CENTER FOR DRUG EVALUATION AND RESEARCH AND CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

APPLICATION NUMBER:

125141/0

MEDICAL REVIEW(S)

MEMORANDUM

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

DATE: April 28, 2006

FROM: Julie Beitz, MD

SUBJECT: Acting Office Director Memo

TO: BLA STN 125141 Myozyme (alglucosidase alfa); Genzyme Corporation

Myozyme is a form of the human enzyme acid α-glucosidase (GAA) that is produced by recombinant DNA technology in a Chinese hamster ovary cell line. Myozyme provides an exogenous source of GAA that is taken up into cells and is transported into lysosomes where it hydrolyzes glycogen. Myozyme has 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 hypertrophic cardiomyopathy and progressive muscle weakness, including impairment of respiratory function. When the 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 when it presents in older patients is slowly progressive. There are no available treatments known to impact the survival or progression of disease in patients with Pompe disease. Current treatment involves supportive measures, such as nutritional therapy and use of respiratory support or other assistive devices. This memo documents my concurrence with the Director of the Division of Gastroenterology Product's recommendation for approval of Myozyme, administered by intravenous infusion, for use in patients with Pompe disease.

Efficacy

On July 27, 2005, Genzyme Corporation submitted BLA STN 125141 which was granted a priority review. Additional clinical and product quality information was requested during the review which upon submission prompted an extension of the review clock. Myozyme was studied in a multicenter clinical trial of 18 infantile-onset Pompe disease patients (Study AGLU01602). Enrollment was restricted to patients aged 7 months or less at first infusion with clinical signs of Pompe disease with cardiac hypertrophy and who did not require ventilatory support at study entry. Patients were randomized to either 20 mg/kg or 40 mg/kg every two weeks for 52 weeks. After 52 weeks of treatment, all 18 patients were alive and 3 required invasive ventilator support. With continued treatment beyond 52 weeks, four additional patients required ventilator support and two of these patients died after receiving 14 and 25 months of treatment, respectively. These outcomes were superior to what was observed in a historical cohort of 61 untreated patients born between 1960 and 2003. Only one of these 61 patients was alive at age 18 months. No difference in outcomes was observed between patients who received 20 vs. 40 mg/kg. Additional clinical observations in evaluable patients included improved motor function in 13 patients and decreases in left ventricular mass index in 15 patients. The majority of patients however remained significantly delayed in motor function compared to normal infants of comparable age.

Interim data were also submitted from an ongoing, multicenter, open-label clinical trial that enrolled 21 patients who were aged 3 months to 3.5 years at the time of first infusion (Study AGLU01702). All patients received 20 mg/kg every two weeks for up to 104 weeks. At the 52-week interim analysis, 16 patients were alive. Sixteen patients were ventilator-free at baseline; ten of these were ventilator-free at 52 weeks, two required ventilator support, and four had died. Five patients required ventilator support at baseline; four of these continued to require this support at 52 weeks, and one patient had died.

Data were presented on an additional twenty-five patients, including one infantile-onset patient, several juvenile-onset patients and 3 patients with symptom onset in their thirties. These patients had received open-label treatment for varying periods of time, the majority on expanded access programs. There was one definite response observed in the infantile-onset patient who had symptom onset at age 6 months and

had received a total of eight years of enzyme replacement therapy that included Myozyme. This patient was wheelchair dependent at the start of therapy, could walk after 72 weeks, and in subsequent years, could run and play sports. Of the remaining 24 patients, six who were treated for periods of 8 months to six years were able to decrease their requirement for ventilatory support from 3-10 hours per day. In addition, three patients with symptom onset at age 30, 33 and 35 years were treated for 17, 14, and 11 months respectively. They remained ventilator-dependent with stable motor function during therapy.

At a CDER Regulatory Briefing held on March 3, 2006, the clinical significance of these data was discussed. The consensus among CDER senior managers and DGP review staff was that the clinical findings supported Myozyme use in infantile-onset Pompe disease patients. In particular, Myozyme use improved ventilator-free survival in these patients as compared to an untreated historical control Pompe disease population which experienced rapid and unrelenting progression of their disease. Furthermore, in my view, the benefits of treatment with Myozyme in these patients outweigh the risk for serious hypersensitivity reactions, including potentially life-threatening anaphylaxis, a safety concern which came to light in the weeks following the briefing (see below).

On the other hand, data presented at the briefing on treatment outcomes in juvenile- and adult-onset patients were viewed as less compelling. Data were not rigorously collected (i.e., derived primarily from case narratives and not from controlled studies). Clinical improvements were far less dramatic than the ventilator-free survival finding observed in patients with infantile-onset disease treated with Myozyme. Rather, there were reports of reduced numbers of hours per day of required ventilatory support and stable motor function over several months' time in a small number of patients. These findings, while suggestive of disease stabilization, are difficult to interpret in the absence of a placebo-treated control group. Improved symptom control and/or disease stabilization in the face of the alternative – slowly progressive morbidity – could be considered clinically meaningful outcomes had they been rigorously assessed in prospective, adequate and well-controlled studies. As this was not the case here, in my view, it is not possible to determine either the magnitude of the treatment effect, or whether the benefits observed in these patients outweigh the risk for serious hypersensitivity reactions, including potentially life-threatening anaphylaxis. As of this writing, controlled data on the efficacy and safety of Myozyme in juvenile- and adult-onset patients is being collected in ongoing Study AGLU02704. This randomized, multicenter, double-blind, placebo-controlled study has completed accrual and will assess patient outcomes after 52 and 104 weeks of treatment. These data, expected to be ready for submission in 2008, should shed light on the benefit vs. risk ratio for Myozyme treatment in these patient populations.

To conclude, my recommendation is to qualify the indication statement that Myozyme be used in patients with Pompe disease with the following statement describing our current state of knowledge, namely that "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 the disease has not been adequately studied to assure safety and efficacy."

Of note, this indication statement is not inconsistent with that approved by the European Union on April 3, 2006, namely that, "Myozyme is indicated for long-term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of Pompe disease (acid α-glucosidase deficiency). The benefits of Myozyme in patients with late-onset Pompe disease have not been established."

Safety

Serious infusion-related hypersensitivity reactions, including anaphylactic reactions, have been reported with administration of Myozyme. The serious nature of these reactions came to light late in the review cycle and was the subject of extensive discussion with the sponsor in teleconferences on April 12, 13, and 18, 2006. Thirty-eight of 280 (14%) patients enrolled in clinical trials or expanded access programs developed infusion reactions involving at least two of three critical body systems, namely, cutaneous, respiratory or cardiovascular systems. Of these cases, 8 experienced severe or clinically significant reactions. Three of these patients (all adults) discontinued Myozyme treatment. These events have been highlighted in a Boxed Warning and in additional bolded warnings which advise that appropriate medical support measures be readily available when Myozyme is administered. Decreasing the infusion rate, temporarily stopping the infusion, and/or administering antihistamines, antipyretics or corticosteroids may

ameliorate the symptoms. If severe hypersensitivity or anaphylactic reactions occur, immediate treatment discontinuation should be considered. Patients who have experienced infusion reactions should be treated with caution when re-administering Myozyme.

Additional bolded warnings highlight: 1) the risk of cardiac arrhythmia and sudden cardiac death in infantile-onset patients with cardiac hypertrophy, that was associated with the use of general anesthesia (in six patients requiring central venous catheter placement or muscle biopsy, one of whom died), and 2) the risk of acute cardiorespiratory failure possibly associated with fluid overload (in a 3-month-old infant with cardiac hypertrophy).

Immunogenicity

The majority of patients (89%) in clinical trials tested positive for IgG antibodies to alglucosidase alfa. There is evidence to suggest that patients developing sustained titers (≥12,800) of anti-alglucosidase alfa antibodies may have a poorer response to treatment, or may lose motor function as antibody titers increase. In addition, infusion reactions were more common in patients with high antibody titers (i.e., reactions involved 8 of 15 such patients) as compared to patients who were antibody negative (i.e., reactions in none of 3 antibody-negative patients).

Product Issues

Genzyme had originally intended to market both a 160 liter and a 2000 liter scale product, however, no safety or efficacy data were presented in the BLA using the latter product. To determine comparability of the two products, the sponsor conducted a study in GAA knockout mice. This study revealed that the 2000 liter scale product resulted in an AUC that was 30% lower than that for the 160 liter scale product. After discussions with the product review team, the sponsor withdrew the 2000 liter scale product from consideration in this BLA when it submitted a major information amendment on December 30, 2005.

Several deficiencies were identified with regard to the enzyme potency assays. The sponsor's assay utilized an artificial substrate instead of a physiologically relevant one, such as glycogen, and did not measure substrate binding or catalysis. There were no potency assays that measured

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discussions with the product review team, the sponsor developed qualified potency assays, and analyzed commercial launch lots using BLA clinical lot data to set provisional release specifications. Genzyme agrees to validate and implement new potency assays in release testing in the coming months. There was general concurrence with this approach at the Center-level briefing in March 2006.

Tradename Review

The tradename "Myozyme" is acceptable.

Phase 4 Studies

The sponsor has committed to conducting the following clinical studies:

- Completing and submitting a final study report for Study AGLU01702 in infantile-onset disease patients
- Completing and submitting a final study report for Study AGLU02704 in juvenile- and adult-onset disease patients
- Implementing a registry of Pompe disease patients treated with Myozyme to collect information on clinical status, including ventilatory status and motor assessments, adverse events, immunogenicity and antibody formation for at least 15 years; cognitive, auditory and visual screening assessments will be performed in patients who are less than one year of age at the start of treatment
- Conducting a study in infantile-onset patients who are less than one year of age at the start of Myozyme treatment to assess growth, cognitive and development, auditory, visual and neuro-imaging assessments, and antibody formation over a 10 year period
- Conducting a study of an immune tolerance regimen in patients who have high antibody titers, or the presence of neutralizing antibody, and are failing Myozyme treatment; and monitoring antibody positive patients, whose immune responses are not associated with loss of efficacy or severe hypersensitivity responses, at regular intervals over an extended period of time (i.e., 18-24

months) to specifically assess if a sub-population of patients becomes tolerant with routine treatment

- Conducting a dose and dose interval exploration study in patients with poor responses to treatment regardless of antibody status; this study will include infantile-, juvenile- and adult-onset patients.

The sponsor also commits to conducting additional preclinical studies, including a six-month chronic toxicity study in neonatal/juvenile mice, a Segment II teratology study in rabbits, histopathologic examination of the testes of male mice in a previously conducted fertility study, and a Segment III prenatal and postnatal study in rats or mice.

In addition, the sponsor commits to addressing several product-related issues, including completing validation of and submitting specifications for its potency assays, finalizing specifications for the drug substance and drug product, incorporating validated assays into its stability protocol, and submitting progress reports on the status of these commitments every 6 months after licensure. The sponsor also commits to providing 1) information from a validated neutralizing antibody assay to evaluate enzyme uptake by human fibroblasts, and 2) results from the validated inhibition of enzyme uptake assay from all patients enrolled in Study AGLU01602 and Study AGLU01702, and all patients treated in clinical studies or on expanded access programs who required invasive ventilation since February 2006.

Julie Beitz MD 4-28-06

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

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

DATE: April 28, 2006

FROM: Brian E. Harvey, M.D., Ph.D.
Division Director, DGP/ODE III/OND

TO: Julie G. Beitz, M.D.
Deputy Director, ODE III/OND

SUBJECT: Division Director Concurrence Memo

APPLICANT: Genzyme Corporation

DRUG: BLA/STN 125141/0
MYOZYME (alglucosidase alfa)

DATE SUBMITTED: July 27, 2005

DIVISION RECOMMENDATION:

The primary Medical Officer, Medical Team Leader and all of the consulting review team members have recommended that BLA/STN 125141/0 for MYOZYME (alglucosidase alfa) be approved. I am in agreement with these recommendations.

