIM status
1702-0107420	3.7	3.7	1.5	1.5	NEGATIVE
1702-8102404	6.1	8.2	3	6.6	POSITIVE
Median ± SD	4.9 ± 1.7	6.0 ± 3.2	2.3 ± 1.1	4.1 ± 3.6	

Study 1702 Baseline/Screening LVMI and LVM-Z score of the two matched patients

Patient ID	Visit	LVMI	LVM-Z
1702-0107420	SCREENING	202.8	6.4
1702-8102404	BASELINE	357.7	8.6
Median ±SD		280.3 ± 109.586	7.5 ± 1.6

Individual Pompe PEDI Functional Mobility Scaled Scores by treatment weeks in the 20 "matched" patients that were analyzed in this review, from the Pivotal-Extension Study (AGLUL01602/2403) and Study 1702 (AGLU01702).

Dashed lines—Lumizyme (2000 L); Arrows—time of product switch from Myozyme (160 L) to Lumizyme (2000 L)

Motor

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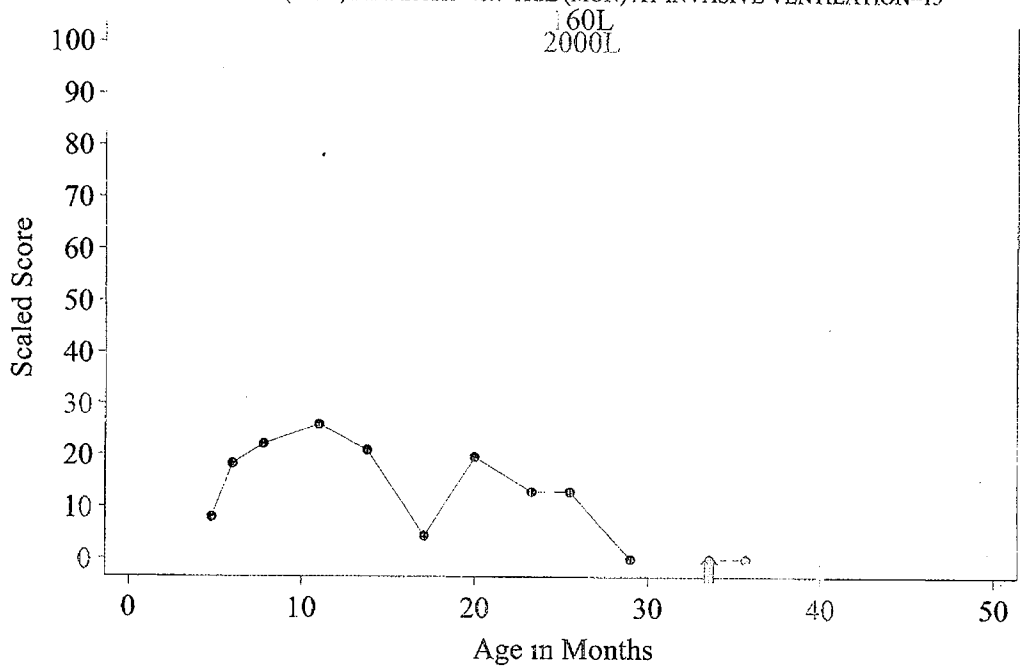
FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=201301 STUDY ID=AGLU01602/2403 DOSE=40 mg/kg CRIM=POSITIVE AGE AT 1st INFUSION=5 Months

AGE (MON) AT DEATH=40.7 AGE (MON) AT INVASIVE VENTILATION=15



⇑ represents the age(in months) at first 2000L infusion.

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Datasets Used: FDA2008.GP1. FDA2008.SURVIVD1 and FDA2008.SURVIVD

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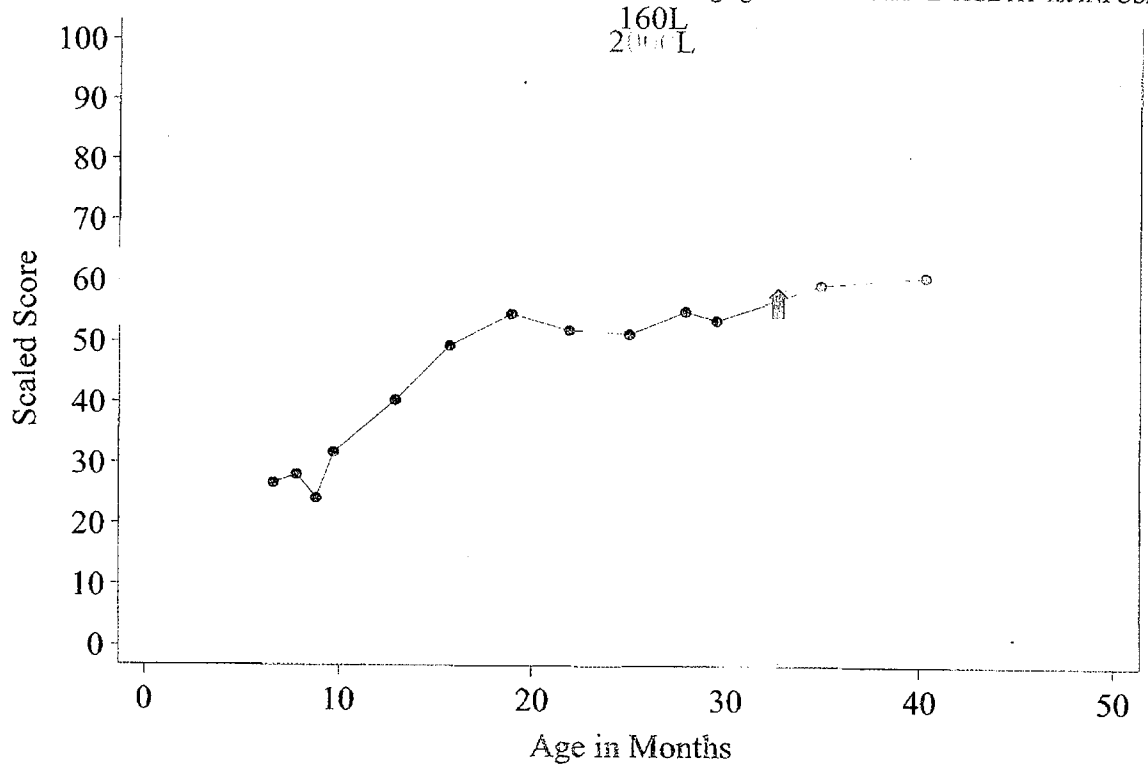
FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=6001302 STUDY ID=AGLU01602/2403 DOSE=20 mg/kg CRIM=POSITIVE AGE AT 1st INFUSION=7 Months



⇧ represents the age(in months) at first 2000L infusion.

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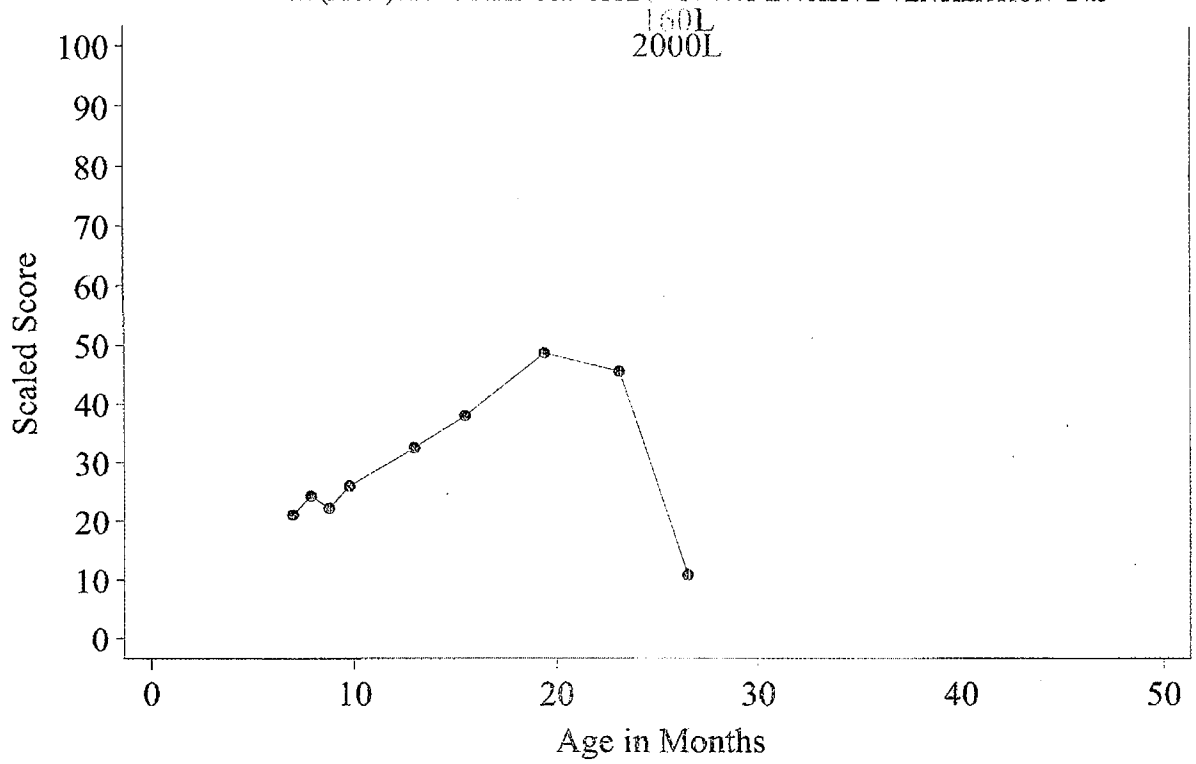
FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=6002303 STUDY ID=AGLU01602/2403 DOSE=40 mg/kg CRIM=NEGATIVE AGE AT 1st INFUSION=7 Months

AGE (MON) AT DEATH=31.9 AGE (MON) AT INVASIVE VENTILATION=24.5



⇧ represents the age(in months) at first 2000L infusion.

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Datasets Used: FDA2008.GP1. FDA2008.SURVIVD1 and FDA2008.SURVIVD

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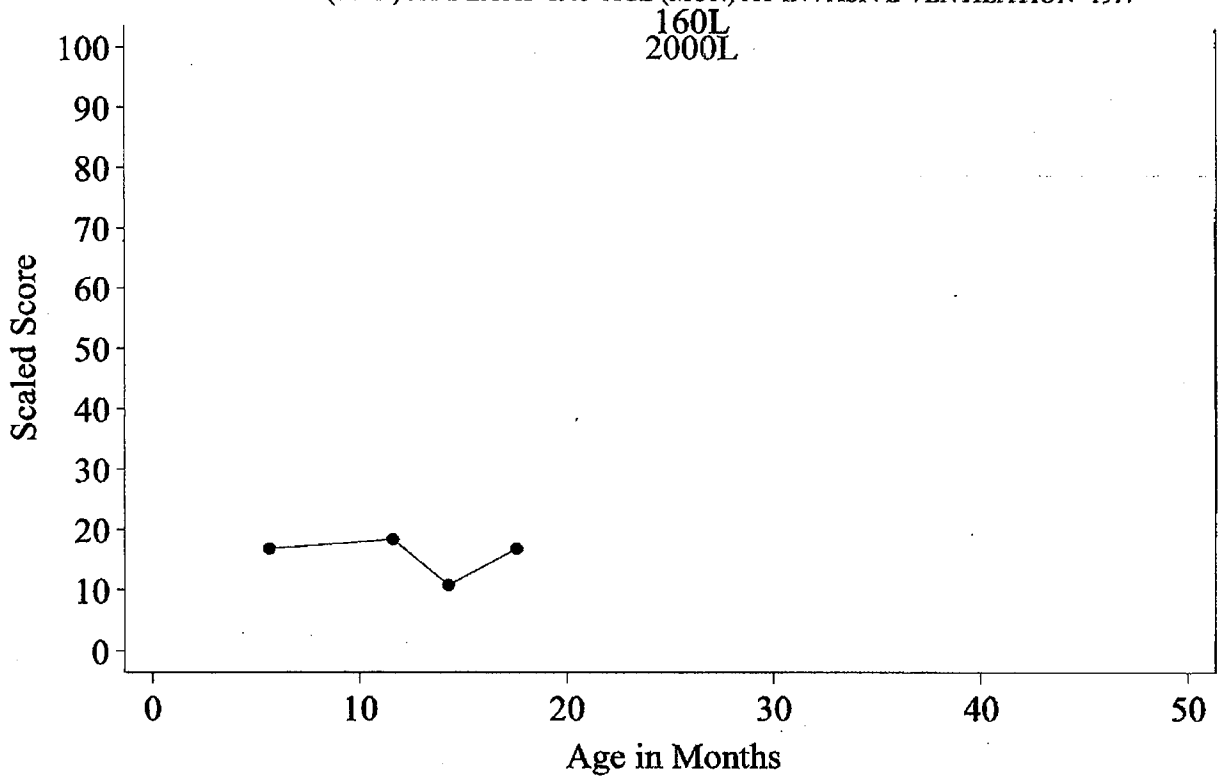
FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=5202305 STUDY ID=AGLU01602/2403 DOSE=20 mg/kg CRIM=POSITIVE AGE AT 1st INFUSION=5.7 Months

AGE (MON) AT DEATH=19.8 AGE (MON) AT INVASIVE VENTILATION=19.4



⬆ represents the age(in months) at first 2000L infusion.

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Datasets Used: FDA2008.GP1. FDA2008.SURVIVD1 and FDA2008.SURVIVD

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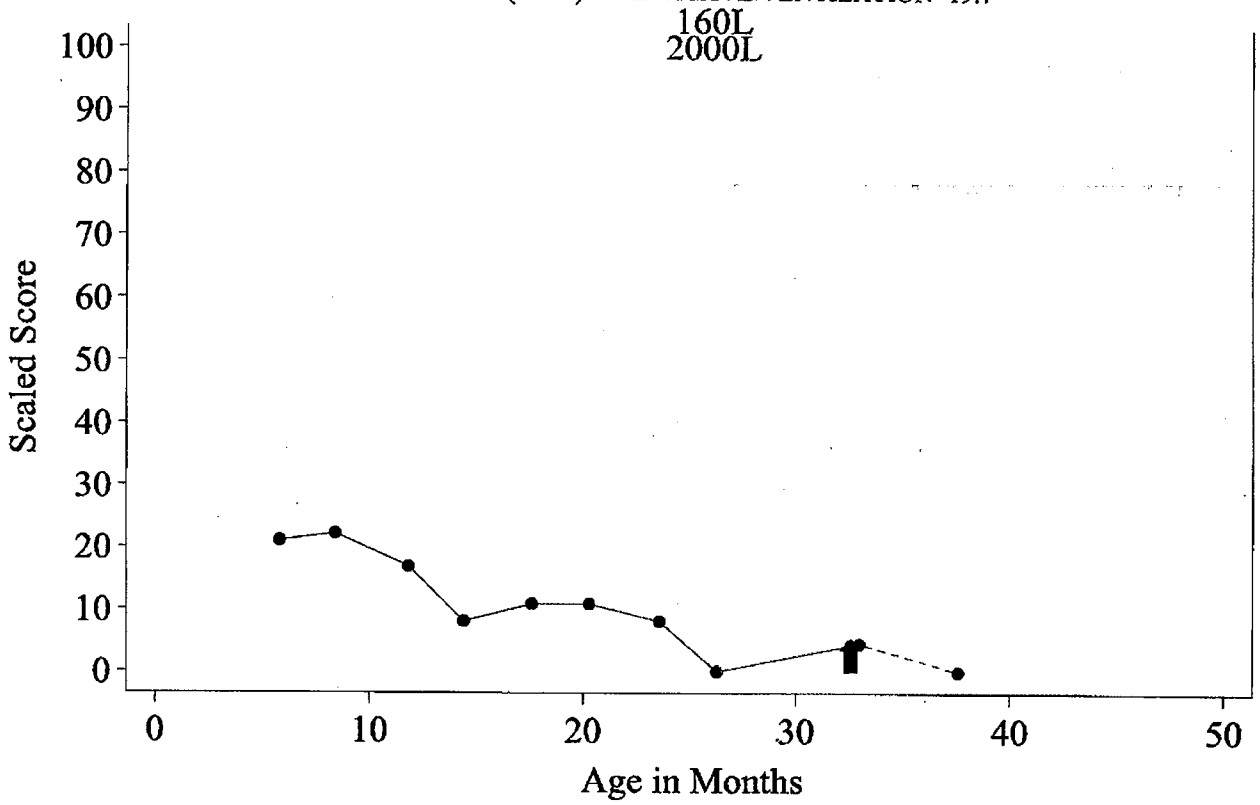
FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=5203306 STUDY ID=AGLU01602/2403 DOSE=20 mg/kg CRIM=POSITIVE AGE AT 1st INFUSION=5.9 Months

AGE (MON) AT INVASIVE VENTILATION=19.7



⬆ represents the age(in months) at first 2000L infusion.

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Datasets Used: FDA2008.GP1. FDA2008.SURVIVD1 and FDA2008.SURVIVD

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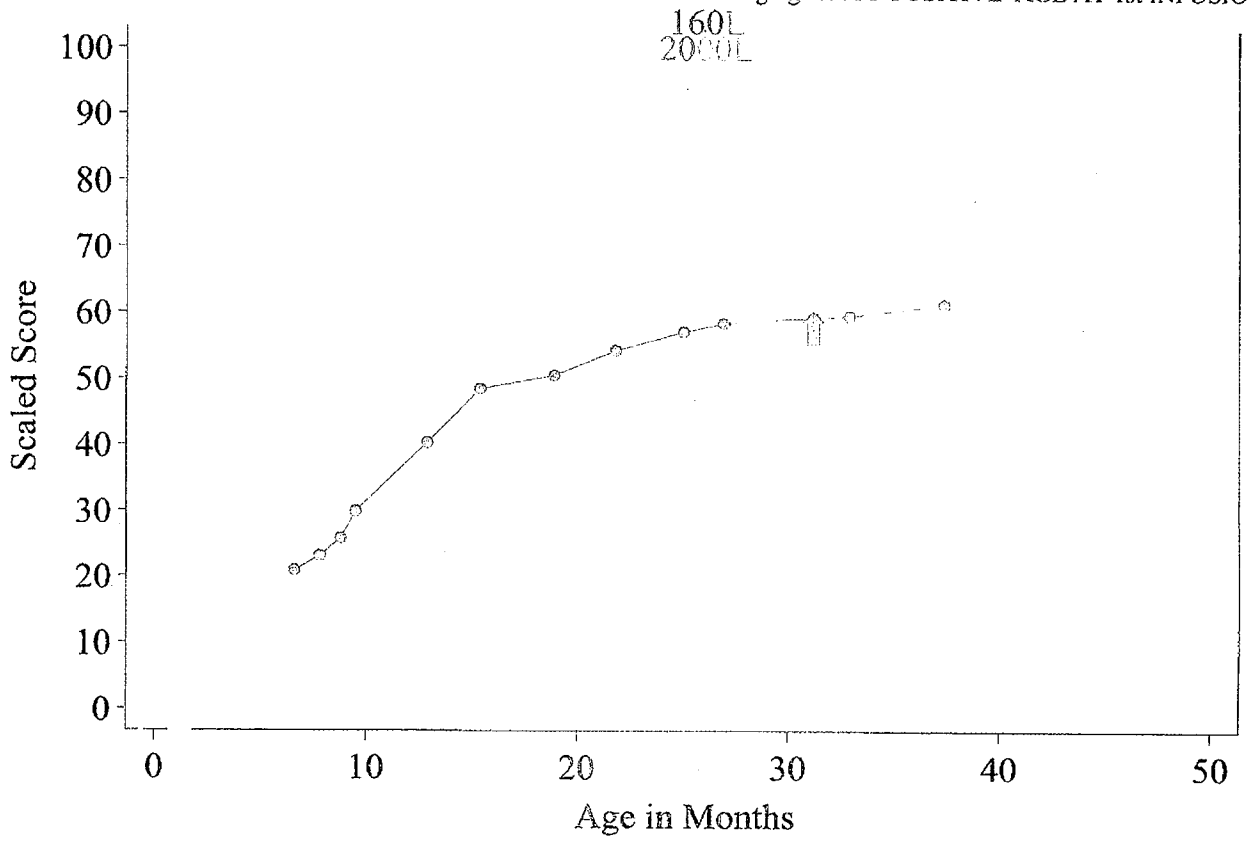
FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=101307 STUDY ID=AGLU01602/2403 DOSE=40 mg/kg CRIM=POSITIVE AGE AT 1st INFUSION=6.9 Months



⇧ represents the age(in months) at first 2000L infusion.

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Datasets Used: FDA2008.GP1, FDA2008.SURVIVD1 and FDA2008.SURVIVD

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FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=202308 STUDY ID=AGLU01602/2403 DOSE=40 mg/kg CRIM=POSITIVE AGE AT 1st INFUSION=4.3 Months

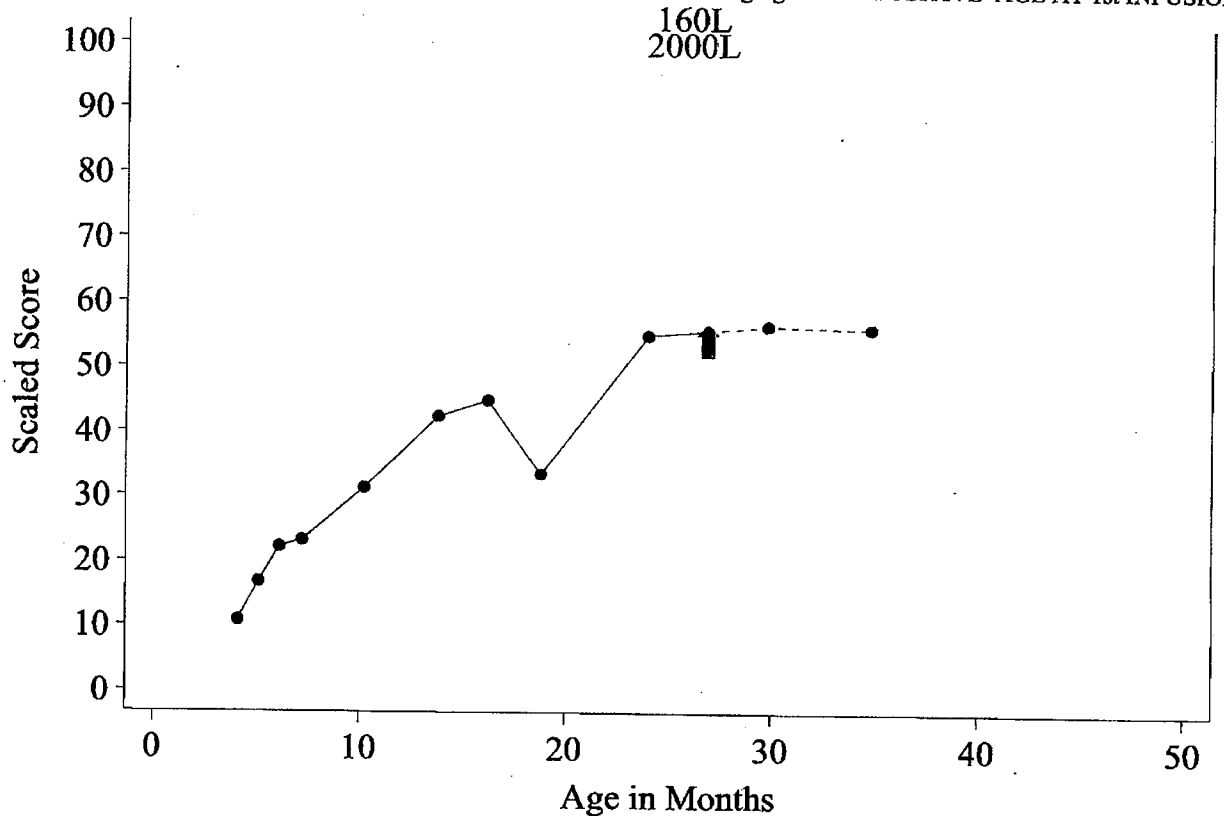

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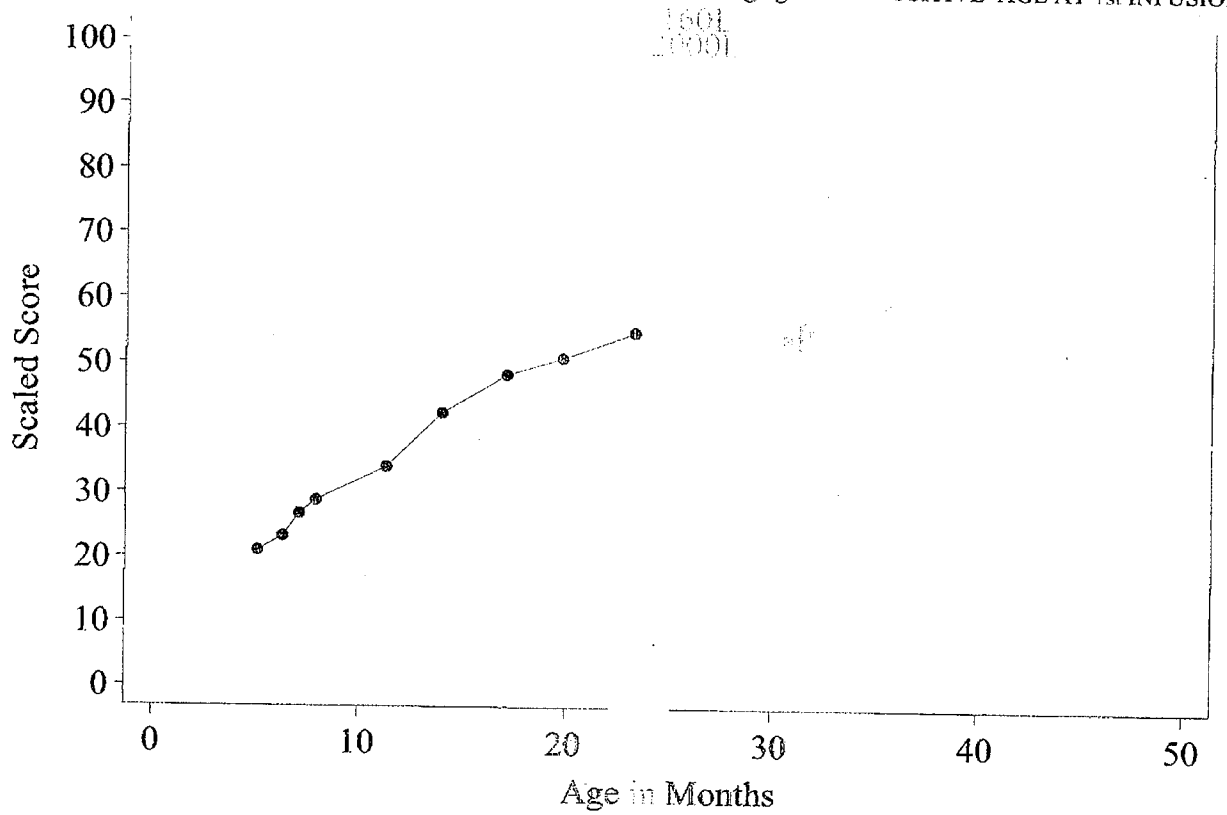
FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=102309 STUDY ID=AGLU01602/2403 DOSE=20 mg/kg CRIM=POSITIVE AGE AT 1st INFUSION=5.3 Months



represents the age(in months) at first 2000L infusion.

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Datasets Used: FDA2008.GP1, FDA2008.SURVIVD1 and FDA2008.SURVIVD

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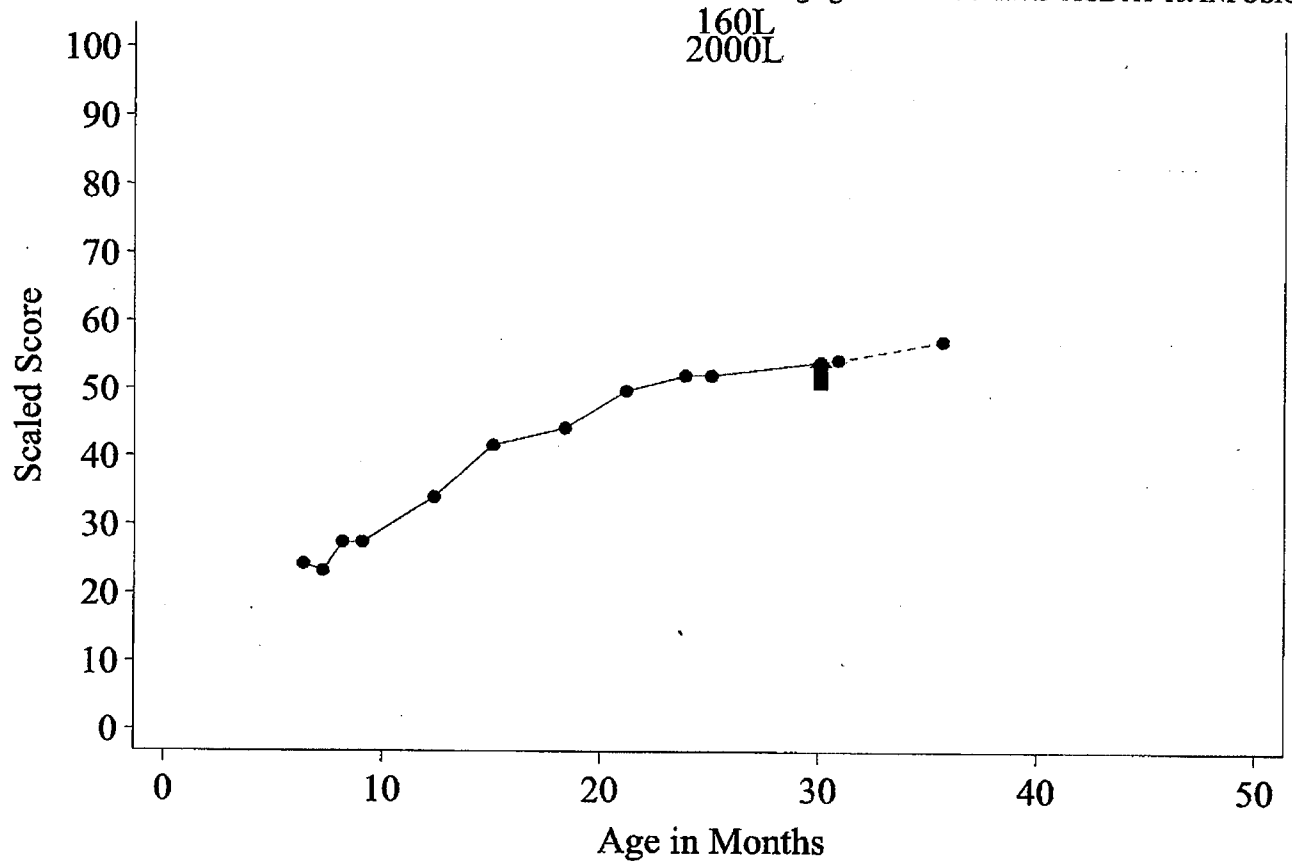
FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=5204310 STUDY ID=AGLU01602/2403 DOSE=20 mg/kg CRIM=POSITIVE AGE AT 1st INFUSION=6.4 Months



⬆ represents the age(in months) at first 2000L infusion.

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Datasets Used: FDA2008.GP1, FDA2008.SURVIVD1 and FDA2008.SURVIVD

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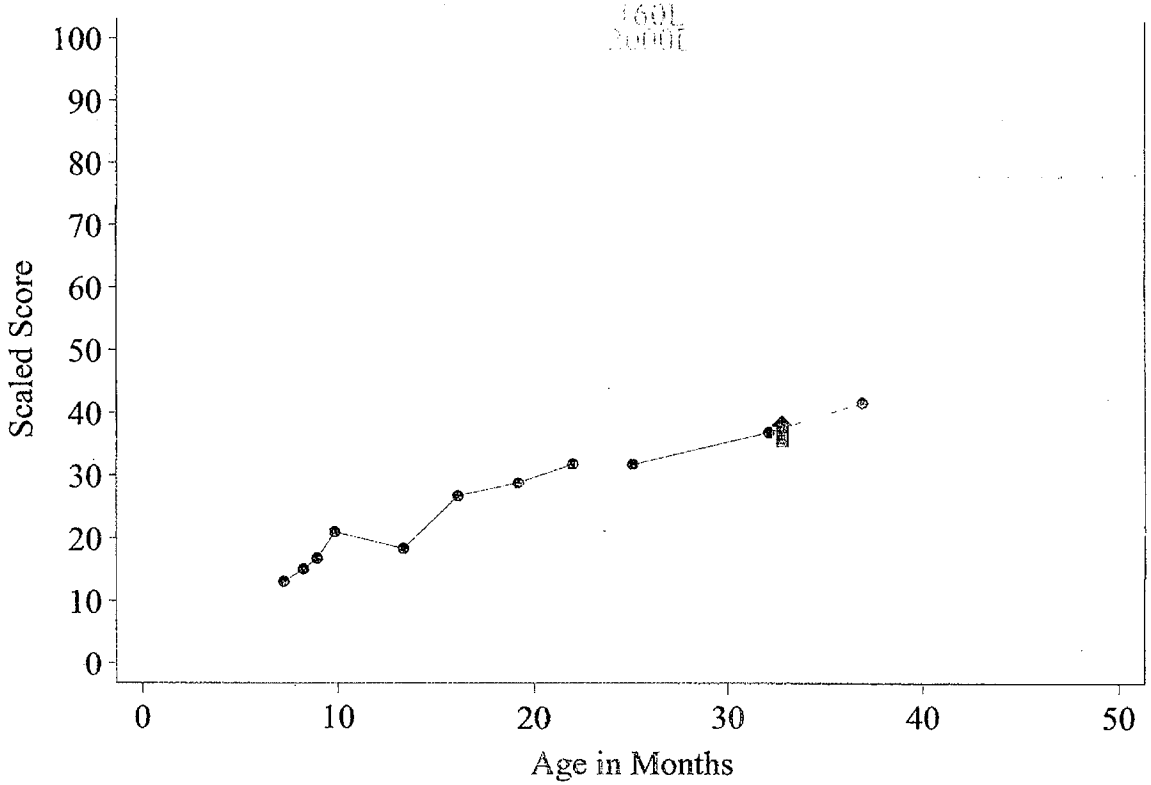
FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=103311 STUDY ID=AGLU01602/2403 DOSE=40 mg/kg CRIM=POSITIVE AGE AT 1st INFUSION=7.3 Months



⬆ represents the age(in months) at first 2000L infusion.

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Datasets Used: FDA2008.GP1, FDA2008.SURVIVD1 and FDA2008.SURVIVD2

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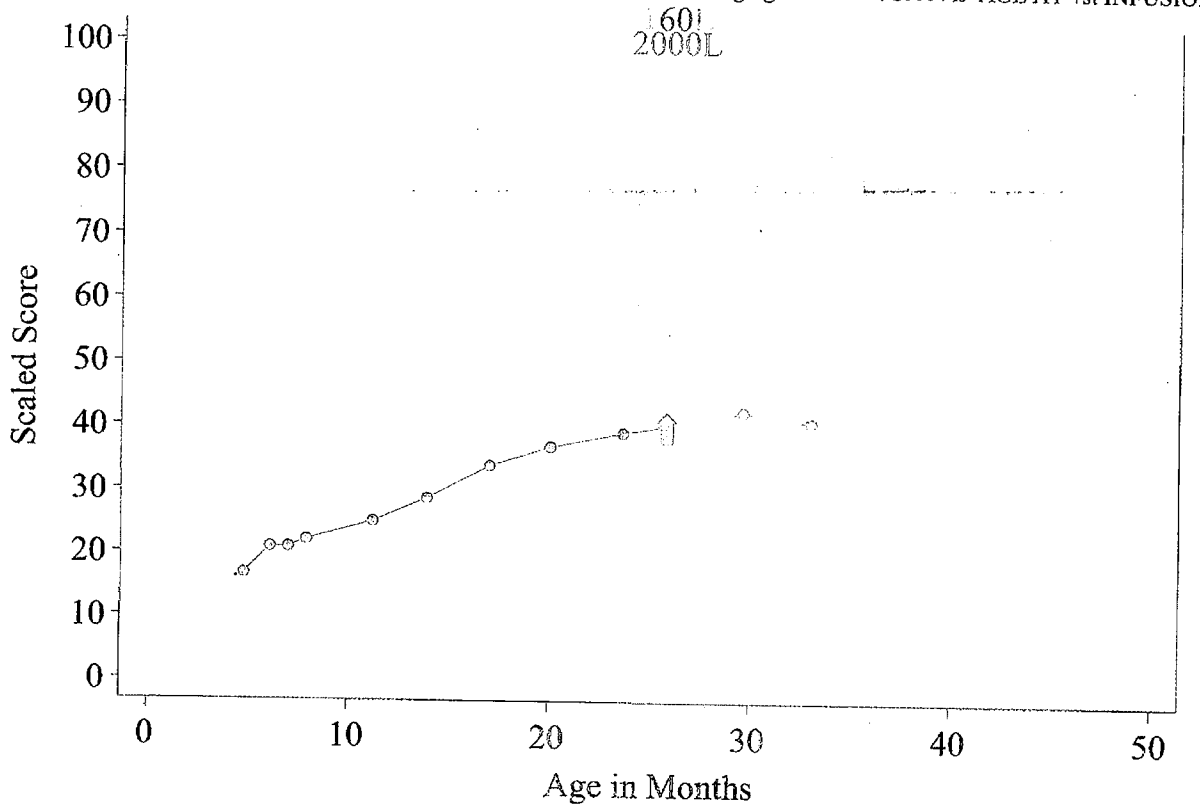
Protocol No. POMPE2000L

FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=8305312 STUDY ID=AGLU01602/2403 DOSE=20 mg/kg CRIM=POSITIVE AGE AT 1st INFUSION=5.1 Months



⇧ represents the age(in months) at first 2000L infusion.

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Datasets Used: FDA2008.GP1. FDA2008.SURVIVD1 and FDA2008.SURVIVD2

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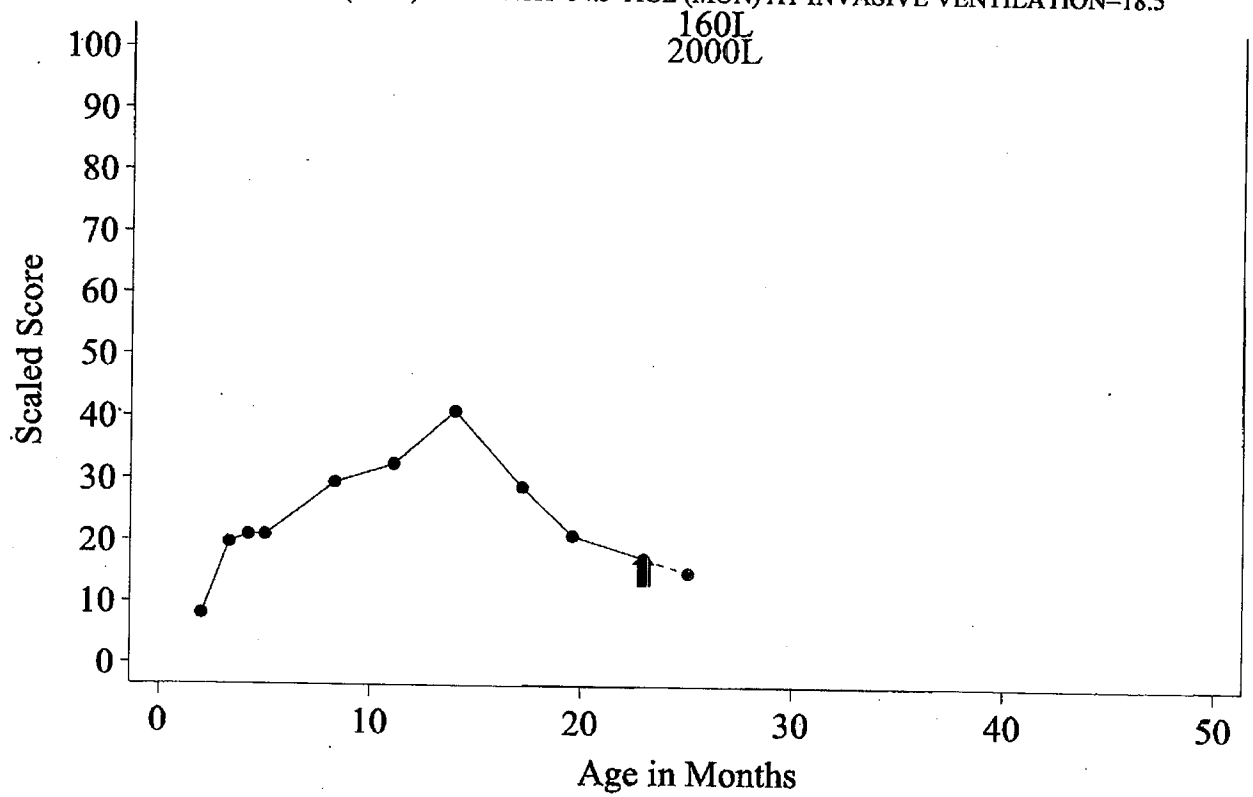
FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=8101313 STUDY ID=AGLU01602/2403 DOSE=40 mg/kg CRIM=NEGATIVE AGE AT 1st INFUSION=2.3 Months

AGE (MON) AT DEATH=34.3 AGE (MON) AT INVASIVE VENTILATION=18.5



⬆ represents the age(in months) at first 2000L infusion.