BACKGROUND:

MYOZYME® (alglucosidase alfa) consists of the human enzyme acid α-glucosidase (GAA), encoded by the most predominant of nine observed haplotypes of this gene. MYOZYME is produced by recombinant DNA technology in a Chinese hamster ovary cell line. Alglucosidase alfa degrades glycogen by catalyzing the hydrolysis of α-1,4- and α-1,6- glycosidic linkages of lysosomal glycogen. MYOZYME provides an exogenous source of GAA and it's binding to mannose-6-phosphate receptors on the cell surface has been shown to occur via carbohydrate groups on the GAA molecule, after which it is internalized and transported into lysosomes, where it undergoes proteolytic cleavage that results in increased enzymatic activity. It then exerts enzymatic activity in cleaving glycogen.

Pompe disease (glycogen storage disease type II, GSD II, glycogenosis type II, acid maltase deficiency) is an inherited disorder of glycogen metabolism caused by the absence or marked deficiency of the lysosomal enzyme GAA. In the infantile-onset form, Pompe disease results in intralysosomal accumulation of glycogen in various tissues, particularly cardiac and skeletal muscles, and hepatic tissues, leading to the development of cardiomyopathy, progressive muscle weakness, and impairment of respiratory function. In the juvenile- and adult-onset forms, intralysosomal accumulation of glycogen is limited primarily to skeletal muscle, resulting in progressive muscle weakness. Death in all forms is usually related to respiratory failure.

The safety and efficacy of MYOZYME were assessed in 2 separate clinical trials in 39 Pompe disease patients, who ranged in age from 1 month to 3.5 years at the time of first infusion.

Study 1 was an international, multicenter, open-label, clinical trial of 18 infantile-onset Pompe disease patients. Efficacy was assessed by comparing the proportions of Myozyme-treated patients who died or needed invasive ventilator support with the mortality experience of an historical cohort of untreated infantile-onset Pompe patients with similar age and disease severity. By the age of 18 months, only one of the 61 historical control patients was alive, indicating the poor outcome of patients who are left untreated. Within the first 12 months of treatment, 3 of 18 MYOZYME-treated patients required invasive ventilatory support; there were no deaths.

Study 2 is an ongoing, international, multicenter, non-randomized, open-label clinical trial that enrolled 21 patients who were ages 3 months to 3.5 years at first treatment. All patients received 20 mg/kg MYOZYME every other week for up to 104 weeks. Five of 21 patients were receiving invasive ventilatory support at the time of first infusion. The primary outcome measure was the proportion of patients alive at the conclusion of treatment. At the 52–week interim analysis, 16 of 21 patients were alive.

Infusion reactions occurred in 20 of 39 (51%) of patients treated with MYOZYME in clinical studies. The most serious adverse reactions reported with MYOZYME were cardiorespiratory failure and anaphylactic reactions.

RECOMMENDATIONS FOR REGULATORY ACTIONS

The review team and consultants for this product have recommended that BLA/STN 125141/0 for MYOZYME® (alglucosidase alfa) be approved and I concur with these recommendations. I also concur with the summary of this review as stated in the Medical Team Leader Memo. There were extensive discussions among the review team members regarding the exact wording of the Indication statement and other important aspects of the product label. The nature of these discussions centered upon the clinical trial data in infants and what extrapolation could be made, if any, to patients whose disease was diagnosed at a later age. These discussions were also informed by the CDER Regulatory Briefing of March 3, 2006, as well as the general discussions of Inborn Errors of Metabolism clinical trials at the Endocrinologic and Metabolic Drugs Advisory Committee on January 13-15, 2003. This process led to the finalized negotiated label for

MYOZYME. I concur with the contents of this label which is based upon the totality of the data present in this BLA.

Specifically, I concur with the wording of the Indications and Usage statement for this product as stated in the finalized negotiated label:

"*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*"

Based upon the data, I also concur with the Black Box Warning as stated in the finalized negotiated label:

"WARNING

RISK OF HYPERSENSITIVITY REACTIONS

LIFE-THREATENING ANAPHYLACTIC REACTIONS, INCLUDING ANAPHYLACTIC SHOCK, HAVE BEEN OBSERVED IN PATIENTS DURING MYOZYME INFUSION.

BECAUSE OF THE POTENTIAL FOR SEVERE INFUSION REACTIONS, APPROPRIATE MEDICAL SUPPORT MEASURES SHOULD BE READILY AVAILABLE WHEN MYOZYME IS ADMINISTERED."

In addition, I concur with the follow negotiated PMC as outlined in the approval letter.

"Postmarketing Studies subject to reporting requirements of 21 CFR 601.70.

1. Genzyme commits to completing the juvenile- and adult-onset Pompe disease study AGLU02704, entitled "A randomized, double-blind, multicenter, multinational, placebo-controlled study of the safety, efficacy and pharmacokinetics of Myozyme, recombinant human acid alpha-glucosidase (rhGAA), treatment in patients with late-onset Pompe disease." Patient accrual is complete, the study is to be completed by September 30, 2007, and a final study report will be submitted to CDER by May 31, 2008.

2. Genzyme commits to conducting the extension to the juvenile- and adult-onset Pompe disease study AGLU02704 through 24 months (AGLU03206), entitled "An open-label extension study of patients with late-onset Pompe disease who were previously enrolled in protocol AGLU02704". Patient accrual is to be completed by December 31, 2007, the study is to be completed by June 30, 2008, and a final study report will be submitted to CDER by November 30, 2008.

3. Genzyme commits to completing study AGLU01702, entitled "An open-label, multicenter, multinational study of the safety, efficacy, pharmacokinetics, and pharmacodynamics of recombinant human acid alpha-glucosidase (rhGAA) treatment in patients > 6 months and ≤ 36 months old with infantile-onset Pompe disease (Glycogen Storage Disease Type II)." This study is to be completed by June 12, 2006, and a final study report will be submitted to CDER by February 28, 2007.

4. Genzyme commits to designing and implementing a registry of patients with Pompe disease being treated with alglucosidase alfa that will be established to obtain long-term clinical status information. Information will be collected on patient demographics, specifics of treatment with alglucosidase alfa, clinical status, ventilatory status, motor assessments, adverse events, assessment of immunogenicity, and potential effects of antibody formation. In patients who are less than one year of age at the start of treatment, information is to be collected on cognitive status, and auditory and visual screening assessments. This registry will be designed so that detailed clinical status information is collected at registry entry and on a 6- to 12-month basis for at least 15 years. Genzyme commits to conducting two sub-studies within the registry: one sub-study that will evaluate the effect of alglucosidase alfa on pregnancy and lactation, and one sub-study that will collect information on the clinical status of patients on ventilatory support at the time of entry into the registry. The registry data will be analyzed at yearly intervals and the results will be submitted in your annual reports for BB-IND 10780. A study protocol will be submitted to CDER by September 29th, 2006, for concurrence, and the study will be initiated by March 31, 2007. The final study report under this registry will be submitted to CDER by September 30, 2022.

5. Genzyme commits to designing and implementing an infantile-onset Pompe disease study to assess growth and development with treatment with alglucosidase alfa, in patients who are less than one year of age at study entry. This study is to include blinded assessments of growth (including standardized measurements of recumbent length, height, weight, and head circumference), developmental testing (the scales used need to be prospectively agreed upon), auditory and visual screening, neuro-imaging, and antibody assessments at 6- to 12-month intervals over a 10-year period. A study protocol will be submitted to CDER by September 29th, 2006, for concurrence, and the study will be initiated by January 31, 2007. The final study report for this study will be submitted to CDER by September 30, 2017.

6. Genzyme commits to designing and implementing an immune tolerance protocol in Pompe disease patients who have significant antibody titers, or the presence of neutralizing antibody, and are failing treatment. Genzyme commits to designing and implementing a preventive immune tolerance protocol in Pompe's patients at high risk of the development of significant immune responses to product. This would involve 1) establishing the correlation among genotype, the level of □-glucosidase protein (non-enzymatic assay), and the presence and levels of binding, IgE, and neutralizing antibodies over time, using validated assays; and 2) developing an immune tolerance regimen that would be implemented before or concomitant with

onset of therapy for those at high risk. Additionally, Genzyme commits to monitoring antibody positive patients, whose immune responses are not associated with loss of efficacy or severe hypersensitivity responses, at regular intervals over an extended period of time (i.e., 18-24 months) to specifically assess if a sub-population of patients become tolerant with routine treatment. Reports from preclinical studies to assess potential tolerance regimens and a commitment for timelines for a subsequent clinical study will be submitted to CDER by December 29, 2006.

Genzyme commits to developing a protocol which will be used to provide guidance to physicians for the use of tolerance inducing regimens for patients who are currently failing treatment because of a robust antibody response and to submit this protocol by October 31, 2006.

7. Genzyme commits to designing and implementing a dose- and dose-interval exploration study in patients with poor responses to treatment, regardless of antibody status. This study is to include patients in the infantile-, juvenile-, and adult-onset patient populations. A study protocol will be submitted to CDER by September 29, 2006, for concurrence, and the study will be initiated by January 31, 2007. The final study report for this study will be submitted to CDER by September 30, 2009.

8. Genzyme commits to initiate a 6-month intravenous chronic toxicity study of Myozyme in neonatal/juvenile mice by September 29, 2006 and submit the full report of the study by September 30, 2007.

9. Genzyme commits to submit by June 30, 2006 the final report of — Study 6354-163 titled "Intravenous Injection Study of Recombinant Human Acid-alfa-Glucosidase (rhGAA) on Female Fertility and Early Embryonic Development to Implantation in Mice".

10. Genzyme commits to conduct a Segment II. Teratology study of Myozyme in rabbits and submit the full report of the study by June 30, 2007. In the interest of clarity and precision for the data obtained, pretreatment of the animals with diphenhydramine should be avoided in the study.

11. Genzyme commits to conduct histopathology examination of the testes of male mice in — Study 6354-155 titled "Intravenous Injection Study of Recombinant Human Acid alfa-Glucosidase (rhGAA) on Fertility and Early Embryonic Development to Implantation in Mice" and submit the full pathology report by October 30, 2006.

12. Genzyme commits to submit the data from the third Segment I reproductive/toxicology study in mice by December 31, 2006, for concurrence. If necessary, Genzyme commits to submit an additional protocol for the study of the effects of Myozyme on spermatocytogenesis and spermiogenesis in male rabbits. In any future protocols, animals should be treated for a minimum of 90 days.

13. Genzyme commits to conduct a Segment III. Prenatal and postnatal study in rats or mice in the third quarter of 2006 and submit the full report of the study by September 30, 2007.

Postmarketing Studies not subject to reporting requirements of 21 CFR 601.70.

14. Regarding method validations:

    a. To complete validation of [redacted] test methods for drug substance and/or product release. Results and proposed specifications will be submitted to FDA by December 31, 2006.

    b. To complete optimization and validation of [redacted] test methods for drug substance and product release. Results and proposed specifications will be submitted by March 31, 2007.

    c. To improve the [redacted] content assay, or to develop, validate, and implement an alternative more accurate and precise assay. Results and proposed specification will be submitted by December 31, 2007.

15. To provide a revised protocol for requalification and confirmation of stability of the primary and working reference standards that incorporates the new panel of validated methods. A revised protocol will be submitted by July 31, 2006.

16. Regarding the drug substance specifications:

    a. To re-evaluate the specification for [redacted] and establish a limit for [redacted] in the specification, following assay re-validation. Results and revised specifications will be submitted by December 31, 2006.

    b. To revise the specification for the [redacted] present in the oligosaccharide mapping analysis and submit by June 30, 2006.

17. Regarding the drug product COA/specifications:

    a. To add the [redacted] proposed specification will be submitted by March 31, 2007.

    b. To explore development of a method for an [redacted] observed in reconstituted drug product and after dilution in saline. Results and a proposal for controlling particle content will be submitted by November 30, 2007.

18. To characterize the composition of the — material observed after reconstitution of drug product and to investigate the nature of particle formation. Results will be submitted by November 30, 2007.

19. —

Validated stability indicating assays will be incorporated into the stability program (including accelerated stability on drug product, and after reconstitution and dilution). Results and revised stability protocol will be submitted by June 30, 2007.

20. To perform a study on formulated bulk drug product to confirm its hold time using the — content assay and other stability-indicating assays. Results will be submitted by November 30, 2007.