Y:\POMPES\POMPE2000L\PROGRAMS\OUTPUT\FDA2008\FPOMPEPEDIBYPATCGM.SAS
Datasets Used: FDA2008.GP1. FDA2008.SURVIVD1 and FDA2008.SURVIVD

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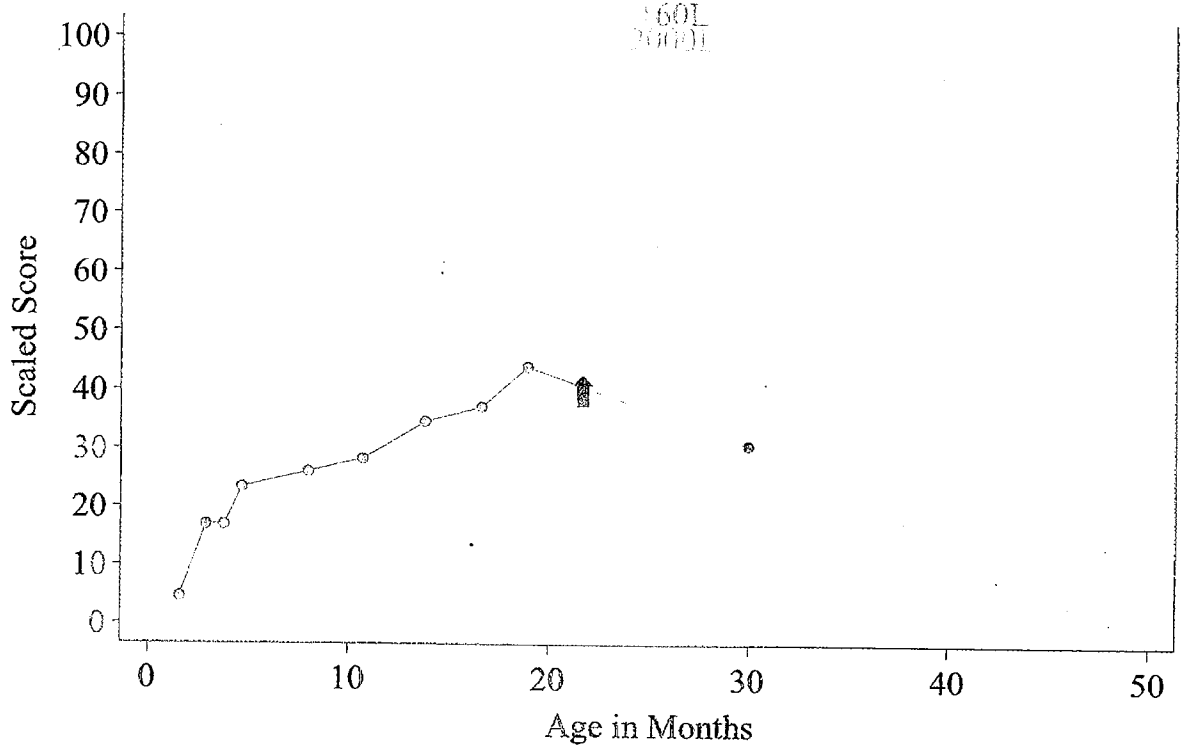
FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=8304314 STUDY ID=AGLU01602/2403 DOSE=20 mg/kg CRIM=POSITIVE AGE AT 1st INFUSION=1.9 Months

AGE (MON) AT INVASIVE VENTILATION=24.4



represents the age(in months) at first 2000L infusion.

Y:\POMPES\POMPE2000L\PROGRAMS\OUTPUT\FDA2008\FPOMPEPEDIBYPATCGM.SAS
Datasets Used: FDA2008.GP1. FDA2008.SURVIVD1 and FDA2008.SURVIVD

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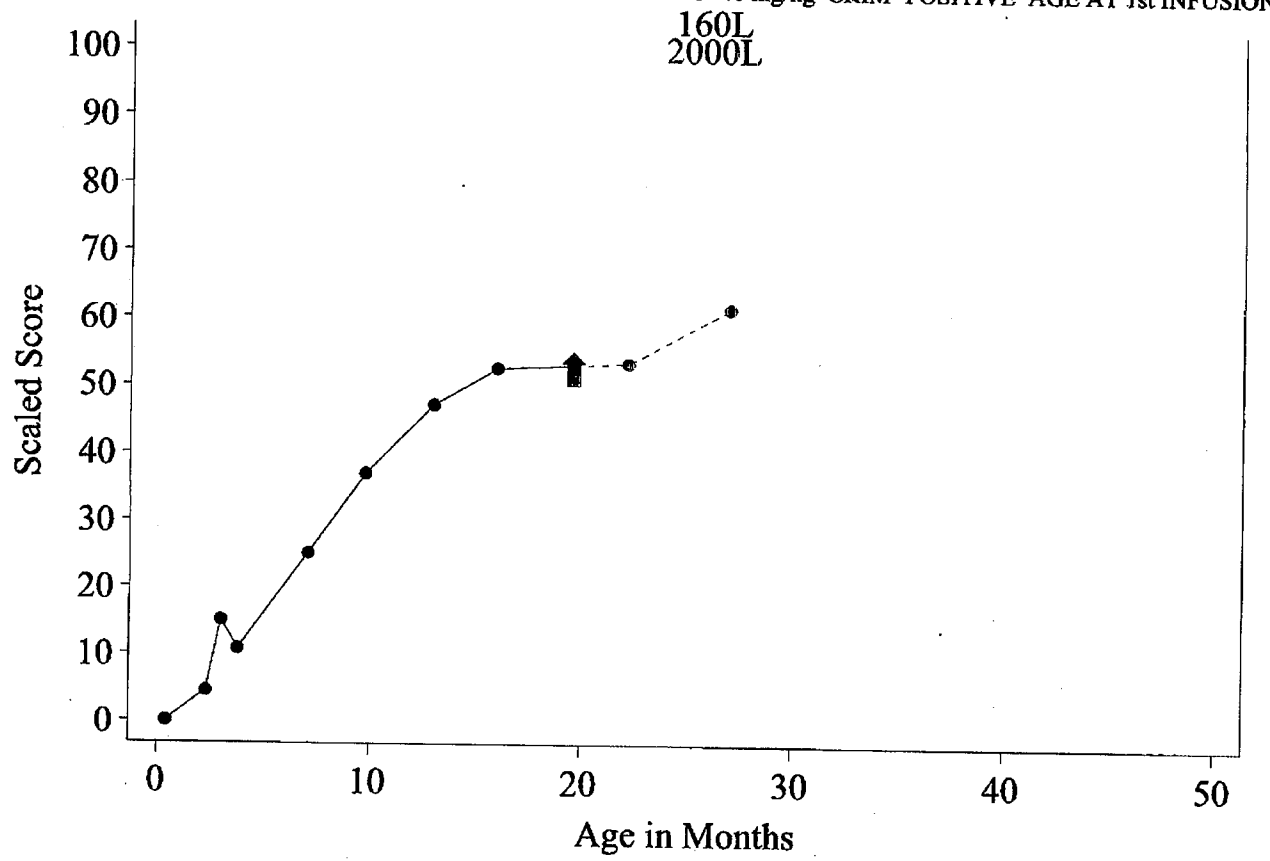
FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=6003315 STUDY ID=AGLU01602/2403 DOSE=40 mg/kg CRIM=POSITIVE AGE AT 1st INFUSION=1.2 Months



⬆ represents the age(in months) at first 2000L infusion.

Y:\POMPES\POMPE2000L\PROGRAMS\OUTPUT\FDA2008\FPOMPEPEDIBYPATCGM.SAS
Datasets Used: FDA2008.GP1. FDA2008.SURVIVD1 and FDA2008.SURVIVD2

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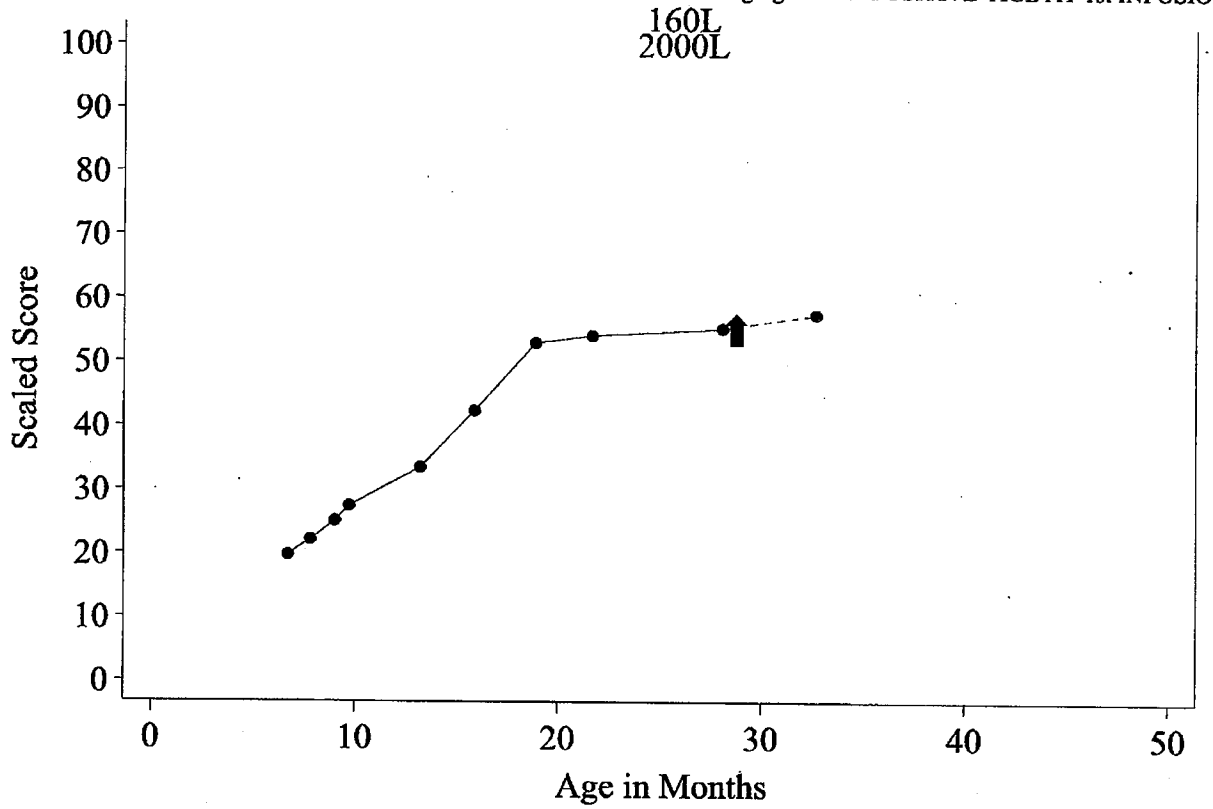
FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=2101316 STUDY ID=AGLU01602/2403 DOSE=20 mg/kg CRIM=POSITIVE AGE AT 1st INFUSION=6.9 Months



⬆ represents the age(in months) at first 2000L infusion.

Y:\POMPES\POMPE2000L\PROGRAMS\OUTPUT\FDA2008\FPOMPEPEDIBYPATCGM.SAS
Datasets Used: FDA2008.GP1, FDA2008.SURVIVD1 and FDA2008.SURVIVD

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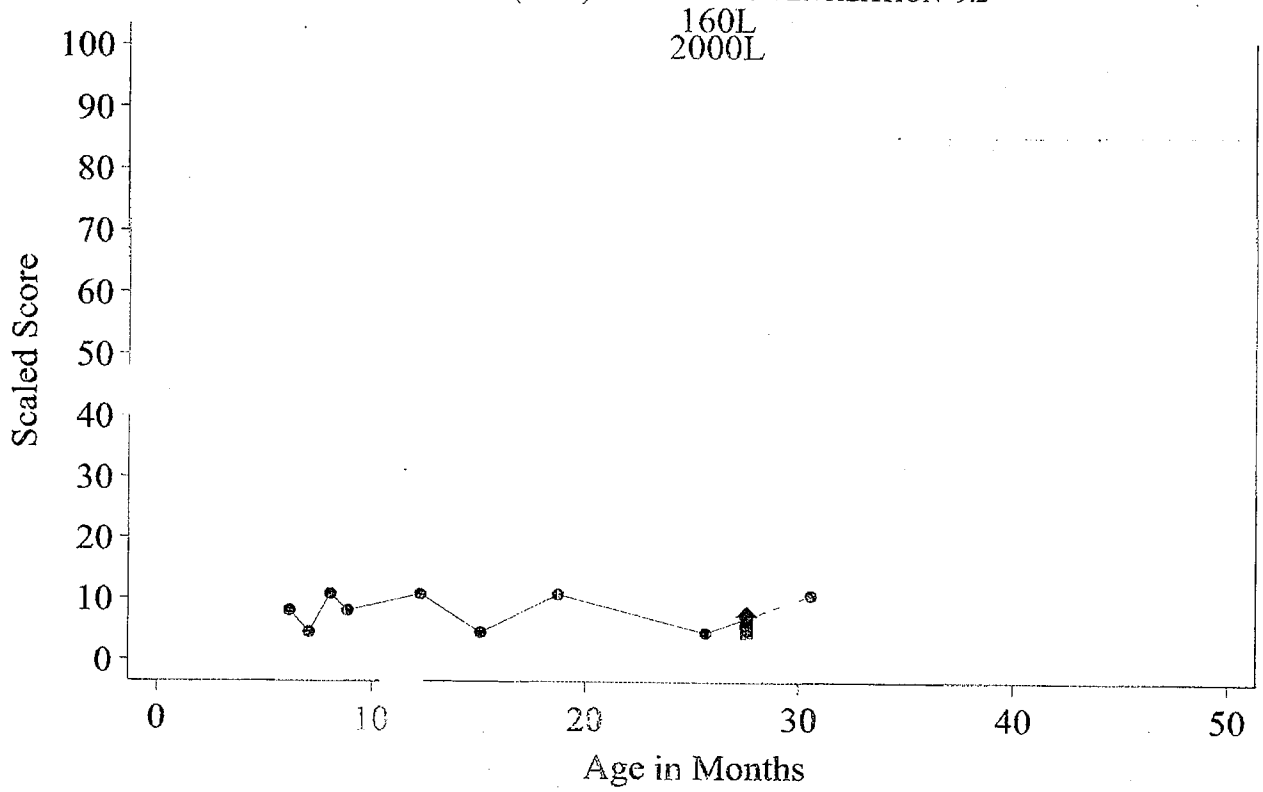
FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=8102317 STUDY ID=AGLU01602/2403 DOSE=40 mg/kg CRIM=NEGATIVE AGE AT 1st INFUSION=6.2 Months

AGE (MON) AT INVASIVE VENTILATION=9.2



⬆ represents the age(in months) at first 2000L infusion.

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Datasets Used: FDA2008.GP1, FDA2008.SURVIVD1 and FDA2008.SURVIVE

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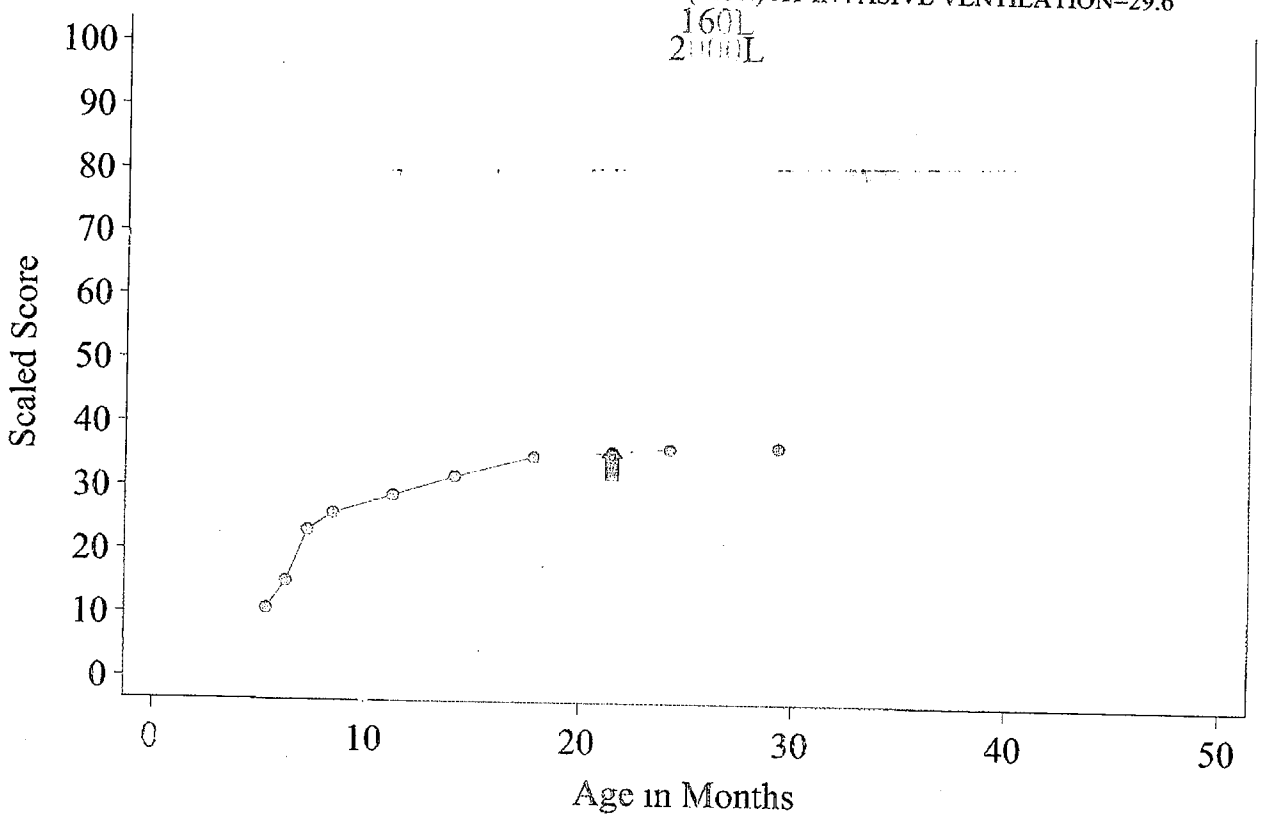
FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=203318 STUDY ID=AGLU01602/2403 DOSE=40 mg/kg CRIM=POSITIVE AGE AT 1st INFUSION=5.4 Months

AGE (MON) AT DEATH=30.1 AGE (MON) AT INVASIVE VENTILATION=29.6



⇧ represents the age(in months) at first 2000L infusion.

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Datasets Used: FDA2008.GP1. FDA2008.SURVIVD1 and FDA2008.SURVIVD2

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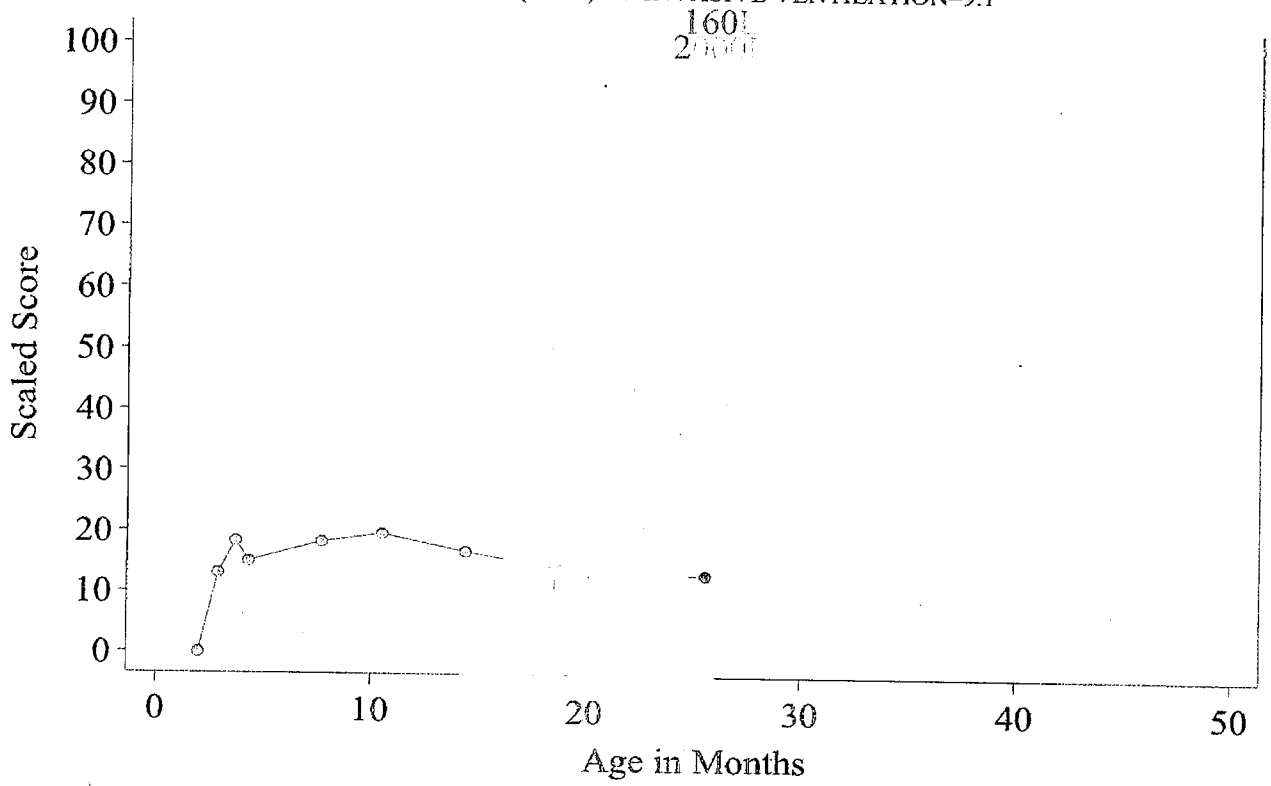
FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=8103319 STUDY ID=AGLU01602/2403 DOSE=20 mg/kg CRIM=NEGATIVE AGE AT 1st INFUSION=2.1 Months

AGE (MON) AT INVASIVE VENTILATION=9.1



represents the age(in months) at first 2000L infusion.

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Datasets Used: FDA2008.GP1 FDA2008.SURVIVD1 and FDA2008.SURVIVE

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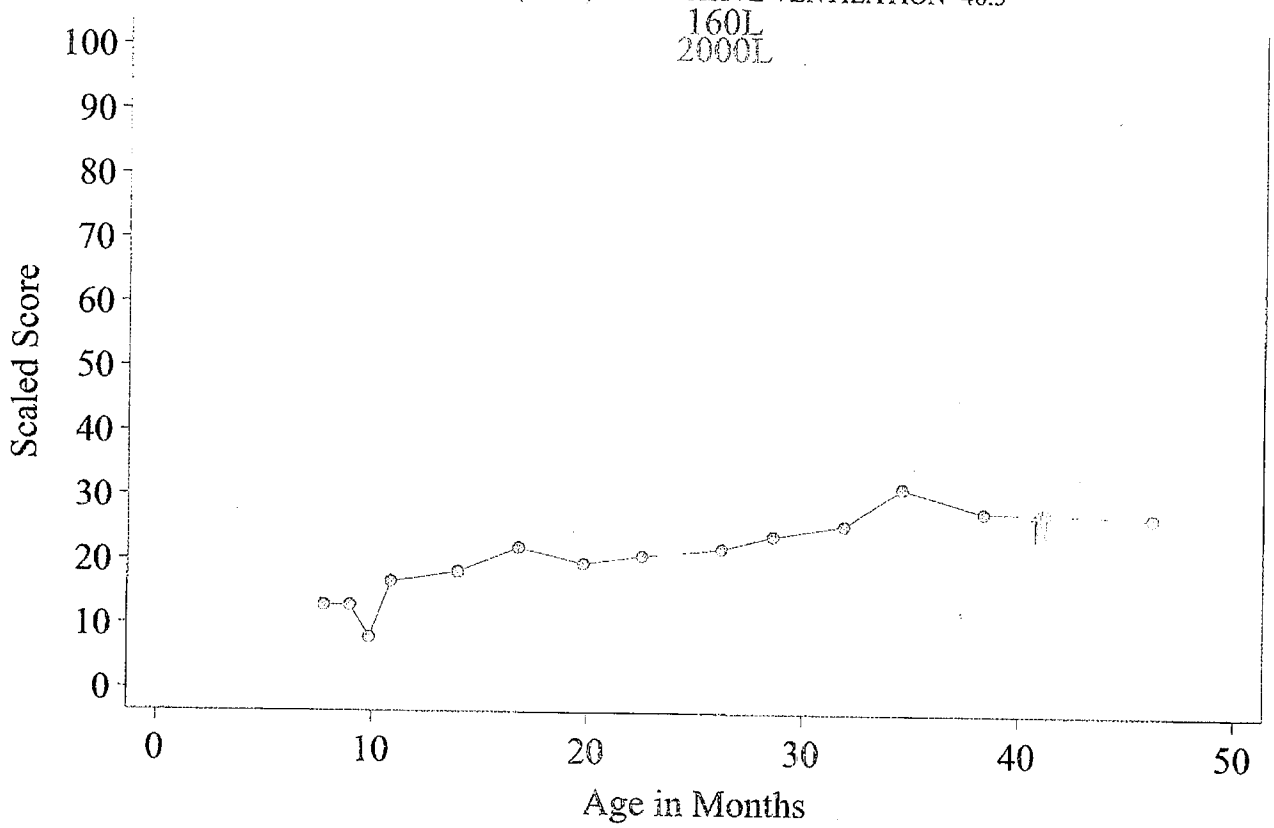
FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=8102404 STUDY ID=AGLU01702 DOSE=20 mg/kg CRIM=POSITIVE AGE AT 1st INFUSION=8.2 Months

AGE (MON) AT INVASIVE VENTILATION=46.5



⇑ represents the age(in months) at first 2000L infusion.

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Datasets Used: FDA2008.GP1. FDA2008.SURVIVD1 and FDA2008.SURVIVD2

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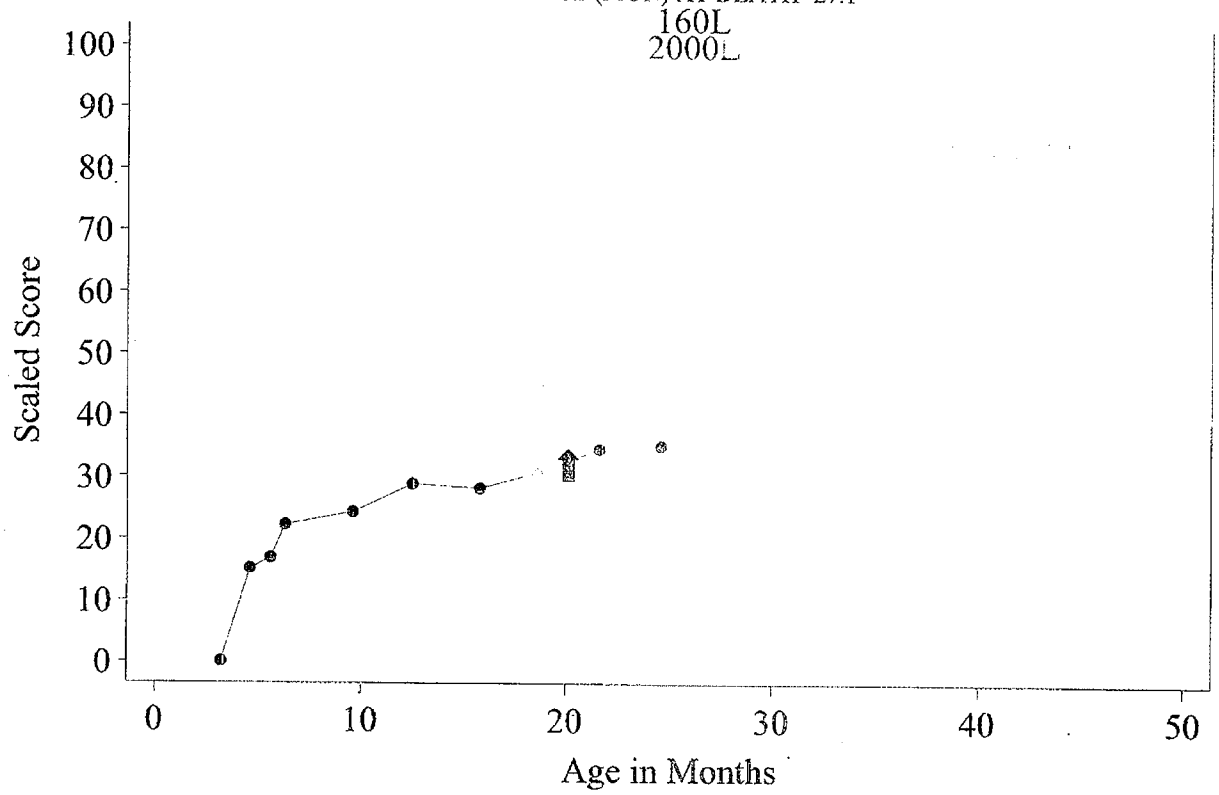
FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=107420 STUDY ID=AGLU01702 DOSE=20 mg/kg CRIM=NEGATIVE AGE AT 1st INFUSION=3.7 Months

AGE (MON) AT DEATH=27.1



⇧ represents the age(in months) at first 2000L infusion.

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Datasets Used: FDA2008.GP1. FDA2008.SURVIVD1 and FDA2008.SURVIVD2

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Individual Pompe PEDI Functional Mobility Scaled Scores by treatment weeks in the 20 "matched" patients that were analyzed in this review, from the Pivotal-Extension Study (AGLUL01602/2403) and Study 1702 (AGLU01702).

Dashed lines—Lumizyme (2000 L); Arrows—time of product switch from Myozyme (160 L) to Lumizyme (2000 L)

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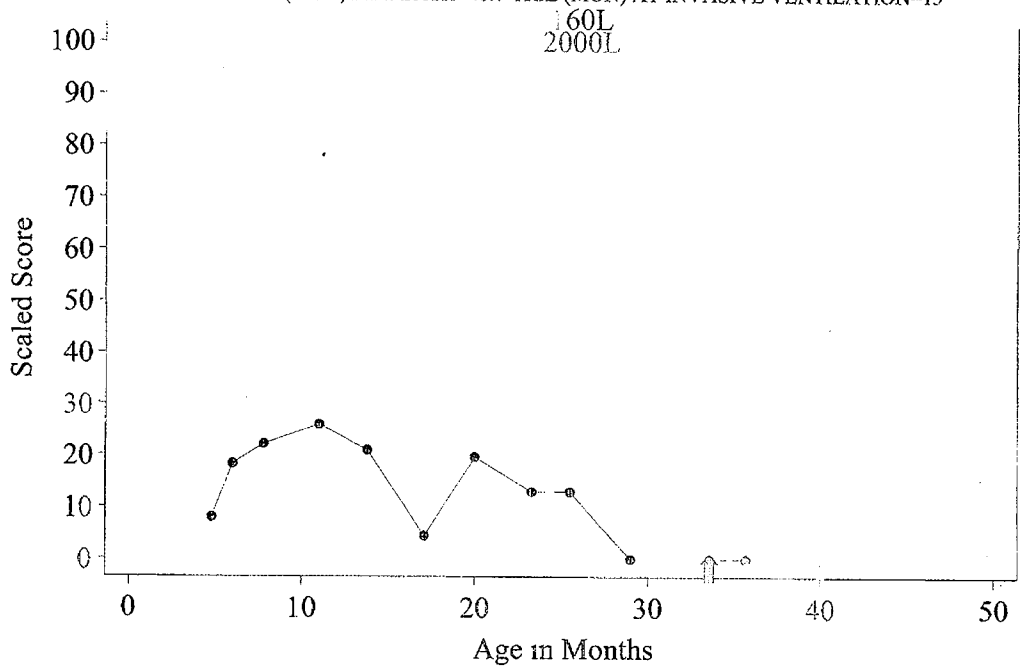
FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=201301 STUDY ID=AGLU01602/2403 DOSE=40 mg/kg CRIM=POSITIVE AGE AT 1st INFUSION=5 Months

AGE (MON) AT DEATH=40.7 AGE (MON) AT INVASIVE VENTILATION=15



⇑ represents the age(in months) at first 2000L infusion.

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Datasets Used: FDA2008.GP1. FDA2008.SURVIVD1 and FDA2008.SURVIVD

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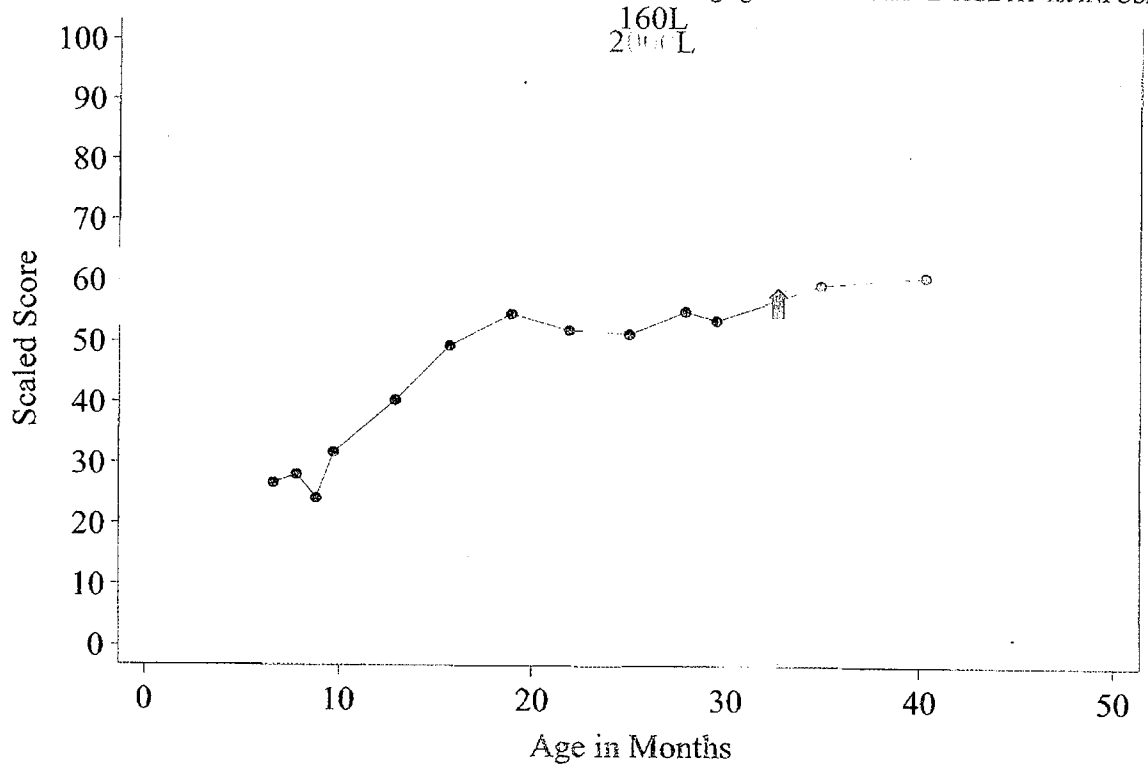
FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=6001302 STUDY ID=AGLU01602/2403 DOSE=20 mg/kg CRIM=POSITIVE AGE AT 1st INFUSION=7 Months



⇧ represents the age(in months) at first 2000L infusion.

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Datasets Used: FDA2008.GP1, FDA2008.SURVIVD1 and FDA2008.SURVIVD

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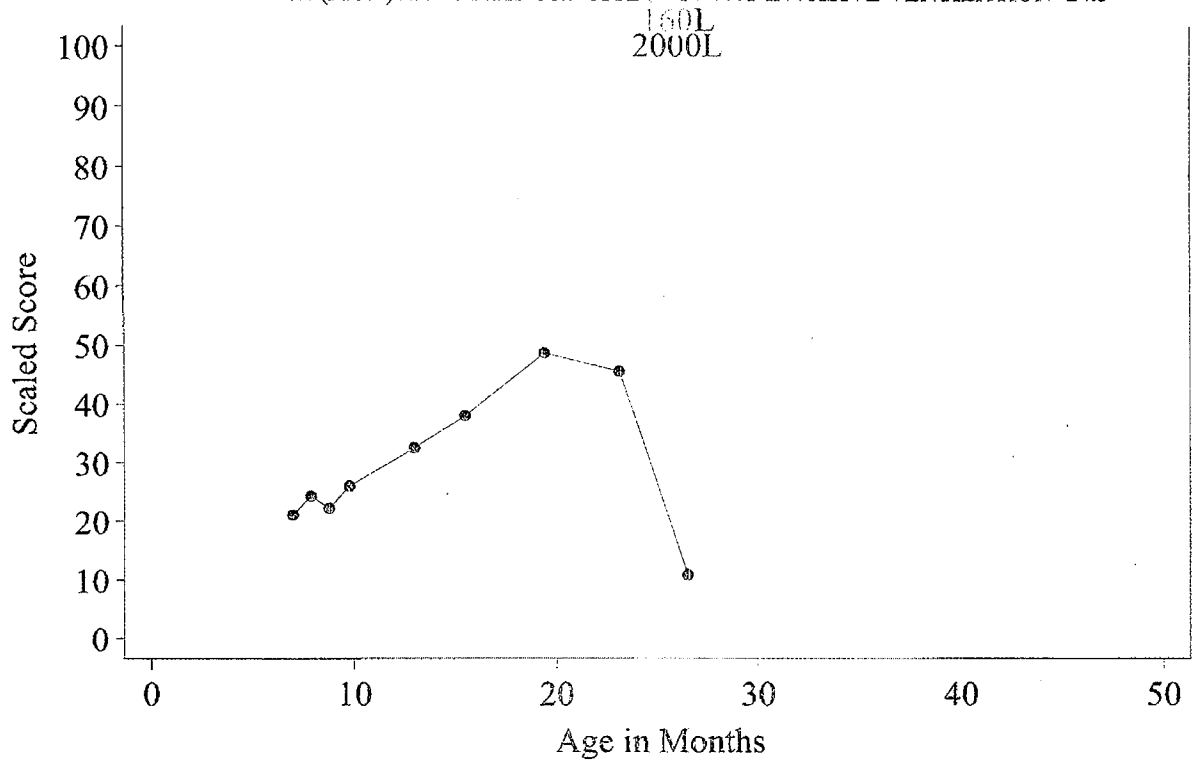
FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=6002303 STUDY ID=AGLU01602/2403 DOSE=40 mg/kg CRIM=NEGATIVE AGE AT 1st INFUSION=7 Months

AGE (MON) AT DEATH=31.9 AGE (MON) AT INVASIVE VENTILATION=24.5



⇧ represents the age(in months) at first 2000L infusion.

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Datasets Used: FDA2008.GP1. FDA2008.SURVIVD1 and FDA2008.SURVIVD

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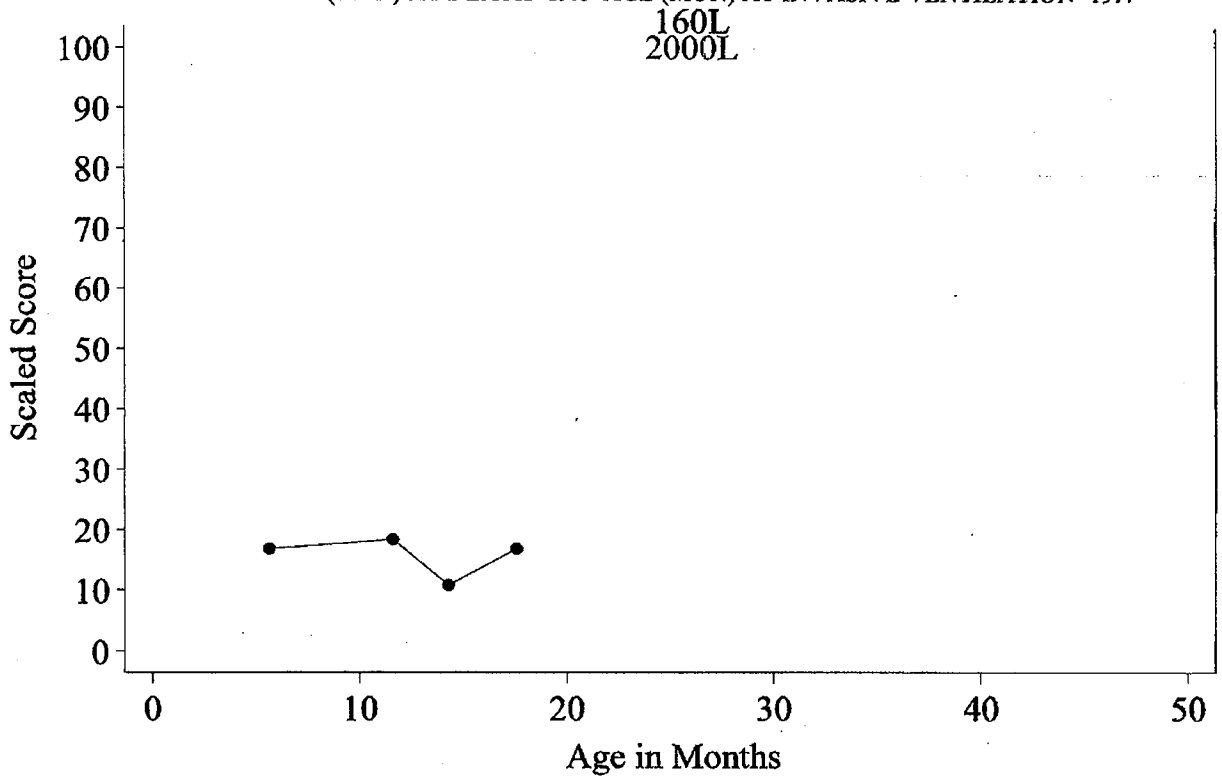
FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=5202305 STUDY ID=AGLU01602/2403 DOSE=20 mg/kg CRIM=POSITIVE AGE AT 1st INFUSION=5.7 Months

AGE (MON) AT DEATH=19.8 AGE (MON) AT INVASIVE VENTILATION=19.4



⬆ represents the age(in months) at first 2000L infusion.

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Datasets Used: FDA2008.GP1. FDA2008.SURVIVD1 and FDA2008.SURVIVD

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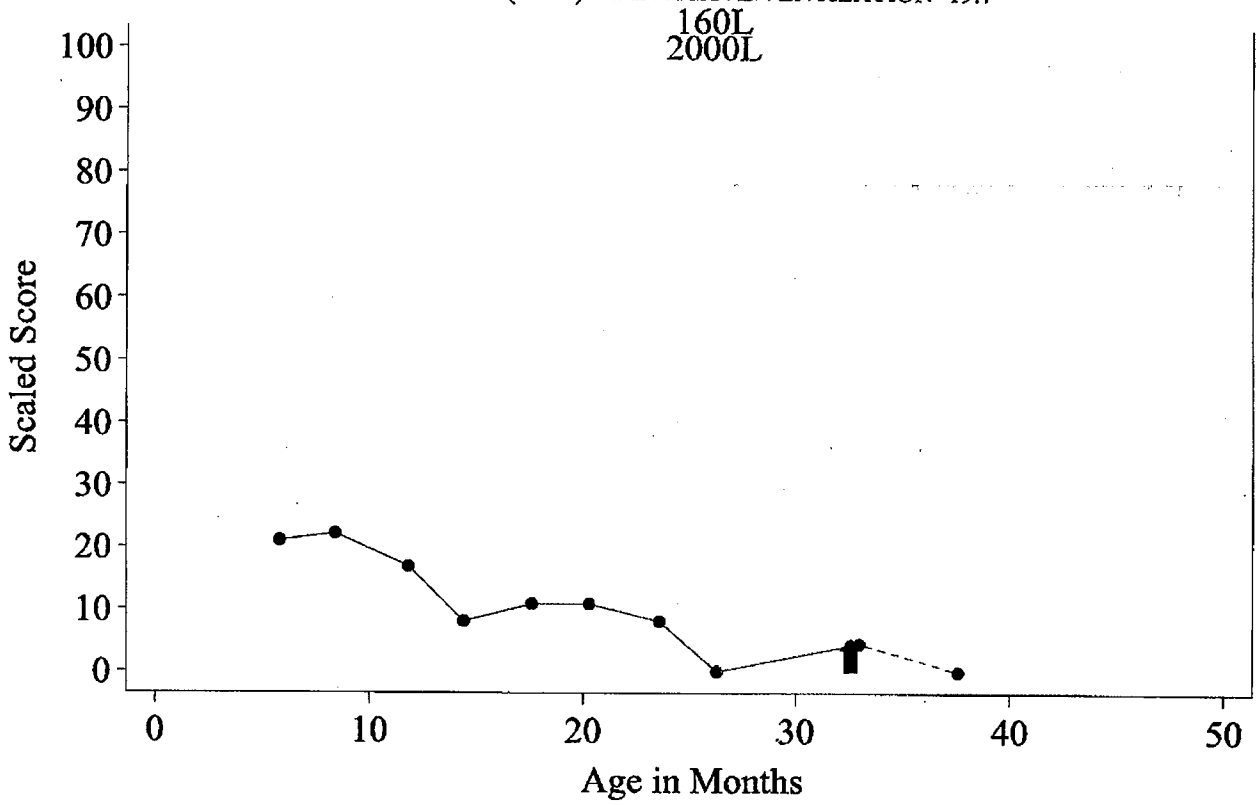
FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=5203306 STUDY ID=AGLU01602/2403 DOSE=20 mg/kg CRIM=POSITIVE AGE AT 1st INFUSION=5.9 Months

AGE (MON) AT INVASIVE VENTILATION=19.7



⬆ represents the age(in months) at first 2000L infusion.

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Datasets Used: FDA2008.GP1. FDA2008.SURVIVD1 and FDA2008.SURVIVD

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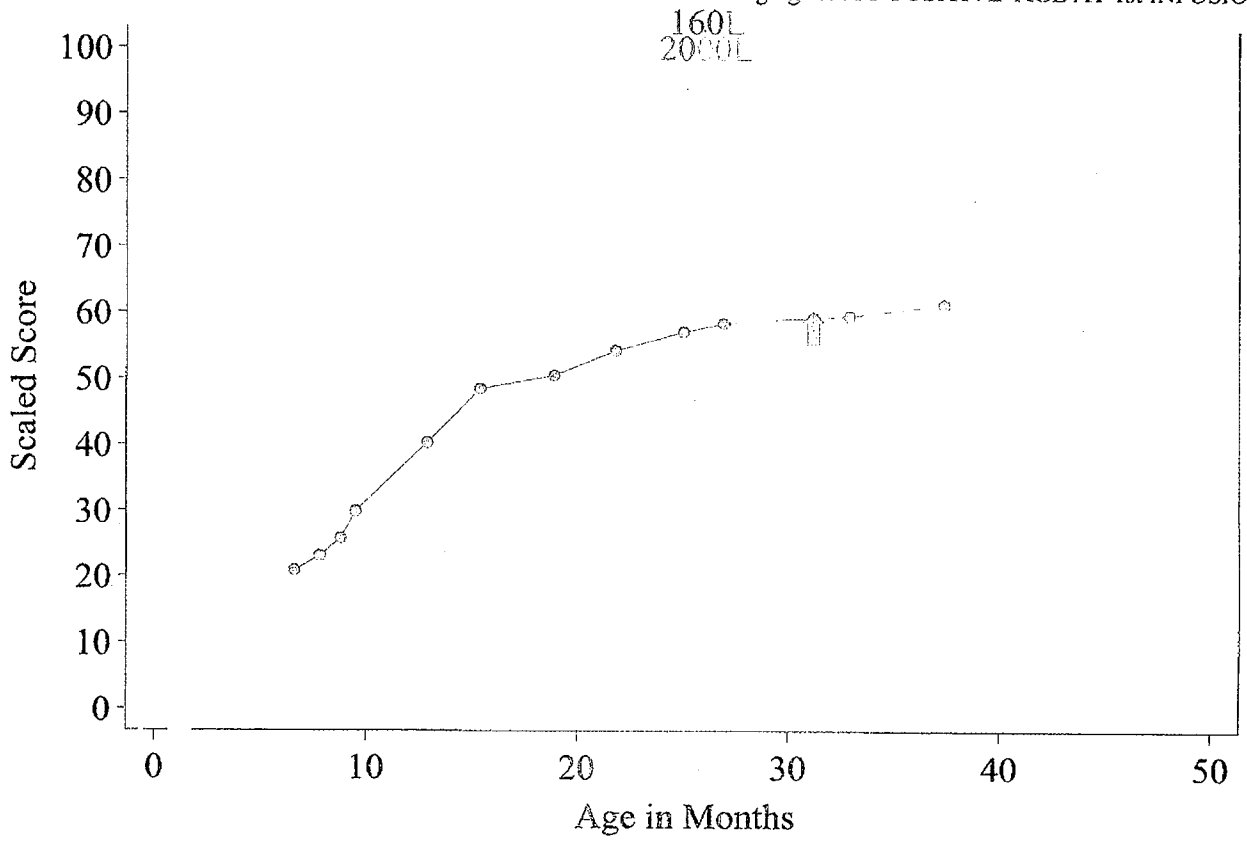
FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=101307 STUDY ID=AGLU01602/2403 DOSE=40 mg/kg CRIM=POSITIVE AGE AT 1st INFUSION=6.9 Months



⇧ represents the age(in months) at first 2000L infusion.

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Datasets Used: FDA2008.GP1, FDA2008.SURVIVD1 and FDA2008.SURVIVD

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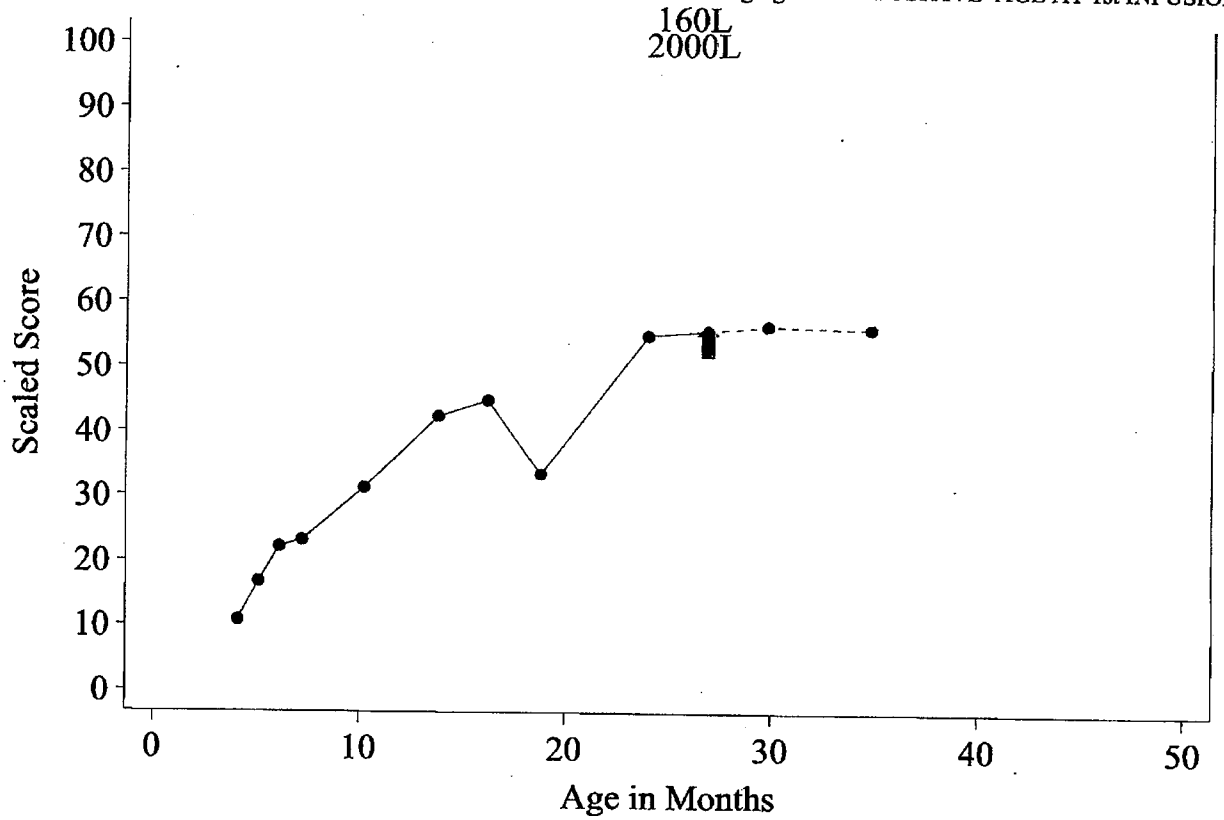
FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=202308 STUDY ID=AGLU01602/2403 DOSE=40 mg/kg CRIM=POSITIVE AGE AT 1st INFUSION=4.3 Months



⬆ represents the age(in months) at first 2000L infusion.

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Datasets Used: FDA2008.GP1, FDA2008.SURVIVD1 and FDA2008.SURVIVI

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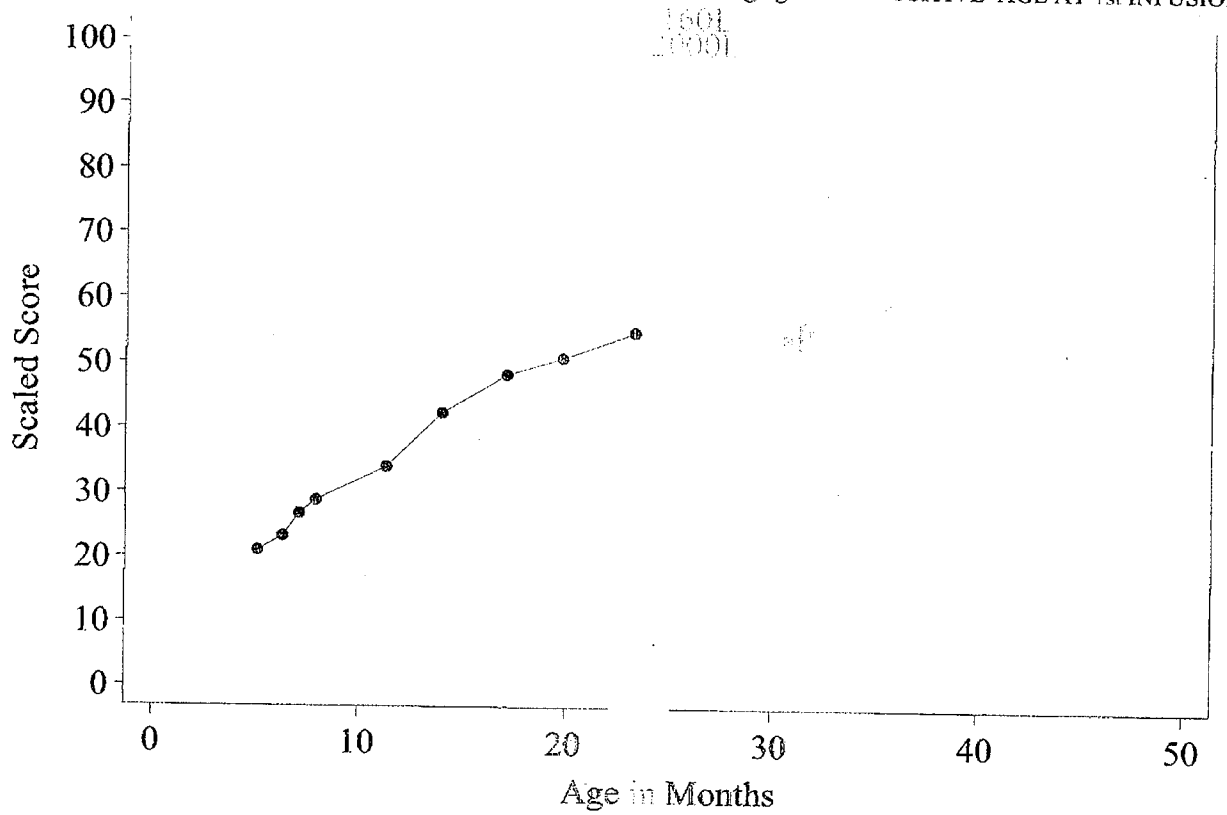
FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=102309 STUDY ID=AGLU01602/2403 DOSE=20 mg/kg CRIM=POSITIVE AGE AT 1st INFUSION=5.3 Months



represents the age(in months) at first 2000L infusion.

Y:\POMPES\POMPE2000L\PROGRAMS\OUTPUT\FDA2008\FPOMPEPEDIBYPATCGM.SAS
Datasets Used: FDA2008.GP1, FDA2008.SURVIVD1 and FDA2008.SURVIVD

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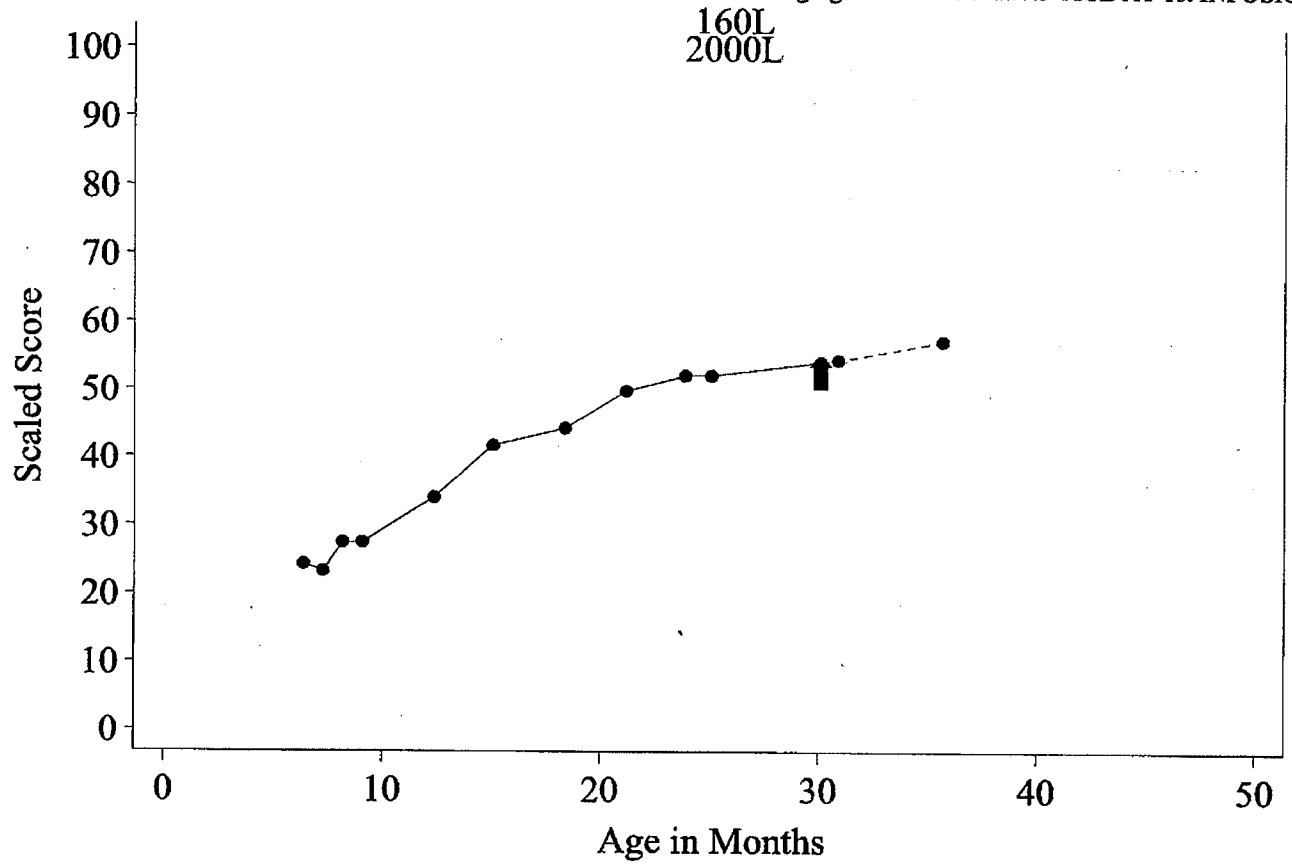
FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=5204310 STUDY ID=AGLU01602/2403 DOSE=20 mg/kg CRIM=POSITIVE AGE AT 1st INFUSION=6.4 Months



⬆ represents the age(in months) at first 2000L infusion.

Y:\POMPES\POMPE2000L\PROGRAMS\OUTPUT\FDA2008\FPOMPEPEDIBYPATCGM.SAS
Datasets Used: FDA2008.GP1, FDA2008.SURVIVD1 and FDA2008.SURVIVD

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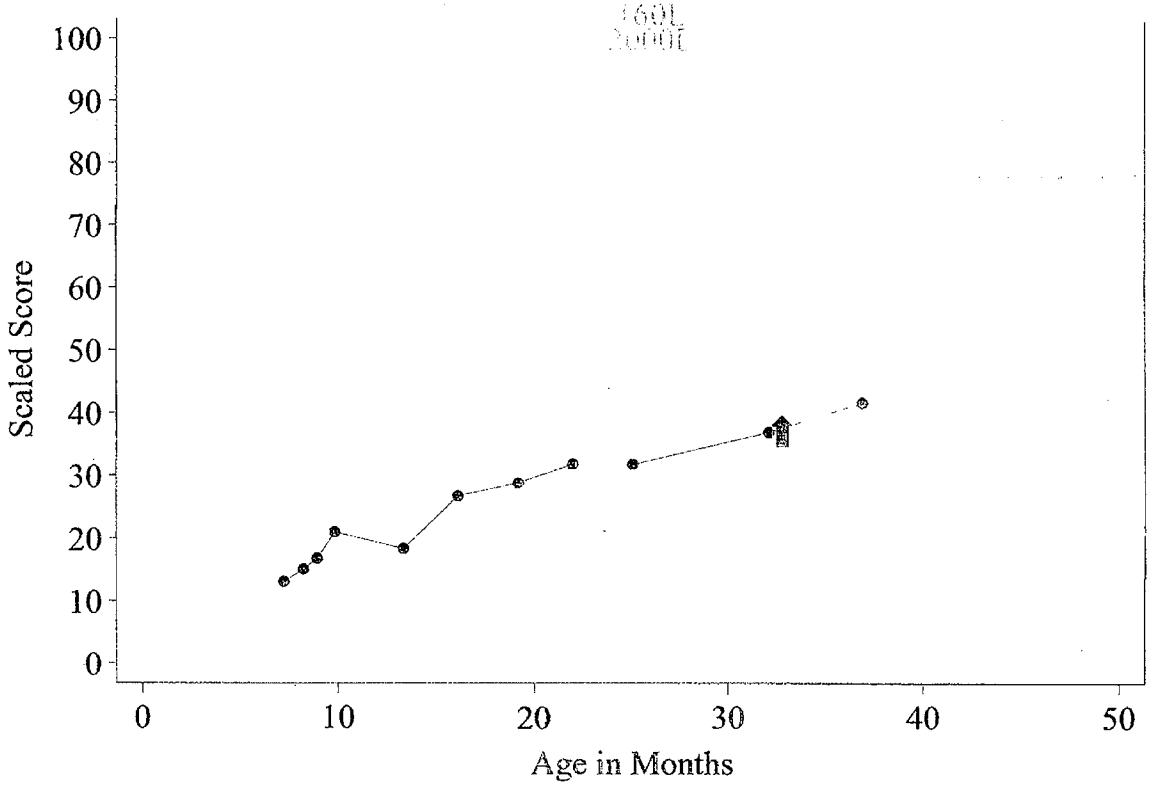
FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=103311 STUDY ID=AGLU01602/2403 DOSE=40 mg/kg CRIM=POSITIVE AGE AT 1st INFUSION=7.3 Months



⬆ represents the age(in months) at first 2000L infusion.

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Datasets Used: FDA2008.GP1, FDA2008.SURVIVD1 and FDA2008.SURVIVD2

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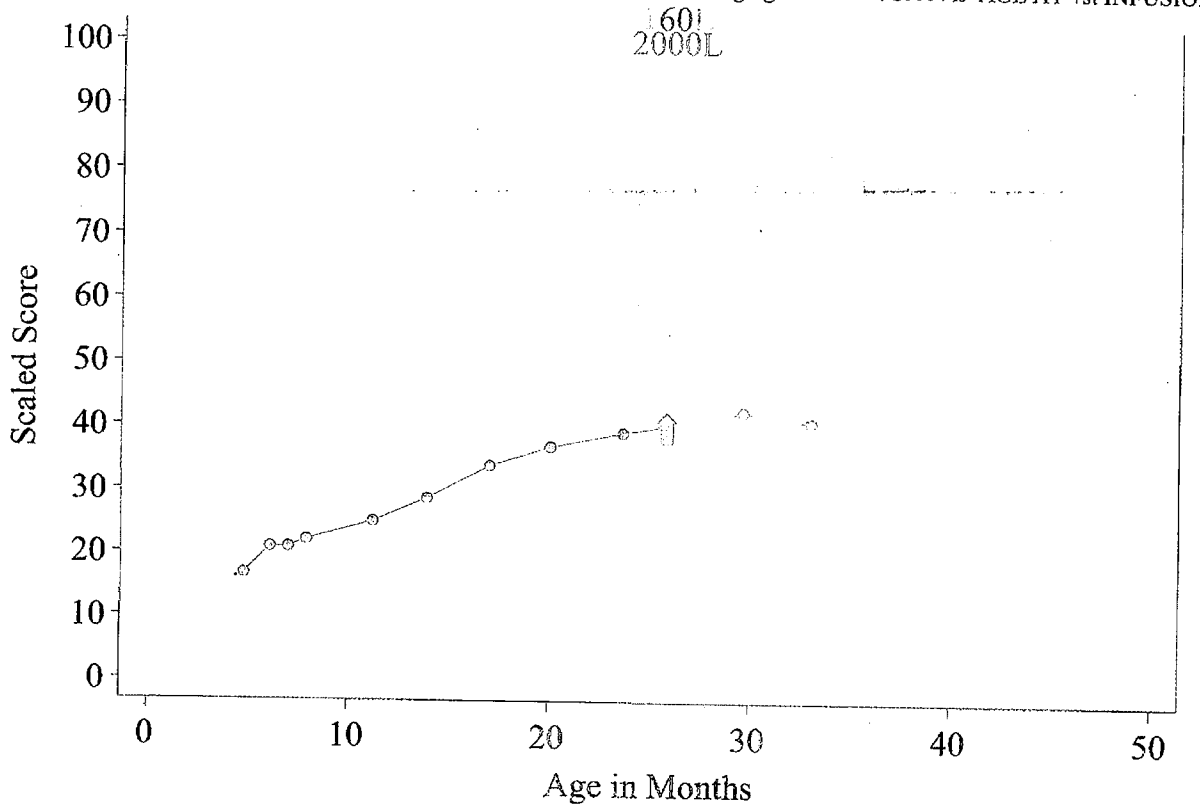
FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=8305312 STUDY ID=AGLU01602/2403 DOSE=20 mg/kg CRIM=POSITIVE AGE AT 1st INFUSION=5.1 Months



⇧ represents the age(in months) at first 2000L infusion.

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Datasets Used: FDA2008.GP1. FDA2008.SURVIVD1 and FDA2008.SURVIVD2

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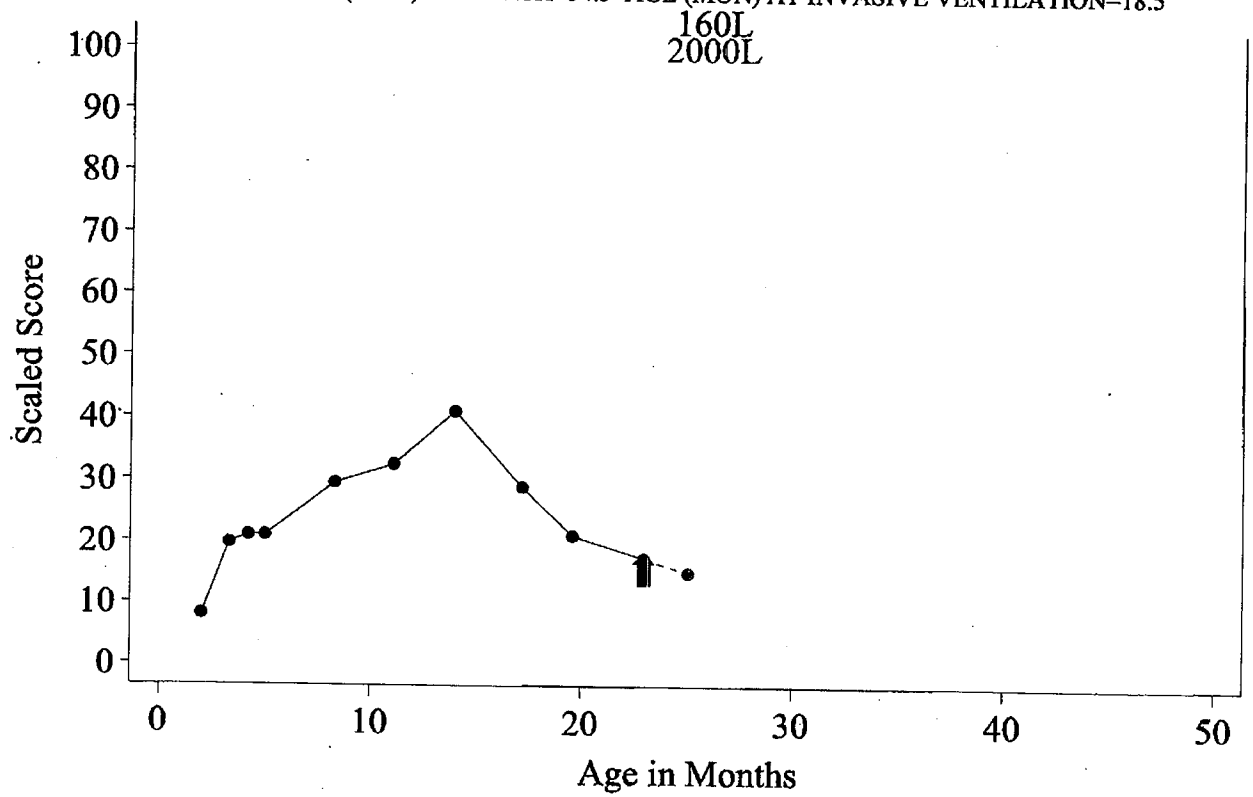
FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=8101313 STUDY ID=AGLU01602/2403 DOSE=40 mg/kg CRIM=NEGATIVE AGE AT 1st INFUSION=2.3 Months

AGE (MON) AT DEATH=34.3 AGE (MON) AT INVASIVE VENTILATION=18.5



⬆ represents the age(in months) at first 2000L infusion.

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Datasets Used: FDA2008.GP1. FDA2008.SURVIVD1 and FDA2008.SURVIVD

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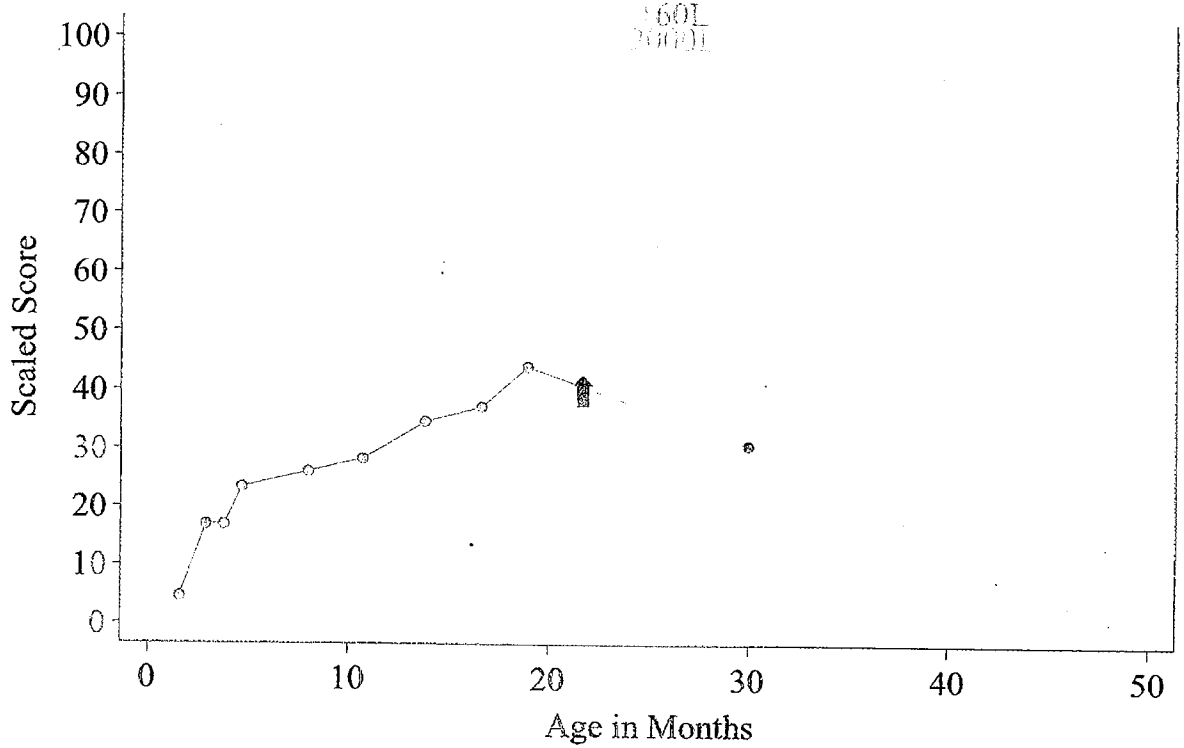
FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=8304314 STUDY ID=AGLU01602/2403 DOSE=20 mg/kg CRIM=POSITIVE AGE AT 1st INFUSION=1.9 Months

AGE (MON) AT INVASIVE VENTILATION=24.4



represents the age(in months) at first 2000L infusion.

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Datasets Used: FDA2008.GP1. FDA2008.SURVIVD1 and FDA2008.SURVIVD

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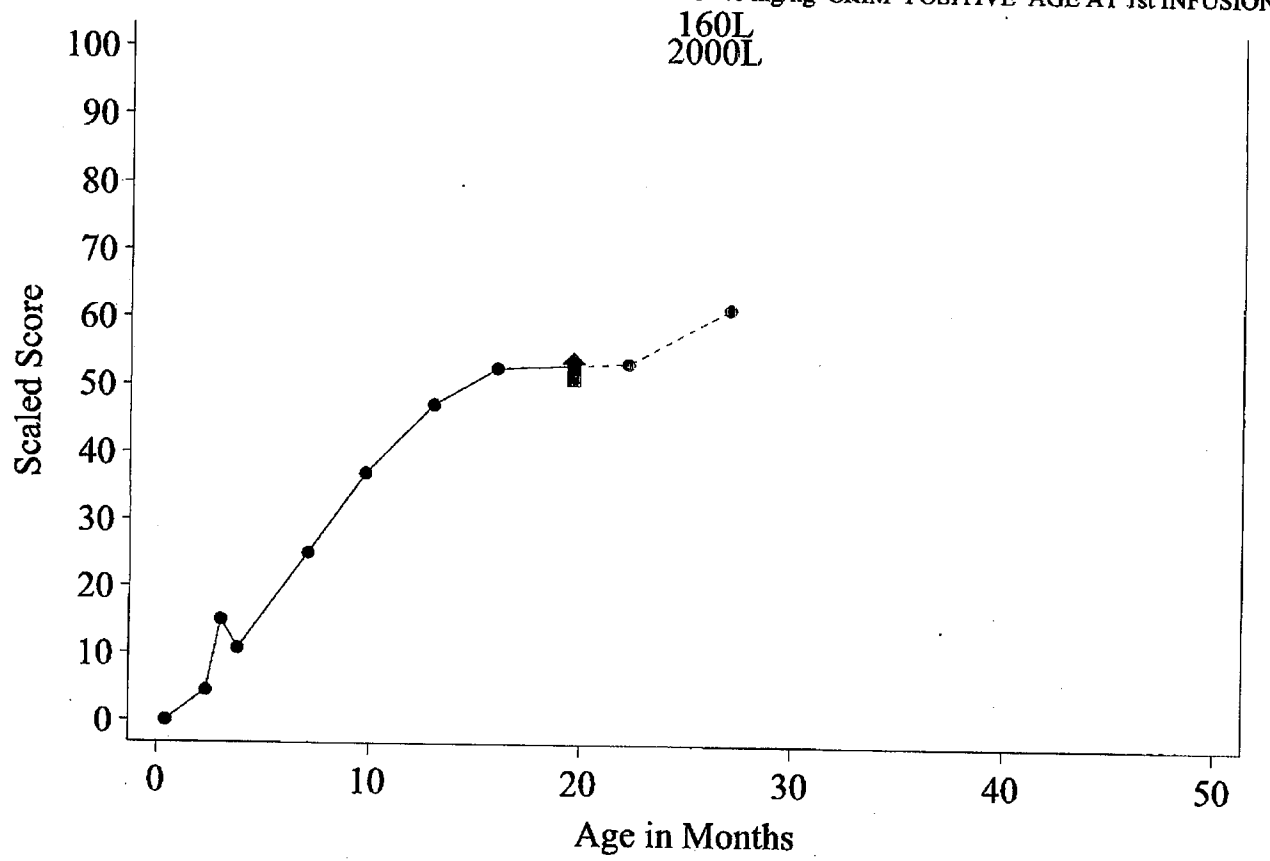
FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=6003315 STUDY ID=AGLU01602/2403 DOSE=40 mg/kg CRIM=POSITIVE AGE AT 1st INFUSION=1.2 Months



⬆ represents the age(in months) at first 2000L infusion.

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Datasets Used: FDA2008.GP1. FDA2008.SURVIVD1 and FDA2008.SURVIVD2

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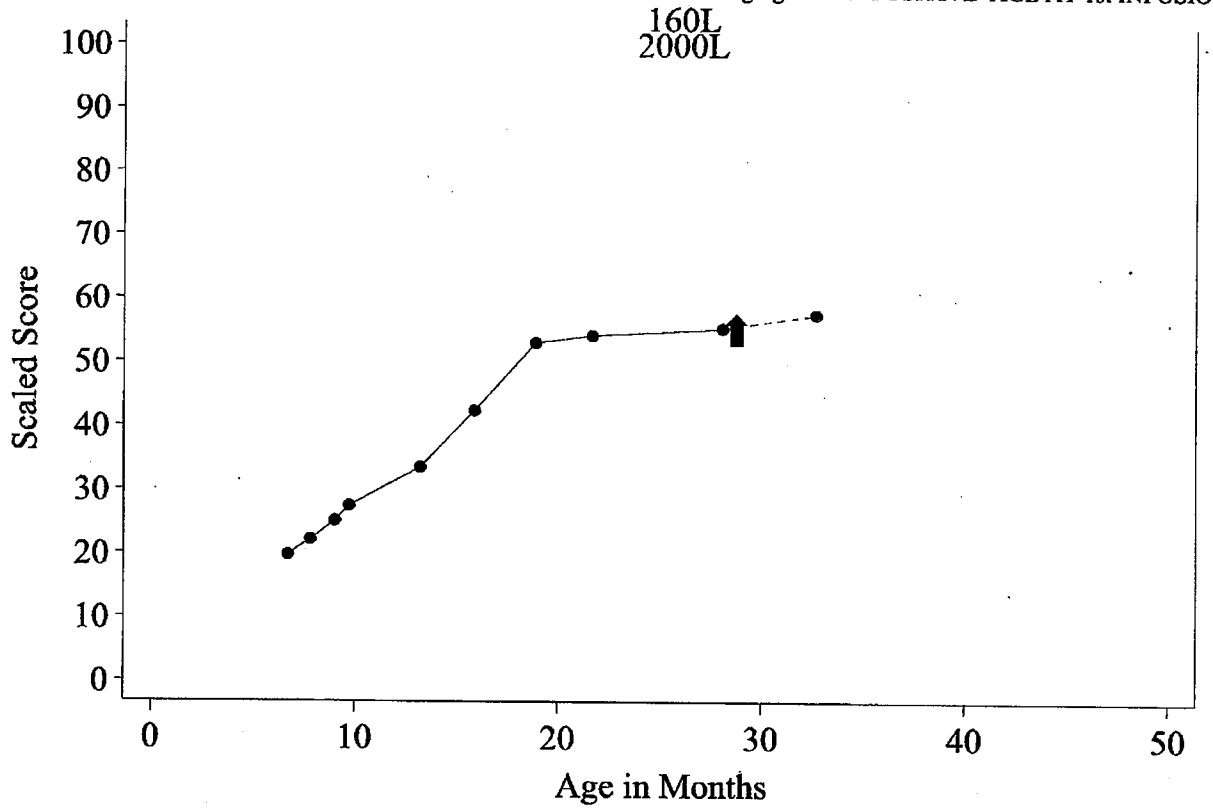
FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=2101316 STUDY ID=AGLU01602/2403 DOSE=20 mg/kg CRIM=POSITIVE AGE AT 1st INFUSION=6.9 Months



⬆ represents the age(in months) at first 2000L infusion.