21. To conduct bracketed, in use photostability studies on product diluted for infusion using current methods. Results will be submitted by December 31, 2006.

22. To provide interim summary reports regarding progress of CMC PMCs every 6 months after licensure.

23. To provide information from a validated cell-based neutralizing antibody assay to evaluate the potential effect of GAA antibody on mannose-6-phosphate receptor dependent enzyme uptake using human fibroblast cells. Results will be submitted by June 30, 2006.

24. To provide results using the validated inhibition of enzyme uptake into human fibroblast assay from all patients in Studies AGLU01602 and AGLU01702, as well as all patients in clinical studies or the expanded access program for Myozyme who have become invasively ventilated since February 2, 2006. Results will be submitted by October 31, 2006."

Brian E. Harvey 4/28/06

Brian E. Harvey, MD, PhD
Director
Division of Gastroenterology Products
Office of Drug Evaluation III
OND, CDER, FDA

DEPARTMENT OF HEALTH AND HUMAN SERVICES | PUBLIC HEALTH SERVICE

Food and Drug Administration

Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993

Division of Gastroenterology Products
HFD-180

Date: **April 27, 2006**

From: **John Hyde, Ph.D., M.D., Clinical Team Leader, DGP** John E. Hyde 4-27-06

Subject: **Clinical Team Leader Summary Review of BLA/STN 125141/0 Alglucosidase Alfa for Glycogenosis Type II (Pompe Disease)**

To: **BLA 125141/0 File**
Brian Harvey, M.D., Ph.D., Division Director, DGP
Julie Beitz, M.D.; Acting Director, ODE 3

Brian E. Harvey 4/28/06 See Divisional Director Mem

Identifying information

BLA/STN#:	125141
Applicant:	Genzyme
Biologic name:	recombinant alglucosidase alfa
Proposed trade name:	Myozyme
Submission date:	July 29, 2005
Stamp date:	July 30, 2005
PDUFA goal date:	April 29, 2006
Formulation:	50 mg alglucosidase alfa, lyophylized, in 20 mL glass vial, for reconstitution in sterile water and dilution in saline for injection
Proposed indication:	
Proposed regimen:	20 mg/kg intravenous infusion every two weeks

Recommended regulatory action: Approval under 21 CFR 601.

Introduction and Regulatory Background

This BLA is for the new molecular entity Myozyme (alglucosidase alfa, rhGAA), an exogenous source of enzyme intended to treat severe deficiency of α-1,4-glucosidase, the defect causing Pompe disease (also known as acid maltase deficiency, glycogen storage disease type II, glycogenosis type II, or generalized glycogenosis). The enzyme, produced by recombinant DNA technology, is one of the normal variants of the human enzyme. The product is to be administered every two weeks at a dose of 20 mg/kg as an intravenous infusion over

approximately four hours. The product is proposed as

Orphan Designation 97-1065 was granted for this product on August 19, 1997, for the "treatment of glycogen storage disease type II." Clinical studies were conducted under Genzyme's BB-IND 10,780. A pre-IND meeting was held on October 15, 2002, and the IND was received on November 22, 2002. Fast Track Designation was granted to Genzyme on February 13, 2003, for "the investigation of Alpha-Glucosidase for its effect in preventing mortality in classical infantile Pompe's disease." An End-of Phase-2 Meeting was held July 22, 2003, and an End-of-Phase 2 Meeting for late-onset Pompe disease was held on April 28, 2005. A CMC pre-BLA meeting was held on May 3, 2005, and a clinical and pre-clinical pre-BLA meeting was held on June 1, 2005. The BLA submission was received on July 30, 2005. The application was granted Priority review status because it was viewed as representing, if approved, a significant improvement over currently available therapies.

During the course of the review of this application, the Division sent three formal information request letters to the applicant to obtain additional safety, efficacy, and manufacturing information that was considered necessary for the review. The last request was made in December 2005, with a request to provide the information by the end of that month. Amendment 008 was received in response to that request on December 30, 2005, and the review clock was extended three months to permit time for the additional review.

No Advisory Committee meeting was convened to discuss this application.

The product was approved by the EMEA April 3, 2006. The indication states:

> Myozyme is indicated for long-term enzyme replacement therapy (ERT) in patents with a confirmed diagnosis of Pompe disease (acid α-glucosidase deficiency).
>
> The benefits of Myozyme in patients with late-onset Pompe disease have not been established (see section 5.1).

The EMEA labeling has a warning about infusion-associated reactions, and the recommended dose is 20 mg/kg every other week.

The primary review disciplines have all written review documents, which should be consulted for more specific details of the application. This memorandum summarizes selected information from these documents. The primary review documents relied upon are the following:

Clinical Efficacy and Safety Review of A. Pariser, dated 4/27
Statistical Review and Evaluation of L. Kammerman, dated 4/27/06
Pharmacology/Toxicology Review and Evaluation of B. Wilcox, dated 3/20/06
Supervisory Pharmacologist memo of J. Choudary, dated 4/14/06
Clinical Pharmacology and Biopharmaceutics Review of A. Rajpal, dated 3/23/06
Immunogenicity Review of J. Wang, dated 4/27/06
Drug Substance Review of F. Mills, dated 4/27/06
Drug Product Review of R. Bernstein, dated 4/27/06
Facility inspection memo of M. Clark-Stuart and J. Li, dated 9/28/05, finalized 3/10/06

In the original submission the applicant presented information on two commercial processes. One used a 160 L fermentation scale and the other a 2000 L fermentation scale. (The clinical studies used the product from the 160 L scale.) The subsequent purification steps differed for the two scales. As a result of deficiencies in the 2000 L process identified during review of this application, the applicant elected to withdrawn the request for approval of the 2000 L process.

The drug substance, rhGAA, is produced in CHO cells — Fermentation takes place in a 160 L bioreactor, and the substance is purified and sterilized by chromatography, — and filtration. To characterize the drug substance adequately, the applicant developed, at FDA's request, five additional assays for release testing. They are not fully validated, but are being used with specifications agreed upon between the applicant and FDA. See the Drug Substance Review for details.

The substance is placed into glass vials without preservative and lyophylized to produce the final drug product. For administration, the product is to be reconstituted in sterile water and diluted in normal saline for infusion. The product from the 160 L process has shown adequate evidence to support a shelf life of 24 months at 2 to 8 °C. The drug product should be designated as "protect from light" Reconstituted material is stable for — at 2 to 8 °C, and diluted material is stable for — at 2 to 8 °C.

Inspection of the drug substance and drug product manufacturing facilities did not identify any issues that would preclude approval.

The immunogenicity reviewer noted a correlation between high binding antibody titer and presence of nonsense/frameshift mutations. Also there appeared to be a relationship between the appearance of high antibody titers and loss of clinical response. Only one patient in 39 evaluated had a neutralizing antibody, but the reviewer had questions about the sensitivity of the assay. Genzyme had developed an assay for antibody inhibiting uptake, but it has only been evaluated on the patient with neutralizing antibody.

Conclusions and Recommendations

The CMC reviewers concluded that the product is approvable using the 160 L commercial process.

The CMC reviewers negotiated post-marketing commitments to improve method validation, to revise the protocol for re-qualification of reference standards using the improved validation methods, to propose additional drug substance specifications for — and for — on the oligosaccharide mapping analysis, to perform specific drug product release tests and develop a — specification, to characterize the — material observed after reconstitution, to investigate the utility of several specified assays for indicating stability, to study bulk drug product using stability-indicating assays, and to perform photostability studies.

The immunogenicity reviewer recommended that the applicant conduct additional investigations to evaluate whether uptake-inhibiting antibody relates to clinical outcome, and to investigate means to induce tolerance in patients who may be at risk for loss of response.

Clinical Inspection Summary memo of J. Tavarez, dated 12/23/05
ODS/DMETS labels and labeling consult memo of N. Roselle, dated 9/12/05
ODS/DDRE pharmacovigilance plan consult memo of A. Brinker et al., dated 12/12/05
ODS/DMETS proprietary name consult memo of C. Hoppes, dated 2/15/06
Neurology Consult of M. Walton, dated 12/16/05
Pediatrics Consult of H. Sachs, dated 3/20/06

Clinical Background

Pompe disease (glycogen storage disease type II, glycogenosis type II, acid maltase deficiency) is a lysosomal storage disease, a category of diseases characterized by a genetic deficiency in production or function of one or more the lysosomal enzymes. In Pompe disease the deficient enzyme is acid α-glucosidase (GAA), which catalyses the breakdown of glycogen in lysosomes by hydrolysis of α-1,4- and α-1,6-glucosidic linkages. Deficiency of the enzyme results in accumulation of glycogen in lysosomes in various tissues. The disorder is autosomal recessive, and numerous mutations have been identified.

Various forms of the disease are described; all involve myopathy, but with a wide range in severity. In the infantile-onset form, symptoms are identified usually in the first few months of life. The features are hypotonia, progressive weakness, and cardiomegaly. Patients also have macroglossia and hepatomegaly. Pulmonary function becomes progressively impaired, and patients usually die of cardiorespiratory failure by two years of age. Glycogen deposition is found in cardiac, skeletal, and smooth muscle, as well as in liver, renal tubular epithelium, and the CNS. Mental development appears normal. A muscular variant of the infantile-onset form also presents with symptoms early in life but does not include cardiomegaly; these patients also have progressive weakness but it may progress more slowly, and the patients can have longer survival.

Juvenile- and adult-onset Pompe disease, sometimes referred to together as late-onset Pompe disease, present later in life, 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. Presenting symptoms are proximal muscle weakness, greater in the lower extremities, which becomes more extensive and progresses. Death is usually secondary to respiratory failure. Glycogen deposition in muscle may be patchy.

The disorder is rare. The incidence is estimated at 1 in 300,000 to 1 in 40,000. Heterozygous carries appear normal.

There is no approved specific treatment for the disease. The currently available therapeutic options are primarily symptomatic and palliative. There is a pressing need for new therapies.

Chemistry, manufacturing, and controls issues

The reader is referred to the Drug Substance review by F. Mills, the Drug Product Review by R. Bernstein, and the Immunogenicity Review by J. Wang.

The immunogenicity reviewer negotiated post-marketing commitments requesting the applicant to do additional work on a neutralizing antibody assay to be able to assess an impact on cell uptake, to investigate the significance of the assay in patients in the two principal studies, and to design and implement an immune tolerance protocol.

Pre-clinical pharmacology and toxicology issues

The reader is referred to the Pharmacology/Toxicology Review and Evaluation by B. Wilcox and to the Supervisory Pharmacologist memo by J. Choudary.

Toxicology studies were performed in rats, dogs, cynomolgus monkeys, and mice. The product was generally well-tolerated. Toxicities noted in mice were a small decrease in WBC and mild dose-related increase in albumin; mildly increased ALT and ST were noted in two females. Studies in rats produced several unscheduled deaths, a number of which were felt to be due to hypersensitivity, but the reviewer felt they were not sufficiently explained. Rats also showed a dose-related decrease in body weight.

Several studies were conducted in GAA knockout (KO) mice, an animal model for Pompe disease. In these studies rhGAA consistently showed efficacy in clearing glycogen from a range of muscles; with cardiac muscle being the most responsive. In a study that dosed 100 mg/kg weekly for four weeks, glycogen was cleared from cardiac muscle at Day 1 after completing dosing and in skeletal muscle at Day 3 after completing dosing. Glycogen re-accumulated in skeletal muscle by Day 28, but in cardiac muscle it was not seen until Day 42. Different skeletal muscles responded differently in a pattern that was consistent across different studies. KO mice that were three months old were more responsive to rhGAA than mice that were 12 months old. In chronic studies, 40 mg/kg qow was as effective as 20 mg/kg weekly. Unscheduled deaths occurred that were thought to be due to hypersensitivity, but some were unexplained. Rodents were routinely pretreated with diphenhydramine. An immunology study in KO mice found elevated IgG, and histamine was elevated after the eighth dose, but IgE was not detected.

Pharmacokinetic parameters in KO mice showed linear behavior over the range 10 to 40 mg/kg. Elimination half-lives were in the range 1 to 3.5 hours for the various species investigated. Animal PK studies found that product from the 160 L and 2000 L production processes did not satisfy criteria for bioequivalence.

Biodistribution studies found the highest level of rhGAA activity in the liver, with lower levels in the spleen, and still lower levels in muscle. Among muscle tissues, cardiac muscle showed the highest levels. The 2000 L process product resulted in higher liver uptake than did the 160 L process product.

A Segment I study was performed in mice. There was a trend toward implantation loss that did not reach statistical significance. Male fertility studies showed increased abnormal sperm and a reduction in sperm counts. A Segment II study in mice showed no pre-implantation loss, but there was a trend (not statistically significant) toward increased late resorptions. There was no statistically significant effect on fetal development.

No genotoxicity or carcinogenicity studies were conducted.

Conclusions and Recommendations

The pre-clinical reviewer concluded that the product was approvable but that the reproductive toxicology data were inadequate to support the late-onset indication. She recommended that the pregnancy category should be – and that the labeling should include . The reviewer recommended that additional reproductive toxicity studies should be done as a post-marketing commitment. She recommended that the applicant should be asked to provide histopathologic evaluation of the deaths in rat studies. She also suggested consideration be given to monitoring AST and ALT, in light of the findings in the monkey study and the known high levels of rhGAA found in the livers of KO mice.

The supervisory pharmacologist also concluded that the product was approvable. Apart from hypersensitivity, he concluded no target organ of toxicity had been identified. He identified that the safety pharmacology study in dogs did not have ECG monitoring, and recommend that the applicant be required He did not feel that the findings of sufficient significance that they needed to be described in labeling. In light of previous agreements regarding the four-week rat toxicology study, he concluded that additional histopathologic examinations for that study were not warranted.

The supervisory pharmacologist's assessment of the reproductive toxicology studies was that that they "do not demonstrate an adverse influence of Myozyme on reproduction in male and female mice." He recommended that the pregnancy category be B; however, he recommended that the applicant be required to conduct additional reproductive toxicology studies.

The supervisory pharmacologist negotiated post-marketing commitments requiring the applicant to do the following:

1. Conduct a six-month intravenous chronic toxicity study in neonatal/juvenile mice.
2. Submit the final report of Study 6354-163, a study of intravenous rhGAA on female fertility and embryonic development to implantation.
3. Conduct a Segment II teratology study in rabbits.
4. Conduct histopathologic examination of the testes of male mice in study 6354-155, a study of the effect of intravenous rhGAA on fertility and early embryonic development, and submit the full pathology report.
5. Submit the results of the third Segment I study, and, if necessary, submit a protocol for a study of the effect of Myozyme on spermatogensis and spermiogenesis in male rabbits.
6. Conduct a Segment III prenatal and postnatal study in rats or mice.

Clinical Pharmacology Issues

The reader is referred to the Clinical Pharmacology review by A. Rajpal.

A subset of patients who received Myozyme in Studies 1602 (severe infantile-onset, dose-ranging) and 1702 (infantile onset) had pharmacokinetic measurements, and these formed the basis for the pharmacokinetic information in the labeling. In study 1602, pharmacokinetic parameters were seen to be proportional between the two doses used. In both studies and at both doses in Study 1602, PK parameters were similar between the first dose and the dose after 12 weeks; however, five patients with high antibody titers (≥ 12,800) had 50% higher clearance after 12 weeks.

In Study 1602, quadriceps muscle biopsy showed greater increase in muscle GAA activity at the higher dose, but no clear trend of skeletal muscle glycogen with dose was appreciated. In muscle biopsies from both Study 1602 and Study 1702 there was no clear trend of skeletal muscle glycogen with time. Plasma and urine oligosacchardies appeared to decrease over time, but no effect of dose (20 mg/kg vs. 40 mg/kg) was observed.

The clinical study material used substance from the 160 L scale process, whereas the applicant initially proposed commercial material using a 2000 L scale process. The lots were deemed not comparable based on pharmacokinetic studies in the GAA knockout mice model. Also in that study, more GAA was seen in the liver and less in quadriceps when using the 2000 L scale product compared to the 160 L scale product. The reviewer speculated that his may be due to the — in the particular lots studied, as — . was found to be correlated with AUC and to a lesser extent inversely related to the fraction of the dose found in the liver.

Based on a limited number of subjects, no obvious differences in PK were seen based on age, gender, race, or body weight. There were no special drug-drug interaction studies. There were no studies of pharmacokinetics in patients with hepatic impairment, renal impairment, or in the elderly.

Conclusions and Recommendations

The Clinical Pharmacology reviewer drew the following conclusions:

1. Pharmacokinetic parameters were proportional when comparing the 20 mg/kg and 40 mg/doses.
2. Clearance was similar on Day 1 and at Week 12 for patients with antibody titers < 12,800, but for the five patients with antibody titers ≥ 12,800, clearance at Week 12 averaged 50% higher than on Day 1.
3. The 2000 L scale product was not pharmacokinetically comparable to the 160 L scale product, so that the 2000 L scale product would not be approvable without additional clinical efficacy and safety studies. (The applicant withdrew its request for approval of the 2000 L scale product during the review period.)

The reviewer recommended labeling changes to include information about the relationship between high antibody titer and clearance in the Clinical Pharmacology section.

No post-marketing commitments were requested.

Clinical/Statistical Issues

The reader is referred to the Clinical Review by A. Pariser, and to the Statistical Review by L. Kammerman.

Historical Study (AGLU-004)

The purpose of this study was to collect natural history data on Pompe disease to provide substantial and numerical specificity for the general notion of the poor prognosis of infantile-onset Pompe disease. The study searched North America, Europe, Israel, and Taiwan for cases of Pompe disease, living or dead, who had not been treated with exogenous enzyme therapy. Data collection included demographics, survival, disease chronology, physical exam data, laboratory data, and treatment data including ventilator use. To be enrolled, patients needed to have a clinical diagnosis of infantile Pompe disease with documented GAA deficiency of GAA gene mutation and symptom onset by age 12 months corrected for gestation.

At total of 300 cases were screened, 172 meet eligibility criteria, and 168 of these were known not to have received exogenous enzyme therapy. Most of the cases were born with in the past 20 years, although 17 of the 168 were born before 1985. The survival experience for the group was poor, with a median age at death of 8.7 months, but it was noteworthy that nearly one quarter survived to one year, and a small percentage also lived past two years.

To provide a control group for the infantile-onset study, the Historical Control Subgroup was selected using the following additional criteria of:

- Documented age at diagnosis ≤ 26 weeks.
- Documented age at first onset of symptoms ≤ 26 weeks, corrected for gestation.
- Documented cardiomyopathy by 26 weeks; if left ventricular mass index (LVMI) was measured it had to be ≥ 65 g/m^2.

Patients were excluded for any of the following:

- Endogenous GAA not markedly reduced (criteria depended on lab, see clinical review).
- Ventilator use before six months of age.
- Major congenital abnormality.
- Significant disease other than Pompe disease.

This identified an historical control group of 62 patients. One had unknown date of death, and only one survived beyond 18 months. The median survival age was 7.5 months, the mean survival age was 8.6 months, and the 18-month survival rate was 1.6% with a 95% confidence interval of (0.0% to 8.8%).

Severe Infantile-Onset Study (AGLU-1602)

This was a multinational, randomized, open-label, dose-ranging study of Myozyme IV 20 mg/kg vs. 40 mg every other week for at least 52 weeks to evaluate safety and the effect on ventilator-free survival. The Historical Control Subgroup was used as a control in lieu of a concurrent

placebo control. The study also included PK/PD assessments and a number of physiologic and developmental assessments.

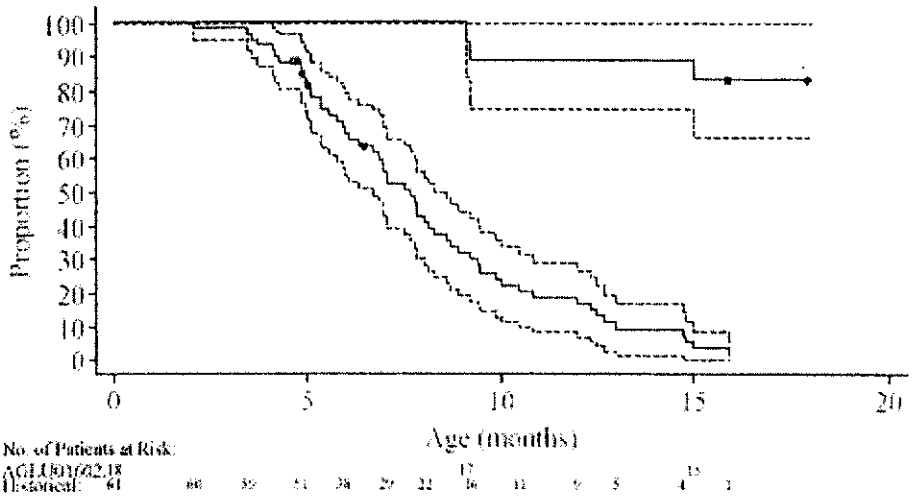
To be eligible, patients were required to have a diagnosis of infantile-onset Pompe disease, defined as GAA deficiency (less than 5% to 10% of normal, depending on assay), clinical signs of disease by age six months, and cardiac hypertrophy. Patients were excluded if they had respiratory insufficiency (defined by use of any form of ventilation and specific blood gas criteria), major congenital abnormality, significant disease other than Pompe disease, or previous exogenous enzyme therapy.

Patients were randomized with equal probability to a dose of 20 mg/kg or 40 mg/kg every other week (qow). Treatment was given biweekly intravenously over four to six hours. During an infusion the rate was increased in a stepwise matter to a maximum of 7/mg/kg/hr. There were no routine prophylactic medications. No concomitant medications were prohibited. At the conclusion of the study period, patients could continue to be treated with Myozyme in an extension study.

The primary endpoint was invasive ventilator-free survival. Ventilator dependence did not include brief periods of ventilator support in association with medical procedures or for management of a temporary acute illness. The primary analysis was based on the pooled Kaplan-Meier estimate of survival to 18 months from data collected through 52 weeks after the last patient entered the study (at which point all but the last few patients would have reached age 18 months or a study endpoint). This was to be compared with the survival estimate from the Historical Control Subgroup. To address some of the concerns about the comparability of historical control data, the analysis was designed to compare ventilator-free survival in the treated groups to survival in the historical control, and the criteria for success were stated as non-overlap of the 95% confidence intervals for the two survival estimates (which roughly corresponds with a difference of 2.8 standard deviations, vs. the customary approximately 2.0 standard deviations).

A total of 19 patients were enrolled at seven sites (3 U.S., France, UK, Israel, and Taiwan). One patient required invasive ventilation during the baseline period and was excluded. The 18 patients were randomized equally to 20 mg/kg and 40 mg/kg biweekly Myozyme infusions. The median age at first infusion was 5.1 months. By the end of the study, all but three patients had reached 18 months of age. Compliance was very high, only a few doses were missed or incomplete. Half of the patients required some sort of premeditation to manage infusion reactions. Protocol deviations were frequent, but the clinical reviewer felt they were of a nature and magnitude that made it unlikely to have a meaningful effect on the results.

At the study conclusion, all patients were alive but three required invasive ventilation, for an estimated proportion of patients alive and ventilator-free at 18 months of 83%; at the September 2005 update, at which point no patients were censored, the 95% confidence interval was (59% to 96%). This was substantially higher than the survival rate in the Historical Control Subgroup (1.6%). The applicant's survival graphic using the pooled treatment groups is shown below:



The reviewers noted a potential selection bias in this analysis, in that patients in ALGU-1602 had to survive long enough to start treatment, whereas that requirement did not apply to the Historical Control Subgroup. However, even if one computes survival to age 18 months in the historical group, conditioned on survival until six months of age, the survival would be calculated as one patient out of 37, for a rate of 2.7% with a CI of (0.1% to 14.2%). The treatment effect still appears dramatic. The statistical reviewer presented additional sensitivity analyses that the applicant performed at the statistical reviewer's request (slight discrepancies between the results here and those in the applicant's sensitivity analyses are likely due to use of an exact method vs. applicant's normal approximation method). The statistical reviewer noted additional problems with the comparison to the Historical Control Subgroup, which are discussed in her review. She felt it was appropriate to analyze the data in terms of time since randomization rather than in terms of chronologic age. An alternative analysis using that approach still showed evidence for a substantial treatment effect of Myozyme. The statistical reviewer concluded that "the quantitation of the treatment difference is almost impossible," but that the data suggested improved outcomes with patients treated with Myozyme compared to the natural history of patients who go untreated. She felt that the applicant's proposed graphic for the labeling was misleading and should not be included.