Y:\POMPES\POMPE2000L\PROGRAMS\OUTPUT\FDA2008\FPOMPEPEDIBYPATCGM.SAS
Datasets Used: FDA2008.GP1, FDA2008.SURVIVD1 and FDA2008.SURVIVD

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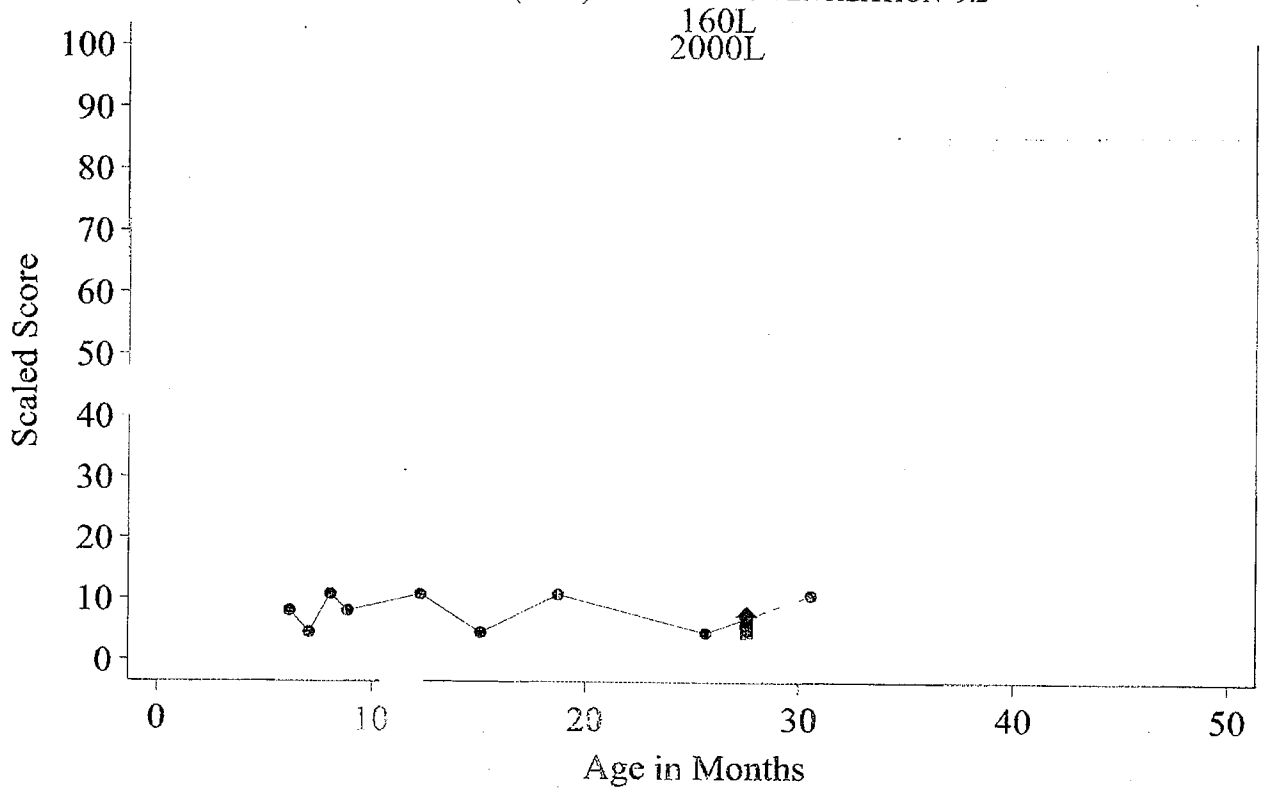
FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=8102317 STUDY ID=AGLU01602/2403 DOSE=40 mg/kg CRIM=NEGATIVE AGE AT 1st INFUSION=6.2 Months

AGE (MON) AT INVASIVE VENTILATION=9.2



⬆ represents the age(in months) at first 2000L infusion.

Y:\POMPES\POMPE2000L\PROGRAMS\OUTPUT\FDA2008\FPOMPEPEDIBYPATCGM.SAS
Datasets Used: FDA2008.GP1, FDA2008.SURVIVD1 and FDA2008.SURVIVE

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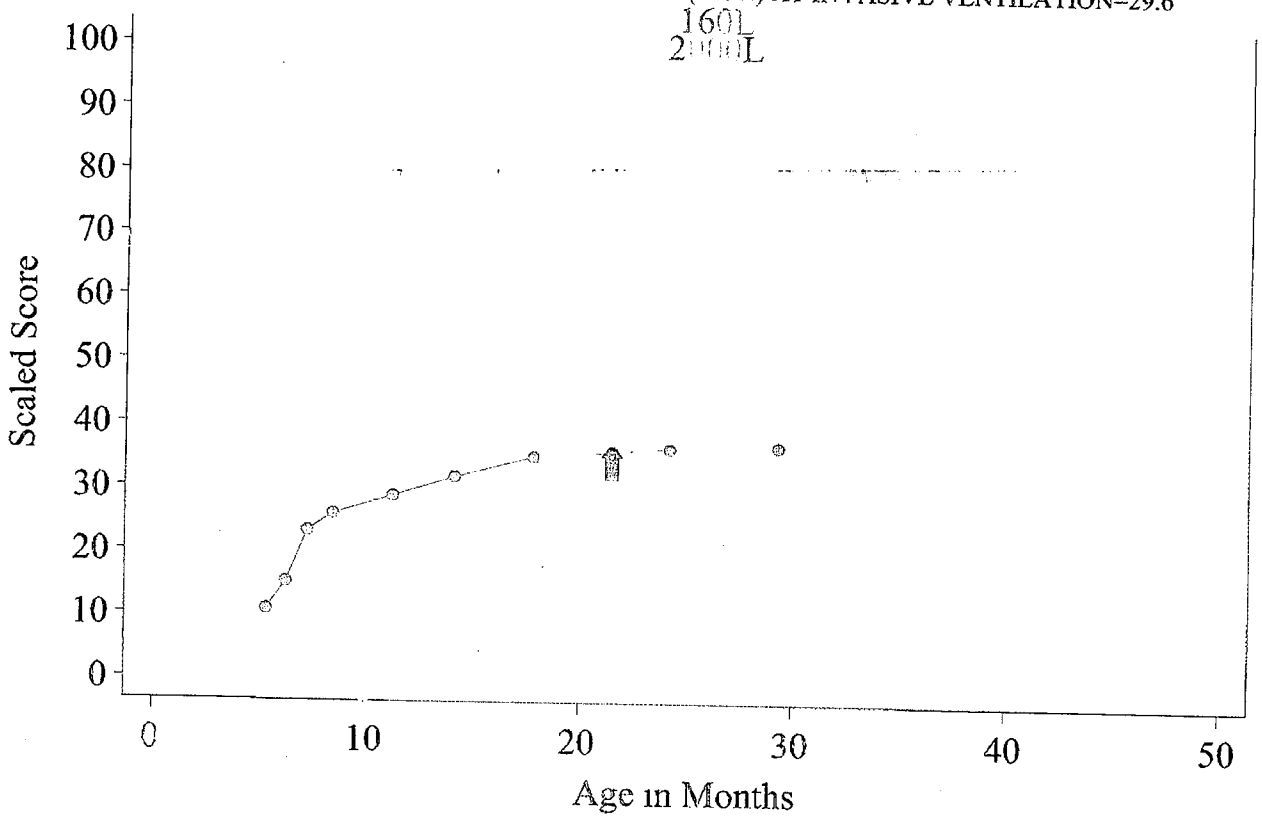
Genzyme Corporation
Protocol No. POMPE2000L

FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=203318 STUDY ID=AGLU01602/2403 DOSE=40 mg/kg CRIM=POSITIVE AGE AT 1st INFUSION=5.4 Months

AGE (MON) AT DEATH=30.1 AGE (MON) AT INVASIVE VENTILATION=29.6



⇧ represents the age(in months) at first 2000L infusion.

Y:\POMPES\POMPE2000L\PROGRAMS\OUTPUT\FDA2008\FPOMPEPEDIBYPATCGM.SAS
Datasets Used: FDA2008.GP1. FDA2008.SURVIVD1 and FDA2008.SURVIVD2

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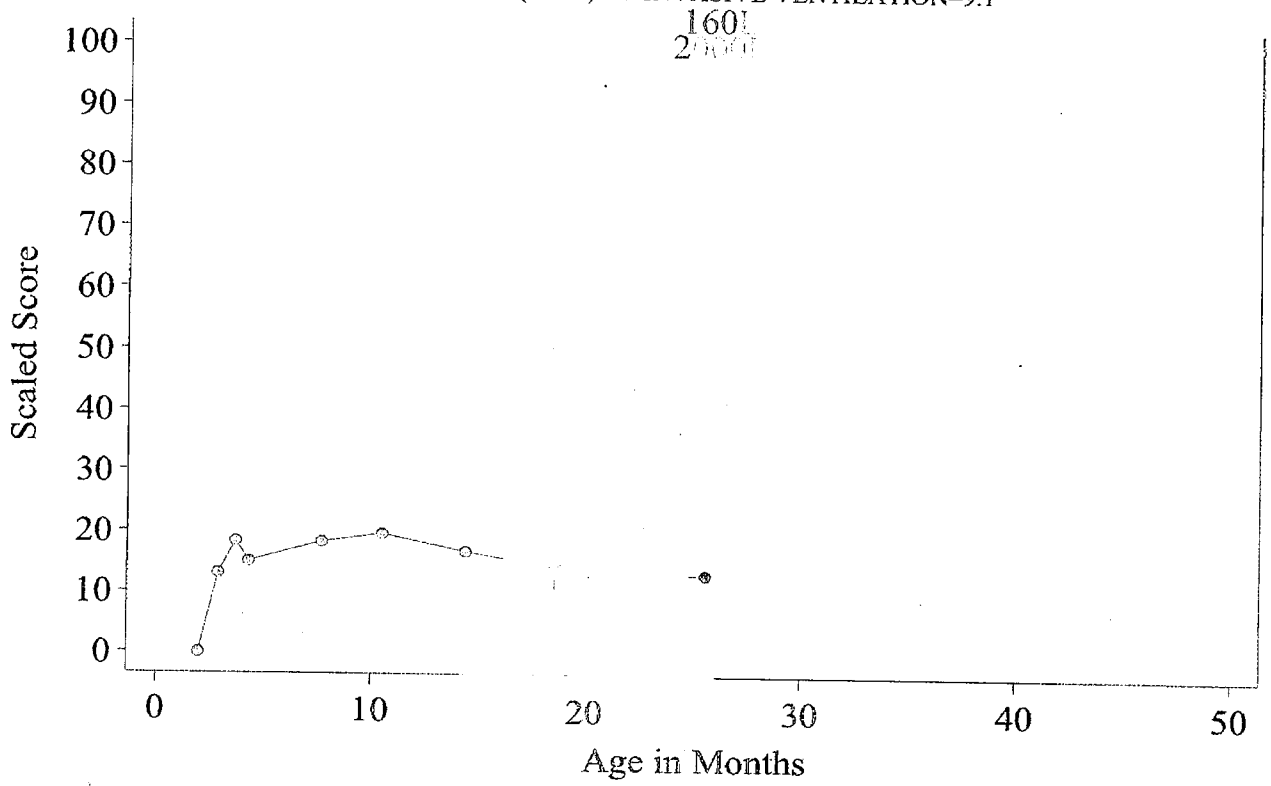
FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=8103319 STUDY ID=AGLU01602/2403 DOSE=20 mg/kg CRIM=NEGATIVE AGE AT 1st INFUSION=2.1 Months

AGE (MON) AT INVASIVE VENTILATION=9.1



represents the age(in months) at first 2000L infusion.

Y:\POMPES\POMPE2000L\PROGRAMS\OUTPUT\FDA2008\FPOMPEPEDIBYPATCGM.SAS
Datasets Used: FDA2008.GP1 FDA2008.SURVIVD1 and FDA2008.SURVIVE

12:27/13MAR08

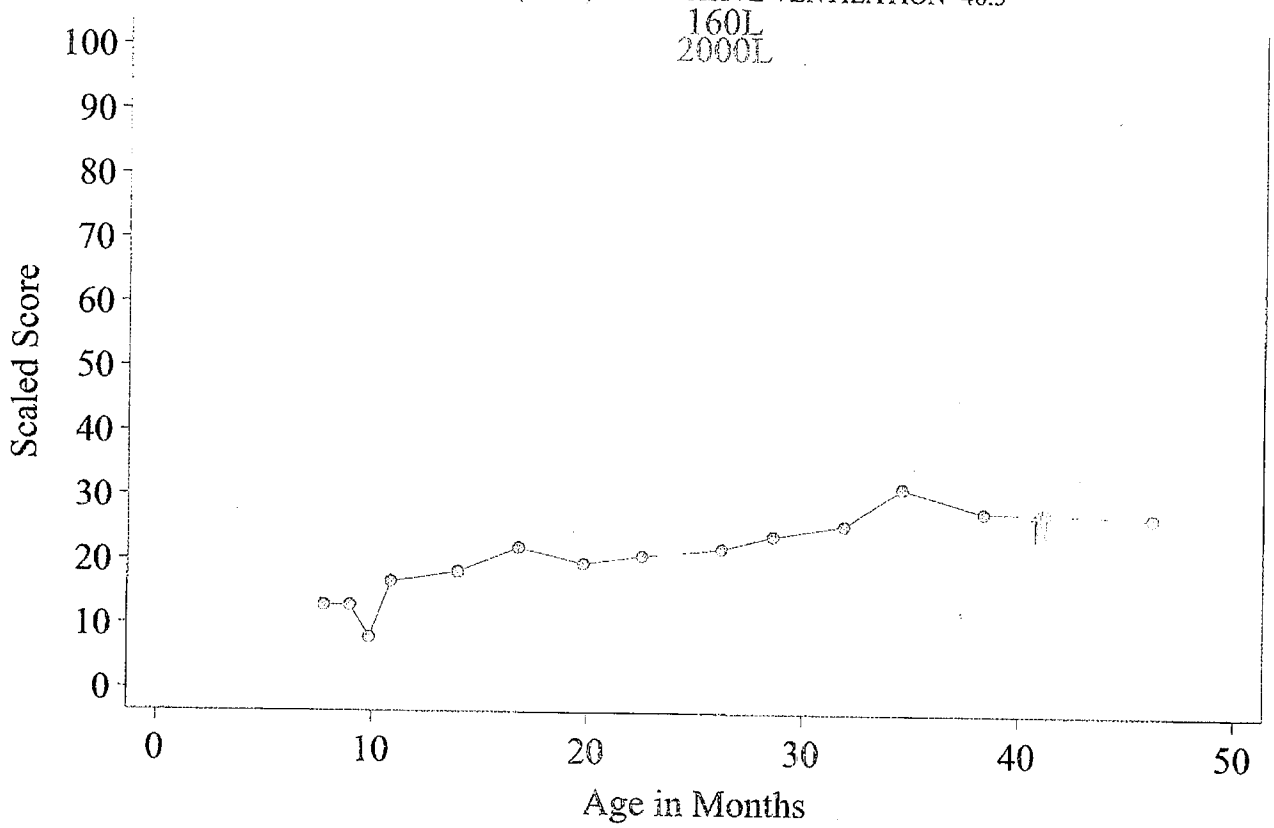
Genzyme Corporation
Protocol No. POMPE2000L

FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=8102404 STUDY ID=AGLU01702 DOSE=20 mg/kg CRIM=POSITIVE AGE AT 1st INFUSION=8.2 Months

AGE (MON) AT INVASIVE VENTILATION=46.5



⇑ represents the age(in months) at first 2000L infusion.

Y:\POMPES\POMPE2000L\PROGRAMS\OUTPUT\FDA2008\FPOMPEPEDIBYPATCGM.SAS
Datasets Used: FDA2008.GP1. FDA2008.SURVIVD1 and FDA2008.SURVIVD2

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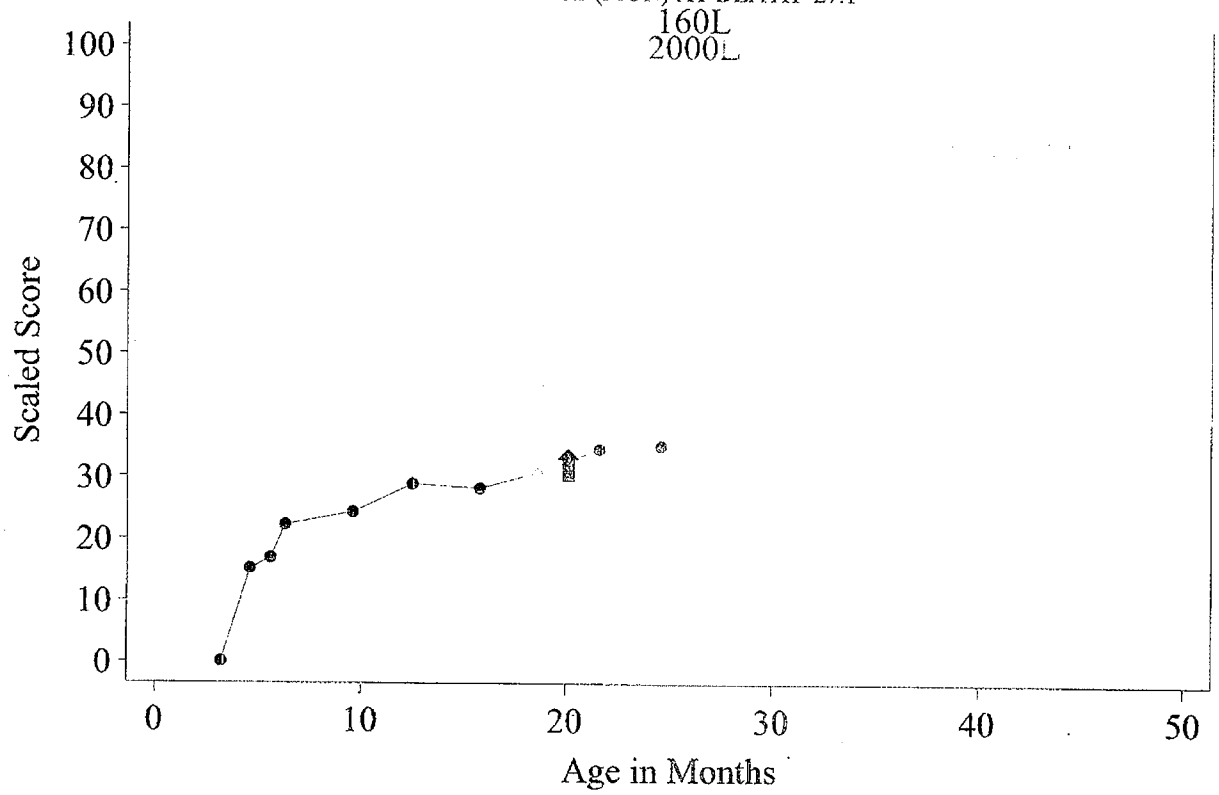
FIGURE 3

POMPE PEDIATRICS EVALUATION OF MOBILITY FUNCTIONAL SKILLS

PATIENT ID=107420 STUDY ID=AGLU01702 DOSE=20 mg/kg CRIM=NEGATIVE AGE AT 1st INFUSION=3.7 Months

AGE (MON) AT DEATH=27.1



⇧ represents the age(in months) at first 2000L infusion.

Y:\POMPES\POMPE2000L\PROGRAMS\OUTPUT\FDA2008\FPOMPEPEDIBYPATCGM.SAS
Datasets Used: FDA2008.GP1. FDA2008.SURVIVD1 and FDA2008.SURVIVD2

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CLINICAL REVIEW

Application Type	BLA 125291
Submission Number	125291/0
Submission Code	N/A
Letter Date	30 May 2008
Stamp Date	30 May 2008
PDUFA Goal Date	27 February 2009
Reviewer Name	Lynne P. Yao, MD
Acting Clinical Team Leader	Joanna W. Ku, MD
Review Completion Date	23 February 2009
Established Name	Alglucosidase alfa
(Proposed) Trade Name	Lumizyme
Therapeutic Class	Enzyme Replacement Therapy
Applicant	Genzyme
Priority Designation	Priority
Formulation	Intravenous Injection
Dosing Regimen	20mg/kg every other week
Indication	Treatment of Pompe Disease (glycogen storage disease type II, acid maltase deficiency)
Intended Population	Late-onset Pompe Disease

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Recommend approving this application under 21 CFR 601 Subpart E, accelerated approval, after agreement with the Applicant to perform a verification study, revision to the proposed labeling, and inclusion of a Risk Evaluation and Mitigation Strategy (REMS).

It is recommended that Lumizyme (alglucosidase alfa, 2000L production scale) treatment be restricted to patients with late onset (non-infantile) Pompe disease 8 years of age and older, who do not have evidence of cardiac hypertrophy. The Agency approved Myozyme, alglucosidase alfa manufactured at the 160L production scale in 2006, and is currently the only approved treatment for Pompe disease. In April, 2008, given the inability to establish product comparability based on chemistry, manufacturing and controls (CMC), pharmacokinetic, or clinical data, the 160 L (Myozyme) and 2000 L (Lumizyme) alglucosidase alfa products were deemed to be different products by the Agency. Therefore, the Agency required the Applicant to submit efficacy and safety data to support separate licensure of Lumizyme. The Agency also informed the Applicant that an Advisory Committee meeting would be convened, and thus, The Endocrinologic and Metabolic Drugs Advisory Committee met on October 15, 2008, to review the information submitted by the Applicant and to request advice regarding the approval of Lumizyme in the treatment of late-onset Pompe disease. A benefit of 3.4% (p=0.004) in % predicted FVC (forced vital capacity) was demonstrated in a double-blind, placebo controlled study (AGLU02704) in patients with late-onset Pompe disease at 78 weeks. Although a difference of 28.1 meters between the Lumizyme and placebo treatment groups was demonstrated in the 6MWT (six minute walk test), the co-primary endpoint of the study, this difference was not statistically significant (p=0.06). Additional information submitted by the Applicant for the advisory committee meeting warned that the worldwide supply of Myozyme was inadequate to meet global demand in the treatment of Pompe disease. Thus, reviewing the totality of evidence supporting a treatment effect of Lumizyme in the context of the likely shortage of Myozyme in the US, the advisory committee voted 16-1 for approval of Lumizyme under CFR 601 Subpart E, with the improvement in % predicted FVC used as a surrogate marker for clinical benefit in Pompe disease. In AGLU02704, the youngest patients eligible for study under this protocol were 8 years of age, although the youngest patient actually enrolled was 10 years of age. Thus, no therapeutic benefit of Lumizyme has been demonstrated in Pompe disease patients less than 8 years of age in adequate and well-controlled trials.

1.2 Risk Benefit Assessment

A summary of the efficacy data for this Application demonstrates that Lumizyme produces a 28.1 meters (p=0.06) increase in estimated change from baseline distance walked during the 6MWT and a 3.4% (p=0.004) 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 Lumizyme-treated patients developed anti-rhGAA IgG antibodies, and eighteen patients (30%) treated with Lumizyme developed *in vitro* neutralizing antibodies.

Important clinical safety issues include allergic and immunologically mediated reactions. Anaphylaxis, as well as immediate and delayed-onset infusion associated reactions, occur at higher rates than placebo. Life-threatening and severe hypersensitivity reactions, including anaphylaxis are present with Lumizyme and have lead to the discontinuation of patients from clinical trials. 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 Myozyme, immune mediated reactions may occur with chronic exposure. These risks are similar to those found with the currently approved product, Myozyme. Thus, the risk appears to be acceptable for patients with Pompe disease 8 years of age and older since there is no other treatment available due to the worldwide shortage of Myozyme and the benefit demonstrated in late-onset patients based on improvement in % predicted FVC, as a surrogate marker in Pompe disease. It remains unknown whether improvement in % predicted FVC in Pompe disease patients leads to improvement in true clinical endpoints such as survival or time to mechanical ventilation. Thus, given this lack of clear clinical benefit of treatment at this time, a verification study will be required by the Applicant to establish the efficacy of Lumizyme.

1.3 Recommendations for Postmarketing Risk Management Activities

1.3.1 Lumizyme Verification Study required under 21 CFR 601.41-46

As described above, under accelerated approval regulations, 21 CFR 601.41-46 (Subpart E), a verification study must be performed to establish the clinical efficacy of Lumizyme. The verification study is being negotiated at the time of the submission of this review. A draft of the current verification study proposal is presented below:

(b) (4)

[redacted]

(b) (4)

1.3.2 Postmarketing Studies Required under 505(o)(3)

Based on the review of the safety data provided by the Applicant, serious adverse reactions, including anaphylaxis and immunologically mediated reactions have been noted. In order to more fully characterize these safety findings, other postmarketing studies that will be required of the Applicant under section 505(o)(3) of the Food Drug and Cosmetics Act. These postmarketing studies have been negotiated with the Applicant and include the following:

1. A retrospective immunogenicity study based on the pattern of antibody responses in patients enrolled in the LOTS and LOTS Extension Studies. (b) (4)

2. A prospective safety study conducted within the ongoing Pompe Registry to assess the known serious risks of treatment with Lumizyme, including anaphylaxis, severe allergic reactions, and signals of severe cutaneous and systemic immune complex-mediated reactions. (b) (4)

1.3.3 Risk Evaluation and Mitigation Strategy

Under Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Food, Drug, and Cosmetic Act (FDCA) the Agency is authorized to require the submission of a REMS (Risk Evaluation and Mitigation Strategy) by the Applicant if it has determined that such a strategy is necessary to ensure that the benefits of the drug outweigh the

risks (section 505-1(a)(1)). Based on the potential for serious allergic reactions, including anaphylaxis, and to ensure that the administration of Lumizyme is limited to the intended population, the Agency recommends that a REMS is necessary for Lumizyme.

The proposed REMS is being negotiated at the time of the submission of this review. Please see the final REMS proposal and supporting document for details of the requirements. A draft of the final REMS proposal is included in Appendix 9.2.

2 Introduction and Regulatory Background

2.1 Product Information

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.

The Applicant manufactures alglucosidase alfa for use in the United States (US) in two production scales, a 160 liter production scale (Myozyme™), and a 2000 Liter production scale (Lumizyme). Currently, the only treatment approved in the US for Pompe disease is Myozyme. Myozyme 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 ≤ 7months at the time of first infusion) as compared to an age-matched, untreated historical control. Approval of Myozyme 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 Myozyme 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 160 L product has not been able to meet the demand for 160 L product in the US and a drug shortage exists. The Applicant has limited access to 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 10,780). However, the Applicant stopped this temporary access program for 2000L product as of April 15, 2008, and Pompe patients over 18 years of age in US are not eligible for treatment under any active IND or access program. It should be noted that Myozyme

is the tradename give to the 160 L product within the US, but outside the US, Myozyme is the tradename used for the 2000 L product. However, given the requirement for separate licensure of these two products in the US, the Agency and Applicant have agreed in the US to name the 160 L product, Myozyme, and the 2000 L product, Lumizyme.

2.2 Tables of Currently Available Treatments for Proposed Indications

Alglucosidase alfa 160L (Myozyme) is the only approved, marketed drug in the United States (US) for the treatment of Pompe disease (see Table 1).

Table 1: Currently Available Treatments for Proposed Indications

Drug (trade name)	Indication	Manufacturer
Alglucosidase alfa 160L product (Myozyme)	Treatment of Pompe disease	Genzyme

2.3 Availability of Proposed Active Ingredient in the United States

The proposed active ingredient, alglucosidase alfa, produced at the 2000 L scale, has not been approved for use in the US. It is available under Investigation New Drug (IND) 10,780. Alglucosidase alfa 2000L has been approved for use in at least 40 other countries outside the US, including Canada.

2.4 Important Safety Issues with Consideration to Related Drugs

Enzyme replacement therapy for lysosomal storage disease was conceived in the early 1960's[1] but it was not until 1974 when purified glucocerbrosidase in the treatment of Gaucher disease was first published.[2] 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). All of the currently studied enzyme replacement therapies are 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 (Table 2).[3]

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

Immunogenicity of enzyme replacement therapies may lead to important safety concerns including the development of anaphylaxis and other allergic reactions. A boxed warning for the risk of anaphylaxis was placed in the label for Myozyme based on a 5% incidence of anaphylaxis in the clinical trial of 18 infantile-onset patients who received Myozyme. Additionally, boxed warnings for the risk of anaphylaxis were required in the labeling for Aldurazyme and Elaprase.

Additionally, delayed-onset infusion reactions have been seen with Myozyme. Finally, chronic immune-mediated skin reactions and glomerulonephritis have been reported in patients receiving rh-GAA.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

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 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 160 L 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 Myozyme was performed in 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 Agency noted that no other commercially available products were approved for use in Pompe disease in the US, and therefore, Myozyme 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 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 Myozyme, 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 product from Myozyme. 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 6 month, priority review would be granted for this BLA. During the current review cycle, the Agency and Applicant agreed upon the trade name, Lumizyme™, for the 2000L product to be marketed in the US. Therefore, for the remainder of this review 2000 L will refer to Lumizyme, and 160 L will refer to Myozyme.

Genzyme submitted BLA (STN 125,291; dated 28-May-2008) seeking approval of Lumizyme 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 Lumizyme in 60 non-infantile-onset Pompe disease patients (age 8 - 70 years) compared with 30 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 % predicted forced vital capacity (FVC). Comprehensive safety data from LOTS was also included in the submission. An open-label, six-month extension of this study (AGLU03206, LOTS extension) is ongoing at the time of this review, and interim safety data to a cut point of April 15, 2008, were submitted as part of an integrated review of safety on September 1, 2008. The integrated safety summary also includes data on patients receiving alglucosidase alfa as part of the AGLU03206 study, a Genzyme sponsored Myozyme Temporary Access Program (AGLU03907, MTAP), several small studies using Lumizyme; (AGLU2603 - 8 patients), (AGLU2804 - 5 patients), (AGLU3105 - 5 patients), and postmarketing safety data from patient treated with Lumizyme outside the US.

2.6 Other Relevant Background Information

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, known collectively as the late onset form, 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 α1,4- and α1,6-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.[4] 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.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Several problems and concerns with this application were noted, and are listed as follows (including but no limited to):

- The Applicant did not effectively integrate the existing safety data submitted in the Integrated Summary of Safety (ISS). Electronic data sets that were provided as part of the ISS were missing important safety information that produced significant time constraints for adequate review. Furthermore, much of the data contained in the ISS was not submitted in the form of electronic data sets; only narrative descriptions of adverse events were provided for three of the studies submitted as part of the ISS.
- Postmarketing safety data were not summarized. The information provided by the Applicant consisted of summary tables, and no electronic datasets were provided for review.
- Changes were made to both the pre-specified primary efficacy endpoints to accommodate an adaptive strategy after the study was initiated. This problem is further discussed in the statistical analysis review section.
- Changes were made to the pre-specified statistical analysis plan after the study was initiated, and changes were made to the statistical analysis plan after the data were unblinded. This problem is further discussed in the statistical analysis review section.
- Several Amendments to the BLA were submitted including errata to the final Clinical Study Report, and amendments to efficacy data sets throughout the review cycle. At the time of this review, 46 amendments to the BLA had been received by the Agency, with the most recent submitted on December 23, 2008. The following table (Table 3) lists some of the significant amendments to the BLA and the dates of their submission.

Table 3: Substantive amendments to BLA 125291

BLA Amendment Sequence	Purpose of submission	Date of submission
125291-007	Submission of labeling	07/18/2008
125291-009	Submission of pharmacology datasets	08/15/2008
125291-0011	Submission of errata to clinical study report affecting primary efficacy endpoints	08/13/2008
125291-0012	Submission of integrated summary of safety and submission of updated labeling	08/29/2008
125291-0014	Submission of cross reference of information to BLA 124141	08/19/2008
125291-0015	Submission of updated safety data sets for AGLU02704 per Agency request	08/15/2008
125291-0022	Submission of updated CMC information per Agency request	09/26/2008
125291-0026	Submission of errata to clinical study report affecting statistical analysis of primary endpoints	09/24/2008
125291-0030	Submission of CMC data regarding (b) (4) (b) (4)	10/08/2008
125291-0037	Submission of data regarding issuance of 483 letter by Agency	11/07/2008
125291-0038	Submission of REMS	11/07/2008
125291-0042	Submission of updated labeling based on information from updated Myozyme label	12/11/2008

The Division of Scientific Investigations (DSI) performed 2 clinical site audits for this application, including: 1) (b) (6) Erasmus Medical Center, Netherlands (site 26 and site 04) Dr. Barry Rosenbloom, Tower Cancer Research Foundation, Beverly Hills, CA (site 29). These sites were selected for inspection because of their high enrollment, geographic location (one foreign and one domestic site). (b) (6) The overall observation noted by the DSI Inspector (Khairy Malek, M.D.) for the two clinical sites was that "The data from the above 3 sites inspected are reliable and can be used in support of the BLA."

Despite problems with the quality of the submission as described above, the overall the quality of the Application was adequate for comprehensive review of the data, and the integrity of the investigators and of the conduct of the trial appear sound.

3.2 Compliance with Good Clinical Practices

The Applicant stated that LOTS was conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP) regulations and clinical research guidelines established by the principles defined in the U.S. 21 CFR Part 312, and ICH E6 "Guideline for Good Clinical

Practice, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use".

3.3 Financial Disclosures

Financial disclosures were included in the submission. For LOTS, notable findings were:

1. [redacted] (b) (6) received grants, equipment payments, consultation payments and retainers totaling over €1,139,000 from 2005-2007, and an additional $940,246.00 in royalties and payments upon FDA and EMEA approval of Myozyme between [redacted] (b) (6).
2. [redacted] (b) (6) has received royalties and payments upon FDA approval of Myzoyme of $7,914,895 and an additional $468,715 in grants, retainers, honoraria, and retainers from [redacted] (b) (6).
3. [redacted] (b) (6) has received $150,000 per year from [redacted] (b) (6).
4. [redacted] (b) (6) received a gift of $336,903 in a research grant from 2006-2008, and $123,255 as a gift for support of work done on genotyping of Gaucher patients in the Gaucher Registry.
5. [redacted] (b) (6) has received an educational grant for $50,000 per year from [redacted] (b) (6)
6. [redacted] (b) (6) received an educational training grant for $80,000 in [redacted] (b) (6)
7. [redacted] (b) (6) received consulting fees and expenses totaling $148993.00 from [redacted] (b) (6)
8. [redacted] (b) (6) received $80,803 from [redacted] (b) (6) in grants, expenses, and honoraria.

The reviewer believes that these financial arrangements do not appear to have impacted the integrity or quality of the Application.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls (CMC)

CMC data have been extensively reviewed by the Product Reviewer (Frederick Mills, Ph.D.); please see the CMC review for the complete review of the product data. The complete product review was not available for the summary at the time of this review but several notable issues have been identified by Dr. Mills and include:

1. The effect [redacted] (b) (4) on immunogenicity of 2000L product. Increase in [redacted] (b) (4) relative to [redacted] (b) (4) may increase susceptibility to proteolysis and increase major histocompatibility complex (MHC)

binding, thus increase in [redacted] (b) (4) may lead to an increase in immunogenicity.

2. The [redacted] (b) (4) of stress-tested material of the 2000L product may be present to a greater degree compared with 160L product. Increases in [redacted] (b) (4) of the product may lead to an increase in immunogenicity.
3. The effect [redacted] (b) (4) level on immunogenicity and efficacy of the 2000L product. The level of [redacted] (b) (4) residues on 2000L product is very low, and lower when compared with the 160L product. [redacted] (b) (4) are known to mediate targeting and uptake of lysosomal enzymes, and decreases in [redacted] (b) (4) of 2000L product may have an effect on efficacy as well as immunogenicity.

Additionally, the Division of Manufacturing and Product Quality (DMPQ) performed a facility inspection of the Applicant's Allston facility, where Lumizyme is manufactured and this inspection uncovered several deviations from current Good Manufacturing Practices including the following:

[redacted] (b) (4)

(b) (4)

These deficiencies were submitted to the Applicant in a 483 letter, dated October, 10, 2008. The Applicant issued a response to these deficiencies; however, at the time of this review, it has not been determined whether the deficiencies will warrant the issuance of a Warning Letter.

4.2 Clinical Microbiology

Clinical microbiology considerations do not apply to this application because Lumizyme is not an antimicrobial agent.

4.3 Nonclinical Pharmacology/Toxicology

The preclinical pharmacology and toxicology were reviewed in depth as part of the review for BLA STN125141 by Niraj R. Mehta, Ph.D. There were 7 new studies evaluating preclinical pharmacology or toxicology submitted in support of BLA STN 125291. Based on previous agreement with the Agency, these studies were submitted to BLA STN 125141 and cross-referenced to the current submission. The major findings of these seven studies are presented below:

1. Repeat-dose toxicity
A study evaluating repeated-dose toxicity was performed in juvenile mice. The NOEL (no observable effects level) was 20mg/kg/qo week and a dose of 50mg/kg/qo week was tolerated by juvenile mice with treatment up to 6 months.

2. Reproductive and developmental toxicology
One study evaluated the effect of doses of rhGAA on male and female mating and fertility. Doses of rhGAA as high as 40mg/kg administered qod did not affect either mating or fertility in both male and female mice. There was a dose dependent decrease in sperm motility and sperm count in the 20 and 40 mg/kg groups when compared to saline control. Another study evaluated the effect of rhGAA treatment on testicular development in male mice treated with up to 40mg/kg qod. There was no major effect on the macroscopic appears of the testicles at week 9.

Two studies in rabbits evaluated the teratogenic potential of rhGAA. Pregnant rabbits were administered doses of rhGAA up to 40mg/kg/day. Based on the visceral and external malformation data from fetuses, there appears to be no teratogenic effect of rhGAA in rabbits, and 40mg/kg/day appears to be a tolerable dose for pregnant rabbits.

One study evaluated effect of fertility in mice at does up to 40mg/kg/qod. There were minor effects of rhGAA on embryonic development in the 40mg/kg group. An increased incidence of gross external alterations (rotated hind limbs) was noted compared to control fetuses. No significant or biologically important differences in values for learning, short-term retention, long-term retention or response inhibition was noted in the F1 generation male and female mice as evaluated by performance in a passive avoidance paradigm.

3. Special toxicology studies
One study was performed in GAA knockout mice to evaluate immune tolerance induction regimens. The study demonstrated the 10mg/kg methotrexate administered at 0, 24, and 40 hours following the first 8 of 16 weekly rhGAA treatments reduced rhGAA-specific IgG titers in these mice.

Based on the nonclinical pharmacology and toxicology review, there were no additional nonclinical studies recommended and the reviewer's final recommendation is for approval of the product.

4.4 Clinical Pharmacology

Information regarding the clinical pharmacology of 2000L product prior to May 30, 2008, was submitted to BLA STN125141 and was cross-referenced in the current BLA. The original clinical pharmacology review was completed by Dr. Tien-Mien Chen.

Clinical pharmacology information submitted to the current BLA STN 125291 includes only information submitted by the Applicant since May 30, 2008. These data have been extensively reviewed by the Clinical Pharmacology and Biopharmaceutics Reviewer, Jang-Ik Lee, Pharm.D., Ph.D., and Justin Earp, Ph.D; please see the clinical pharmacology and biopharmaceutics review for the completed review of these data. A brief review of the clinical pharmacology data are presented below.

4.4.1 Mechanism of Action

Acid alpha-glucosidase is a hydrolase that degrades lysosomal glycogen to glucose. During trafficking to the lysosome, acid alpha-glucosidase is proteolytically processed, resulting in the formation of an enzymatically active multi-subunit complex. Acid alpha-glucosidase degrades glycogen by catalyzing the hydrolysis of α-1,4- and α-1,6-glycosidic linkages of lysosomal glycogen. 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.

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.

4.4.2 Pharmacodynamics

Clinical pharmacodynamic studies were not conducted for Lumizyme.

4.4.3 Pharmacokinetics

The pharmacokinetic profiles of 32 late-onset Pompe disease patients were studied as part of LOTS. All patients received 20mg/kg/dose body weight every other week, and data were analyzed using a 2-compartment linear pharmacokinetic model with a zero-order input. Patient's age and sex had no significant impact on the pharamocokinetic parameters. Cmax (Maximum clearance), Clearance (CL) and the central volume of distribution (V1) were affected by body weight; however, weight did not affect the effective half-life of rhGAA.

4.4.3.1 Immunogenicity

The development of anti-rhGAA antibody and its effect on PK and PD parameters was assessed by the pharmacology reviewer. Both high binding antibody titers and inhibitory antibody status (positive for uptake inhibition) are indicative of an increased systemic clearance (CL) of rhGAA. Additionally, the presence of inhibitory antibodies is associated with higher binding antibody titers: 5 patients with the highest binding antibody titer also had positive inhibitory antibody status in Study AGLU02704.

The Applicant claims no difference in rhGAA CL with antibody titers; however, there is a clear trend toward increased CL estimate at binding antibody titers at or above 10,000, which suggests that clearance increases with higher binding antibody titers (see Figure 1). Additionally, Figure 2 shows the changes in rhGAA CL over time in the 5 inhibitory antibody positive patients with the highest binding antibody titer. There was a clear increase rhGAA CL in 4 patients between Week 0 and Week 52. In one patient, the clearance increased by as much as 100% (from approx. 600 to approx 1200 mL/hr). The results clearly indicate that the onset of inhibitory antibodies increases the clearance of rhGAA. Although these 5 inhibitory positive patients also had the highest IgG antibody titer in the study, it is unclear whether binding or inhibitory antibodies are the cause for increased clearance. It can only be stated that inhibitory antibody status is associated with high binding antibody titers.

Figure 1: Individual plots for tendency of rhGAA clearance across anti-rhGAA IgG antibody titer

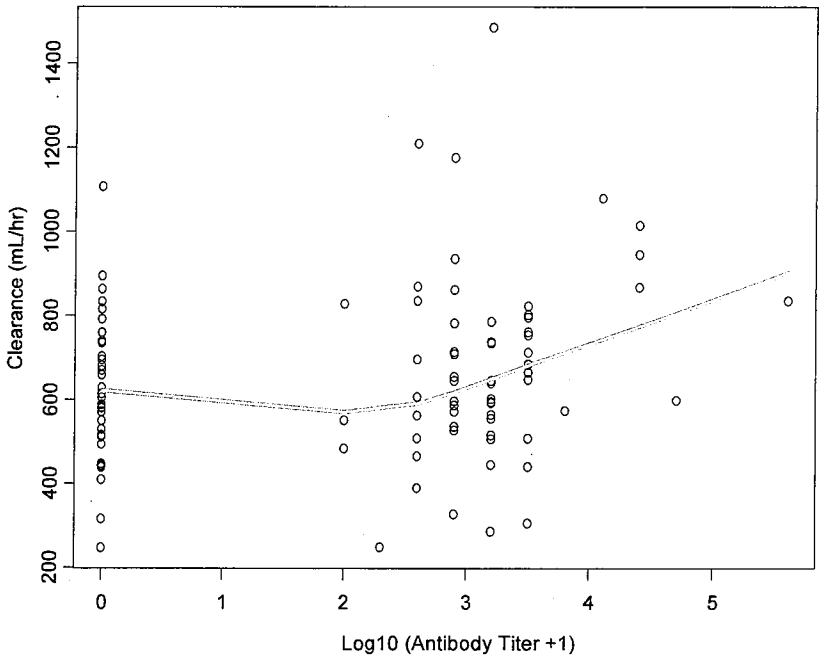
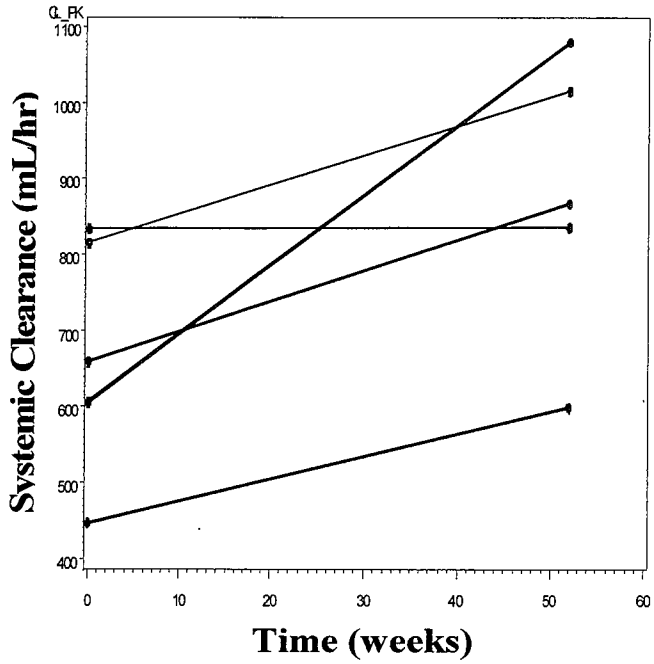


Figure 2: Time Course of rhGAA Clearance in patients with high anti-rhGAA IgG antibody titers and positive inhibitory antibody status at Week 52



In summary, the rhGAA pharmacokinetics were best described by a linear 2-compartment model. However, the Applicant used an abbreviated sample scheme, which was terminated ~20 hours after dosing, and therefore, the volume of the peripheral compartment could not be precisely estimated. No significant difference in pharmacokinetics was observed by either the Applicant or the

pharmacology reviewer across visits suggesting that rhGAA pharmacokinetics were stationary over time.

Additionally, both high anti-rhGAA IgG antibody titers and inhibitory antibody status (positive for uptake inhibition) are associated with a change in rhGAA pharmacokinetics. Inhibitory antibody status is associated with the highest anti-rhGAA IgG antibody titers: 5 patients with the highest binding antibody titer also had positive inhibitory antibody status in Study AGLU02704. Those five patients also had higher clearance (CL), lower Cmax, and lower AUC than 29 patients with negative inhibitory antibody status. The clinical significance of high antibody titers or positive uptake inhibition status is unclear.

5 Sources of Clinical Data

5.1 Table of Clinical Studies

The following table (see Table 4) lists the clinical studies submitted by the Applicant for review in support of the 2000L product. By prior agreement with the Agency, one clinical study, AGLU02704, A randomized, double-blind, placebo-controlled, adaptive, multicenter, multinational, placebo-controlled study of the safety, efficacy, and pharmacokinetics of Lumizyme, recombinant Human Acid alpha-Glucosidase (rhGAA), treatment in patients with late-onset Pompe Disease (LOTS),was the only study that was submitted for review to establish efficacy for the Applicant's requested indication. However, several other studies have been submitted to this application, largely to provide additional safety information regarding the 2000L product. Information from a non-GCP, investigator sponsored retrospective case series in 11 infantile-onset patients treated with 2000L product was also submitted by the Applicant. However, these data were not reviewed, as the information pertains only to infantile-onset patients, and provide no information supported the Applicant's proposed indication in late-onset patients only.

Table 4: Table of Clinical Studies

Study	Trial Design	Comments
AGLU02704	LOTS: Randomized, DB, PC study of late-onset Pompe patients ages 8-70 years; 2000L 20mg/kg/qow, n=90	Submitted to BLA 125291
AGLU03206	LOTS extension: OL extension of 80 patients who participated in AGLU02704 (LOTS); 2000L 20gm/kg/qo week, Study on-going	Only safety data to 15 April 2008 provided, No efficacy data
AGLU3907	MTAP*: OL, expanded access protocol to treat US patients >18 years of age until commercial treatment was available, n=138	Only safety data to 15 April 2008 provided, No efficacy data
AGLU2603	OL, expanded access study to treat severely affected late-onset patients who did not qualify for other studies until commercial treatment was available., n=9, 20mg/kg/qow	CSR submitted to BLA 125291
AGLU2804	Single center, OL, bridging study, late-onset Pompe disease, age 5-18 years, n=5, 20mg/kg/qow for 74 weeks	CSR submitted to BLA 125141
AGLU3105	Single center, OL, exploratory study in patients with advanced late-onset Pompe disease, age 17-50 years, n=5, 20mg/kg/qow for 52 weeks	CSR submitted to BLA 125291
Study in Taiwanese infants	Single center, uncontrolled, retrospective case series of infantile-onset patients treated with 2000L, n=11	Non-GCP investigator sponsored study

LOTS = Late Onset Treatment Study, DB = double blind, PC = placebo controlled, OL = open label, MTAP = Myozyme Temporary Access Program, US EAP = United States Expanded Access Program, qow = every other week.
*Myozyme refers to the 2000 L product, Lumizyme

5.2 Review Strategy

Brief Overview of Clinical Development Program

The original IND 10,780 was received by the Agency on November 22, 2002. There have been at least nine Phase 2/3/4 studies evaluating Lumizyme in late-onset Pompe disease. Information on six of these studies has been included in the current submission. There are 5 other studies evaluating Lumizyme or Myozyme in late-onset Pompe disease that are completed or on-going, and 2 studies involving the Pompe disease Registry:

1. AGLU02103: An open-label extension study of the long-term safety and efficacy of recombinant human acid α-glucosidase (rhGAA) given as enzyme replacement therapy to a single patient with Pompe disease (glycogen storage disease Type II) who was previously enrolled in a Genzyme-sponsored enzyme replacement therapy study. This was a phase 2, open-label extension study that enrolled one patient, a 20 year-old female patient, and evaluated 2000L product. The patient had previously received rhGAA derived from both transgenic rabbits [redacted] (b) (4) and [redacted] (b) (4) cell line [redacted] (b) (4) The dose of Lumizyme received was 30mg/kg/qow. The objective of this study was to provide access to treatment to this patient until commercial treatment was available.
2. AGLU02503: A clinical program to provide access to treatment for severely affected patients diagnosed with late-onset Pompe disease with recombinant human Acid α-Glucosidase (rhGAA). This study was conducted in three centers in Europe and enrolled a total of three patients.
3. AGLU04107: Observation study about the evolution of severe late-onset Pompe disease patients with pulmonary dysfunction and receiving Lumizyme.
4. AGLU03707: An exploratory study of the safety and efficacy of immune tolerance induction (ITI) in patients with Pompe disease with sustained high antibody titers or with antibodies that inhibit Myozyme activity or uptake.
5. AGLU3306: An exploratory, open-label study of the safety and efficacy of high dose or high dosing frequency 2000 L treatment in patients with Pompe disease who do not have an optimal response to the standard dose regimen. This study is evaluating the safety and efficacy of alternate dosing regimens of the 2000 L product in patients who have not demonstrated an optimal response to standard 20mg/kg every other week. Patients have been randomized to either 20mg/kg weekly or 40mg/kg every other week. The study was initiated in January, 2007. No further data are available at this time.
6. AGLU3406: A sub-registry to determine the presence of Myozyme (alglucosidase alfa, 160 L) in breast milk from women with Pompe Disease treated with Myozyme. No patients are currently enrolled in this study.
7. AGLU3506: A sub-registry to observe the effect of Myozyme (alglucosidase alfa, 160 L) treatment on pregnancy and infant growth in women with Pompe Disease. No patients are currently enrolled in this study.

Studies submitted for review with Application.

1. AGLU02704 is discussed in detail in section 5.3, Discussion of Individual Studies.

2. AGLU03206 is an open-label extension study of patients with late-onset Pompe disease who were previously enrolled in AGLU02704 (LOTS extension). A total of 81 patients enrolled in this study and preliminary efficacy and safety data were submitted as part of this review. This study evaluated the efficacy and safety of patients previously enrolled in LOTS for an additional 6 months (a total of 104 weeks) with placebo treatment patients converted to alglucosidase alfa 2000L product for 6 months. Safety data through 15 April, 2008 were submitted on 1 September 2008 as part of the integrated summary of safety.

3. AGLU02603 (not previously submitted) is an expanded access use of alglucosidase alfa 2000L in patients with late-onset Pompe disease. Nine patients were enrolled in this study,

and 8/9 received 2000L product for 52 weeks. One patient in the study received 160 L product for the first 6 infusions and then was changed to 2000 L product. The objective of this study was to provide access to treatment to this patient until commercial treatment was available.

4. AGLU02804: A single center, open-label, bridging study of the safety, pharmacokinetics and efficacy of recombinant human acid α-glucosidase (rhGAA) treatment in patients with late-onset Pompe disease (glycogen storage disease Type II). This study enrolled 5 patients between the ages of 5 and 18 years of age. All patients received 2000 L product at a dosage of 20mg/kg every other week for 74 weeks. All patients completed the study.

5. AGLU03105 (not previously submitted) was a prospective, open-label, single-arm exploratory study of the effect and safety of rhGAA in patients with advanced late-onset Pompe disease who are receiving respiratory support. This study was also performed in Europe with a total of only five patients enrolled in this study. All patients received 2000 L product for 52 weeks.

6. AGLU03907, "Myozyme" (Lumizyme) Temporary Access Program, has enrolled 137 patients with late-onset Pompe disease as of 15 April 2008. Safety data on these patients, many of whom have received 160L product in the past are being treated with 2000L product. The objective of this study was to provide access to treatment to this patient until commercial treatment was available. This study is ongoing, and patients in this treatment protocol have received Lumizyme for up to 11 months at the time of the submission of safety data through 15 April, 2008 as part of the integrated summary of safety.

5.3 Discussion of Individual Studies

By agreement with the Agency, one clinical study, AGLU02704, a randomized, double-blind, placebo-controlled, multicenter, multinational, placebo-controlled study of the safety, efficacy, and pharmacokinetics of Lumizyme, recombinant human acid alpha-glucosidase (rhGAA), treatment in patients with late-onset Pompe Disease (LOTS), was the only study that was submitted for review to establish efficacy for the Applicant's requested indication.

5.3.1 Methods

The efficacy information available for the medical review includes clinical efficacy or outcomes measures from one clinical study, LOTS. Efficacy data were available in 90 patients (60 patients randomized to Lumizyme and 30 patients randomized to placebo), all of whom had late-onset Pompe disease. Section 5.3.1 describes the design, study population, treatment, objectives and outcome measures, inclusion and exclusion criteria, concomitant medications, pertinent protocol amendments, and statistical plan.

5.3.1.1 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 Lumizyme 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).

5.3.1.2 Study objectives

The primary objectives of LOTS included the assessment of the efficacy, safety, pharmacokinetic profile, and tolerability of Lumizyme treatment over a 78 week period in patients with late onset Pompe disease patients.

Secondary objectives included the determination of the efficacy of Lumizyme treatment over a 26 week period, as well as the effect of Lumizyme on quality of life, and proximal and respiratory muscle strength.

Tertiary and exploratory objectives included the effect of Lumizyme on respiratory muscle weakness, various patient reported outcomes, and potential pharmacodynamic markers of Pompe disease.

5.3.1.3 Patient population/eligibility

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 ≤ 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 [(FVC supine (L) – FVC upright (L))/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.

5.3.1.4 Concomitant meds

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 sponsor has 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.

5.3.1.5 Visits and procedures

Study visits and procedures are shown in Tables 5-7 (tables were electronically copied from Applicant Protocol dated 16 August 2006, pgs. 30-34/84)

Table 5: 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[5,6]	X[5,6]
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 6: Schedule of Study Events: Treatment Period

Study Event[1a]	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
Physical Examination			X		X		X							X						X							X
Serum chemistry and hematology		X	X		X		X							X						X							X
Urinalysis		X	X		X		X		X		X		X		X		X		X		X		X		X		X
Oligosaccharides in blood			X		X		X							X						X							X
Oligosaccharides in urine			X		X		X							X						X							X
Anti-rhGAA antibody (IgG)	X		X		X		X		X		X		X		X		X		X		X		X		X		X
Pharmacokinetics testing[8]	X						X																				X
Height							X							X						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	Continuous Monitoring																										
Adverse Event Assessment	Continuous Monitoring																										
Concomitant and Pre-Infusion Medication/Therapy Monitoring[11]	Continuous Monitoring																										

Table 7: Schedule of Study Events—Treatment Period from week 54-week 78/End of Study

Study Event[1,2]	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)[6]						X							X[13]
Fatigue Severity Scale (FSS)[6]						X							X[13]
Rotterdam 9-Item Handicap Scale[6]						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

Randomizations and controls
LOTS was conducted as a double-blind, placebo-controlled study with randomization in a 2:1 ratio of Lumizyme 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 Lumizyme 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).

Study medication dose selection

The selection and timing of Lumizyme 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 Myozyme is 20mg/kg every other week, and the same dose was selected for use of Lumizyme in LOTS. No other doses of Lumizyme were used in this study.

Efficacy and endpoint measures
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 Lumizyme 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.

Secondary efficacy endpoints
1. Determination of effect of Myozyme treatment of 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 Myozyme 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 Myozyme 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 Myozyme 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 Myozyme treatment on inspiratory muscle weakness as measured by Maximal Inspiratory Pressure (MIP)
2. Determination of the effect of Myozyme treatment on expiratory muscle weakness as measured by Maximal Expiratory Pressure (MEP)
3. Determination of the effect of Myozyme 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 Myozyme 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 Myozyme 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 Myozyme 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 Myozyme treatment on muscle strength as assessed by Manual Muscle Testing (MMT)
5. Evaluate the effect of Myozyme treatment on patient-reported fatigue as measured by Fatigue Severity Scale (FSS)
6. Evaluate the effect of Myozyme treatment on the patient's functional ability as measured by the Rotterdam 9-item Handicap Scale
7. Evaluate the effect of Myozyme treatment on the change in oligosaccharide levels in plasma and urine

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.

PK and PD measures

The pharmacokinetic profiles of 32 late-onset Pompe disease patients were studied as part of LOTS. All patients received 20mg/kg/dose body weight every other week, and data were analyzed using a 2-compartment linear pharmacokinetic model with a zero-order input. Patient's age and sex had no significant impact on the pharamacokinetic parameters. Cmax (Maximum clearance), Clearance (CL) and the central volume of distribution (V1) were affected by body weight, however, weight did not affect the effective half-life of rhGAA.

5.3.1.6 Additional statistical considerations

There were several statistical and design issues that were uncovered during the course of the review. These issues include the following:

- Change from a fixed design to the use of an adaptive strategy

- Change in the endpoint from 6MWT (FVC) at 52 weeks to average change in 6MWT (FVC) as measured by a linear slope
- Change in statistical analysis methods after data were shown to violate assumptions of prespecified model
- Use of a minimization algorithm to allocate patients
- Results of re-randomization analyses

The statistical analysis plan was also amended three times, and the major changes to this plan are summarized below (from statistical review, Lisa Kammerman, PhD):

In the various statistical analysis plans, discussed below, the 6MWT (distance in meters) and FVC upright (% predicted) assessments formed the co-primary endpoints. A protocol amendment changed the definition of the endpoints to accommodate the adoption of an adaptive design strategy. In all plans, the measurement of the 6MWT was to be examined first. If the treatment effect were statistically significant at 0.05, then FVC upright would be evaluated.

1. **Original Statistical Analysis Plan, dated 27 September 2005**

The original statistical analysis plan specified two co-primary 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)

The treatment effect at 52 weeks for the 6MWT was to be assessed by a repeated measures linear model with covariates. The model was to have the following characteristics:

- Site is an explanatory variable
- Distance walked at baseline is a continuous covariate
- Time of assessment is an explanatory variable (categorical) in the model
- The model includes a term for the interaction between time and treatment, i.e., to assess evidence about whether the time effect is different for each treatment
- Response covariance is modeled by a compound symmetry structure
- The model contains a parameter for the treatment effect between Lumizyme and placebo at Study Week 52, adjusted for baseline.

The parameter for the treatment effect at Study Week 52 would be tested to assess the significance of the treatment effect.

The model parameters would be estimated by a restricted maximum likelihood method (REML). Assumptions regarding the normality of errors and the form of the covariance matrix would be assessed. If the data indicated that model assumption of normality of errors were likely to be violated, then non-parametric methods may be used to carry out the significance testing.

Assessment of FVC upright would be carried out in a similar manner.

The sample size calculations for the original fixed design were based on variability in FVC over time in untreated patients with late-onset Pompe disease in Study AGLU02303; there was no longitudinal data on 6MWT. With a 2:1 treatment allocation (Lumizyme:Placebo), a sample size of 63 (Lumizyme, n=42; placebo n=21) would have 80% power to detect a treatment difference of 0.75 standard deviations using a two-sample t-test with a Type I error rate of 5%. The plan was to enroll at least 72 patients (2000L, n=48; placebo n=24) to account for a 10 to 15% dropout rate.

2. Statistical Analysis Plan Amendment 2, dated 29 September 2006

In May 2006, while the study was ongoing, the protocol was amended to an adaptive clinical trial design, and the primary endpoint was changed to a linear rate of change in distance walked estimated from a longitudinal model where response was to be modeled as a linear function of time of assessment. The rationale for these changes was to determine the optimal duration of the study and to "compare the two treatments over the course of the study, rather than focusing on comparisons at 52 weeks."

The statistical analysis plan contained methods and plans for the implementation of the adaptive design.

The adaptive design required changes to the primary endpoints. The co-primary efficacy variables were changed to slopes (average monthly increase):

- Average monthly increase in 6MWT.
- Average monthly increase in FVC upright (% predicted).

The interim analysis for the adaptive design was to be done when the last patient enrolled and continuing in the study completed Week 38 or when the statistical criterion for the analysis had been achieved. The study could continue to 52 weeks, as originally planned, or extended an additional 3 or 6 months. The maximum length of time any patient could participate in the study was 78 weeks.

The changes in the average monthly increases in 6MWT (and FVC upright) among patients randomized to Lumizyme compared with changes in average monthly increases in 6MWT (and FVC upright) among patients randomized to placebo were 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)

The model would be used to estimate the rate of change for each patient. Model assumptions would be assessed. Differences between the average monthly increase between patients randomized to Lumizyme and to placebo would be tested by a Wald statistic. The Haybittle-Peto alpha-spending function would adjust for the implementation of the adaptive design, resulting in a final nominal alpha of 0.04999 for declaring statistical significance.

Supportive analyses were to include a re-randomization analysis, which was to consist of running the minimization algorithm used for the treatment assignments 10,000 times. The LME would be applied and the p-values for the test of the treatment effect recorded. The resulting empirical distribution for the p-values would be compared with the observed p-value.

An analysis of covariance model (ANCOVA) was an additional supportive analysis. The ANCOVA would model the change from baseline and, separately, relative change from baseline to the last observed assessment. The model would include the baseline strata used in the minimization algorithm, the baseline observation, and treatment indicator.

3. Changes to statistical analysis methods after data were unblinded

The Applicant further changed the statistical analysis plan after the data were unblinded. The pre-specified analysis using LME with model based variance was performed. After fitting the pre-specified LME to the data, diagnostics were done to determine the appropriateness of the LME model. These diagnostics were pre-specified in the SAP. Examination of the 6MWT data indicates significant departures from linearity and violations of the assumption of normality. Moreover, the applicant asserts the observed non-linearity also compromises the estimate of the model-dependent variance-covariance matrix.

Because of these findings, the Applicant chose to use a sandwich estimator of the variance-covariance matrix. In addition, the applicant decided to test the difference in the monthly rate of change using GEE models and the repeated measures Wei-Lachin test, a nonparametric procedure. The applicant claims that GEE models relax the assumptions of linearity and a correctly specified variance-covariance matrix. Their GEE model uses a compound symmetric working correlation matrix. ANCOVA models were used in place of LME models to estimate treatment effects in subgroups.

The FVC efficacy analysis did not violate any of the assumptions of the LME model. However, GEE, Wei-Lachin and ANCOVA models were used to analyze FVC to maintain consistency with the analyses of the 6MWT.

The statistical reviewer agrees that the sandwich estimator of the variance-covariance matrix in the LME model is more appropriate for these data than is a model-based estimator. However, because of the numerous violations of the assumptions underlying the pre-specified LME model, the statistical reviewer favors the use of the ANCOVA model to assess the efficacy of the 2000L product. The ANCOVA model makes fewer assumptions. Additionally, it answers the clinical question of interest: does the change from baseline to the last assessment in the 6MWT among patients treated with Lumizyme differ from the change from baseline to the last assessment in the 6MWT among patients treated with placebo. Therefore, the assessments between the baseline and the last visit are not needed to answer this question.

Based on the review of the statistical and design issues, the FDA statistical reviewer made the following conclusions:

From a statistical perspective, this application is unusual in several ways. While the study was ongoing, the study was changed from a fixed design to a design with an adaptive strategy. This necessitated a change to the endpoint, which became the linear rate of change over the duration of the study. For each patient, this rate of change was estimated by a slope. Thus, instead of comparing the 6MWT at 52 weeks, the primary analysis became a comparison of the slopes.

To evaluate the slopes, the primary analysis method was a linear mixed effects model, where the patient-level intercepts and slopes were random effects and other effects (e.g., treatment, baseline strata) were fixed effects. The statistical analysis plan specified a model-dependent estimator of the variance-covariance matrix.

The statistical analysis plan also specified ANCOVA models and re-randomization tests as supportive analyses. The re-randomization tests were included to address the minimization algorithm that was used to allocate patients in a 2:1 ratio to either Lumizyme or placebo.

When the data were analyzed, diagnostic tests determined the 6MWT departed from the assumption of linearity and the assumption of normality as well. Moreover, the applicant asserts the observed non-linearity also compromises the estimate of the model-dependent variance-covariance matrix.

As a result, the applicant proposed the use of a "sandwich" estimator of the variance-covariance matrix. While I agree the "sandwich" estimator is more appropriate, its use leaves some unanswered questions. If the model assumptions are correct, the model-based estimator of the variance-covariance matrix is more efficient than a "sandwich" estimator". Had the results been statistically significant, I wonder whether the applicant would have explored the use of the "sandwich" estimator and argued for its use if the results had been statistically non-significant.

The applicant also included results from analyses that were not pre-specified: generalized estimating equation (GEE) models and non-parametric assessment of the data. These tests gave statistically significant results for the 6MWT. However, I question the use of models that were not prespecified.

Because of the violations of the assumptions underlying the linear mixed effects model and the changes to the model after the data were unblinded, I believe the results of the ANCOVA should be emphasized. The ANCOVA is consistent with the clinical question of interest, which is whether the change from baseline to the last observation differs between Lumizyme -treated patients and placebo-treated patients.

Further complicating the interpretation of the study results is the scheme used to allocate patients to 2000L and placebo. Instead of a blocked randomization, the study used a minimization allocation in order to maintain a 2:1 (Lumizyme: placebo) ratio within study sites and within strata defined by baseline values for the 6MWT and FVC.

Re-randomization tests are the appropriate approach for assessing statistical significance when a minimization algorithm used. Usually, the result from a re-randomization test is consistent with the

result from the classical test. However, that is not the case in this submission. For the ANCOVA of the 6MWT, the p-value changes from 0.035 to 0.06; and for the LME with the sandwich estimator, the p-value changes from 0.046 to 0.15. I discount the applicant's argument that patients can be assumed to have arrived in a random order, an assumption which leads to statistically significant results for the 6MWT. The results for FVC are statistically significant regardless of the test used.

The clinical team believes the 6MWT is the relevant parameter for deciding the efficacy of Lumizyme. The results for FVC were to be assessed only if the result for the 6MWT was statistically significant.

Although the p-value of 0.06 for the re-randomization test, which I believe is the appropriate test, corresponding to the ANCOVA is not statistically significant at the traditional alpha level of 0.05, I believe the orphan status of the indication needs to be entertained when deciding on the efficacy of this product for the treatment of adult patients with Pompe disease.

5.3.1.7 Protocol amendments

Three protocol amendments and three statistical analysis plan amendments were submitted by the Applicant during the course of LOTS (see Figure 3). The major changes in each protocol amendment were summarized by the Applicant:

1. **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 ≥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 he Investigator would significantly interfere with study compliance, including all prescribed evaluations and follow-up activities.

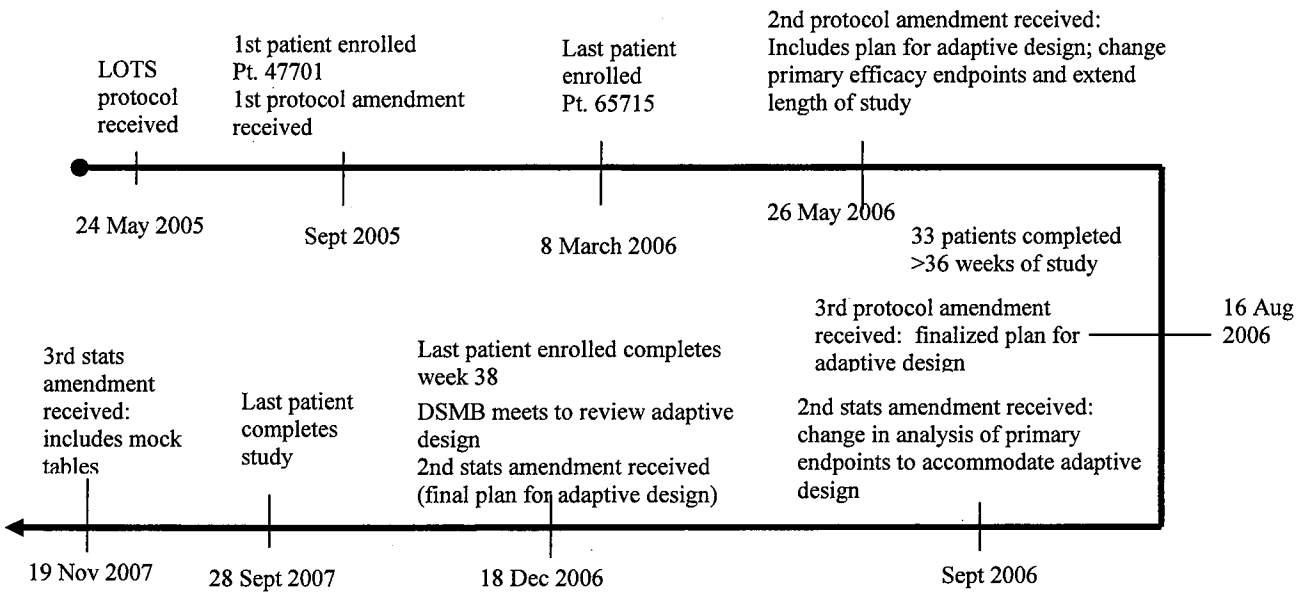
2. **Protocol Amendment 2, dated 26 May 2006**
    - This amendment was submitted after 33 patients had completed at least 36 weeks of the study.

- 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.

3. 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).

Figure 3: Timeline of Protocol and Statistical Analysis Plan Amendments



5.3.1.8 Study conduct

Use of Concomitant Medications

There are 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. Table 8 shows the most concomitant medication use in the study. There were no major differences in concomitant medication use between the treatment groups. Additionally, data

regarding the use of other support (e.g. ventilator, assistive walking devices) was also reviewed. There were a greater percentage of patients in the placebo group that required the use of bi-pap during the study (see Table 9). The effect of additional respiratory support on the primary efficacy endpoints was analyzed (see Table 10). Patients in the placebo group who received respiratory support performed worse than the overall mean for the placebo group. Also, patients in the Lumizyme treatment group did not perform as well as the overall mean, but there was an average 18 meter improvement in 6MWT. Thus, it appears that there was a treatment effect in patients who were receiving respiratory support. The number of patients in this subgroup analysis is small, and therefore, no clear conclusions regarding the presence of additional respiratory support on the efficacy outcomes can be determined.

Table 8: Most common concomitant medications overall

Medication	Total (%)	Lumizyme group Total (%)	Placebo group Total (%)
Paracetamol	57 (63)	37 (62)	20 (67)
Ibuprofen	48 (53)	29 (48)	19 (63)
Influenza vaccine	28 (31)	20 (33)	8 (27)
Loperamide HCl	25 (28)	15 (25)	10 (33)
Multivitamin, plain	21 (23)	15 (25)	6 (20)
Influenza vaccine, polyvalent	18 (20)	13 (22)	5 (17)
Acetylsalicylic acid	17 (19)	12 (20)	5 (17)
Guaifenesin	17 (19)	11 (18)	6 (20)

Table 9: Patients receiving respiratory support as concomitant therapy

Type of support	Total (%)	Lumizyme (%)	Placebo (%)
Bi-PAP	31 (34)	17 (28)	14 (47)
Oxygen	10 (11)	8 (13)	2 (7)
Ventilator	4 (4)	3 (5)	1 (3)
More than 1 therapy	8 (9)	6 (10)	2 (7)

Table 10: Effect of concomitant respiratory support on primary efficacy endpoints

	Lumizyme (n=21)	Placebo (n=11)
Change from baseline %FVC mean (± SE)	0.2 (0.5)	-2.6 (0.5)
Change from baseline 6MWT mean (± SE)	18.4 (3.8)	-14.9 (6.0)

Compliance with Medications

During the course of the study, 35 (58%) patients in the Lumizyme group and 17 (57%) patients in the placebo group missed at least 1 infusion. There were a total of 101 missed infusions in 52 patients in the entire study. The most common reasons given for missing infusions included scheduling issues and logistical issues. Also, in patients that missed more than 1 infusion (18 total), 13 (22%) patients were in the Lumizyme group, and 5 (16%) were in the placebo group. This group includes 3 patients in the Lumizyme group who dropped out of the study, and 1 patient in the placebo group who withdrew from the study. These missed infusions do not appear to have made a

substantial difference in the outcome of the trial as the missed infusions between the groups was similar.

Protocol deviations
Protocol deviations were frequent, and predominantly consist of out-of-window infusions or assessments, deviations in rates of infusion, and missed assessments. These deviations were felt to be minor and unlikely to impact on the overall study results. Protocol violations reported were notable for:

1. Patient 18713 developed anaphylaxis beginning with week 28 infusion. The patient missed infusions from week 34 to 40. Afterward, the patient received 20mg/kg infusion at week 42, but developed another anaphylactic reaction. The patient then missed week 44 infusion, and was administered week 46 infusion, and 5 subsequent infusions of 10mg/kg.
2. Patient 4705 in the placebo treatment group received one dose of Lumizyme at study visit 2. This drug was allocated for patient 26705. It is not stated whether patient 26705 received placebo treatment or Lumizyme.
3. There were six patients identified, in whom the Sponsor states as having completed the study that did not have complete 6MWT data. Specifically, patients 26703, 29707, 65707, 90707, 65711, and 18713 had incomplete 6MWT data. Furthermore, two of these patients, 26703 and 29707 did not have 6MWT data at the 78 week time point. Patient 26703 was randomized to receive Lumizyme, and patient 29707 was randomized to receive placebo. Additionally, patients 65707, 90707, 65711, and 18713 were all randomized to receive Lumizyme.

5.3.2 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 11), the age at first infusion was weighted toward patients ≥ 40 years of age, with 71% of the patients in the Lumizyme 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 2 patients in the Lumizyme treatment group were less than 18 years of age at the time of the first infusion, and 2 patients in the placebo group were less than 18 years of age at the time of enrollment (Table 11).

Table 11: Number of patients (% of total) by age at first infusion, by treatment group

Age at First Infusion	Lumizyme	Placebo
<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 12 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 Lumizyme. The majority of both the placebo and Lumizyme 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 12: 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 (Lumizyme)

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 Lumizyme in this Pompe disease population cannot be definitively determined. Further analysis of the juvenile-onset subgroup is presented in 5.3.7.1.

Patient enrollment based on site

Two centers enrolled 33% or 30/90 patients in the LOTS trial. The number of patients enrolled by site and by treatment group is presented in Table 13. There are no major discrepancies in the percentages of patients enrolled by treatment group at each center.

Table 13: Number of patients enrolled by site

SITE	Total patients	Lumizyme	Placebo
04 (Netherlands)	2 (2%)	1 (2%)	1 (3%)
16 (Pittsburgh)	10 (11%)	7 (12%)	3 (10%)
18 (Washington, DC)	10 (11%)	7 (12%)	3 (10%)
26 (Netherlands)	20 (22%)	13 (22%)	7 (23%)
29 (Los Angeles)	14 (16%)	9 (15%)	5 (17%)
47 (St. Louis)	12 (13%)	8 (13%)	4 (13%)
65 (New York)	12 (13%)	8 (13%)	4 (13%)
90 (France)	10 (11%)	7 (12%)	3 (10%)

There was considerable variability in the performance in the primary efficacy endpoints, 6MWT and % predicted FVC based on site of enrollment (see Tables 14 and 15). However, a review of two sites, 26 and 29, by the Division of Scientific Investigation found no concerns regarding the conduct of the study at these two sites. A full review of the efficacy analysis for LOTS is provided in section 5.3.4.

Table 14: Mean change in 6MWT (± SD) from baseline to end of study based on site of enrollment

SITE	Lumizyme	Placebo
04	14 (18.3)	-51.5 (9.2)
16	8.9 (46.2)	-48.6 (53.9)
18	35.7 (44.3)	2.9 (22)
26	50.1 (74.4)	-1.0 (31)
29	13.3 (24)	0.3 (22.6)
47	28 (52.9)	17.2 (31.8)
65	5.8 (27.8)	6.6 (36.2)
90	21.4 (30)	26.7 (21.5)

Table 15: Mean hange in % predicted FVC (± SD) from baseline to end of study based on site of enrollment

SITE	Lumizyme	Placebo
04	-0.5 (2.6)	2.5 (2.1)
16	0.2 (5.3)	-5.6 (3.1)
18	0.3 (5.9)	-2.4 (5.7)
26	1.9 (4.4)	-1.2 (5.6)
29	0.56 (4.0)	-1.3 (2.5)
47	1.6 (5.9)	-1.3 (4.0)
65	3.6 (4.3)	-1.0 (3.2)
90	1.2 (5.9)	-1.6 (3.5)

Additionally, there appears to be a gender imbalance based on the site of enrollment (Table 16). Site 26 appears to have enrolled more men in the treatment group and more women in the placebo group. The affect of gender on treatment is discussed in a later section (section 5.3.7.5), but imbalances in the enrollment of women and men at different sites may play a role in the statistical issues relating to re-randomization inference.

Table 16: Enrollment by treatment group and gender by site

		Lumizyme		Placebo	
SITE	Total	Female	Male	Female	Male
04	2	0	1	1	0
16	10	5	2	2	1
18	10	2	5	2	1
26	20	4	9	6	1
29	14	5	4	3	2
47	12	3	5	2	2
65	12	3	5	1	3
90	10	4	3	2	1

5.3.3 Patient Disposition

A total of 108 patients with late-onset Pompe disease signed the informed consent form, and were eligible for screening (Figure 4). 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:

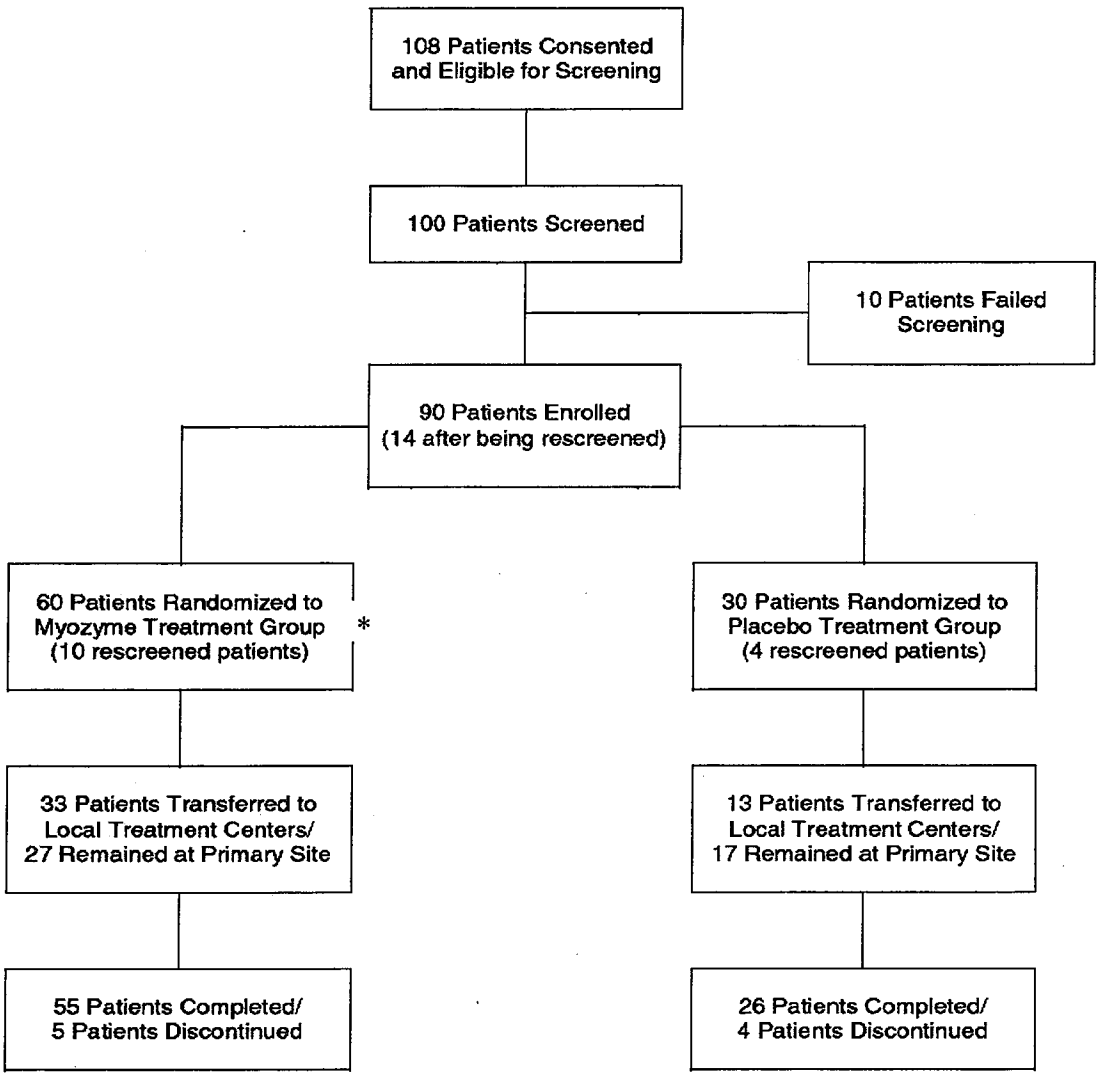
- Failed to meet enrollment criteria based on investigator's discretion (10 patients)
- Failed to qualify based on pre-screening results (5 patients)
- Investigational site was already fully enrolled at the time patients were consented (2 patients)
- Chose not to participate after consenting, but prior 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 4: Patient Disposition ALGU02704



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* Myozyme refers to the 2000 L product (Lumizyme)

5.3.4 Analysis of Primary Endpoint(s)

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 Lumizyme 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).