The graphic above also fails to reflect some events that occurred after 18 months. With continued treatment after the end of the initial study period, four additional patients required invasive ventilation. Two of these patients subsequently died, after 14 and 25 months of treatment.

An analysis of left ventricular mass index (LVMI) showed progressive improvement in the cardiomegaly over the 52 weeks of the study. However, there was significant variation present at 52 weeks, with a few patients in the normal range but other still having very high LVMI. Ejection fraction showed a small increase from baseline to Week 52. Change in cardiac findings did not have any obvious correlations with clinical outcome. The review team felt that the

LVMI index is most appropriately considered a pharmacodynamic measure of effect, rather than an efficacy outcome.

Data on physical growth, motor function, and development were assessed. The growth data were found to contain obvious outliers and other apparently erroneous values, and the clinical reviewer did not consider the data to be reliable. Data on motor function showed that the patients did generally exhibit progressive development of motor function, but that a majority still lagged significantly behind normal children by the end of the study. The Bailey Scale of Infant Development II (BSID II), an assessment of cognitive, language, and personal/social development, found generally increasing raw score over the course of treatment, but the distribution of age-normalize index scores was similar at the beginning and end of the study, with about half of patients in the normal range, and half showing varying degrees of delay.

Sixteen of the 18 patients developed antibody, eight in each dose group. None subsequently became antibody negative. More high titers were seen in the 40 mg/kg group. Attempts to correlated antibody titers with clinical outcome found a tendency for patients with poorer outcomes to have a higher peak antibody titers. Two patients who appeared to be making progress in motor development but later regressed were found to have loss of milestones and ventilator dependence that correlated with markedly elevated peak antibody titers.

No benefit of the higher dose (40 mg/kg vs. 20 mg/kg) was seen in the primary analysis or with the secondary endpoints. In light of the higher rates of infusion reactions (see under Safety below) and the higher antibody titers seen with the 40 mg/kg dose, the recommended dose is 20 mg/kg.

Ongoing Infantile-Onset Study (ALGU-1702)

This study is a multinational, non-randomized, uncontrolled, open-label study of the safety and efficacy of Myozyme 20 mg/kg qow for 52 weeks, to be followed by a 52-week maintenance phase. The study also includes PK and PD assessments. The initial 52-week treatment period has been completed and the maintenance phase is ongoing; only the data from the initial 52-week period were available for review.

To be eligible for the study, patients had to be between 6 and 36 months of age at time of first infusion and they had to have a diagnosis of infantile-onset Pompe disease (defined here as symptom onset by 12 months of age), GAA deficiency, and cardiac hypertrophy. Patients were excluded for clinical cardiac failure with EF < 40%, major congenital abnormality, significant other disease, or prior exposure to exogenous GAA therapy.

Myozyme was administered at a dose of 20 mg/kg every other week as an IV infusion over approximately four hours. There was no recommended routine prophylactic therapy, and no concomitant medications were prohibited.

The primary endpoint was proportion of patients alive, with non-completers treated as deaths. The experience from the historical study was offered as a comparison group. However, the

Division has been unwilling to stipulate to the adequacy of an historical control for this study, in part because of the increased heterogeneity of outcomes in patients in this age range. Secondary endpoints were ventilator status, cardiac status as measured by LVMI and clinical cardiac failure, and motor development. Measures of growth and function were also included.

Twenty-two patients were enrolled from six sites. Mean age at first symptoms was 3.9 months, mean age at diagnosis was 8.9 months, and mean age at first infusion was 15.8 months. At first infusion, 5 of 22 (24%) were on invasive ventilation, and 2 (5%) were on noninvasive ventilation. Compliance with medication was very high. Five patients required some pre-meditation at some point during the study. Protocol violations were frequent, and they did increase the heterogeneity of the study population, but otherwise the clinical reviewer felt the violations were unlikely to have significant impact in the overall assessment.

At Week 52, 17 of the 21 patients were alive, providing a survival rate of 81%, with a confidence interval of (58% to 95%). A subset of 86 patients from the Historical Study was selected as a potential reference group. An analysis of this reference group showed a wide range in time to death. It was observed that survival rates in treated patients appeared to be highly dependent on age at first infusion. Certain stratified and matched analyses were performed (see Table A2-10 of the Clinical Review), but there was substantial overlap in confidence intervals for the 52-week survival. Given these findings, and the inherent difficulties in using historical controls, it was deemed that despite the favorable trend, the findings did not provide evidence of efficacy in this study.

Of the five patients on invasive ventilation at baseline, one died and the others remained on invasive ventilation. Of 16 who were not invasively ventilated at baseline, four died and two went onto invasive ventilation. One patient on noninvasive (nasal) ventilation at baseline was able to discontinue ventilation.

Studies of LVMI showed decreases over the course of treatment, starting at around Week 8, but these reductions were not indicative of clinical improvement. Measures of motor development and mobility showed a modest favorable group trend, but were still variable. However, without an adequate control group, these data do not provide support of efficacy.

Almost all (19 of 21) patients developed antibodies, but the two who did not had only limited data. Only one patient out of the 19 had no measurable antibody at the end of the study.

Other Clinical Efficacy Data

The applicant has several active open-label, expanded access studies, mostly in patients with juvenile- and adult-onset Pompe disease (see Clinical Review for details), and some limited data are available from earlier investigations with other formulations. In this application, data on 24 additional patients were provided. None of the experience is controlled, and the data are mainly narrative reports of variable quality and completeness.

One report is worthy of note. Patient ' — had symptoms noted at six months and appeared to have the muscular variant of infantile-onset Pompe disease. By age 11 years he was wheelchair bound but not ventilator dependent. Initially he was treated with a formulation by Pharming made using transgenic rabbit milk. Over three years he had dramatic improvement in motor function to the point where he was able to walk, and subsequently he became able to run, ride a bike, and play soccer. He presently has normal strength and is being maintained on Myozyme.

Data from the remaining 23 cases are much less clear regarding benefit. No ventilator-dependent patient has been able to discontinue ventilatory support. For five patients, there are reports of reduced hours per day on the ventilator, but objective data were not provided. No case similar to that of — was reported for a juvenile- or adult-onset patient.

Late-Onset Study (LOTS), Ongoing

The applicant is conducting a randomized, placebo-controlled study in 70 juvenile- and adult-onset patients to investigate the safety and efficacy of Myozyme. The duration is one year. Endpoints will be six-minute walk test and %FVD analyzed in a sequential fashion. Enrollment is near or at completion. No results from this study were available for review.

Clinical Site Inspections

The clinical sites at the University of Florida in Gainesville, Florida, and at Duke University in Durham, North Carolina, were inspected. The inspections did not reveal any significant issues regarding the conduct of the study, and the DSI Reviewer recommended that data from these sites appeared acceptable for use in support of the BLA.

Safety

The reader is referred to the Clinical Review for full details of the safety analysis. The safety database consisted of safety information on 44 patients from GCP studies as well as information on an additional 17 patients from uncontrolled experience in non-GCP studies under the expanded access program, for a total of 61 patients. However, additional patients have been exposed to Myozyme in international experience (the exact numbers were not reported), and some additional information, such as serious adverse event (SAE) reports, have been received on those patients.

Identification of drug-related toxicity in these studies is challenging, because Pompe disease patients have significant underlying morbidity. Serious adverse events would be expected in the course of a 52-week study, and there was no systematic collection of adverse events in a placebo comparison group (the historical data were not adequate for that purpose). Dr. Pariser reviewed reports of deaths and non-fatal SAEs, and she performed additional, treatment-blinded categorization analyses of all adverse events reported in the clinical studies, pooling events in related groups to increase the sensitivity of the analysis.

A total of 14 deaths was reported in this application as of a March 8, 2005, cutoff. The deaths occurred in the principal studies described above as well as from the several small studies comprising the international expanded access program. An additional death occurring around September 2005 was also reported by the applicant. These deaths were consistent with being due to the patients' underlying disease; none was attributed to Myozyme.

An additional death was noted in an infantile-onset Pompe disease patient not treated with Myozyme, but who was in Study AGLU-1702. While undergoing general anesthesia for placement of the catheter to be used for Myozyme infusion, the patient had ventricular fibrillation and cardiac arrest. This case is of significance in light of other reports of cardiac arrhythmias noted in infantile-onset patients who received anesthesia for catheter placement or muscle biopsy (see below).

Of the 39 patients in the two principal trials, 35 had at least one SAE. These generally were a reflection of the underlying disease. A comparison of the two dose groups in study ALGU-1602 did not demonstrate any relationship between dose and SAE rates.

Four patients who participated in Study AGLU-1602 and four patients in Study AGLU-1702 had cardiac arrhythmia associated with anesthesia, in two cases the event was before the patients started receiving Myozyme. Also, as noted above, one patient died prior to receiving Myozyme during anesthesia to place the infusion catheter. These events led to a change in the investigator brochure to advise investigators of the risk of using anesthesia for study procedures in these patients. In infantile-onset Pompe disease, which involves cardiomyopathy, it appears that anesthesia may pose a risk for cardiac arrhythmia. Because these patients may require central catheter placement as a necessary prerequisite for receiving Myozyme therapy, the clinical reviewer recommended that a warning about the use of anesthesia for placement of the catheter be included in the Myozyme labeling.

One three-month-old patient developed acute cardiac failure and required intensive intervention. The clinical reviewer's assessment of the case was that the failure may have be a consequence of the volume of fluid needed for the Myozyme administration, in conjunction with the patient's cardiomyopathy. The reviewer recommended that this risk be described in a warning.

Several cases of significant hypersensitivity reactions have been received, involving both infantile- and late-onset patients. In at least a couple of cases the patients have been found to be IgE positive and the events were judged by the reviewer team to be anaphylaxis. There are four reports of patients with reactions of such severity or seriousness that they have discontinued therapy. As noted below, under Outstanding Safety Issues, some significant information regarding hypersensitivity reactions was received very late in the review cycle, and the issue has not been resolved fully. Given the current understanding of these events, the clinical reviewer recommended that the labeling include a boxed warning for this adverse event.

The predominant safety finding was of infusion reactions associated with Myozyme, some severe, a finding that would be expected based on experience with other exogenous enzyme products. Rash, flushing, urticaria, cough, tachypnea, tachycardia, vomiting, agitation, increased

blood pressure, cyanosis, hypertension, irritability, pallor, pruritus, retching, rigors and tremor were the common presentations. The less common but severe reactions included pyrexia, decreased oxygen saturation, and hypotension. Slower infusions, or temporary interruption of the infusion, sometimes with additional medications, were usually sufficient to manage the reactions. In Study ALGU-1602, the frequency of infusion reactions was about 3-fold higher in the 40 mg/kg group than in the 20 mg/kg group, reinforcing the selection of 20 mg/kg as the recommended dose. The infusion reactions were of sufficient significance that a warning is appropriate.

The size of the clinical study patient population is severely limited by the rarity of the disease. This limitation underscores the importance of asking the applicant to conduct a post-marketing registry study for systematic collection of additional safety data.

Outstanding Safety Issues

Subsequent to the applicant's response, on December 30, 2005, to the Division's latest formal information request, significant new safety information has been received regarding Myozyme. In April 2006 the Division received a report of a patent in her 30's who had an anaphylactic reaction of such severity that the independent Allergy Review Board recommended that the patient stop being treated with Myozyme. Also, the Division received a report of an infantile-onset patient who appears to have "coded" during an infusion. In response to inquiries from the clinical reviewer, the Division received updated/corrected information about the extent of antibody testing that the applicant had available, and after requesting additional information about patients who had positive test for IgE antibodies, cases were uncovered that appear to be anaphylaxis.

From discussions between the Division and the applicant about these and related cases, the review team has come to have concerns that the applicant applied an overly narrow interpretation as to what safety information should be presented to the FDA. The review team also has serious concerns that significant safety information that should have been clearly identified, analyzed, and discussed in the Integrated Summary of Safety was effectively obscured by the way it was presented in the application: The Division learned from a third party about a case in which a patient chose to stop treatment following an infusion reaction that led to an ICU stay; the case apparently was only represent in the application as withdrawal of patient consent rather than discontinuation due to an adverse event. Another discontinuation due to an adverse event was only briefly identified as such at the end of a long case report.

It is the opinion of the review team that in order to evaluate the safety of this product adequately it will be necessary to obtain additional information from the applicant, and additional time will be needed to assess the significance of the new information. Until that work is completed, it would be prudent to remain very cautious about what can be said about the safety of this product, and to present the product safety information in the labeling from a conservative viewpoint.

Clinical Consults

Consulting reviews were requested from the Division of Neurology Products and from the Division of Pediatric Drug Development.

Neurology

The Neurology Reviewer (M. Walton) reviewed Study 1602 in conjunction with the historical control data, and concluded that the submission provided a solid basis for acceptance of the historical control in that the substantially longer avoidance of mortality was unlikely to be attributable to concerns about non-comparability for the historical control.

The consultant also concluded that there was evidence that the functional capability of the treated Pompe infants showed some advancement over the course of the study, but the infants remained severely impaired. The consultant felt that the observations could not be interpreted as evidence that the treatment permitted infants to begin development along normal lines, rather, only that advancement occurred during the period of treatment and into the period when death would have been expected to have already occurred. The consultant recommended that continued follow-up of these patients would be valuable.

Pediatrics

The Pediatric Reviewer (H. Sachs) considered the application from the perspective of extrapolatability, adequacy of the assessment tools, and proposals for postmarket studies.

The consultant concluded that the course of disease in infantile-onset patients differed from that of the other Pompe variants in that the infantile form involved more rapidly progressive disease and had cardiac symptomatology. The consultant also noted that the effect of neutralizing antibody in patients dependent on endogenous enzyme was unknown. The consultant recommended that data in the ongoing Late-Onset Study were needed to establish efficacy and safety in the late-onset patient population.

The consultant generally felt that the motor scales used in the studies were appropriate, but that not all would be as useful in older patients. The consultant also felt that the cognitive scales were generally appropriate.

For the postmarketing studies, the consultant recommended assessments of fine and gross motor function, language, growth, neuro-imaging, hearing screening, vision screening, and antibody status. The specific tools recommended can be found in the Pediatric Consult Review.

Clinical Conclusions and Recommendations

The clinical reviewer concluded that the application provided adequate evidence of efficacy for Myozyme in infantile-onset Pompe disease, but that there was not substantial evidence that Myozyme had efficacy in juvenile- or adult-onset Pompe disease. The statistical reviewer concluded that the data suggested improved survival and invasive-ventilator-free survival among subjects treated with Myozyme compared with the untreated historical subgroup.

The clinical reviewer concluded that the safety of Myozyme was an acceptable risk for treating infantile-onset Pompe disease patients, but the risk of serious hypersensitivity reactions was significant, and that there should be a boxed warning for that risk.

The clinical reviewer recommended that the labeling include a warning for cardiac arrhythmia during anesthesia for catheter placement; a warning for cardiorespiratory failure, possibly as a consequence of volume overload, in patients with cardiac hypertrophy; and a warning for infusion reactions . The statistical reviewer recommended that the proposed be removed from the labeling because the selection bias with the historical control group (not accounting for the need to survive until infusions could begin) gave a misleading impression of the relative benefit.

The clinical reviewer negotiated post-marketing commitments to require the applicant to do the following:

1. Complete the juvenile-onset Pompe disease study AGLU-02704, an ongoing randomized double-blind study of safety efficacy and PK in patients with late-onset Pompe disease.
2. Conduct an extension to the study AGLU-02704 (extension protocol number ALGU-03206), as an open-label extension study through 24 months of total time on study.
3. Complete study ALGU-1702, an ongoing open-label study of infantile-onset Pompe disease patients aged 6 to 36 months at entry.
4. Design and implement a registry of Pompe patients being treated with Myozyme, to run for 15 years. It should collect information on auditory and visual assessment for patients less that one year at entry. It should include a substudy on pregnancy and lactation and substudy on patients on ventilator support at time of entry into the registry.
5. Conduct an infantile-onset disease study to assess growth and development during treatment with Myozyme in patients less that one year at entry. It should include assessment of growth and development, auditory and visual screening, neuro-imaging, and antibody assessments over 10 years.
6. Design an implement an immune tolerance protocol in Pompe patients who have significant antibody titers of neutralizing antibody and who are failing treatment.
7. Design and implement a dose and dose-interval exploration study in patients with a poor response to treatment.

Advisory Committee

This application was not presented to an Advisory Committee. The application was discussed at a CDER Regulatory Briefing on March 3, 2006.

Office of Drug Safety

Review of the trade name "Myozyme" by DMETS identified some similarity to the approved product Naglazyme (an exogenous enzyme for treating MPS VI) when scripted. However, DMETS concluded that the potential for confusion was minimal and that the name was acceptable. DMETS also recommended that the applicant develop patient information for this product, similar to what was done for Aldurazyme (laronidase).

DMETS reviewed the labels and labeling and made several recommendations to improve clarity and reduce the risk of error.

DDRE reviewed the applicant's plans to conduct a voluntary post-market registry, and concluded that the pharmacovigilance plan was adequate. In a pre-approval safety conference, the Division apprised DDRE that its post-market monitoring concerns were that the Agency should give particular attention to hypersensitivity reactions, and well as monitoring the other adverse events relating to the warnings that had been added in the labeling.

Pediatrics

This product has received an orphan designation for the proposed use, and is therefore exempt from the requirements of the PREA. The approval recommendation is for a pediatric population. However, good information about the older pediatric population is lacking. One of the postmarketing commitments is to complete the controlled study in late-onset Pompe disease, which includes older pediatric patients. In addition, Genzyme has committed to perform a study looking at growth and development in pediatric patients being treated with Myozyme. (See also the comments from the Pediatric Consult Review under the Clinical Consults subsection of Clinical/Statistical Issues above.)

Discussion

The application provides adequate evidence of efficacy for improved survival in infantile-onset Pompe disease. However, the efficacy in later-onset variants of Pompe disease has not been shown, and there is an inadequate basis for extrapolating from the infantile onset population to the other populations, because of differences in the nature of disease and because it is unclear what benefit would be extrapolated. Extrapolation of improved survival to late-onset disease seems speculative, and the benefit one might wish to confer on late-onset patients, improved motor function, was not what was directly demonstrated in the infantile-onset population.

Significant new information about the safety of this product has come to light since the receipt of the response to the information request made in December 2005. The need to have a thorough assessment of product safety could be used to make the case for acting on the present application with a complete response letter citing the inability to determine the acceptability of the risk of the product because of incomplete information about the extent and nature of serious infusion reactions.

However, patients with infantile-onset have a rapidly fatal disease with no currently approved therapeutic options, and Myozyme has demonstrated the ability to prolong life in severely affected infantile-onset Pompe patients. Even if thorough review of the safety information regarding hypersensitivity reactions finds it to be as adverse as it could reasonable be expected to be, given what is currently known, it still appears that Myozyme could still be considered an acceptable risk for infantile-onset Pompe patients, provided patients and physicians were informed as fully as possible about the potential serious risks. Thus, it would be reasonable to

approve Myozyme for patents with infantile-onset Pompe disease. Given the current questions about safety, including a boxed warning regarding the potential for anaphylaxis or anaphylactoid reactions would be prudent until such time that the questions about safety are answered adequately and the Division is able to determine that such a warning would not be necessary. Given the lack of evidence of efficacy in the later-onset forms of disease, and the unanswered questions about the safety and risk of significant adverse events, there is presently inadequate justification for indicating Myozyme for the juvenile- and adult-onset Pompe disease populations.

Regulatory Conclusions

In the opinion of this reviewer, the data in this application support approval of Myozyme under 21 CFR 601 for treatment of infantile-onset Pompe disease at a dosage of 20 mg/kg intravenously every other week, and the data provide a basis for construction of product labeling that contains the essential scientific information needed for the safe and effective use of Myozyme in that population. The efficacy for juvenile- and adult-onsets forms of disease has not been demonstrated, and is not readily extrapolated from the infantile-onset group. Unanswered questions surrounding serious safety issues add further reason to be reluctant to extend the indication beyond the infantile-onset form. Therefore the indication should be for treatment of infantile-onset Pompe disease, and the labeling should identify that the benefit obtained was improved survival. The pediatric section should indicate the lack of information about safety and efficacy for the juvenile-onset form of Pompe disease.

The labeling should contain a warning about the risk in the infantile-onset Pompe population of using general anesthesia to place the central venous catheter for product infusion, a warning about the risk of acute cardiorespiratory failure that may be related to volume overload during infusion in patients with cardiomyopathy, and a warning about the risks and management of infusion reactions. There also should be a warning about the risk of anaphylaxis and serious anaphylactoid reactions. Until the Agency obtains sufficient information to provide assurance that it is adequate to do otherwise, this warning should be presented as a boxed warning.

Genzyme has agreed to appropriate and adequate post-marketing commitments as outlined in the discipline-specific sections above.

CLINICAL REVIEW

Application Type	BLA
Submission Number	125141
Submission Code	0
Letter Date	07/29/2005
Stamp Date	07/30/2005
PDUFA Goal Date	04/28/2006
Reviewer Name	Anne R. Pariser, M.D.
Through	John Hyde, M.D., Ph. D., Clinical Team Leader
Review Completion Date	04/27/2006
Established Name	recombinant alglucosidase alfa
(Proposed) Trade Name	Myozyme®
Therapeutic Class	Enzyme Replacement Therapy
Applicant	Genzyme Corp
Priority Designation	P
Formulation	for 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	Pompe disease

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Recommend approving this application with revision to the proposed label.

It is recommended that Myozyme's treatment indication be restricted to patients with infantile-onset Pompe disease. A ventilator-free survival benefit with Myozyme treatment was demonstrated in a clinical study (AGLU01602) that was limited to the youngest, most severely affected Pompe disease patient population. In AGLU01602, a ventilator-free survival benefit at age 18 months was seen in infantile-onset Pompe disease patients who received their first dose of Myozyme prior to the age of seven months, who had cardiac hypertrophy, and who did not require ventilatory support at study entry, as compared to an untreated, historical-control cohort that was similar in age and disease severity.

No therapeutic benefit of Myozyme has been demonstrated in any other Pompe disease patient population, and no adequate and well-controlled studies with Myozyme in the treatment of patients with juvenile- and adult-onset Pompe disease have been completed.

Safety results from clinical trials with Myozyme have shown a concerning safety signal for the risk of hypersensitivity reactions, some of which have been life-threatening and have lead to the discontinuation of patients from clinical trials. In infantile-onset Pompe disease, this risk appears to be acceptable given the risk of the underlying disease and the nearly universal progression to death by 18 months of age in untreated patients, and with a clear ventilator-free survival benefit having been demonstrated with Myozyme treatment. The risk/benefit profile of Myozyme in the juvenile- and adult-onset Pompe disease patient population has not been defined. Thus, given the known risks of treatment with Myozyme, and the lack of any evidence of a treatment benefit available at this time, the treatment of patients with juvenile- and adult-onset Pompe disease with Myozyme outside of a clinical trial or other monitored clinical program cannot be recommended.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

None warranted at the present time.