Six-Minute Walk Test

A. 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 meter 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).[5] 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 difference 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).[6, 7]

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 validated surrogate markers for a clinical benefit outcome such as time to death or ventilator dependency.

B. Results

Summary statistics
A review of the primary efficacy data from the 6MWT was performed to determine differences between the Lumizyme (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 5.3.1.5). 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 17 shows summary statistics based on the original statistical plan. Baseline data for distance walked between the Lumizyme and placebo treatment groups was not different. On average, patients in the Lumizyme treatment group could walk 26 meters more at the end of treatment than at the beginning of treatment (Table 17). 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 17, a difference between the

"*mean distance walked at baseline*" and "*median distance walked at baseline*" should be noted. In the Lumizyme 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 5.3.7.6. 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 (Lumizyme 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 17.

Table 17: Change from baseline in distance walked in 6MWT in meters

	Lumizyme N=60	Placebo N=30	Difference
Summary statistics:			
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
Results of ANCOVA:*			
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)

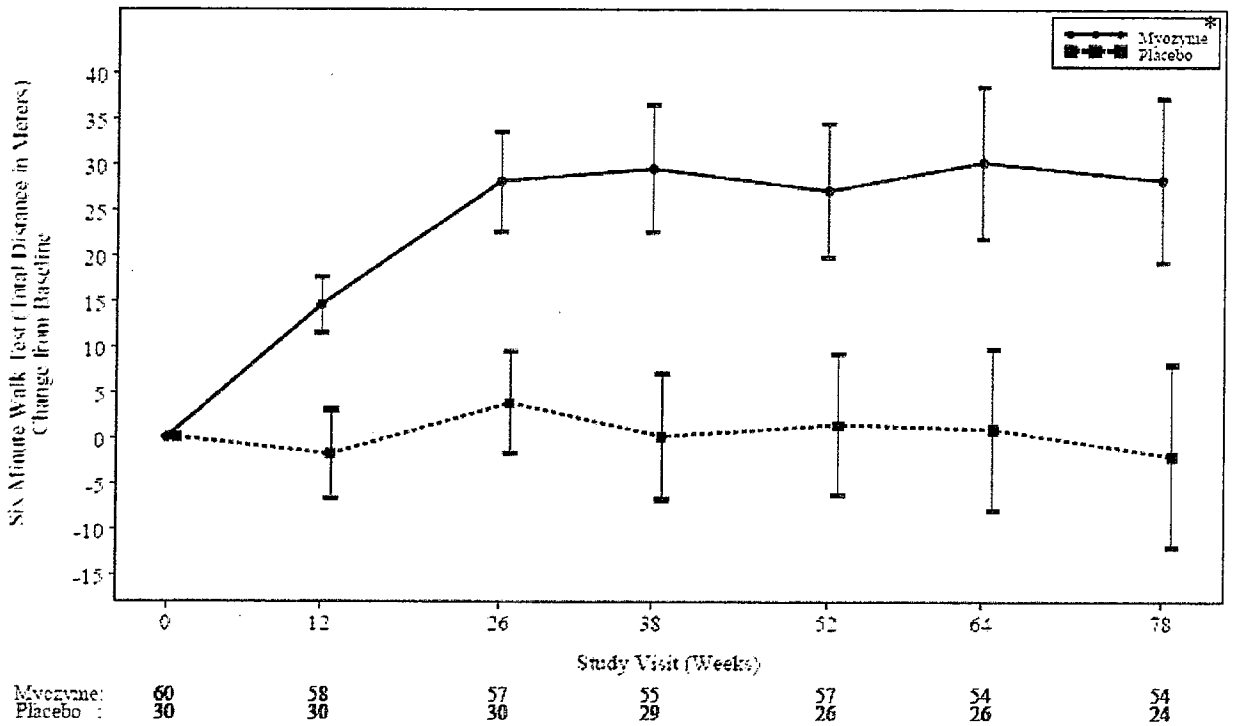
*Copied from Applicant Clinical Study Report pg. 106/1841

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 18 and depicted in Figure 5. Among subjects in the Lumizyme 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.[8]

Table 18: Mean/median change from baseline (± SD) 6MWT to last observation in meters

Visit	Lumizyme	Placebo
Screening/Baseline		
Week 12	14.7/12 (23.4)	-1.8/0 (26.5)
Week 26	28.1/21 (41.0)	5.9/4 (28.6)
Week 38	29.4/23 (51.4)	1.1/4 (38.4)
Week 52	27.7/17.5 (55.1)	1.4/0 (39.9)
Week 64	30.2/13 (61.3)	1.0/-1.5 (45.4)
Week 78/Early Termination	27.1/15.5 (65.6)	-5.0/-7 (47.7)
Overall Mean Difference	32.1	
Overall Median Difference	22.5	

Figure 5: Change from Baseline 6MWT 2000 L vs. Placebo



* Myozyme refers to the 2000 L product (Lumizyme)
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C. 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 Lumizyme 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 Lumizyme 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 Lumizyme 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 19.

Table 19: Monthly change in distance walked (m) 6MWT LME with model based variance and robust variance estimation

Parameter	Summary Statistic	Placebo (N= 30)	Lumizyme (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	0.8883	0.0124	0.0464

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However, after apply re-randomization inference to these data, the Applicant regenerated p-values for the 6MWT LME and showed that after re-randomization using a fixed patient arrival sequence, the p-value changed to 0.15. The statistical reviewer believes that this p-value is the correct p-value for the LME analysis (Table 20).

Table 20: Corrected re-randomization p-values for primary efficacy endpoint statistical analyses

Endpoint	Model	Reported primary efficacy result p-values	Corrected Re-randomization p-value with fixed patient arrival sequence	Re-randomization p-value with random patient arrival sequence	Stratified permutation test p-value
6MWT	LME with robust variance estimation	0.0464	0.1500	0.060	0.065
	GEE	0.0326	0.1040	0.042	0.045
	ANCOVA	0.0347	0.060	0.033	0.035
FVC upright	LME with model-based variance estimation	0.0084	0.0130	0.009	0.012
	ANCOVA	0.0055	0.004	0.005	0.005

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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 Lumizyme group compared with the placebo treatment group (p=.035). However, when the re-randomization inference is applied to the ANCOVA analysis, the p-value again increases significantly to 0.06. Thus, the ANCOVA analysis also fails to demonstrate a statistically significant difference between the 2000L treatment and placebo groups for 6MWT (Table 20).

D. Summary of results for the 6MWT

The Applicant performed four analyses of the data for 6MWT:

1. LME with robust variance (post-hoc)
2. GEE (post-hoc)
3. LME with model-based variance (pre-specified)
4. ANCOVA (pre-specified as a sensitivity analysis only)

Of these four post-hoc analyses of the data, none achieved statistical significance after applying the re-randomization inference using a fixed patient arrival sequence. The FDA statistical reviewer agrees that the most appropriate analysis is ANCOVA. Using this analysis, the difference of 28.1 m between the Lumizyme treatment group and placebo group at the end of the study adjusted for baseline differences (ANCOVA, p=0.06) is not statistically significant.

Additionally, 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.

FVC Analysis

A. Description

Forced Vital Capacity (FVC) % predicted 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.[9] 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.[10] 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, nor has it been used

previously as 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 Lumizyme treatment group and -0.16 for the placebo group. The difference in monthly change in FVC (% predicted) was 0.18 (Table 21) and the change from baseline to last observation between the groups was 3.4% (Table 22). 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 Lumizyme-treated and placebo of 0.18% is unclear.

Table 21: FVC Upright (% Predicted)

	Lumizyme 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)		
Wilcox-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)		

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Table 22: Change from baseline in upright FVC (% predicted)

	Lumizyme N=60	Placebo N=30	Difference
Summary statistics:			
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
Results of ANCOVA:*			
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)

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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 23).

Table 23: Mean (± SD) Change in FVC (% predicted) from baseline by visit

Visit	Lumizyme	Placebo
Screening/Baseline		
Week 12	1.8 (3.8)	-0.8 (4.0)
Week 26	1.6 (4.3)	-0.4 (3.7)
Week 38	1.4 (4.8)	-2.6 (4.7)
Week 52	1.6 (5.1)	-2.0 (4.5)
Week 64	0.5 (6.1)	-3.0 (5.2)
Week 78/Early Termination	1.4 5.6)	-2.4 (4.3)
Overall Mean Difference	3.8%	

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.

5.3.5 Analysis of Secondary Endpoints(s)

Quantitative Muscle Testing (QMT) was assessed during the study as a secondary endpoint. QMT is a standardized measure of muscle force production during maximal voluntary isometric muscle contraction. This test has not been used to evaluate Pompe disease patients previously, but has been used in other various diseases in which muscle weakness is a symptom, i.e., spinal muscular atrophy, Duchenne's muscular dystrophy, and amyotrophic lateral sclerosis. In this study, the Applicant studied the QMT of the proximal leg muscle groups, the knee flexors (hamstrings) and extensors (quadriceps), to assess the effect of alglucosidase alfa on the strength of the proximal leg muscles. The results were reported by the Sponsor as a QMT leg score. This score is defined by the Sponsor as the average of the bilateral means for the percent predicted of normal values for the knee flexors and extensors. This reviewer notes that this scoring system has not been used before to test muscle weakness in Pompe disease patients, and has not been used consistently in other diseases where muscle weakness is present as described above. The normative values for QMT that the study bases the percent predicted calculations [11] has not been used to study Pompe disease patients previously and has not been clearly tested in children.

The QMT leg score data are presented in Table 24 below. The rate of change monthly change in QMT leg score was not statistically significant in any analysis used by the Sponsor. The mean monthly change in QMT leg score (% predicted) was 1.18 in the treatment group and -2.0 in the placebo group for a difference of 3.18, but again, this was not statistically significant. The Sponsor also provided the relative change from baseline to last available observation and demonstrated a 12.44 % predicted difference that was statistically significant. This importance of the QMT score in establishing efficacy for the treatment is difficult as this test has not been used previously to evaluate clinical outcome in Pompe disease patients. Additionally, the data collected only included the QMT leg score as a measure of the % predicted of normal. Raw QMT leg score data (actual force of muscle contraction in Newtons) were not provided by the Sponsor nor were the raw data analyzed. The data appear to demonstrate a slight early improvement in the treatment group, but at the last observation at week 78, both groups show a declining trend in QMT leg score (see Figure 6). The reviewer believes that these data do not provide any meaningful support for the clinical efficacy of alglucosidase alfa.

Table 24: QMT Leg score (% predicted) Electronically copied from Sponsor submission

	Lumizyme	Placebo	Difference	P value
Mean Baseline QMT Leg Score, % predicted	37.69	32.49		
Mean QMT Leg Score at Last Available Observation, % predicted	39.05	30.40		
Estimates/Tests of Monthly Change in QMT Leg Score % Predicted (Repeated Measures Analysis)				
LME with model-based variance, % predicted (95% CI)	0.00 (-0.13, 0.13)	-0.13 (-0.32, 0.06)	0.13	0.2615
Wei-Lachin test				0.0295
Estimates/Tests of Change in QMT Leg Score % Predicted From Baseline to Last Observation				
ANCOVA Estimated Mean Change from Baseline to Last Available Observation, % predicted (95% CI)	1.18 (-1.07, 3.42)	-2.00 (-5.16, 1.17)	3.18 (-0.73, 7.08)	0.1093
ANCOVA Relative Change from Baseline to Last Available Observation, % (95% CI)	2.86 (-2.09, 7.81)	-9.58 (-16.54, -2.61)	12.44 (3.84, 21.03)	0.0051
Nonparametric Median Change from Baseline to Last Observation, % predicted (95% CI)	0.50 (-1.25, 2.25)	-2.13 (-3.54, -0.75)		
Wilcoxon-Mann-Whitney test				0.0224

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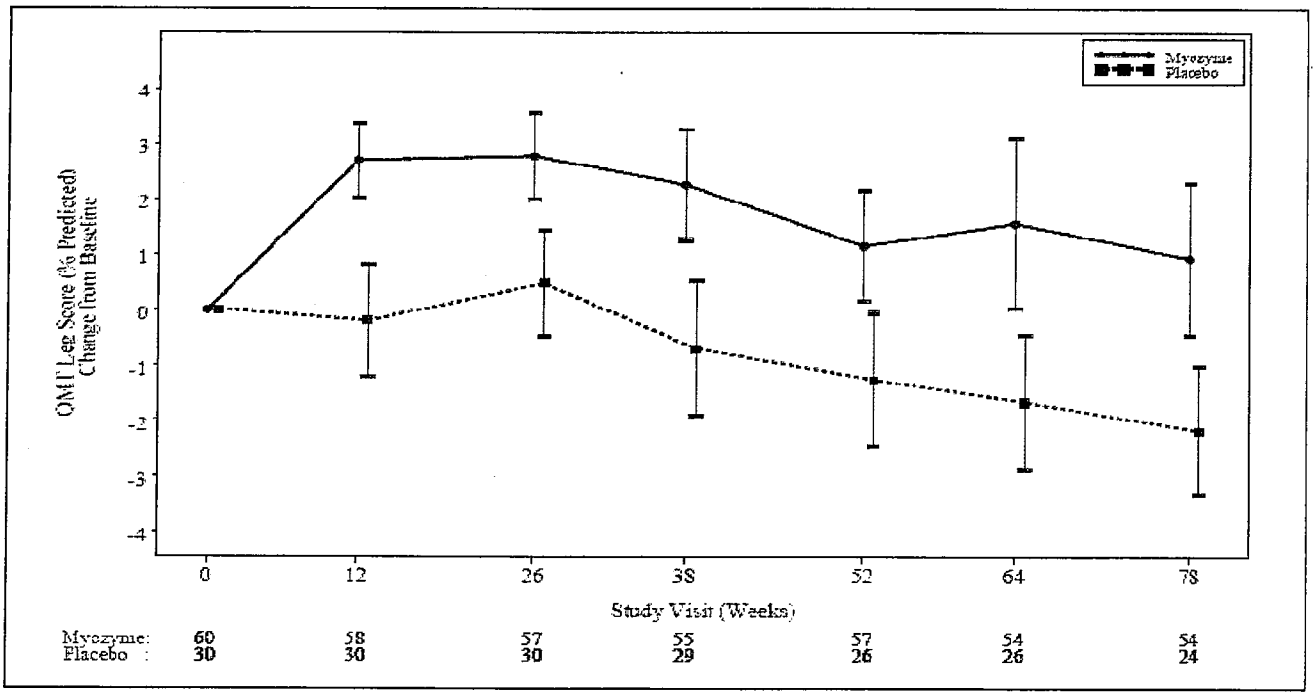
Figure 6: Mean (± SEM) Change from baseline over time in QMT leg score (% predicted)



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* Myozyme refers to the 2000 L product (Lumizyme)

5.3.6 Other Endpoints

Multiple secondary, tertiary, and exploratory endpoints were collected and analyzed as part of AGLU02704. None of these endpoints were used to establish evaluate the efficacy or safety of Lumizyme in late-onset Pompe disease, and therefore, due to time constraints, these endpoints were not analyzed for this review.

5.3.7 Subpopulations

5.3.7.1 Age at enrollment

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 25), the age at first infusion was weighted toward patients ≥ 40 years of age, with 71% of the patients in the Lumizyme 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 Lumizyme 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 25).

Table 25: Number of patients enrolled by age at first infusion, by treatment group

Age at First Infusion	Lumizyme (% of total)	Placebo (% of total)
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)

Table 26: Patient Demographics and Baseline Characteristics

	Lumizyme (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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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 Lumizyme 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 27).

Table 27: Estimate of mean change from baseline to last observation 6MWT by Age

Factor	n	Lumizyme Estimate (95%CI)	n	Placebo Estimate (95% CI)	Treatment eff. (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 Lumizyme in smaller subgroups based on age at enrollment, age at diagnosis, and age at first symptoms.

Because patients with juvenile-onset Pompe disease generally have earlier onset of symptoms and faster progression of disease, the efficacy of Lumizyme 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 28), age 30-50 years (Table 30), age 50-70 years (Table 31). 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 28). However, the overall estimated treatment effect (the difference in mean distance walked at last observation between Lumizyme and placebo groups) of Lumizyme is 40.1 meters which is consistent with the overall treatment effect.

Table 28: Patients less than 30 years of age 6MWT mean (±SD) change from baseline

Visit	2000L Mean (±SD)	PlaceboMean (±SD)
Week 12	7.6 (17.1)	-38 (17.8)
Week 26	14.8 (23.9)	-5.8(10.2)
Week 38	-21.3 (88.0)	2 (2.8)
Week 52	-6.4 (32.0)	-1.5 (2.1)
Week 64	14.8 (21.5)	1 (4.2)
Week 78/Early Termination	-4.6 (44.1)	-35.5 (25.2)

Individual patient data for the five Lumizyme-treated patients less than 30 years of age is listed below in Table 29. Patient 4701was the only patient in this subgroup with a change in baseline walked at or above the average for the entire Lumizyme-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 29). Patients aged 30-49 constitute the largest subgroup of patients based on age, with 51/90 patients in this age range. Results of their 6MWT are presented in Table 30. At the end of the study, there was a treatment effect of 35.1 meters, which is slightly higher than the overall treatment effect seen in the study of 28.1 meters. In the oldest patient subgroup, patients age 50-70, 31 patients were enrolled. A treatment effect of 24.3 meters was observed, which is slightly lower than the overall treatment effect of 28.1 meters (see Table 31).

Table 29: Lumizyme-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	15.9	9.9	5.3	5.8	Male	626	36.5
29701	25.8	8.6	16.4	17.2	Female	389	-7.5
29712	17.5	1.9	8.9	15.3	Male	84	18.5
65706	28.2	16.4	10.6	11.6	Female	210	12.5
65707	20.7	6.5	9.8	14.2	Male	280	-83

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

Visit	Lumizyme Mean (±SD)	Placebo Mean (±SD)
Week 12	7.2 (25.8)	-3.2 (30.0)
Week 26	20.0 (47.4)	1.6(33.1)
Week 38	23.6(50.2)	-3.3 (43.4)
Week 52	26.3(59.2)	-9.9 (57.5)
Week 64	21.9(70.7)	-6.5(50.1)
Week 78/Early Termination	24.6(71.2)	-10.5(53.3)

Table 31: Patients age 50-70 6MWT mean (±SD) change from baseline

Visit	Lumizyme Mean (±SD)	Placebo Mean (±SD)
Week 12	13.3(18.9)	-9 (24.1)
Week 26	26.8 (34.0)	-10.8 (35.5)
Week 38	30.4(50.9)	-4.3 (32.8)
Week 52	17.7 (63.1)	0.6(32.3)
Week 64	28.9(56.9)	4 (34.5)
Week 78/Early Termination	25.5 (61.9)	-0.8(39.6)

5.3.7.2 Age at diagnosis of disease

As stated above, only four patients were under the age of 18 at the time of enrollment participated in LOTS, and only two of four patients under age 18 were assigned to the Lumizyme treatment group. 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 32. It should also be noted that 2 patients in the Lumizyme 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. These patients were diagnosed based on a family member who was previously diagnosed. Therefore, this reviewer believes that these 2 patients do not represent true

juvenile-onset disease patients as their age at first symptoms was over the age of 20 (see Table 32). The Applicant did not include an analysis of 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. Results of 6MWT are presented in Table 33. Although a treatment effect of 20 meters is demonstrated, both the Lumizyme group and the placebo group deteriorated by the end of the study. There was a small treatment effect of 0.5% in % predicted FVC between the treatment groups.

Table 32: 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	Lumizyme	5.8	5.3	15.9
65706	Lumizyme	11.6	10.6	28.2
18710	Lumizyme	12.0	28.3	36.9
65707	Lumizyme	14.2	9.8	20.7
26710	Lumizyme	14.6	22.6	30.3
29712	Lumizyme	15.3	8.9	17.5
16708	Lumizyme	16.0	16.0	31.7
29701	Lumizyme	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

Table 33: Patients 18 years of age or younger

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

	6MWT (M)		% predicted FVC	
Visit	Lumizyme (n=5)	Placebo (n=3)	Lumizyme (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	-2.2 (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	15.6 (29.8)	26 (0)	-4.6 (3.8)	-3 (0)
Week 78/Early Termination	-0.8 (51.8)	-20.3 (36.6)	-1.5 (4.4)	-1 (2.6)

1. 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 34). 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.

Table 34: Demographic characteristics of patients with onset of symptoms prior to age 18 (n=14)

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	Lumizyme	12.3	18.3	31.8
16709	Lumizyme	17.8	27.8	32.6
47702	Placebo	10.1	26.8	33.3
26721	Placebo	14.7	24.8	35.3
29702	Lumizyme	9.9	28.3	40.3
65715	Lumizyme	10.2	34.2	41.9
29707	Placebo	7.6	27.3	44.9
18703	Lumizyme	17.3	31.1	48.0
90710	Lumizyme	17.9	39.3	48.5
16701	Lumizyme	16.1	42.8	49.7
16707	Placebo	16.3	49.3	50.9
65702	Placebo	11.4	20.5	52.0
29704	Placebo	13.7	37.7	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 Lumizyme treatment group compared to placebo, but overall younger patients had smaller changes from baseline compared to older patients.

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 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 Lumizyme 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 35).

Table 35: Patients with age at first symptoms < 18 years of age 6MWT mean (±SD) change from baseline

Visit	Lumizyme Mean (±SD)	Placebo Mean (±SD)
Screening/Baseline		
Week 12	6.7 (26.0)	-16.6 (20.4)
Week 26	18.1 (23.7)	-7.8 (21.8)
Week 38	2.3 (32.2)	-17.3 (25.9)
Week 52	7.9 (26.8)	-15.0 (27.5)
Week 64	25.3 (16.6)	-17.1 (34.3)
Week 78/Early Termination	5.4 (38.1)	-28.3 (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 Lumizyme treatment is attenuated This subgroup analysis only included small numbers of patients and, therefore, clear conclusions based on these observations cannot be made.

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 Lumizyme. 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 Lumizyme compared with Myozyme, the potential for increased immunogenicity of Lumizyme (see section 5.3.7.3), and the lack of data regarding efficacy of Lumizyme in the juvenile-onset patients, strong consideration should be given to limiting the indication of Lumizyme to adult-onset patients only.

5.3.7.3 Immunogenicity

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 Lumizyme-treated patients developed anti-rhGAA IgG antibodies by week 20 of the study. Below Table 36 and 37 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 36: Effect of Mean IgG titer category on 6MWT and FVC

Parameter	Mean IgG TiterCategory 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 37: Effect of Peak IgG titer category on 6MWT and FVC

Parameter	Peak IgG TiterCategory 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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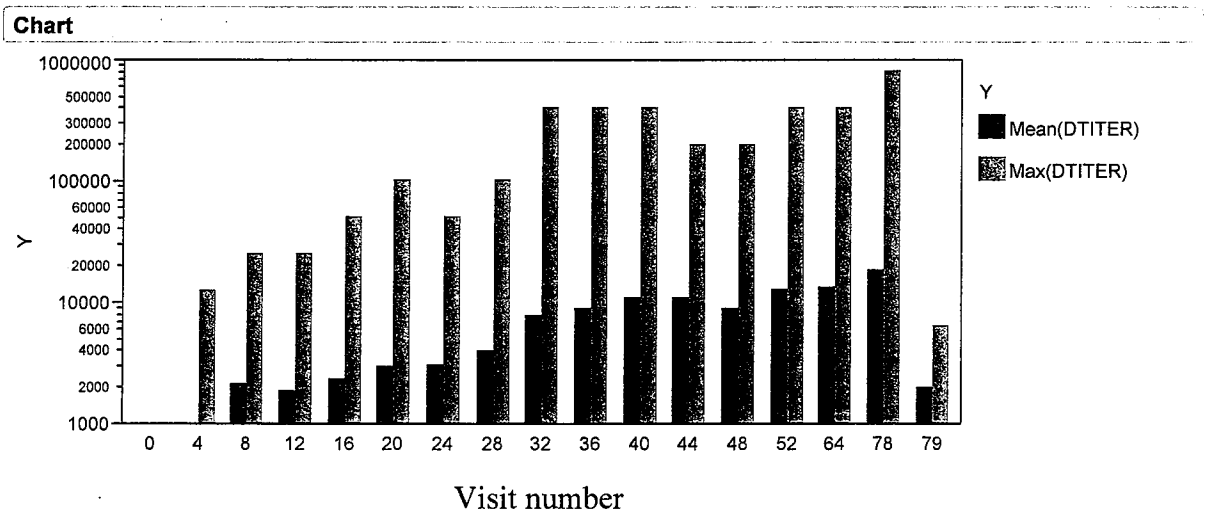
Figure 7 : Mean and maximum anti-rhGAA antibody responses over time



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 with Lumizyme. 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 Lumizyme. 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 Lumizyme 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 at the end of the study. The demographics of these 9 patients are presented below (Table 38). This subgroup's overall improvement was approximately 7.4 meters less than the overall Lumizyme treatment group (Table 39 and Table 40). Additionally, there is a loss of treatment effect in this group of patients after Week 52 (Table 40). 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 Lumizyme treatment group.

Table 38: 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	5.3	5.8	9.9	15.9
18701	Female	35.5	40.4	1.8	42.3
18704	Male	34.5	35.3	16.6	51.8
18710	Male	28.3	12.0	24.8	36.9
26712	Male	29.3	39.8	10.0	50.0
29713	Female	40.1	41.6	3.7	45.4
47713	Female	39.8	39.8	3.3	43.2
65701	Male	36.3	39.1	0.5	39.8
90705	Male	48.3	61.3	7.5	68.9

Table 39: Mean change from baseline 6MWT in 9 patients with rising IgG titer at week 78

	Lumizyme Overall (n=60)	Rising IgG at week 78 (n=9)
Mean Change from baseline in meters (±SD)	26.1 (51.3)	18.8 (25.0)
Difference in Change from baseline	7.4	

Table 40: 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	12.4 (19.9)
Week 26	21.8 (16.9)
Week 38	19.1 (20.0)
Week 52	26.3 (23.2)
Week 64	16.0 (29.3)
Week 78/Early Termination	17.8 (40.2)

Lumizyme, 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 (Table 41).[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 Myozyme, 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 as compared with 30% of late-onset (non-infantile) patients treated with Lumizyme.

Table 41: Immune responses in patients receiving enzyme replacement therapy

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 Lumizyme 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 Lumizyme than that seen with Myozyme 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 Lumizyme. These findings may suggest a higher immunogenicity of Lumizyme compared to Myozyme.

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*.

Eighteen patients (30%) developed inhibitory antibodies to Lumizyme during the study. This compares with 2.5% of infantile-onset patients treated with Myozyme. The demographic characteristics of these patients are listed below in Table 42. 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 (Tables 42 and 43).

Table 42: 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	31.5	35.3	8.1	43.5
Male	10	33.4	38.0	11.0	49.1

Table 43: 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	35.5	40.4	1.8	42.3
18703	Female	17.3	31.1	16.6	48.0
26705	Female	35.2	42.7	1.0	43.8
26715	Female	36.3	36.8	14.8	51.7
29701	Female	16.4	17.2	8.6	25.8
29713	Female	40.1	41.6	3.7	45.4
47713	Female	39.8	39.8	3.3	43.2
65709	Female	31.4	32.4	15.3	48.2
18704	Male	34.5	35.6	16.6	51.8
18713	Male	41.2	48.9	6.8	55.9
26712	Male	29.3	39.8	10.0	50.0
26718	Male	26.3	29.3	18.5	47.8
29709	Male	18.6	22.6	7.4	30.0
47706	Male	34.9	35.3	15.9	51.3
47711	Male	37.4	39.0	15.7	54.9
65701	Male	36.3	39.1	0.5	39.8
90703	Male	26.8	29.3	11.1	40.3
90705	Male	48.3	61.3	7.5	68.9

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

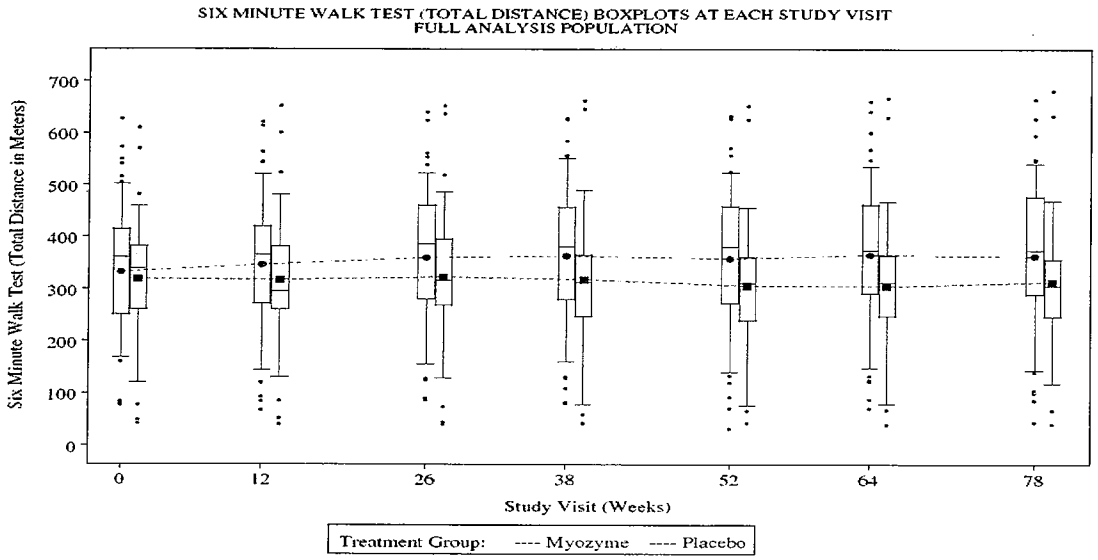
Table 44: Mean change (± SD) from baseline 6MWT in meters; inhibitory antibody positive patients (n=18)

Visit	Mean
Screening/Baseline	
Week 12	16.3 (25.9)
Week 26	41 (63.4)
Week 38	46 (72.5)
Week 52	41.5 (78.4)
Week 64	40.7 (79.3)
Week 78/Early Termination	39.1 (83.9)

"High performers"

A small of group of patients in the Lumizyme-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 8) 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 9).

Figure 8: Boxplot graph of total distance walked during 6MWT full analysis population.



* Myozyme refers to the 2000L product (Lumizyme)
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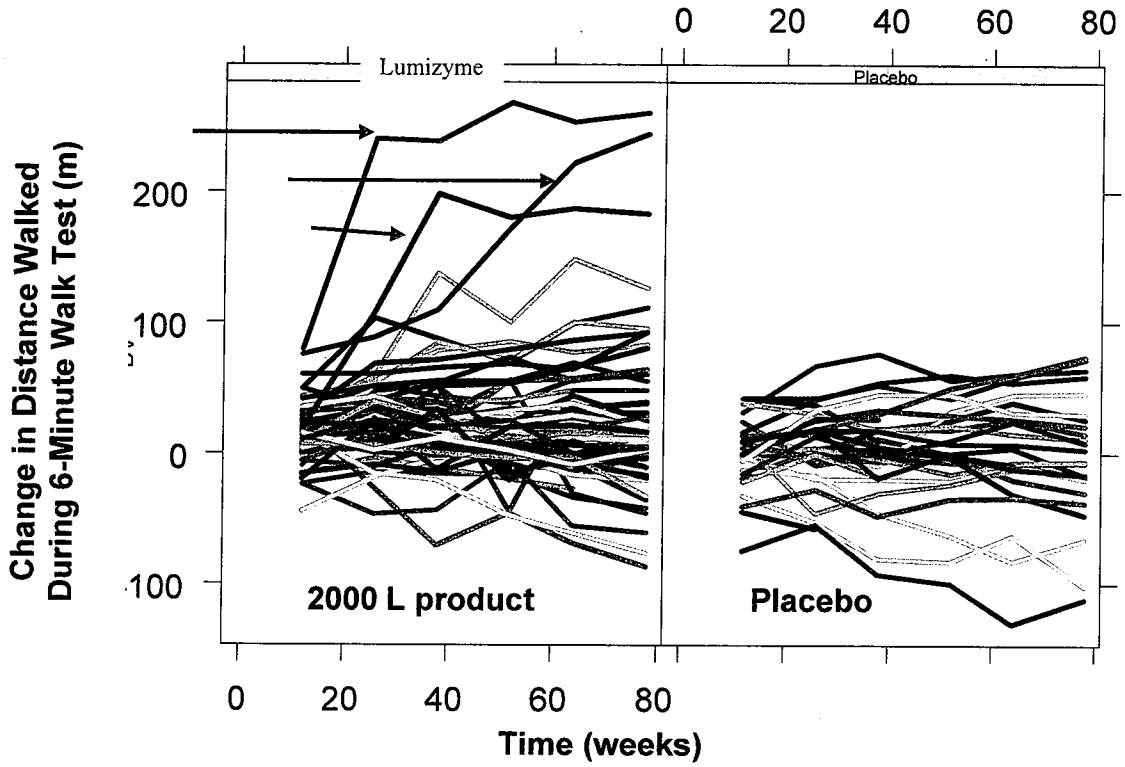
Figure 9: Individual 6MWT data



Clinical and demographic characteristics of the four patients identified as high performers in figure 5 were reviewed. Interestingly, three of these "high performers" developed inhibitory antibody titers to Lumizyme. Thus, presence of inhibitory antibody appears to be associated with a dramatic improvement in at least three patients treated with Lumizyme. The individual 6MWT test data on these three patients is presented below in Table 45. 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 Lumizyme treatment may be especially beneficial.

Table 45: Mean (± SD) change from baseline 6MWT in 3 "high performers" with inhibitory antibody

Patient ID	Mean (± SD)
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 were 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 46. There were three female patients and one male patient in this group, and disease characteristics are not significantly different.

Table 46: 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	35.5	40.4	1.8	42.3
26712	Male	29.3	39.8	10.0	50.0
29713	Female	40.1	41.6	3.7	45.4
47713	Female	39.8	39.8	3.3	43.2

These four patients performed substantially worse in both primary efficacy outcomes when compared to the overall Lumizyme treated group. This group's mean change from baseline walked at the end of the study was -8.75 meters (compared with the overall Lumizyme 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 47).

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 47) 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 47: Patients with rising anti-GAA IgG titer at end of study and positive inhibitory antibodies (n=4)

	Change in 6MWT Mean (± SD)	Change in FVC (% Predicted) Mean (± SD)
Week 12	6.0 (6.7)	1 (4.5)
Week 26	16.3 (10.2)	1.3 (5.7)
Week 38	11.8 (3.4)	-0.3 (6.0)
Week 52	23.3 (22.5)	0.8 (5.0)
Week 64	-7.0 (17.6)	-1.0 (8.8)
Week 78/Early Termination	-8.8 (28.2)	-0.5 (8.4)

In summary, inhibitory antibody formation is increased (30%) in patients receiving Lumizyme compared to infantile-patients that received Myozyme (10%). The development of inhibitory antibodies to Lumizyme appears to produce two disparate effects; one subgroup of patients with inhibitory antibody appears to improve substantially compared to the overall Lumizyme 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 Lumizyme 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 Lumizyme.

Overall immunogenicity findings

In summary, the immunogenicity of Lumizyme remains a concern. All patients treated with Lumizyme 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 Myozyme (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 Lumizyme, and this incidence is substantially higher than the 10% incidence in infantile-onset patients treated with Myozyme. 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. Thus, these immunogenicity findings suggest a higher immunogenic potential in Lumizyme compared with Myozyme. The higher immunogenicity of Lumizyme 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 Lumizyme. Further study will be required to verify the preliminary findings based on these exploratory analyses. Finally, exploratory analyses suggest that there may be a subgroup of patients with specific antibody profiles whose response to Lumizyme treatment may be enhanced. Although this finding does not point toward a specific safety or efficacy concern, further study of this finding may lead to improvements in efficacy of enzyme replacement therapies and better understanding of the pathogenesis of specific phenotypes of Pompe disease.

5.3.7.4 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 48). The overall average change from baseline in each of the primary efficacy endpoints was worse than the overall average in both treatment groups (Table 49). However, the patients in the Lumizyme 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 nine of ten 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 5.3.7.5). Additionally, lower GAA activity also appears to be associated with younger age.

Table 48: 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 49: Mean Change from Baseline 6MWT and % predicted FVC in patients with GAA activity <1%

	Lumizyme (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 Lumizyme. Six of ten patients with GAA activity < 1% were randomized to receive Lumizyme. 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. Only one patient with GAA activity < 1% developed inhibitory antibodies to GAA.

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, and not respond as well to treatment with Lumizyme.

5.3.7.5 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 Lumizyme 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 50). Furthermore, at 78 weeks, male patients in the placebo group showed larger increases in distance walked when compared to the female patients in the Lumizyme treatment group

(see Table 51 and Figure 10). 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 5.3.7.4, nine of ten patients with GAA activity (% normal) < 1% were women, and this subgroup performed worse than the overall mean for both treatment groups (Table 52).