1.2.2 Required Phase 4 Commitments

The recommended indication for Myozyme is limited by the narrow scope of the clinical data submitted in support of this application, and a number of clinical areas need to be addressed by post-marketing commitments. It is recommended that Myozyme undergo further clinical evaluation and study in:

- The juvenile- and adult-onset Pompe disease patient population.
- A broader infantile-onset Pompe disease population than was defined by AGLU01602, to include final data from clinical study AGLU01702 (up to 104 weeks of Myozyme treatment). Study AGLU01702 included infantile-onset Pompe disease patients ages 3 months to 3.5 years at time of first dose of Myozyme, who may have been on ventilatory support at study entry.
- The growth and development of infantile-onset Pompe disease patients over time.
- Pompe disease patients of any age failing treatment. This is to include poor responders with and without high anti-rhGAA IgG antibody titers.
- The long-term evaluation of Myozyme treatment in a Pompe disease registry.
- Evaluation of sub-populations of Pompe disease patients, including pregnant or lactating females exposed to Myozyme, and ventilator-dependent patients of any age, as clinical status in these patients will need to be followed over many years. These patients may be followed in sub-studies as part of the registry.

Therefore, the following clinical post-marketing actions are recommended:

1. Completion of the juvenile- and adult-onset onset Pompe disease study AGLU02704, entitled "A randomized, double-blind, multicenter, multinational, placebo-controlled study of the safety, efficacy and pharmacokinetics of Myozyme, recombinant human acid alpha-glucosidase (rhGAA), treatment in patients with late-onset Pompe disease" (LOTS). Enrollment in this study has been completed, the study is ongoing, and the study is expected to be completed in March 2007.

2. Conduct and completion of study AGLU03206, the 52-week extension study to LOTS (AGLU02704) in juvenile- and adult-onset Pompe disease patients, entitled "An open-label extension study of patients with late-onset Pompe disease who were previously enrolled in protocol AGLU02704" (this is a draft title supplied by the sponsor). Patient accrual is expected to be completed by March 31, 2007, and the study completed by March 31, 2008.

3. Completion of study AGLU01702, entitled "An open-label, multicenter, multinational study of the safety, efficacy, pharmacokinetics, and pharmacodynamics of recombinant human acid alpha-glucosidase (rhGAA) treatment in patients >6 months and ≤36 months old with infantile-onset Pompe disease (Glycogen Storage Disease Type II)." This study is ongoing, and is expected to be completed by June 12, 2006.

4. Design and implementation of a long-term registry that will be established to obtain long-term clinical status information in patients of all ages with Pompe disease who are being treated with alglucosidase alfa. Information will be collected on patient demographics, specifics of treatment with alglucosidase alfa, clinical status, ventilatory status, motor assessments, adverse events, assessment of immunogenicity, and potential effects of antibody formation. In patients who are less than one year of age at the start of treatment, information is to be collected on cognitive status, and auditory and visual screening

assessments. This registry will be designed so that detailed clinical status information is collected at registry entry and on a 6- to 12-month basis for at least 15 years. Two sub-studies within the registry are to be performed: one sub-study that will evaluate the effect of alglucosidase alfa on pregnancy and lactation, and one sub-study that will collect information on the clinical status of patients on ventilatory support at the time of entry into the registry. The registry data will be analyzed at yearly intervals and submitted in annual reports to the Myozyme IND (#10780). The registry is expected to be initiated by January 31, 2007, and run through January 31, 2022.

5. Design and implementation of an infantile-onset Pompe disease study to assess growth and development with treatment with alglucosidase alfa, in patients who are less than one year of age at study entry. This study is to include blinded assessments of growth (including recumbent length, height, weight, and head circumference), cognitive (language and cognition) and motor (fine and gross motor) development (scales to be used are to be prospectively agreed upon), auditory and visual screening, neuro-imaging, and antibody assessments at 6- to 12-month intervals over a 10-year period. This study is expected to be implemented by January 31, 2007.

6. Design and implementation of 1) an immune tolerance protocol in Pompe disease patients who have significant antibody titers, or the presence of neutralizing antibody, and are failing treatment; and 2) the design and implementation of a preventive immune tolerance protocol in Pompe disease patients at high risk of development of significant immune responses to Myozyme.

7. Design and implementation of a dose- and dose-interval exploration study in patients with poor responses to treatment, regardless of antibody status. This study is to include patients in the infantile-, juvenile-, and adult-onset patient populations.

1.2.3 Other Phase 4 Requests

None recommended at the present time.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Recombinant human acid α-glucosidase (alglucosidase alfa, rhGAA) is the investigational agent studied in this application, and the sponsor intends to market rhGAA under the trade name Myozyme®. Endogenous acid α-glucosidase (GAA) is a lysosomal hydrolase 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. Deficient activity of acid α-glucosidase results in intralysosomal accumulation of glycogen. Myozyme is a new molecular entity (NME) being proposed as an enzyme replacement therapy (ERT) for the treatment of Pompe disease (Glycogen Storage Disease II, GSD II, acid maltase deficiency, glycogenosis type II), an inherited disorder of glycogen metabolism resulting from absent or deficient activity of acid α-

glucosidase. Myozyme is produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells.

Absent or deficient activity of endogenous acid α-glucosidase in Pompe disease results in intralysosomal accumulation of glycogen in numerous tissues, particularly muscle, which results in progressive muscle weakness and impairment of respiratory function. The rapidity of progression of the disease appears to depend, at least in part, on the magnitude of the deficiency of the enzyme and the age at onset of clinical symptoms, and Pompe disease is classified by the age at onset of clinical signs and symptoms of the disease. Infantile-onset Pompe disease is most commonly defined as age of onset by six months of age or younger (but has been defined to include patients with age of onset up to 12 months), childhood- or juvenile-onset is most commonly defined as age of onset after age six to 12 months and by the age of 16 years, and adult-onset is defined as symptom onset after 16 years of age. The infantile-onset population is further sub-divided into the classic infantile-onset form, including patients with signs and symptoms of Pompe disease at six months of age or younger AND cardiac hypertrophy, and the muscular-variant infantile-onset form, including patients with signs and symptoms of Pompe disease at six months of age or younger, but without the cardiac involvement.

This biologics licensing application (BLA) includes clinical efficacy or outcomes measures from ten clinical studies and expanded access programs (EAPs), in which all patients received treatment with open-label Myozyme. There were no placebo or concurrent controls in any of these studies or programs. Five clinical studies and EAPs were conducted in infantile-onset Pompe disease patients, and five studies and EAPs were conducted in juvenile- and adult-onset Pompe disease patients. Safety information was submitted from the same ten clinical studies and EAPs as for efficacy, with additional, limited information obtained from an ongoing, double-blind, placebo-controlled, safety and efficacy study in juvenile- and adult-onset Pompe disease (Study AGLU02704).

The entire Myozyme clinical program was conducted in Pompe disease patients, and given the rarity of this disease, the entire Myozyme-exposed population in this submission was small. Comprehensive efficacy and safety results that permitted substantive review were available in about 44 patients, 39 of whom were infantile-onset patients. There was additional safety and outcomes information available for review in about 40 additional patients; however, this information was mainly from EAPs, and was of limited utility in defining either the effects of Myozyme treatment or the safety of Myozyme administration.

A retrospective, international, observation, natural history study was also conducted in infantile-onset Pompe disease patients, whereby a retrospective chart review of 168 untreated infantile-onset patients were identified, and demographic and survival data on these patient were summarized. This observational study was conducted to better characterize the natural course of infantile-onset Pompe disease. No patient in this natural history study received treatment with rhGAA. This historical study population formed the basis of the historical control reference populations that were used for comparison in studies AGLU01602 and AGLU01702 in lieu of a placebo or concurrent control.

Infantile-Onset Pompe Disease

Five clinical studies and EAPs were performed in the infantile-onset patient population, and information was available for review in the application for 52 infantile-onset patients. These studies are:

1. Study AGLU01602, n=18
2. Study AGLU01702, n=21
3. Study AGLU02203, n=5
4. Study AGLU02003, n=7
5. Study AGLU1205-02, n=1

Study AGLU01602 was the pivotal clinical study submitted in support of the Myozyme BLA. Study AGLU01602 was a multicenter, international, open-label, safety and efficacy study performed in 18 patients with classic infantile-onset Pompe disease. In this study, patients were treated with Myozyme 20 mg/kg or 40 mg/kg every other week (qow) for from 52 to 106 weeks. Enrollment was restricted to patients diagnosed with Pompe disease by six months of age, who were age 7 months or younger at the time of first infusion, who had cardiac hypertrophy, and who did not require ventilatory support at study entry. The primary efficacy endpoint was the proportion of patients who were alive and free of invasive ventilator support at 18 months of age, as compared to an historical control that was similar to the study patients in age and severity of disease. Other major efficacy outcome measures included changes from baseline after 52 weeks of treatment in measures of cardiac status (left ventricular mass index [LVMI], ejection fraction [EF]), physical growth (length, weight, and head circumference), and achievement of motor and mental developmental milestones assessed by the Alberta Infant Motor Scale (AIMS), the Bayley Scales of Infant Development II (BSID-II), and the Pompe Pediatric Evaluation of Disability Inventory (Pompe PEDI). As infantile-onset Pompe disease is a uniformly fatal disease for which there are no established treatments, no placebo treatment was administered, and all patients received active treatment with Myozyme.

Study AGLU01702 was the largest study submitted in support of the Myozyme BLA (n=21), and included comprehensive safety and efficacy outcomes measures that permitted substantive clinical review. Study AGLU01702 is an ongoing, multicenter, international, open-label, safety and efficacy study performed in 21 patients with Pompe disease. Patients were treated with Myozyme 20 mg/kg qow for up to 104 weeks; however interim data only (to 52 weeks of treatment for most patients) were submitted to the application. Enrolled patients were ages three months to 3.5 years at time of first infusion, had onset of signs and symptoms of Pompe disease by 12 months of age, had cardiac hypertrophy, and five of 21 patients were receiving invasive ventilatory support at the time of first infusion. The primary outcomes measure was the proportion of patients alive over the course of treatment, which was compared to an historical control reference group that was similar in age and severity of disease. This study did not have a placebo- or concurrent-control group.

The remaining three infantile-onset studies and programs were of lesser importance to the review, as they contained limited safety and outcomes assessments. These studies were:

- Study AGLU02203: AGLU02203 is an ongoing, open-label, expanded access safety and efficacy study of Myozyme 20 mg/kg qow in five infantile-onset Pompe disease patients at an advanced stage of disease progression (mean age of 10.3 years at study entry, range 7-16 years). The objective of the study was to provide ERT with Myozyme to these patients.
- Study AGLU02003: AGLU02003 is an open-label, international, long-term, safety and efficacy, extension study of Myozyme (10 mg/kg per week, or 20, 30, or 40 mg/kg qow) in seven infantile-onset patients (mean age 22 months at first rhGAA treatment, range 2 to 73 months, and 41 months, range 24 to 76 months at first Myzoyme treatment) who were previously enrolled in clinical trials of ERT with other formulations of rhGAA (Pharming and Synpac). The objective of the study was to monitor the long-term safety and outcomes of rhGAA treatment in these patients.
- Study AGLU1205-02, Amendments 4 & 5: AGLU1205-02 is an ongoing, open-label, extension study of Myozyme 20 to 40 mg/kg qow administration to a single infantile-onset Pompe disease patient, who had previously received rhGAA (Synpac and Pharming formulations) for three years under IND: [redacted] This patient was age 3 months at first rhGAA infusion and 41 months at first Myozyme infusion.

Juvenile- and Adult-Onset Pompe Disease
Information on safety and outcomes measures for 24 juvenile- and adult-onset Pompe disease patients was available for review in the application. Information on only four of these patients (from EAPs) had been submitted in the original BLA application, with additional information, predominantly in the form of narratives, submitted late in the review cycle (Amendments 002 and 007, submitted in November and December 2005, respectively). This information was of limited utility in defining either the effects of Myozyme treatment or the safety of Myozyme administration in the juvenile- and adult-onset Pompe disease populations, and included:

- Study AGLU02804: AGLU02804 was an open-label, nonrandomized, uncontrolled, single-center, 26-week, safety and efficacy study of five juvenile-onset Pompe disease patients ages 6 to 15 years at study entry (median age 12.7 years), with onset of first symptoms at ages 1 to 12 years. All patients were able to ambulate at least 10 meters (m) at baseline, and patients on invasive ventilation at baseline were excluded. All patients received Myozyme 20 mg/kg qow for 26 weeks. The primary efficacy measures were changes from baseline at Week 26 in distance walked in six minutes (six-minute walk test, 6MWT), and pulmonary function test (PFT) parameters.
- Expanded Access Programs: Narratives for 19 juvenile- and adult-onset Pompe disease patients participating in EAPs were submitted. The patient population was extremely diverse, and the length of treatment, safety and efficacy assessments, and scope of information provided in the narratives were highly variable and subjective.