Table 50: Mean (± SD) baseline 6MWT based on gender (meters)

Gender	Treatment	Mean
Female (n=45)	Lumizyme (n=26)	318.4 (117.1)
	Placebo (n=19)	303.4 (119.4)
Male(n=45)	Lumizyme (n=34)	342.7 (132.6)
	Placebo (n=11)	343 (148.9)

Table 51: 6MWT mean (± SD) based on gender at 78 weeks

		Baseline (M)	Change from baseline (M)
Gender	Treatment	Mean	Mean
Female	Lumizyme (n=25)	337.7 (117.8)	7.3 (36.4)
	Placebo (n=17)	284 (107.1)	-27.9 (43.7)
Male	Lumizyme (n=34)	382.8 (156.0)	33.6 (79.5)
	Placebo (n=10)	375.9 (168.2)	17.5 (41.7)

Figure 10 : Mean Change from Baseline 6MWT (M) by gender

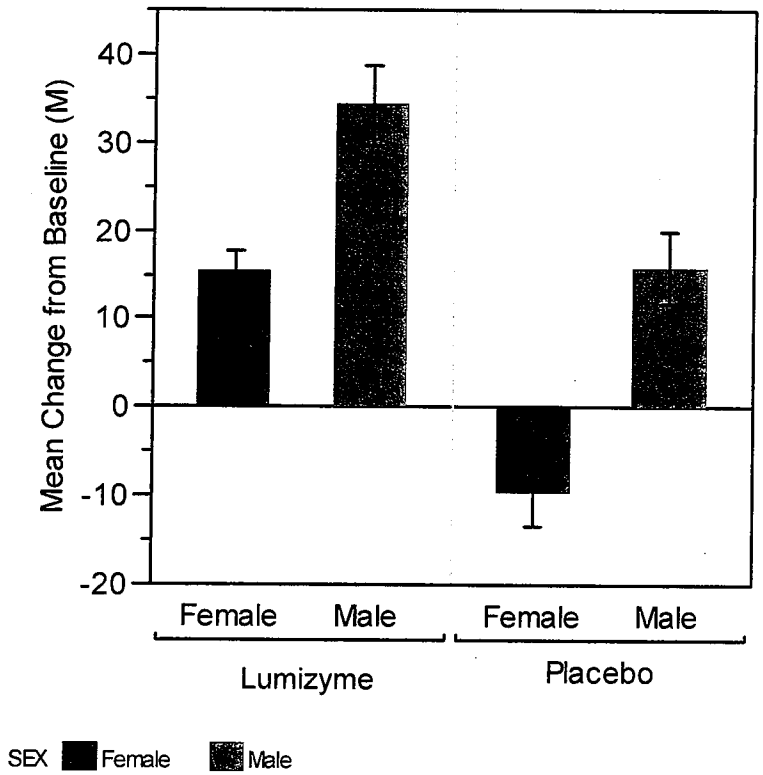


Table 52: Mean (± SD) % GAA activity female vs. male

Gender	Lumizyme	Placebo
Female	12.6 (10.2)	9.6 (7.9)
Male	9.5 (5.9)	11.2 (7.5)

5.3.7.6 Effect of baseline walk test

An evaluation of the effect of baseline 6MWT was performed to assess the possibility that Lumizyme may have different efficacy in patients with more severe or mild disease at baseline. Therefore, patients were stratified based on more mild disease (normal 6MWT or >500m at baseline) or more severe disease (baseline 6MWT <100m). Results of these analyses are presented in Table 53 and Table 54. Patients who had less severe disease at baseline improved by 27 meters in the Lumizyme group (n=7) and was similar to the overall mean, but placebo treated patients improved by 68 meters (n=2) (see Table 53). Thus, it appears that patients in the placebo group performed better, suggesting that Lumizyme may not be as effective in mild disease states. Interestingly, patients with more severe disease improved in both groups. However patients treated with Lumizyme improved by only 18 meters compared with the overall improvement of 25 meters. However, placebo treated patients improved by 9 meters, while the overall placebo mean was -3 meters (see Table 54). Again, these analyses are exploratory in nature, and given the small numbers of patients in each group, firm conclusions cannot be made based on these observations.

Table 53: Mean Change (±SD) in patients with "normal" baseline 6MWT (500m or greater)

Visit	Lumizyme (n=7)	Placebo (n=2)
Screening/Baseline		
Week 12	13.6 (23.6)	36.5 (7.8)
Week 26	19.1 (25.5)	54.5 (17.8)
Week 38	22.1 (35.1)	64 (17)
Week 52	21 (30.8)	49 (10)
Week 64	30.9 (41)	59.5 (2.1)
Week 78/Early Termination	26.7 (38.8)	68 (5.7)

Table 54: Mean Change (±SD) in patients with baseline 6MWT < 100m

Visit	Lumizyme (n=5)	Placebo (n=3)
Screening/Baseline		
Week 12	15.8 (21.3)	3.7 (4.5)
Week 26	30.2 (21.2)	-3 (1.7)
Week 38	25.4 (25.5)	4 (12.4)
Week 52	9 (38.4)	6.3 (16.2)
Week 64	20.8 (26.7)	7.3 (27.4)
Week 78/Early Termination	18.4 (41.8)	9.5 (23.3)

5.3.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The selection and timing of Lumizyme 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 Myozyme is 20mg/kg every other week, and the same dose was selected for use of Lumizyme in LOTS. No other doses of Lumizyme were used in this study.

5.3.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

A positive trend in the change in distance walked is seen between the Lumizyme group and the placebo group. However, this improvement continues only to approximately week 26 and plateaus at that distance. Additionally, all Lumizyme treated patients developed IgG titers to rhGAA by week 12. Anti-rhGAA antibody titers were obtained pre-infusion at week 2, 4 and every 4 weeks after this. IgG antibody binding was analyzed by Enzyme-linked Immunosorbent Assay (ELISA) and confirmed by radioimmunoprecipitation assay (RIP). IgG inhibitory antibody testing was performed after week 78 on all IgG seropositive patients using two methods. Inhibition of rhGAA enzymatic activity by antibody present in patient serum was performed by diluting patient sera and incubating with constant activity rhGAA enzyme in microtiter plates. The assay limit of detection was set at 20% (the lowest percent inhibition that could be discriminated from background). Flow cytometry based assay was also performed to evaluate whether patient antibodies interfered with uptake of rhGAA by human fibroblast cells in culture. Patient serum at different dilutions was pre-incubated with GAA conjugated to a fluorescent marker and added to fibroblast cells. Cells were harvested and analyzed by flow cytometry. Positive test was defined as inhibition of enzyme uptake in fibroblasts greater than 20% at two or more ser dilution starting at 1:10. Borderline samples were defined as a titer of 20 and positive samples were defined as ≥40. Eighteen of sixty patients treated with Lumizyme developed inhibitory IgG antibody titers. The average time to development of inhibitory IgGs was approximately 36 weeks or 30 weeks after first positive IgG titer.

A subgroup analysis was performed by the reviewer evaluating the effect of rising titer with and without development of inhibitory antibody activity (see section 5.3.7.3). Subgroup analysis was performed in patients who had peak titers anti-rhGAA IgG at the end of the study (week 78). Five patients had peak IgG titers at 78 weeks. The mean change from baseline walked in the 6MWT was 18 meters. Four of these five patients also developed inhibitory antibodies to rh-GAA in the presence of rising anti-rhGAA IgG at 78 weeks. In these patients, their mean change from baseline in the 6MWT was 0.8 meters, which was clearly worse than the overall change of 26.1 meters in the overall Lumizyme treatment group. Additionally, the change in baseline distance walked at 78 weeks was -13 meters, and was worse than even the placebo group. These data suggest that in a subgroup of Lumizyme treated patient may develop antibody profiles that lead to deterioration during Lumizyme treatment. This is particularly worrisome given that their decline appears to be accelerated compared with those receiving placebo, suggesting a potential deleterious effect of Lumizyme in some Pompe patients. However, given the small number of patients in this group, it is difficult to draw clear conclusions from these data. Nevertheless, the patients who develop rising anti-GAA antibody titers and the presence of inhibitory antibody may be a group of patient in whom

alglucosidase alfa treatment may not be beneficial. These patients appear not to develop tolerance to GAA. GAA is a lysosomal enzyme, but is also found outside of cells. Some investigators have found that in patients who maintain some degree of endogenous enzyme activity (CRIM negative) that presence of enzyme outside of cells in the general circulation may be neutralized by inhibitory antibody and are prevented from returning to the lysosome for activity, thus, producing an overall decrease in enzyme activity and potential worsening of clinical symptoms in the context of Lumizyme treatment. Based on these findings, this reviewer would recommend additional studies to evaluate the long term effect of alglucosidase alfa, especially in those who develop persistently high IgG titers and/or inhibitory antibodies. In addition, this reviewer would recommend risk mitigation strategies that include routine monitoring for development of both anti-GAA antibodies and inhibitory antibodies. This reviewer also believes that discontinuation of treatment should be considered in these patients to prevent the potential for acceleration of deterioration in their disease. However, the presence of inhibitory antibody appears to be associated with a dramatic improvement in at least three Lumizyme treated patients. In fact, three of five patients that had an improvement greater than 100 meters at any point during the study were inhibitory antibody positive. There is a biologic plausibility in this situation as well, and it is possible that "inhibitory antibodies" may actually increase the activity of the enzyme.[15]

5.3.10 Additional Efficacy Issues/Analyses

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 the 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).[16] 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.[17] 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 Lumizyme group was 26.1 meters, and the mean change in upright FVC (% predicted) was 3.4%. Neither of these overall means met the definition of responder at the least stringent level based on the Applicant's classification. However, if these definitions are used to evaluate individual patient response, some differences between Lumizyme and placebo are apparent. For each responder level of 6MWT established by the Applicant, there were a greater percentage of patients in the Lumizyme group who achieved the clinical threshold. In the Lumizyme 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. Additionally, there were seven patients in the Lumizyme treatment group that improved by 15% from baseline % predicted FVC compared to no patients in the placebo group (Table 55). 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 55: Number (n) of responders based on clinical threshold definitions

Clinical Threshold	Lumizyme (% of total)	Placebo (% 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%	7 (11.7)	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 Lumizyme 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.

5.4 Overall Efficacy Conclusions

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 Lumizyme and placebo treatment. Although a difference of 28.1 meters between the Lumizyme and placebo treatment groups was demonstrated in the 6MWT (six minute walk test) at 78 weeks, this difference was not statistically significant (p=0.06, ANCOVA, with re-randomization inference). However, based on both the pre-specified and original statistical analysis plans, there was a 3.4% difference (p=0.004) in % predicted upright FVC in favor of Lumizyme.

The Applicant has proposed that the Lumizyme be indicated for late-onset Pompe disease patients. However, only four 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 Lumizyme in this patient group. Currently, Myozyme is approved in the US for juvenile-onset Pompe disease patients. However, there have been no controlled clinical trials to date evaluating either Myozyme or Lumizyme in juvenile-onset Pompe disease patients. Thus, given the concerns regarding the potency of Lumizyme compared with Myozyme, the potential for increased immunogenicity of Lumizyme, and the lack of data regarding efficacy of Lumizyme in the juvenile-onset patients, strong consideration should be given to limiting the indication of Lumizyme to patients 8 years of age and older.

While treatment with Lumizyme produces statistically significant difference in % predicted FVC compared to placebo in LOTS, the clinical meaning of these differences remains unclear. Despite the use of the 6MWT and % predicted FVC as 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 Lumizyme may also contribute to differences in efficacy of Lumizyme in certain subgroups. All patients treated with Lumizyme developed anti-rhGAA antibodies by 12 weeks, compared with no patients in the placebo group. This incidence is also higher compared to infantile-onset patients treated with Myozyme. Additionally, 18 patients in the Lumizyme treatment group developed inhibitory antibody. Again, this incidence is higher compared to both the placebo group and to infantile-onset patients treated with Myozyme. Persistently rising IgG titers in a subgroup of patients treated with Lumizyme 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. 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 with Lumizyme.

Exploratory analyses of the effect of age, baseline GAA activity, and gender also demonstrated differences between the Lumizyme group and placebo group. However, there was a persistent treatment effect for Lumizyme 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 during discussions regarding postmarketing studies and labeling.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The Sponsor is proposing that Lumizyme receive the following indication:

(b) (4)

The reviewer proposes the following indication for Lumizyme:

"Lumizyme (alglucosidase alfa) is indicated for patients 8 years and older with late onset (non-infantile) Pompe disease (GAA deficiency) who do not have evidence of cardiac hypertrophy. The effectiveness of Lumizyme is based on stabilization of % predicted forced vital capacity. Improvements in survival or ventilator-free survival have not been evaluated in trials."

For a final version of the indication for Lumizyme, please see final product labeling.

Efficacy is discussed in section 5 of this review.

7 Review of Safety

Safety Summary

7.1 Methods

The primary safety information for this clinical review includes data from one clinical study, AGLU02704, Late Onset Treatment Study (LOTS). Additional safety data for Lumizyme was submitted to the Agency on September 1, 2008 by the Applicant.

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 were treated for 52 weeks; 8/9 received 2000 L product only. One patient in the study received Myozyme 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 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 (2000 L, Lumizyme) 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 Lumizyme while the product is under review, and to divert the remaining supply of Lumizyme to infantile-onset patients. Safety data on these patients were submitted to a cutoff date of 15 April 2008 and include approximately 11 months of observation.

6. Postmarketing safety data through April 15, 2008, for Lumizyme. A total of 32 adverse events reports in late-onset Pompe disease patients were submitted by the Applicant.

Because Lumizyme is not commercially available in the US, these postmarketing data reflect the postmarketing safety data collected in the EU and Canada.

The most comprehensive safety data submitted to the application were the safety data collected as part of the GCP-compliant LOTS and LOTS extension studies. Safety data in these studies were collected in a rigorous and comprehensive manner, including regular AE assessment and documentation at scheduled study visits, clinical laboratory evaluations, physical examinations, site monitoring and DSMB and ARRB oversight. Data from AGLU02603 (n=9), AGLU02804 (n=5), AGLU 03105 (n=5) were not pooled by the Sponsor, but were also collected according to GCP-compliant protocols. Interim safety data was provided in the two ongoing clinical studies, AGLU03206 (LOTS extension) and AGLU03907 (MTAP). The post-marketing safety data collected are not a part of a GCP study and therefore, safety data were collected predominantly through spontaneous report of Serious Adverse Events (SAEs) outside of the US.

The Sponsor coded AEs by System Organ Class (SOC) and AE preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). The MedDRA coding system contains greater than 15,000 AE preferred terms that can result in substantial granularity, fragmentation, and dilution of AE terms. AE preferred terms and SOC terms were revised by this Reviewer (with notification to the Sponsor) so that AE terms were clustered together to allow for a more meaningful description of the AE profile of Myozyme. Example: abdominal discomfort abdominal pain abdominal pain lower and upper, all classified as abdominal pain.

7.1.1 Clinical Studies Used to Evaluate Safety

There were 6 studies that were reviewed that included safety data in support of the 2000L product. These studies are summarized in Table 56.

Table 56: Safety data studies

Study	Trial Design	Comments
AGLU02704	LOTS: Randomized, DB, PC study of late-onset Pompe patients ages 8-70 years; 2000L 20mg/kg/qow, for 78 weeks, n=90	Final clinical study reports includes electronic safety data sets
AGLU03206	LOTS extension: OL extension of 80 patients who participated in AGLU02704 (LOTS); Lumizyme, 20gm/kg/qo week for 26 weeks, Study on-going	Safety data to 15 April 2008 provided in electronic data sets
AGLU3907	MTAP: OL, expanded access protocol to treat US patients >18 years of age until commercial treatment was available, n=138, Study on-going, data include approximately 11 months of exposure.	Safety data to 15 April 2008 provided. Final study report not completed.
AGLU2603	OL, expanded access study to treat severely affected late-onset patients who did not qualify for other studies until commercial treatment was available, length of study 52 weeks, n=9, 20mg/kg/qow	Final clinical study report includes safety data
AGLU2804	Single center, OL, bridging study, late-onset Pompe disease, age 5-18 years, n=5, 20mg/kg/qow for 74 weeks	Final clinical study reports includes safety data
AGLU3105	Single center, OL, exploratory study in patients with advanced late-onset Pompe disease, age 17-50 years, n=5, 20mg/kg/qow for 52 weeks	Final clinical study report includes safety data

7.1.2 Adequacy of Data

Reporting of adverse events by LOTS includes important review information such as classification of AE using standard medical terminology (MedDRA), system organ class (SOC), timing of AE in relationship to the infusion, classification of relationship to study medication, classification of severity of AE, and date of onset and resolution of AE. These appear to be adequate to assess the safety profile of the drug.

7.1.3 Pooling Data across Studies to Estimate and Compare Incidence

Safety data from the various studies were not pooled as the types and quality of safety data were variable, and therefore, pooling of data was not performed in this review. Only data from three studies (LOTS, LOTS extension and MTAP) were submitted in electronic datasets. However, the safety data from LOTS extension study was not complete, as this study is on-going. Therefore, further information regarding specific adverse events collected from the LOTS extension case report forms was not available for review. The Applicant stated that these forms would be made available after the study completed and data locked, thus making some estimates of the frequency of adverse events such as anaphylaxis difficult. Safety data from other sources including the postmarketing

experience were not submitted electronically, and largely consist of case report forms. Therefore, pooling of these data was not performed.

7.2 Adequacy of Safety Assessments

Safety assessments occurred in LOTS at specified intervals and included laboratory, physical examination, echocardiography, and immunologic measurements. These appear to be adequate to assess the safety profile of the drug.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Overall, 2/3 of both the treatment group and placebo group completed at least 78 weeks of treatment. Table 57 below presents the numbers of patients in each treatment group and the length of exposure to treatment up to 78 weeks. Descriptive statistics relating to the total length of exposure are presented in Table 58. The mean exposure length for LOTS was 115 weeks with a median exposure of 112 weeks. The minimum exposure was 105 weeks and the maximum exposure during LOTS was 135 weeks.

Table 57: Exposure length (weeks) by treatment group LOTS

Weeks in Study	Myozyme Patients (N=60) n (%)	Placebo Patients (N=30) n (%)
< 4 weeks	1 (1.7)	0 (0.0)
>= 4 weeks to < 12 weeks	1 (1.7)	0 (0.0)
>= 12 weeks to < 26 weeks	1 (1.7)	1 (3.3)
>= 26 weeks to < 38 weeks	0 (0.0)	2 (6.7)
>= 38 weeks to < 52 weeks	1 (1.7)	1 (3.3)
>= 52 weeks to < 64 weeks	0 (0.0)	0 (0.0)
>= 64 weeks to < 78 weeks	17 (28.3)	7 (23.3)
>= 78 weeks	39 (65.0)	19 (63.3)

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* Myozyme refers to 2000L product (Lumizyme)

Table 58: Total exposure to Lumizyme (weeks) in LOTS extension

Characteristic/Statistic	Placebo Double-Blind/ Myozyme Extension	Myozyme Double-Blind/Myozyme Extension	
		Total Exposure	3206 Exposure
Myozyme Exposure (weeks)			
n	26	55	55
Mean	32.5	114.7	33.4
Standard Deviation	6.45	8.53	9.05
Median	27.9	111.9	27.6
Min, Max	25.1, 52.0	104.9, 134.7	25.1, 53.9

Note: Exposure time derived by computing the difference between the data cutoff date of April 15th, 2008 or the date of discontinuation (if discontinuation occurred prior to data cutoff date) and the date of first myozyme infusion (or first myozyme infusion during ASLU03206 for 3206 exposure).

* Myozyme refers to 2000L product (Lumizyme)

7.2.2 Explorations for Dose Response

There was only one dose of alglucosidase used; 20mg/kg/dose, qo week for the pivotal study. This is the dose used in the commercially approved Myozyme. Therefore, no explorations of dose response were included in this submission.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or *in vitro* testing was conducted.

7.2.4 Routine Clinical Testing

Routine safety laboratory studies were performed as part of AGLU02704. These results are discussed in section 7.4.7.

7.2.5 Metabolic, Clearance, and Interaction Workup

Studies evaluating metabolic, clearance, and interaction were not conducted.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Enzyme replacement therapy is approved for use in several metabolic diseases including Mucopolysaccharidoses I, II, VI, Gaucher disease, and Fabry disease.[18] These therapies all have significant potential to produce anaphylaxis and other severe hypersensitivity reactions and have lead to a boxed warning for each of these therapies. Alglucosidase alfa 160L, approved in April, 2006 for use in Pompe disease also carries a boxed warning relating to anaphylaxis. Infusion associated reactions are also commonly found in these treatments. Risk of cardiac failure is also a prominent warning in the 160L product, but patients who received this product in the pivotal trial all had infantile onset Pompe disease, in which there is a significant cardiac disease component. Patients with late-onset Pompe disease do not have the same underlying risk profile.

7.3 Major Safety Results

The major safety results reviewed in this section are from LOTS except when pooling of data was possible with the LOTS extension study. Safety data from other studies submitted to this application are also reviewed and are presented in section 7.4, supportive safety results.

Overview of Adverse Events in LOTS
Overall, 1479 adverse events were collected in the Myozyme treated group and 870 adverse events were collected in the placebo group. There were a total of 658 treatment related events with 438 treatment related adverse events noted in the Lumizyme treatment group, and 220 treatment related averse events in the placebo group. All patients during LOTS reported at least 1 adverse event, and the numbers of patients reporting serious adverse events, treatment related adverse events is presented in Table 59.

Table 59: Number (%) Patients reporting Treatment Emergent AEs

	Lumizyme (n=60)	Placebo (n=30)
Patients with Any AE	60 (100)	30 (100)
Patients with Treatment Related AE	50 (83.3)	23 (76.6)
Patients with SAEs	13 (21.7)	6 (20.0)
Patients with Severe AEs	14 (23.3)	10 (33.3)
Patients who discontinued due to AEs	3 (5.0)	1 (3.3)
Patients who Died	1 (1.7)	0 (0)
Number of Treatment related AEs	479	229

Serious Adverse Events (SAEs) were defined by the Applicant in the study protocol as any AE that results in death, life-threatening experience, prolonged or significant hospitalization, persistent or significant disability, congenital anomaly, new ventilator use, or an important medical event, based on medical judgment, that may jeopardize the patient or lead to medical or surgical intervention to prevent an outcome listed above. This definition is consistent with the regulatory definition of SAEs as noted in the International Conference on Harmonization (ICH E2A).

Thirteen patients developed serious adverse events in Study AGLU02704. One patient, 16709, died during the study, and the summary of this patient's clinical course is described below. Three of the thirteen patients withdrew from the study due to their serious adverse event, one due to death, and two due to anaphylaxis. There were seven patients receiving placebo who developed serious adverse events, and one withdrawal due to a serious adverse event in the placebo group (headache).

There were 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 Lumizyme 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 60. Ten of these SAEs (8 in the Lumizyme 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 7.3.4, 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.

7.3.1 Deaths

One death occurred during the LOTS clinical trial. This death occurred in patient 16708, a 33 year-old Caucasian woman [redacted] (b) (6) 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 Lumizyme on February 23, 2006. In [redacted] (b) (6), 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 (b) (6) and two coils were placed, one on (b) (6), and the second on (b) (6)

The patient developed dizziness, nausea and sweating on the morning of (b) (6), (b) (6) 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 contract demonstrated multiple foci of old hemorrhage 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 that the death was likely unrelated to treatment with Lumizyme.

7.3.2 Serious Adverse Events

There was a total of 27 serious, adverse events occurred in 19 patients in the LOTS (see Table 60). There were 13 patients who sustained at least one SAE in the treatment group, and 6 patients who sustained at least one SAE in the placebo group. As described above in section 7.3.1, on patient developed brainstem ischemia due to a cerebral aneurysm and died as a result of this. Overall, the following SAEs occurred at a higher incidence in the Lumizyme group than placebo: anaphylaxis, brain stem ischemia, coronary artery disease, angioneurotic edema, throat tightness, intervertebral disc protrusion, cerebral aneurysm, supraventricular tachycardia, gastroenteritis, chest pain/discomfort, pneumonia, dehydration, and lung disorder.

Table 60: Number (n) of Nonfatal Serious Adverse Events by treatment group

System Organ Class	Preferred Term	Lumizyme	Placebo
Cardiac disorders	Coronary artery disease	2	0
	Supraventricular tachycardia	1	0
Gastrointestinal disorders	Abdominal pain	1	1
General disorders and administration site conditions	Chest discomfort	1	0
	Non-cardiac chest pain	1	0
Immune system disorders	Anaphylaxis	2	0
Infections and infestations	Brain stem ischemia	1	0
	Diverticulitis	0	1
	Flank pain	0	1
	Gastroenteritis	1	0
	Pneumonia	1	0
Injury, poisoning and procedural complications	Fall	1	1
	Humerus fracture	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
	Throat tightness	1	0
Skin and subcutaneous tissue disorders	Angioneurotic edema	1	0
	Septal panniculitis	0	1
Vascular disorders	Aneurysm	1	0
Total		20	7

7.3.3 Dropouts and/or 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 Lumizyme treatment group, one patient died (see section 7.3.1), 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 61). 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 Lumizyme infusion. The patient tested positive for anti-rhGAA IgE antibodies and complement activation with significantly

elevated serum tryptase. 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 Lumizyme 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.

- 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 61: Patient dropouts or discontinuations (n=9)

Patient ID	Treatment group	Reason for Drop out or Discontinuation
16708	Lumizyme	Death
16709	Lumizyme	Adverse Event (Anaphylaxis)
29706	Lumizyme	Withdrew for "personal reasons"
65701	Lumizyme	Wish to receive commercial product
90701	Lumizyme	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 61, four patients dropped out of the study (one patient in the Lumizyme 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 62) 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 62: 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 in meters
Screening/Baseline	
Week 12	-17.5 (20.7)
Week 26	12.5 (19.1)
Early Termination	-28 (26.5)

7.3.4 Significant Adverse Events

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 Myozyme based on a 5% incidence of anaphylaxis in the clinical trial of 18 infantile-onset patients who received Myozyme. 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).[19] 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 63.

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 for a total incidence of 6.7%. All of the patients identified by the reviewer with anaphylaxis (4/60, 6.7%) were in the Lumizyme 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 64).

Table 64: Laboratory values in 4 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

Anaphylaxis was also reviewed in data submitted from the LOTS extension study. The applicant includes one additional patient, 18708, randomized to the placebo group who developed anaphylaxis after beginning treatment in the extension study. This reviewer has uncovered four other patients that have symptoms consistent with anaphylaxis, with the onset of these symptoms occurring during the infusion with 2000L product. These cases cannot be confirmed with the Applicant as the study is on-going and the case report forms were not available at the time of the review. The clinical findings in these four additional patients are listed below in Table 65.

Table 65: Patients in LOTS extension with suspected anaphylaxis

Patient ID	Treatment group	Clinical findings
18703	Lumizyme	dyspnea and urticaria
29705	Lumizyme	dizziness and urticaria
29708	Lumizyme	pruritis, chest pain, edema
29704	Placebo	urticaria and falls

If these four patients are included in the analysis of anaphylaxis, then the total incidence of anaphylaxis in the LOTS extension trial is 7/80 patients or 8.8%, slightly higher than the incidence in LOTS.

Infusion Reactions

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 66).20 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 "hypersensivity/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 67 lists some of the signs and symptoms of infusion associated reactions.[21]

Table 66: Grading of Reactions according to the NCI CTCAE

	Grade				
	1	2	3	4	5
Hypersensitivity (allergic reaction)	Transient flushing or rash; drug fever <38°C (<100.4°F)	Rash; flushing; urticaria; dyspnea; drug fever ≥38°C (≥100.4°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.

Infusion reactions 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, hyperhydrosis, diarrhea, somnolence, Raynaud's syndrome, hematuria, and proteinuria.

Based on the Applicant's classification of infusion reactions found in the electronic dataset, there were a total of 214 IARs, with 167 events occurring in 13 patients in the Lumizyme treatment group, and 47 events occurring in 5 patients in the placebo group. However, the total number of adverse events that occurred during or within 2 hours of completion of the infusion without regard for investigator assignment of relationship to study medication is different from the Applicant's classification (see Table 68). There were a total of 469 AEs in 74 patients during or within 2 hours of the infusion, with 358 events occurring in 50 patients in the Lumizyme group, and 111 AEs in 24 patients in the placebo group. Data from LOTS extension was not substantially different in terms of

the numbers of patients in each treatment group that sustained an AE during or within 2 hours of completion of the infusion (Table 69).

Table 68: Number (% of total) of AEs within 2 hours of infusion completion by treatment group LOTS

	Total	Lumizyme	Placebo
AE onset during or within 2 hours of completion of infusion	469	358 (76%)	111 (24%)
Number of patients experiencing	74 (52%)	50 (83%)	24 (80%)

Table 69: Number of AEs within 2 hours of infusion completion by treatment group LOTS extension

	Total	Lumizyme	Placebo
AE onset during or within 2 hours post completion	168	101 (60%)	67 (40%)
Number of patients experiencing	51 (64%)	34 (63%)	17 (71%)

The types of AEs differed between the Lumizyme treatment group and placebo group. Table 70 lists all adverse events occurring in at least 3% of patients in the 2000L group 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. Notable differences between the 2000 L and placebo group included the presence of hypersensitivity (allergic) reactions, skin reactions, including urticaria, and parasethesias, nausea, vomiting, stomach discomfort, chills, flushing, and throat tightness that were not present in the placebo group. Other interesting adverse events that occurred during this observation period in increased incidence compared with placebo include hypoacusis, ear discomfort, neck pain, tendonitis, hyporeflexia, areflexia, musculoskeletal tightness, and pain, hematoma, and hematuria. There is no clear explanation for the increased incidence of these infusion associated reactions, however, further study may be warranted to assess whether these adverse events may be related to the infusion or some epiphenomenon.

Table 70: Adverse events occurring in at least 3% of patients during or within 2 hours of completion of infusion

System Organ Class	Preferred term	Lumizyme N (%)	Placebo N (%)	% Difference between groups
Ear and labyrinth disorders	Hypoacusis	6 (10)	1 (3)	7
	Ear discomfort	3 (5)	0 (0)	5
Gastrointestinal disorders	Diarrhea	4 (7)	0 (0)	7
	Vomiting	4 (7)	0 (0)	7
	Stomach discomfort	5 (8)	0 (0)	8
General disorders and administration site conditions	Chest discomfort	6 (10)	0 (0)	10
	Local swelling	4 (7)	0 (0)	7
	Feeling hot	3 (5)	0 (0)	5
	Chills	2 (3)	0 (0)	3
	Edema peripheral	2 (3)	0 (0)	3
Immune system disorders	Hypersensitivity	4 (7)	0 (0)	7
Injury, poisoning and procedural complications	Fall	12 (20)	5 (17)	3
	Procedural pain	2 (3)	0 (0)	3
Investigations	Blood pressure increased	2 (3)	0 (0)	3
Musculoskeletal and connective tissue disorders	Neck pain	3 (5)	0 (0)	5
	Tendonitis	4 (7)	0 (0)	7
	Pain in extremity	5 (8)	1 (3)	5
	Muscle tightness/twitching/stiffness	6 (10)	2 (7)	3
Nervous system disorders	Dizziness	5 (8)	1 (3)	5
	Areflexia/hyporeflexia	2 (3)	0 (0)	3
	Syncope	2 (3)	0 (0)	3
Renal and urinary disorders	Hematuria	3 (5)	0 (0)	5
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain	6 (10)	0 (0)	10
	Dyspnea	4 (7)	0 (0)	7
	Throat tightness	2 (3)	0 (0)	3
Skin and subcutaneous tissue disorders	Urticaria	6 (10)	0 (0)	10
	Pruritis	3 (5)	0 (0)	5
	Rash	7 (12)	0 (0)	12
	Hyperhidrosis	2 (3)	0 (0)	3
Vascular disorders	Flushing	3 (5)	0 (0)	5
	Hematoma	3 (5)	0 (0)	5

This table may be further analyzed to demonstrate those infusion reactions that occurred at an incidence of at least 5% greater in Lumizyme treated patients compared to placebo. These infusions reactions include: anaphylaxis, urticaria, diarrhea, vomiting, dyspnea, pruritis, rash/erythema, pharyngolaryngeal pain, neck pain, local swelling, hypoacusis, ear discomfort, tendonitis, hematuria, flushing/feeling hot, pain in extremity, stomach discomfort, and chest discomfort.

Delayed-onset infusion reactions, defined by the medical reviewer as those occurring from 2-48 hours after 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.[22] 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 reactions in patients receiving Myozyme; 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 Lumizyme.

Delayed onset adverse reactions were evaluated based on the timing of the adverse event in relation to the completion of the infusion. As shown in Table 71, there were a total of 40 patients (66%) who sustained delayed onset adverse reactions in the 2000L group, and 23 patients (76%) in the placebo group. However, the types of AEs also differ between the 2000 L group and placebo group. Table 71 also lists the most common delayed-onset adverse events occurring in at least 3% of treated patients. In the Lumizyme group, the most common delayed onset AEs were headache, musculoskeletal pain and stiffness, falls, and diarrhea. Two episodes of urticaria occurred in two patients (16710 and 29705) in the Lumizyme treatment group. No episodes of delayed-onset anaphylaxis or urticaria were identified in the placebo group. The most common delayed-onset infusion reactions in the placebo group were headache and falls.

Table 71: Delayed adverse events occurring in at least 3% of patients (between 2 and 48 hours after completion of infusion)

System Organ Class	Preferred term	Lumizyme N (%)	Placebo N (%)
Gastrointestinal disorders	Abdominal discomfort	4 (7)	3 (10)
	Diarrhea	6 (10)	3 (10)
	Nausea	3 (5)	3 (10)
	Vomiting	3 (5)	1 (3)
General disorders and administration site conditions	Neck pain	2 (3)	0 (0)
	Chest discomfort	2 (3)	1 (3)
	Chills	1 (2)	1 (3)
	Influenza like illness	1 (2)	1 (3)
	Malaise	2 (3)	0 (0)
Infections and infestations	Nasopharyngitis	6 (10)	4 (13)
Injury, poisoning and procedural complications	Fall	8 (13)	8 (27)
	Procedural pain	3 (5)	0 (0)
Musculoskeletal and connective tissue disorders	Arthralgia	2 (3)	4 (13)
	Back pain	4 (7)	2 (7)
	Musculoskeletal pain	12 (20)	2 (7)
	Musculoskeletal stiffness	8 (13)	3 (10)
	Musculoskeletal weakness		
Nervous system disorders	Dizziness	4 (7)	1 (3)
	Headache	9 (15)	6 (20)
Psychiatric Disorders	Insomnia	2 (3)	0 (0)
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain	3 (5)	0 (0)
	Cold sweat	1 (2)	0 (0)
	Skin nodule	1 (2)	0 (0)
	Urticaria	**2 (3)**	**0 (0)**
Total		40 (66%)	23 (77%)

Additionally, delayed infusion reactions that occurred in Lumizyme treated patients at an incidence of ≥ 3% compared to placebo treated patients included urticaria, dizziness, procedural pain, pharyngolaryngeal pain, malaise, muscle spasms, musculoskeletal pain, musculoskeletal weakness, musculoskeletal stiffness, neck pain, insomnia, and epistaxis.

As stated earlier, a total of 74 patients in the study had infusion reactions, 50 in the Lumizyme-treated group and 24 in the placebo group. Of these 74 patients, 5 patients had at least 10 infusion reactions (4 of these patients were randomized to the Lumizyme group, and 1 patient was in the placebo group). One of the Lumizyme-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 measures. Or, patients themselves might have been "unblinded" and thus performed differently on the 6MWT, a test that is patient-effort dependent. Table 72 shows the mean change from baseline in the 6MWT in all patients reporting at least 10 infusion reactions. Interestingly, patients with more infusion reactions in the placebo treatment group performed much better than the overall placebo treatment group mean, and in fact performed better than patients in the Lumizyme

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 72: Overall change from baseline 6MWT for 5 patients with at least 10 infusion reactions

Treatment	Mean (± SD)
Lumizyme	26.35 (45.6)
Placebo	59.17 (15.3)

Skin Reactions and other Potential Immune-mediated AEs

Skin reactions have been noted in postmarketing safety data collected as part of Myozyme, and the Myozyme labeling has been updated to reflect this safety finding. Skin reactions identified in the postmarketing data collected include reactions that may be immunologically mediated (see section 8.1). Therefore, a review of skin findings reported in the LOTS trial was performed using the following preferred terms: angioneurotic edema, rash (and several subcategories of rash including erythema and pruritis), urticaria, and septal panniculitis. Clearly, skin reactions are more common in the 2000 L group (50%) compared with the placebo group (10%). Table 73 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.

Table 73: Total number of patients (%) with Skin Reactions by treatment group

Preferred term	Lumizyme (%)	Placebo (%)
Angioneurotic edema	1 (2)	0
Hyperhidrosis	5 (8)	0
Photosensitivity reaction	2 (3)	0
Rash	16 (27)	5 (8)
Septal panniculitis	0	1 (3)
Urticaria	6 (10)	0
Total	30 (50)	6 (10)

Additionally, although small in number, there is evidence of possible glomerular injury as manifested by hematuria and/or proteinuria in patients treated with Lumizyme. Seven patients in the Lumizyme treatment group developed hematuria and/or proteinuria, and only two patients in the placebo group. Two patients in the Lumizyme 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 Myozyme.[23] While this condition was not observed in the LOTS study, immune mediated kidney disease should be considered as potential long-term safety issue.

Cataracts

Six patients (4 patient in the Lumizyme group and 2 in the placebo group) developed cataracts during the study. The demographic characteristics are listed below in Table 74. The mean time to development of the cataracts was not different between placebo treated and Lumizyme. There is

also no clear difference between the patients' age at onset of the cataract between the groups. It is unclear whether Lumizyme is associated with the development of cataracts.

Table 74: Characteristics of 6 patients who developed cataracts during the study

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

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 Lumizyme treated patients. There were no arrhythmias noted in the placebo group.

7.3.5 Submission Specific Primary Safety Concerns

Based on this review, allergic and immune mediated reactions are the main safety concern with Lumizyme. 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 to78 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 Lumizyme is generally similar to Myozyme and other enzyme replacement therapies for lysosomal storage diseases, there are data that suggest that Lumizyme may be more immunogenic than Myozyme.

Finally, should Lumizyme be approved for use in late-onset Pompe disease, administration of Lumizyme in unapproved populations must be avoided. Safeguards are being discussed (a Risk Evaluation and Mitigation Strategy; REMS, see section 9.2) with the Applicant in order to avoid misuse of Lumizyme, should it be approved, to infantile-onset patients, for whom safety and efficacy have not been demonstrated, and for whom Myozyme has previously been approved.

7.4 Supportive Safety Results

Safety data from three GCP studies evaluating Lumizyme in late-onset Pompe disease patients as well as data from a retrospectively collected, case series of infantile patients treated with Lumizyme from a single center in Taiwan were also submitted by the Sponsor in support of the application. Efficacy data were not provided in support of the proposed indication in any of these studies. Safety data were collected and submitted to the Agency in the form of narrative reports only for these studies. Thus, incorporation of these data into an integrated safety review was not performed.

7.4.1 AGLU03907

This study included 125 patients enrolled in a temporary access program to allow patients 18 years of and older to be treated with Lumizyme due to a drug shortage of the approved product, Myozyme. The mean exposure in this study to a cutoff date of 15 April 2008 was 19.4 weeks, with a minimum of 2 weeks and a maximum of 47 weeks. The Applicant provided safety data in electronic form, but did not provide any summary of adverse events. This medical reviewer's tabulation of adverse events from the datasets differs somewhat from the tabular presentation of data provided by the Applicant. The data presented here are based on the medical reviewer's tabulations only.

In study AGLU2907 (MTAP) a total of 318 adverse events were noted in 92 patients through a cutoff date of 15 April 2008. Upon review of the data submitted by the Applicant, 46 adverse events were reported without a reported term, preferred term, or system organ class assignment. Therefore, these AEs were not able to be included in the analysis of safety for this study. Thus, the total number of adverse events reported in this study was 272. The total time of exposure to Lumizyme ranged from 3weeks to 47 weeks with a mean time of exposure of 22 weeks.

The Applicant reported 38 SAEs in 15 patients. All of these SAEs were assessed by the site investigator as either not-related or remotely related to treatment with Lumizyme. There is no record of anaphylaxis or hypersensitivity reactions reported as an SAE. However, a review of the datasets reveals the possibility of anaphylaxis in at least two patients (see Table 75). The Applicant reported 12 patients with infusions reactions, but these data are not able to be reviewed as the adverse event in relationship to the timing of the infusion was not provided.

Table 75: Suspected cases of anaphylaxis in AGLU03907 MTAP

Patient ID	Preferred terms
50039	Pyrexia, hypotension, cardiac failure
10401	Fever, seizure, cardiac arrest, hypotension, wheezing

The most common adverse events reported are listed in Table 76. These adverse events are similar to the most common adverse events reported from LOTS and LOTS extension studies. Arrhythmia was not previously reported as a common adverse event, and in MTAP, there were five patients with arrhythmias including palpitations, sinus tachycardia and an irregular hear rate. Only one of these adverse events was reported by the site investigator as possibly related to Lumizyme.

Table 76: Adverse events occurring in at least 5 patients in AGLU03907 MTAP

Preferred term	Number of patients
Nasopharyngitis	10
Rash	9
Fall	8
Nausea	8
Diarrhea	7
Muscular weakness	7
Myalgia	7
Arrhythmia	6
Influenza	5
Pneumonia	5
Sinusitis	5

However, a slightly different pattern of adverse events emerges if the adverse events are listed by number of occurrences (see Table 77). When evaluated in this manner, urticaria becomes the most commonly reported adverse event in this study, and is likely related either to anaphylaxis or infusion reactions. However, the Applicant did not provide any information on these adverse events in relationship to the timing of the infusion and, therefore, these events cannot be classified as infusion related with any certainty.

Table 77: Most common adverse events in AGLU03907 MTAP

Preferred term	Number of episodes
Urticaria	21
Hypoaesthesia	12
Nasopharyngitis	12
Rash	11
Fall	10
Nausea	10
Pneumonia	9
Arrhythmia	7
Diarrhea	7
Muscular weakness	7
Myalgia	7
Influenza	6
Sinusitis	6
Headache	5
Non-cardiac chest pain	5

There appears to be a substantially lower percentage of patients reporting adverse events, as well as a substantially lower incidence of adverse events in this study compared with other clinical studies evaluating the safety of Lumizyme. This finding is likely related to underreporting of AEs in the MTAP clinical trial. Required study visits were much less frequent in MTAP compared with the LOTS or LOTS extension protocols, and despite the requirement to report all adverse events, the

decreased frequency of required study visits in MTAP may have produced some underreporting of adverse events. Additionally, there appears to be a substantially higher incidence of urticaria reported as a percentage of the total adverse events, that suggests that potentially immune-mediated or infusion related adverse events were reported more frequently than less significant adverse events. Therefore, this medical reviewer did not pool the data from this study with the LOTS safety data.

7.4.2 AGLU02603

This study included nine patients enrolled in a US expanded access protocol that provided Lumizyme to severely affected patients (i.e., ventilator-dependent and wheelchair-bound) with non-infantile onset Pompe disease, until commercial therapy was available. One patient in the study received Myozyme for the first six infusions and then was switched to Lumizyme. The study was conducted from November 23, 2004 to August 13, 2006. Safety data submitted to the Application included only paper listings of adverse events for these nine patients. Electronic datasets were not submitted, and therefore, thorough review of adverse events in this study was not possible due to time constraints. The total exposure to 2000l product ranged from 23 weeks to 82 weeks, with a mean exposure of 43 weeks, and a median exposure of 37 weeks. The Applicant reported a total of 47 treatment-emergent adverse events occurring in eight patients.

One patient death occurred during the study, in a 39.9 year old male patient (patient 819) due to mucus plugging of his tracheostomy tube. The death was assessed as unrelated to treatment with Lumizyme. Another patient died after completion of the study due to multiple cerebral infarcts secondary to cerebral aneurysm. This patient death was also assessed to be unrelated to Lumizyme by the site investigator. This medical reviewer agrees with the Applicant's classification of these two patient deaths based on the information provided.

A total of five SAEs in three patients were reported in this study. SAEs reported in patient 819 above led to the patient's death. The other three SAEs occurred in two patients. Hypotension related to anaphylaxis was reported in patient 831, and dyspnea with bronchial obstruction was reported in patient 811. Both of these patients recovered.

Two patients discontinued treatment due to adverse events. One patient died, as described above, and the other patient developed anaphylaxis and was withdrawn from the study by the site investigator. Additionally, infusion reactions were reported in 3 of 9 patients, including one patient (patient 831) who developed anaphylaxis and was withdrawn from the study.

7.4.3 AGLU02804

This bridging study included five patients enrolled in a single center in the Netherlands, evaluating the safety and efficacy of Lumizyme until it was commercially available in Europe. Safety data submitted to the Application included only paper listings of adverse events for these five patients. Electronic datasets were not submitted, and therefore, thorough review of adverse events in this study was not possible due to time constraints. All patients completed the 74 week study and thus, the total exposure was 74 weeks for all patients. There were a total of 137 treatment-emergent AEs, and 100% of patients experienced at least one AE.

No deaths occurred during the study period, and there were three SAEs reported in three patients during the study. The SAEs included two patients who required Achilles tendon release due to contracture, and one patient who was injured (cuts to head and neck pain) due to an automobile accident. All patients recovered, and none of these SAEs led to discontinuation from the study. All three SAEs were assessed as not-related to treatment with Lumizyme and based on the information available, this medical reviewer agrees with the Applicant's assessment. The Applicant's clinical study report states that no infusion reactions or episodes of anaphylaxis were reported during the study. Given the limited ability to review the data listings and no classification of the AEs in relationship to the timing of the infusion, it is impossible to report the incidence of these AEs with any degree of certainty. However, there at least three patients who developed pyrexia, and but no reports of rash, urticaria, hypotension, or edema.

7.4.4 AGLU03105

This study included five patients enrolled in a single center in France, evaluating the safety and efficacy of 2000L product in patients with advanced late-onset Pompe disease who were receiving respiratory support. Safety data submitted to the Application included only paper listings of adverse events for these five patients. Electronic datasets were not submitted, and therefore, thorough review of adverse events in this study was not possible due to time constraints. The total exposure to Lumizyme was 52 weeks in 3/5 patients. One patient received only 25 infusions over 52 weeks, and the other patient died prior to the last infusion. The Applicant reported a total of 59 treatment-emergent, and 100% of patients experienced at least one AE.

One patient death in a 41 year-old male occurred due to a "massive tracheal hemorrhage" one day after his 26th infusion with Lumizyme. The site investigator assessed the AE as unrelated to the treatment, and based on the limited information available, this medical reviewer agrees with this classification.

A total of nine SAEs were reported in two patients in this study. There were 8 SAEs reported in one patient (196003), a 62 year-old male. The reported SAEs included increased respiratory difficulties, flushing, asthenia, bronchitis, gastroenteritis, dizziness, dyspnea, and ventilator difficulty. All of these SAEs led to hospitalization and were assessed as unrelated to treatment with Lumizyme. The patient recovered from all SAEs. The other SAE was described above as a patient death due to massive tracheal hemorrhage. There were three infusions reactions reported in two patients in this study. There were no cases of anaphylaxis reported. The only patient that was discontinued from the study; this was due to patient death as described above.

7.4.5 Safety data from Taiwan experience

This study included 11 infantile-onset patients in a single center in Taiwan, evaluating the safety and efficacy of Lumizyme in infantile-onset Pompe disease patients. These data were not collected as part of GCP study, and were collected as a retrospective case series. Of the 11 infantile-onset patients, 10 patients were ≤ 6 months of age at the time of the first infusion of Lumizyme. There were six male patients and five female patients. The overall drug exposure for the 11 patients in the study is as follows: 4 patients received treatment for < 52 weeks, and 7 had received at least 52 weeks of treatment. The longest exposure was 130 weeks. There were no patient deaths reported,

and there were two serious adverse events. One episode of anaphylaxis was reported in one patient, for an incidence in this small cohort of 9%. There was also one episode of Torsade de pointes, a serious ventricular arrhythmia that occurred during intubation of one patient for RSV bronchiolitis.

7.4.6 Common Adverse Events

Overall, 2349 were AEs reported during the study period; 1479 AEs in the Lumizyme 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 78.

Table 78: Overall number of patients (%) with adverse event by treatment group

	Lumizyme (n=60)	Placebo (n=30)
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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The most common AEs (AEs occurring in > 20% of the patients in LOTS) are summarized in Table 79. 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. The most common AEs in the LOTS extension study data submitted by the Applicant are similar (see Table 80).

Table 79: AEs occurring in at least 20% of patients LOTS

Preferred term	Total (%)	Lumizyme (%)	Placebo (%)
Fall	59 (66)	39 (65)	20 (67)
Musculoskeletal pain/myalgia	57 (63)	39 (65)	18 (60)
Nasopharyngitis	43 (48)	27 (45)	16 (53)
Headache	40 (44)	25 (42)	15 (50)
Diarrhea	30 (33)	17 (28)	13 (43)
Arthralgia	27 (30)	18 (30)	9 (30)
Hypoacusis	27 (30)	20 (33)	7 (23)
Dizziness	22 (24)	16 (27)	6 (20)
Back pain	22 (24)	14 (23)	8 (27)
Nausea	21 (23)	11 (18)	10 (33)
Rash	18 (20)	16 (27)	5 (17)
Gastroenteritis	18 (20)	9 (15)	9 (30)
Pharyngolaryngeal pain	17 (20)	12 (20)	5 (17)

Table 80: AEs occurring in at least 20% of patients in LOTS extension study

Preferred term	Total (%)	Lumizyme (%)	Placebo (%)
Fall	37 (41)	26 (43)	11 (37)
Nasopharyngitis	37 (41)	24 (40)	13 (43)
Hypoacusis	26 (29)	18 (30)	8 (27)
Headache	24 (27)	14 (23)	10 (33)
Arthralgia	20 (22)	14 (23)	6 (20)
Back pain	18 (20)	13 (22)	5 (17)
Myalgia	18 (20)	11 (18)	7 (23)

The Applicant also submitted data regarding the incidence of the most common adverse reactions. Adverse reactions were defined by the Applicant as an adverse event that is possibly associated with treatment with Lumizyme. Table 81 shows the most common adverse reactions by system organ class and preferred term based on the Applicant's assessment of relationship to treatment. However, the reviewer's classification of relationship of adverse event to treatment with Lumizyme differed from the Applicant. Specifically, as described above, some adverse events that occurred during the infusion period or within two hours of the completion of the infusion were re-classified by the reviewer as possibly related to the study drug. Therefore, in the opinion of this reviewer, the number of adverse reactions is greater than that reported by the Applicant. shows the most common adverse reactions based on a difference of at least 5% in the Lumizyme treatment group compared with the placebo group. The reviewer notes that some preferred terms have been combined to reflect adverse events that would be clinically considered similar. These reactions include includes infusion site events (bruising, pain, paraesthesia, reaction and phlebitis), musculoskeletal pain (musculoskeletal pain, musculoskeletal discomfort, musculoskeletal chest pain, non-cardiac chest pain, and myalgia), and rash (contact dermatitis, drug eruption, erythema, heat rash, rash, rash macular, rash, maculo-papular, rash pruritic, skin nodule, and subcutaneous nodule). It should be noted that the reviewer did not had access to all CRFs to review for details regarding these adverse reactions, as full CRFs on all patients in the study were not included in the submission.

Table 81: Most common Adverse Reactions (> 5% of patients) based on Applicant's assessment of relationship

System Organ Class	Preferred Term	Total N (%)	Lumizyme (%)	Placebo N (%)
Nervous system disorders	Headache	11 (12)	5 (8)	6 (20)
	Dizziness	6 (7)	4 (7)	2 (7)
Skin and subcutaneous tissue disorders	Rash	11 (12)	6 (10)	5 (17)
	Hyperhidrosis	5	5 (8)	0
	Urticaria	5	5 (8)	0
Immune System Disorders	Hypersensitivity	4	4 (7)	0
Gastrointestinal disorders	Nausea	8 (9)	5 (8)	3
	Vomiting	3	3	0
General disorders and administration site conditions	Fatigue	7 (8)	3 (5)	4
	Chest discomfort	5	4 (7)	1
Eye disorders	Cataract	5 (6)	4 (7)	1
Musculoskeletal and connective tissue disorders	Muscle twitching	5	4(7)	1
	Myalgia	4	3 (5)	1 (3)
Ear and labyrinth disorders	Hypoacusis	4	2 (3)	2 (7)
Investigations	Blood pressure increased	3	3	0
Vascular disorders	Flushing	3	3	0

Table 82: Adverse reactions occurring in 2000L treated group ≥ 5% compared with Placebo treatment

System Organ Class	Preferred Term	Lumizyme n=60(%)	Placebo n=30(%)
Blood and lymphatic system disorders	Lymphadenopathy	5 (8.3)	0 (0)
Ear and labyrinth disorders	Hypoacusis	20 (33.3)	7 (23.3)
	Vertigo	4 (6.7)	0 (0)
	Ear discomfort or pain	7 (11.7)	2 (6.7)
Eye disorders	Vision blurred	3 (5.0)	0 (0)
Gastrointestinal disorders	Constipation	6 (10.0)	0 (0)
	Dyspepsia	5 (8.3)	0 (0)
	Vomiting	13 (21.7)	3 (10.0)
General disorders and administration site conditions	Chest discomfort or pain	10 (16.7)	2 (6.7)
	Infusion site reactions	8 (13.3)	0 (0)
	Malaise	3 (5.0)	0 (0)
	Edema, peripheral	10 (16.7)	3 (10.0)
	Pain	5 (8.3)	1 (3.3)
Immune system disorders	Anaphylaxis	4 (6.7)	0 (0)
Infections and infestations	Gastroenteritis	6 (10.0)	1 (3.3)
	Respiratory tract infection	3 (5.0)	0 (0)
	Upper respiratory tract infection	11 (18.3)	3 (10.0)
Injury, poisoning and procedural complications	Procedural pain	9 (15.0))	3 (10.0)
Metabolism and nutrition disorders	Hypokalemia	3 (5.0)	0 (0)
Musculoskeletal and connective tissue disorders	Muscle twitching	5 (8.3)	1 (3.3)
	Musculoskeletal pain	22 (36.6)	10 (33.3)
	Musculoskeletal stiffness or tightness	10 (16.6)	2 (6.6)
Nervous system disorders	Somnolence	3 (5.0)	0 (0)
	Tremor	4 (6.7)	0 (0)
Renal and urinary disorders	Nephrolithiasis	3 (5.0)	0 (0)
Respiratory, thoracic and mediastinal disorders	Dyspnea, exertional	4 (6.7)	0 (0)
	Epistaxis	3 (5.0)	0 (0)
Skin and subcutaneous tissue disorders	Hyperhidrosis	5 (8.3)	0 (0)
	Pruritis	6 (10.0)	1 (3.3)
	Rash	12 (20.0)	3(10.0)
	Urticaria	6 (10.0)	0 (0)

In summary, the most common adverse reactions in the study based on at least a 5% difference between the Lumizyme group and placebo group are listed in Table 82. Other notable differences are adverse reactions that were not reported in the placebo group at all but were seen in at least 5% of the Lumizyme treatment group. These adverse reactions included anaphylaxis, lymphadenopathy, vertigo, blurred vision, dyspepsia, malaise, respiratory tract infection, hypokalemia, somnolence, tremor, nephrolithiasis, exertional dyspnea, epistaxis, and hyperhidrosis.

7.4.7 Laboratory Findings

Laboratory testing, including chemistry and hematology panels, and urinalysis testing were performed according to the study schedules outlined in the study visits and procedures section of the clinical review. Clinically significant worsening in any laboratory parameter was documented as an AE and these AEs have been considered in the overall review of AEs.

No other notable, relevant or remarkable findings for changes in vital signs were seen; however, there was insufficient time available in the review period to thoroughly review these data.

7.4.8 Vital Signs

Vital signs were performed according to the study schedules outlined in the study visits and procedures sections of the protocol for AGLU02704. Clinical significant worsenings in vital signs were documented as AEs, and have been considered in the overall review of AEs. Notable vital sign changes that were reported as AEs tended to be associated with 2000l product infusion (e.g. tachycardia, hypotension, hypertension, tachypnea) and are additionally noted in the review of infusion associated reactions and anaphylaxis.

No other notable, relevant or remarkable findings for changes in vital signs were seen; however, there was insufficient time available in the review period to thoroughly review these data.

7.4.9 Electrocardiograms (ECGs)

Changes in ECGs were evaluated as part of the efficacy evaluation in AGLU02704, LOTS. A review of cardiac AEs including arrhythmias is included in the integrated review of safety. Please refer to this section 7.3.4 for a discussion of the cardiac findings noted in AGLU02704.

No other notable, relevant or remarkable findings for changes in vital signs were seen; however, there was insufficient time available in the review period to thoroughly review these data.

7.4.10 Special Safety Studies

No special safety studies were conducted.

7.4.11 Immunogenicity

See section 7.3.4 (Anaphylaxis and Infusion Reactions)

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Only one dose of drug (20mg/kg/dose) was administered for this study. Therefore, dose dependency for AEs cannot be adequately assessed. The dose used in this study is the dose that is approved for commercial use.

7.5.2 Time Dependency for Adverse Events

There was not specific time dependence of the development of adverse events. Many adverse events documented occurred with the initial infusion of drug, and adverse events occurred throughout the course of the study. Chronic immune reactions have also been noted in postmarketing experience with Lumizyme.

7.5.3 Drug-Demographic Interactions

No drug-demographic interaction studies were conducted by the Applicant.

7.5.4 Drug-Disease Interactions

No drug-disease interaction studies were conducted by the Applicant.

7.5.5 Drug-Drug Interactions

No drug-drug interaction studies were conducted by the Applicant.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

No animal or human studies were conducted to assess the carcinogenic or mutagenic potential of 2000L product.

7.6.2 Human Reproduction and Pregnancy Data

No formal studies with Lumizyme have been conducted in pregnant women, and there are no reports of pregnancy in any patients treated to date with Lumizyme.

7.6.3 Pediatrics and Effect on Growth

Growth was not assessed as a primary efficacy endpoint in any of the studies submitted by the Applicant for Lumizyme. Pediatric patients were studied as part of AGLU02704 (LOTS), but only

four patients under the age of 18 at the time of enrollment participated in the study. Only two of four patients under 18 years of age received treatment with Lumizyme. Therefore, no conclusions can be made regarding pediatric patients and the effect of Lumizyme on growth.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There are no withdrawal/rebound phenomena or abuse potential issues identified with Lumizyme. There have been no reports of overdose with Lumizyme.

7.7 Additional Submissions

There were no additional submissions reviewed for this application.

7.8 Overall Safety Conclusions

Important clinical safety issues include those related to the immunogenicity of the Lumizyme. Anaphylaxis, as well as immediate and delayed-onset infusion associated reactions, occurs at higher rates than placebo. Infusion reactions, including delayed infusion reactions, after treatment with Lumizyme have also been uncovered during this review. Chronic exposure to Lumizyme has not been adequately studied, but both skin reactions and urinary abnormalities reported in LOTS suggest that, as with Myozyme, immune mediated reactions may occur with chronic exposure.

Finally, should Lumizyme be approved for use in late-onset Pompe disease, administration of Lumizyme 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 Lumizyme, should it be approved, to patients less than 8 years of age, for whom safety and efficacy have not been demonstrated, and for whom Lumizyme has previously been approved.

8 Postmarketing Experience

Postmarketing experience is limited to the use outside the US as the 2000L product has been approved in at least 40 countries outside the US based on information provided by the Applicant. Use of Lumizyme within the US is limited to patients enrolled in clinical trials including the Myozyme (Lumizyme) Temporary Access Program. Safety data from MTAP were reviewed above under study AGLU03907. Because Lumizyme is not commercially available in the US, these postmarketing data reflect the postmarketing safety data collected in the EU and Canada. The Agency requested that postmarketing safety information submitted by the Applicant should be separated by diagnosis, as the data relating to infantile-onset patients receiving Lumizyme would not support the Applicant's proposed indication. An incidence for adverse events reported in the postmarketing setting was not able to be calculated as the Applicant was not able to provide a reliable estimate of the total number of late-onset patients treated with Lumizyme since Lumizyme is approved for use outside the US for the treatment of both infantile-onset and late-onset patients. Additionally, the Applicant did not summarize the postmarketing findings, but rather, presented all information in tabular form and without reviewable datasets. Therefore, an exhaustive review of

these data was not possible. Nevertheless, a summary of safety data from the postmarketing setting is provided below.

8.1 Deaths

The applicant reported a total of ten patient deaths with Lumizyme treatment in the postmarketing setting. Adverse events resulting in death included cardiorespiratory arrest, respiratory failure (2 patients), hemothorax, pneumothorax, cardiac failure, sepsis, aortic dissection, cerebrovascular accident, and skin necrosis. Specific details regarding these patient deaths were not available for review, and due to the nature of these postmarketing reports, detailed information is not likely to be available.

8.2 Serious and Significant Adverse Events

In postmarketing experience with Lumizyme, serious adverse reactions have been reported, including anaphylaxis. The most frequently reported serious adverse reactions were infusion reactions. In addition to the infusion reactions the following adverse reactions have also been reported in at least two patients during postmarketing use of Lumizyme: dyspnea, respiratory failure, bronchospasm, stridor, decreased oxygen saturation/hypoxia, pharyngeal edema, chest discomfort, chest pain, hypotension, hypertension, erythema, flushing, lung infection, tachycardia, cyanosis, and hypersensitivity. Systemic and cutaneous immune medicated reactions, including ulcerative and necrotizing skin lesions have been reported in postmarketing safety experience with Lumizyme. Again, the data submitted by the Applicant are in tabular form only, and the total number of patients that have received Lumizyme in the post-marketing setting remains unclear. Therefore, it is not possible to estimate the frequency of these adverse events based on the data provided.

8.3 Common Adverse Events

The Applicant did not submit any data regarding the incidence of common adverse events from in the postmarketing setting.

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9.3 Advisory Committee Meeting

An Endocrinologic and Metabolic Drugs Advisory Committee Meting (EMDAC) was convened on October 21, 2008 to discuss the safety and efficacy of the 2000L product for the treatment of late-onset Pompe disease. The EMDAC was given the following questions from the Agency to consider, and the votes by the committee members with reviewer comments are included at the end of each question below:

1. Do you believe LOTS has established the effectiveness of the 2000L product? (Vote: Yes or No)

    a. If not, should an additional study be conducted to determine whether the 2000L product is effective in treating late-onset Pompe Disease? (Discuss)

    b. If additional study is recommended, should a head-to-head study vs. the 160L product be conducted, or an alternate study design? (Discuss)

Committee vote: 16 yes, 1 no, 0 abstentions.

Reviewer comments: See comments to question 2, below.

2. Please consider the following decisional options for the 2000L product and state which option, based on the evidence presented, is most appropriate: (Choose a, b, or c)

    a. Not approved. If no approval is recommended, then the 2000L product can be made available to adult-onset patients under a treatment IND, whereby the Applicant may charge for product as part of the conduct of an additional study or studies. These studies would be conducted to further evaluate the 2000L product. (Discuss)

    b. Approval under Accelerated Approval (Subpart E), whereby the 2000L product can be approved using the FVC as a surrogate endpoint reasonably likely to predict clinical benefit, and a verification study to demonstrate clinical benefit of the 2000L product would be required of the Applicant during the post-marketing period. If you believe this is the most appropriate decision, please recommend a study design for the verification study, such as a head-to-head comparison vs. the 160L product. (Discuss)

    c. Regular Approval based on the 6MWT findings in LOTS. (Discuss)

Committee vote: 2a: 1 vote; 2b: 11 votes; 2c: 4 votes.

Reviewer comments: The majority of the committee voted for approval under 21CFR601 Subpart E, with approval based on benefit demonstrated in FVC used as a surrogate marker and requiring a verification study to demonstrate clinical benefit of the 2000L product. The majority of those who voted for Subpart E approval also commented that the study design should include a head-to-head comparison of the 2000L product with the 160L product.

3. If an Accelerated Approval or a regular Approval (2.b. or 2.c.) is recommended, please consider the following:

    a. The LOTS trial enrolled an inadequate number of patients with juvenile-onset Pompe disease. Only four patients were under 18 years of age at the time of enrollment in the study, one of whom was exposed to 2000L product (one patient aged 16 years). Only nine patients in LOTS developed symptoms and were diagnosed with Pompe disease under the age of 18, six of whom were exposed to 2000L product. Should the indication for the 2000L product be restricted to the adult-onset population only (i.e., patients who were diagnosed and had symptom onset over 18 years of age)? (Vote: Yes or No)

Committee vote: Yes: 0 votes; No: 16 votes; Abstension: 1 vote.

Reviewer comments: The committee did not feel that there should be a limited indication for the product based on the Agency's proposed limitation to patients aged 18 years of age or older. The committee members comments reflected the opinion that any age cutoff in the late-onset disease population would be arbitrary. However, this reviewer recommends that the indication for this product be limited to patients 8 years of age and older based on the limited data available in the use of this product in Pompe disease patients less than 8 years of age, and that there remains an available product (160L) that may be used to treat patients less than 8 years of age.

    b. If you recommend approval for a restricted age group (e.g., adults only), what safeguards should be implemented to avoid use of the 2000L product in patients less than 18 years of age, such as communication plans or restricted distribution? See attached REMS template. (Discuss)

Reviewer comments: Since the vote on question 3a was unanimously no, there was no formal voting for this question. However, several of the committee members agreed that a REMS should be required to ensure the safe use of the 2000L product.

    c. Should additional studies be required as post-marketing commitments to assess efficacy? (Vote: Yes or No)

Committee vote: Yes: 15 votes; No 2 votes.

Reviewer comments: Many of the committee members stated that post-marketing studies should be required for the 2000L product, however, some committee members expressed concern regarding the quality of studies that could be performed in the post-marketing setting.

        i. If yes, please describe the design of the study(ies). (Discuss)

Reviewer comments: Committee members stated that the design of the study should be rigorous, and that the study should include younger patients who have not been previously studied. Committee

members also stated that the choice of an endpoint for this study should include a clinically relevant endpoint and should be designed to measure a robust effect. Since a placebo controlled study is not likely feasibly, a dose ranging study was also stated as an alternative study design.

d. Should additional studies be required as post-marketing requirements to assess safety? (Vote: Yes or No)
   ii. If yes, please describe the design of the study(ies). (Discuss)

Committee vote: Yes: 17 votes.

Reviewer comments: Committee members stated that the safety study should be conducted to evaluate long term safety issues with an emphasis on the immunopathologies that may be present with chronic administration (e.g., glomerulonephritis, vasculitis). Committee members also stated that safety studies should be performed to evaluate the development of anaphylaxis with a high level of sensitivity and specificity, and the effect of pertinent biomarkers (e.g. antibody levels) on immunogenicity and safety. Other safety issues that were recommended include specific studies in children regarding follow up measurements of growth, development, and impact on hormonal influences (e.g. impact on puberty).

The full transcript of the Open portion of the AC meeting is available on the FDA website.

9.4 Literature Review/References

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DIVISION OF PULMONARY AND ALLERGY PRODUCTS
MEDICAL OFFICER CONSULTATION

Date:	September 18, 2008
To:	Wes Ishihara, Division of Gastrointestinal Products
From:	Susan Limb, MD, Medical Reviewer
Through:	Sally Seymour, MD, Medical Team Leader 9/18/08
Through:	Badrul Chowdhury, MD, PhD, Division Director 9/18/08
Subject:	Alglucosidase-alfa-associated anaphylaxis

General Information

BLA#:	125291, N000
Sponsor:	Genzyme Corporation
Drug Product:	Alglucosidase
Protocol:	n/a
Request From:	Wes Ishihara, Division of Gastrointestinal Products
Date of Request:	September 9, 2008
Date Received:	September 9, 2008
Materials Reviewed:	Case narratives, CRFs

Executive Summary

This is a medical officer review in response to a consultation request from the Division of Gastrointestinal Products (DGP) regarding alglucosidase-alfa (GAA). A 160L alglucosidase-alfa enzyme replacement therapy is currently marketed under the tradename Myozyme® for the treatment of Pompe disease, a glycogen storage disorder resulting from acid maltase deficiency. Myozyme was first approved in April 2006 on the basis of two clinical trials in 39 pediatric patients that demonstrated improved mortality/ventilator-free survival. The current product label contains a boxed warning on the risk of hypersensitivity reactions, including anaphylaxis (<1%) and other severe infusion reactions.

The Applicant has submitted a new BLA for a 2000L alglucosidase-alfa product with the proposed indication of treatment of late-onset Pompe disease. The 2000L and original 160L (Myozyme) product differ in terms of scale of production of the recombinant human enzyme. Based on CMC, preclinical, and clinical pharmacology data, the 2000L and 160L products differ substantially so as to render the 2000L a new product, requiring a separate BLA. (b) (4)

As a result, the Applicant conducted a single safety and efficacy trial to support the 2000L product. During the conduct of the pivotal study, 3 cases of anaphylaxis were identified, resulting in an anaphylaxis rate of 5%. An additional 4 cases of suspected anaphylaxis have been identified by DGP, which would increase the estimated frequency of anaphylaxis to 11.7%. DGP has been unable to come to an agreement on the categorization of the 4 additional cases with the Applicant. DGP requested that DPAP review the four cases to assess for anaphylaxis and requested feedback on the following question.

DGP considers the following 4 patients to have experienced anaphylaxis, and intends to present this conclusion at the Advisory Committee Meeting on October 21, 2008, and include this information in the Advisory Committee background package that is due on September 23, 2008. We are seeking an opinion from the DPAP consultant regarding whether you agree that these 4 patients sustained an episode of anaphylaxis based on the clinical definition of anaphylaxis set forth by the Network Symposium or any other standard clinical definition.

After review of the 4 suspected cases, DPAP agrees with the determination that Patient 29708 meets criteria for anaphylaxis, using criteria outlined by the joint NIAID/Food Allergy and Anaphylaxis Network symposium (Sampson HA et al. Second symposium on the definition and management of anaphylaxis: Summary Report – Second NIAID/FAAN Symposium. *J Allergy Clin Immunol.* Feb 2006; p 391-7). This patient experienced both acute skin-mucosal and respiratory involvement in the form of oral pruritus and chest tightness in a time course consistent with an anaphylactic reaction. The other 3 cases are suggestive of drug hypersensitivity to varying degrees but do not meet criteria for anaphylaxis. After inclusion of Patient 29708 as 1 of 4 total cases, the new estimated rate of anaphylaxis for the 2000L product is 6.7%.

Background

A 160L alglucosidase-alfa is currently marketed under the tradename Myozyme® for the treatment of Pompe disease, a glycogen storage disorder resulting from acid maltase deficiency. Patients with Pompe disease suffer from lysosomal glycogen accumulation in multiple tissues, particularly cardiac and skeletal muscle. The infantile-onset form of the disease is typified by early death due to hypotonia, cardiomyopathy, and respiratory failure, usually by 18 months in untreated patients. The adult-onset form of Pompe disease is characterized by a slow, progressive myopathy. Death usually results from respiratory failure. A spectrum of phenotypes between the typical infantile-onset and late-onset forms are also observed.

The Myozyme label contains a boxed warning on risk of hypersensitivity reactions, including anaphylactic reactions and other severe infusion reactions. In the clinical trials, the rate of anaphylaxis and/or cardiac arrest was estimated as <1% patients. However, an infusion reaction frequency of 51% (20 of 39 patients) is reported, including classical anaphylactic signs and symptoms such as hypotension, wheezing/bronchospasm, hypoxia, throat tightness, angioedema, and urticaria. These infusions reactions were noted to occur up to 2 hours after drug administration and were associated with higher

infusion rates. Based on the product label, it is unclear how infusion reactions were distinguished from anaphylaxis, as signs and symptoms may overlap. To some degree, "infusion reaction" is a catch-all term that encompasses a wide range of drug reactions which may or may not have an immunologic basis. In the safety database that includes clinical trials and an expanded access program, a frequency of 14% (38 of 280 patients) is reported for infusion reactions involving at least 2 of 3 body systems.

For the BLA for 2000L alglucosidase-alfa, the Applicant conducted a single, randomized, placebo-controlled, double-blind study in 90 patients ranging in age from 8-70 years, 78 weeks in duration. The patients were randomized 2:1 drug product:placebo. A total of 60 patients received the 2000L product, which was administered as an IV infusion at a dose of 20 mg/kg every other week. The primary efficacy variable was a six-minute walk test, as well as change from baseline in %predicted FVC. Review of the safety data shows at least 3 patients with anaphylaxis, based on diagnostic criteria outlined by a joint NIAID/Food Allergy and Anaphylaxis Network symposium held in 2006. These criteria are based on evidence of multi-organ involvement following an appropriate time-course after exposure to a likely or known allergen. The criteria do not make distinctions in terms of the "severity" of anaphylaxis. The criteria are summarized as follows:

Anaphylaxis is highly likely when any one 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 (e.g., generalized hives, pruritus or flushing, swollen lips-tongue- uvula), and at least one of the following:*
    a. *Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)*
    b. *Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)*
2. *Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):*
    a. *Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)*
    b. *Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)*
    c. *Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)*
    c. *Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)*
3. *Reduced BP after exposure to known allergen for that patient (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*

Three cases of anaphylaxis have been identified by the Applicant.

- **Patient 16709** experienced urticaria after her first infusion. After her second infusion two weeks later, she experienced chest discomfort, throat tightness, urticaria, flushing, nausea, decreased oxygen saturation, and pruritus consistent with anaphylaxis. She tested positive for anti-rhGAA IgE antibodies following the event, as well as having an elevated serum tryptase 23.7 mcg/L consistent with mast cell degranulation. This patient was discontinued from the study.
- **Patient 18713** experienced non-cardiac chest pain, urticaria, flushing, scalp swelling, pruritus, lip swelling, and macular rash during his 14th infusion at Week 28. He initially tested negative for anti-rhGAA IgE after the anaphylactic event, but tested positive on several subsequent tests, first testing positive at Week 30. Serum tryptase was not elevated. The patient underwent a successful drug desensitization procedure over a period of 6 consecutive weeks.
- **Patient 90701** experienced severe angioedema of the tongue, dysphagia, and "oppression" 15 minutes after the 3rd infusion and was discontinued from the study. This patient did not test positive for IgE antibodies. Skin testing was recommended for Patients 16709 and 90701 but was declined in both cases due to potential for reaction. *(Although the case narrative as written does not clearly meet the outlined criteria, DPAP considers the case to be a case of anaphylaxis. For the purposes of safety review, any cases identified by the investigator/sponsor as anaphylaxis are considered to be true cases.)*

DGP has identified 4 additional potential cases of anaphylaxis but has been unable to come to an agreement with the Applicant on the categorization of these adverse events as anaphylaxis. As a result, DGP has requested that DPAP review the 4 suspect cases. DGP has posed the following question to DPAP:

> *DGP considers the following 4 patients to have experienced anaphylaxis, and intends to present this conclusion at the Advisory Committee Meeting on October 21, 2008, and include this information in the Advisory Committee background package that is due on September 23, 2008. We are seeking an opinion from the DPAP consultant regarding whether you agree that these 4 patients sustained an episode of anaphylaxis based on the clinical definition of anaphylaxis set forth by the Network Symposium or any other standard clinical definition.*

These cases are described and a discussion follows.

Anaphylaxis cases

Patient 29705

Patient 29705 is a 44 year-old male with a history of depression, anxiety associated with need sticks, obsessive compulsive disorder, swollen tongue, hearing loss, lactose intolerance, and erectile dysfunction. The patient received his first dose of alglucosidase-alfa on December 9, 2005. He reported a range of adverse reactions on subsequent

infusions. These reactions and accompanying laboratory testing are summarized in the table below:

Patient 29705: Timeline of adverse events and laboratory testing					
Infusion date	**AE date** (b) (6)	**MedDRA PT**	**Serum tryptase** (mcg/L, ref range <14.7)	**Complement activation***	**Anti-rhGAA IgE antibody***
3/31/2006		Hematuria			
4/14/2006		Chest discomfort	7.8	+	- (4/20/2006)
4/28/2006		Chest discomfort Dizziness			
5/11/2006		Chest discomfort			
5/26/2006		Headache[a] Nausea Hematuria	8.8	+	-
7/19/2006		Chest discomfort			
7/19/2006		Burning sensation Fall Loss of consciousness[b]			
8/2/2006		Stress			
8/16/2006		Stress			
9/27/2006		Stress Headache			
1/19/2007		Fall			
3/16/2007		Infusion site reaction			
4/27/2007		Stress			
5/11/2007		Urticaria			
5/25/2007		Urticaria	9	-	- (5/30/2007)
6/8/2007		Urticaria			

* details of assay and/or numerical results not provided
[a] Headache and nausea resolved after infusion rate slowed from 250 → to 125 ml/hour.
[b] Reported as secondary to fall.

No further infusions were administered after the June 8, 2007, dose as the study was completed. Of note, urticaria was observed on the last two infusions despite premedication with diphenhydramine and systemic steroids. Based on the AE narratives, the urticaria appeared to be more diffuse and severe on the last two occasions. No relative hypotension was observed with any of the episodes.

Patient 29708

Patient 29708 is a 40-year-old female with asthma, seasonal allergies, allergic sinusitis, eczema, depression, and anxiety. The patient received her first dose of alglucosidase-alfa on November 4, 2005 at a dose of 20 mg/kg every other week. The patient reported a range of adverse reactions on subsequent infusions, including dizziness, chest discomfort, cold sweat, paresthesias, sensation of heaviness, photophobia, and somnolence. During her infusion on November 15, 1005, she experienced dizziness approximately 3 hours after the infusion was started. The infusion rate was decreased from 125 ml/hr to 62.5 ml/hr, and the dizziness began to resolve. The dizziness was accompanied by the sensation of chest tightness, which the patient reported to be similar to her asthma. The chest discomfort was alleviated by 1 puff of albuterol, and self-limited oral pruritus

which resolved within 2 minutes. At pre-infusion, heart rate was 92 bpm and blood pressure 112/73 mmHg. Thirty minutes into the infusion, the blood pressure was decreased to 97/63 while the heart rate remained stable at 88bpm. Vital signs recorded at the time of pruritus and chest tightness showed a heart rate of 87 bpm, blood pressure 108/76, respiratory rate 20, and temperature 97.3. Laboratory testing was positive for complement activation, serum tryptase was 3.2 mcg/L, and anti-rhGAA IgE antibodies were negative. The patient reported one additional episode of oral pruritus following infusion on January 10, 2006, but went on to receive multiple infusions subsequently without further skin-mucosal involvement or other clear evidence of drug hypersensitivity.

Patient 26710

Patient 26710 is a 30-year-old male who received his initial dose of alglucosidase-alfa on March 13, 2006, at a dose of 20mg/kg every other week. On August 14, 2006, he experienced pyrexia (38°C) 1.5 hours after the start of the infusion. Thirty minutes after infusion completion, the patient experienced an increase in systolic blood pressure (137/81 → 157/108 mmHg), increase in heart rate (89 → 98 bpm), dizziness, and diaphoresis. One hour after infusion, the patient had a single episode of vomiting. The patient recovered and vital signs returned to close to baseline without intervention within 30 minutes of vomiting. Serum tryptase and complement activation labs were not obtained as the investigator classified the reaction as a mild event. Anti-rhGAA IgE antibody testing was negative on August 28, 2006,. The patient remained enrolled and completed the study.

Patient 26712

Patient 26712 is a 50-year-old with a history of hypertension. He received his first dose of alglucosidase-alfa on March 13, 2006. On August 14, 2006, the patient experienced chills and malaise during drug infusion, coincident with an increase in the infusion rate. Blood pressure and temperature increased from pre-infusion baseline (134/84 → 164/102 mmHg and 36.8 →38.4°C 87 bpm). No clinically significant changes in heart rate were reported during the chills and malaise although a transient tachycardia up to 102 bpm was observed during the infusion. Laboratory testing was positive for complement activation, negative for anti-rhGAA IgE antibodies, and serum tryptase was 3.8 mcg/L. On August 13, 2007, the patient experienced gagging 3 hours after the start of the infusion, which lasted approximately 6 minutes. No clinically significant changes from pre-infusion baseline vital signs were recorded for this event. The patient tolerated the rest of the infusion. The patient remained enrolled and completed the study.

Discussion

Based on diagnostic criteria outlined by the joint NIAID/FAAN symposium, one of the four suspected cases meets criteria for anaphylaxis. Patient 29708 experienced skin-mucosal involvement (oral pruritus) and respiratory compromise (chest tightness/bronchospasm) during drug infusion with a time-course consistent with anaphylaxis. The severity of the individual symptoms is not part of the diagnostic criteria; given the multi-organ involvement and unpredictable nature of anaphylaxis, all

anaphylactic reactions are considered potentially life-threatening. Based on the information provided, Patient 29708 meets the joint symposium's criteria.

The other cases, however, do not meet criteria based on the information provided. These events were characterized primarily by a single sign or symptom. While a sign such as the urticaria observed in Patient 29705 is suggestive of drug hypersensitivity and may indicate a patient at risk for anaphylaxis upon repeat exposure, this skin manifestation alone does not meet diagnostic criteria for anaphylaxis. Similarly, symptoms such as vomiting or chills are difficult to categorize as anaphylaxis without documentation of accompanying skin-mucosal involvement, respiratory compromise, or derangement in vital signs.

The improvement of some of these symptoms with a slower infusion rate suggests a non-immunologic, non-specific activation of the complement cascade. This interpretation is supported by the lack of serum tryptase elevation and anti-rhGAA IgE antibodies in the cases, as well as successful rechallenges. However, negative test results do not rule out an immunologic mechanism, as serum tryptase measurement is time-sensitive and IgE antibody titers are occasionally low or undetectable immediately following an anaphylactic event.

In conclusion, the 2000L product appears to cause anaphylaxis as has been previously reported for the 160L product. Including Patient 29708, the calculated rate of anaphylaxis for the 2000L product is 6.7% (4 out of 60 patients who received alglucosidase alfa). This rate is higher than the <1% rate reported in the Myozyme product label but not significantly greater than the estimated 5% based on cases identified by the Applicant, especially given the small sample size. The higher rate may be attributable to the structural differences between the 160L and 2000L product. Alternatively, cases of anaphylaxis for the original Myozyme product may have been underreported or may have been categorized as infusion reactions, given the overlap in clinical symptoms and signs.