1.3.2 Efficacy

The recommendation for approval of Myozyme as a treatment for Pompe disease is based entirely on the results of the pivotal Study AGLU01602 conducted in 18 classic infantile-onset patients, who received their first infusion of Myozyme by age seven months and were not

receiving ventilatory support at study entry. The results from Study AGLU01602 show a clear and compelling ventilator-free survival benefit at 18 months of age in Myozyme-treated patients as compared to an untreated historical control of similar age and disease severity. No substantial evidence of a benefit of treatment with Myozyme has been demonstrated in any other Pompe disease patient population. No adequate and well-controlled studies with Myozyme in the treatment of juvenile- and adult-onset Pompe disease patients have been completed, and no efficacy data permitting substantive review have been submitted to this application to date in support of a treatment indication for Myozyme in the juvenile- and adult-onset Pompe disease population.

Efficacy results from the Myozyme clinical program are summarized as follows:

1. The efficacy results from Study 1602 show:
    a. A clear ventilator-free survival advantage in Myozyme-treated patients at 18 months of age as compared to an untreated historical control of similar age and disease severity.
    b. Evaluation of cardiac parameters, including LVMI, left ventricular mass (LVM) Z-scores and EF were notable for decreases in LVMI and LVM Z-scores in all patients through Week 52, consistent with the pharmacodynamic (PD) effect of rhGAA on cardiac muscle; however, no clear clinical effect on overall cardiac function could be discerned, and the clinical relevance of the PD effect of rhGAA on cardiac function is unknown.
    c. Physical growth measurements of body weight and length, and head circumference were notable for numerous missing and inconsistent datapoints, making interpretation of the data unreliable; however, despite these limitations, weight, length, and head circumference appeared to increase in all patients throughout the study.
    d. Motor development results were notable in that the majority of patients treated with Myozyme experienced clinically meaningful gains in motor developmental milestones; however, the majority of patients remained significantly delayed compared to normal age-matched peers. A worrisome signal was noted in two patients who initially showed the achievement of new motor milestones that were almost completely lost during continued treatment. Motor milestone losses coincided with the development of markedly elevated antibody titers, suggesting interference from antibody with clinical response.
    e. Cognitive developmental results from the BSID-II test were encouraging, with most patients demonstrating increases in BSID-II scores from baseline at Week 52.
    f. Immunogenicity data showed 89% of patients developed anti-rhGAA antibody at anytime during the study, usually by Week 12, and antibody titers tended to be high (arbitrarily designated as >6,400, maximum 409,600). More patients in the 40 mg/kg dose group developed high titers than in the 20 mg/kg group, and many patients continued to show sustained or increasing antibody titers throughout the study. A concerning signal was seen in patients with high-risk mutations (frameshift or deletion mutations and absent or near-absent endogenous protein) and high anti-rhGAA IgG antibody titers. These patients were more likely to

have poor clinical outcomes than patients with lower risk mutations and lower antibody titers.

2. The efficay results for Study 1702 show:
    a. The proportion of Myozyme-treated patients alive at Week 52 overlapped with the survival ranges in the historical control reference populations of similar age and disease severity. Due to the highly heterogeneous rate of progression to death in this Pompe disease patient population, and as there was no concurrent control group for the study, it is not possible to state whether survival was prolonged in patients treated with Myozyme.
    b. Evaluation of respiratory status at baseline and Week 52 showed seven patients had a worsening status, including five patients who died, and two patients who became invasive-ventilator dependent. In no case did a patient on invasive ventilatory support at baseline discontinue this support over the duration of the study. The findings for the respiratory status endpoint appeared to be at least partially dependent on the patients' ages at diagnosis and first infusion, and it was extremely difficult to determine whether there was a treatment effect of Myozyme in this population, or if the findings were consistent with the natural progression of the underlying disease.
    c. Evaluation of cardiac parameters (LVMI, LVM Z-score, and EF) showed that most patients had decreases from baseline in LVMI at Week 52 consistent with the pharmacodynamic effect of rhGAA treatment; however, there was no clear benefit on cardiac or clinical outcome seen.
    d. Motor development assessments showed that about half of the patients had modest gains in gross motor function (i.e., predominantly proximal, lower extremity muscle strength and function), but these patients were delayed compared to non-disabled, same-age peers. The other half of patients had little to no meaningful gains (or regression) in gross motor function. Fine motor function (i.e. predominantly distal, upper extremity muscle function) was much more preserved, however, with most patients demonstrating gains in fine motor function. These motor development results are generally consistent with the natural progression of the underlying disease, and it is not known if the motor results, particulatory for fine motor assessments, are the results of treatment with Myozyme.
    e. Cognitive development results were encouraging as most patients scored within a normal to mildly delayed range; however longer-term follow-up is needed.
    f. Immunogenicity data showed that 90% of patients developed anti-rhGAA antibodies at anytime during the study, and that antibody titers tended to be high (>6400) and to remain elevated throughout the study. High antibody titers also tended to be associated with high-risk mutations (e.g., frameshift or nonsense mutations in at least one allele), and patients with the highest titers tended to have poorer outcomes.

Outcomes measures in the remaining clinical studies and expanded access programs were of limited utility in determining the effect of Myozyme in Pompe disease. These results tended to

be highly subjective with few objectively or consistently collected outcomes measures available for review. It is especially noted that there was a lack of objective data submitted in the juvenile- and adult-onset patient population, and as there have been no adequate and well-controlled studies completed to date in this population. Thus, no assessment of the effect of Myozyme treatment on juvenile- and adult-onset Pompe disease patients is possible.

In summary, the treatment of infantile-onset Pompe disease patients with Myozyme at or prior to the age of seven months results in an invasive ventilator-free survival benefit at 18 months of age as compared to an untreated historical control of similar age and disease severity. Clinically meaningful gains in motor function were also demonstrated in these patients, although the majority of these patients were substantially delayed compared to same-age, non-disabled peers. It is not known if these results are sustained, especially in patients developing elevated anti-rhGAA antibody titers. No substantial evidence of a treatment effect of Myozyme in the Study AGLU01702 patient population could be determined. Discerning anything less than a dramatic treatment effect in this Pompe disease population would have been difficult due to the highly heterogeneous presentation and progression of the disease in this Pompe disease age group, and the study results, not surprisingly, overlapped with the outcomes in an historical control reference population similar in age and disease severity. No assessment of the effect of Myozyme treatment on juvenile- and adult-onset Pompe disease patients is possible, as no data from adequate and well-controlled studies in this population have been submitted to the application to date.

1.3.3 Safety

The safety results from the Myozyme clinical development program are notable for the following safety signals and concerns that are to appear prominently in the product labeling:

1. A safety signal for severe hypersensitivity reactions during Myozyme infusion was noted late in the review cycle. Some of these hypersensitivity reactions have been life-threatening, including anaphylactic shock (cyanosis, hypoxia, hypotension, and bronchoconstriction, requiring unspecified life support measures), anaphylactic and anaphylactoid reactions (IgE and non-IgE mediated), angioedema, and numerous cases of infusion reactions associated with two of the three organ systems of cardiac, respiratory and skin (consistent with anaphylaxis/hypersensitivity). Recognition of this signal lead to a request to the Sponsor to query their pharmacovigilence database for similar cases, and the frequency, incidence, and magnitude of this problem is still being defined. However, hypersensitivity reactions have occurred in infantile- through adult-onset patients, have lead to the discontinuation of at least three adult patients from Study AGLU02704 (LOTS protocol in juvenile- and adult-onset Pompe disease) and AGLU02603 (US expanded access protocol), and appear to have occurred in about 15% of patients treated in clinical trials with Myozyme to date. This safety signal is noteworthy, and it is recommended that a boxed warning appear in the product labeling.
2. One case of acute cardiorespiratory failure requiring intubation and inotropic support has been observed in an infantile-onset Pompe disease patient with underlying cardiac hypertrophy, possibly associated with fluid overload.

3. Multiple instances of cardiac arrhythmia and sudden cardiac death during general anesthesia for central venous catheter placement (needed for Myozyme infusion) have occurred in infantile-onset patients, who are at risk for arrhythmia due to underlying cardiac hypertrophy. These arrhythmias included ventricular tachycardia, ventricular fibrillation, bradycardia, and cardiac arrest, and required intervention such as cardiac defibrillation.

Safety results are otherwise summarized as follows:

1. Deaths reported in clinical studies and expanded access programs were predominantly due to underlying disease, and included respiratory and cardiac failure, cardiac arrest, and infectious causes.
2. Adverse Events (AEs) were frequently reported in clinical studies, and tended to reflect underlying disease or were AEs commonly seen with enzyme/protein infusions (e.g., allergic and hypersensitivity reactions, and AEs such as pyrexia). Serious Adverse Events (SAEs) also tended to be consistent with underlying disease (e.g., respiratory and infectious SAEs), or treatment intervention complications (e.g., catheter-related complications). The most commonly reported SAEs in clinical studies (pooled results of AGLU01602 and AGLU01702, n=39) were pneumonia, respiratory failure, respiratory syncytial virus infection, and catheter-related infection.
3. Infusion reactions were common. Pooled results from AGLU01602 and AGLU01702 showed that 51% of patients treated with Myozyme experienced infusion reactions, some of which were severe, such as oxygen desaturation, pyrexia, urticaria, hypotension, and wheezing/bronchospasm, among others.
4. Hearing loss at Screening/Baseline and during treatment was reported in many patients in the rhGAA clinical development program, including infantile-, juvenile- and adult-onset patients in clinical trials and in expanded access programs. Hearing loss was described as hypoacousis, sensorineural, mixed, and conductive in these patients, and it was additionally noted that middle ear effusions were present in many patients, which complicated the interpretions of the results. Hearing loss has been described in the medical literature as associated with Pompe disease, possibly secondary to glycogen deposition in the cochlea. Hearing loss has also been reported in other lysosomal storage diseases. It appears likely that the hearing loss reported in this study is secondary to underlying disease and not to treatment with rhGAA, although it is not possible at this time to determine whether rhGAA treatment modifies the progression or development of hearing loss in this patient population. It is recommended, therefore, that longer-term follow-up of hearing be performed in patients receiving rhGAA.

In summary, safety results from clinical trials with Myozyme have shown a concerning safety signal for the risk of hypersensitivity reactions in all age groups, some of which have been life-threatening and have lead to the discontinuation of patients from clinical trials, and for cardiac complications (cardiac failure and arrthymia) in infantile-onset patients. In infantile-onset Pompe disease, this risk appears to be acceptable given the risk of the underlying disease and the nearly universal progression to death by 18 months of age in untreated patients, and with a clear ventilator-free survival benefit having been demonstrated with Myozyme treatment. The

risk/benefit profile of Myozyme in the juvenile- and adult-onset Pompe disease patient population has not been defined. Thus, given the known risks of treatment with Myozyme, and the lack of any evidence of a treatment benefit available at this time, the treatment of patients with juvenile- and adult-onset Pompe disease with Myozyme outside of a clinical trial or other monitored clinical program cannot be recommended.

1.3.4 Dosing Regimen and Administration

Doses of Myozyme ranged from 10 mg/kg every other week to 40 mg/kg every week by intravenous infusion. Most patients in the Myozyme clinical development program received treatment with Myozyme in a dose of 20 mg/kg every other week. The next most frequently administered dose was 40 mg/kg every other week. Information available on patients receiving doses of Myozyme less than 20 mg/kg and greater than 40 mg/kg every other week was extremely limited, and was not of sufficient detail to provide any assessment of safety or efficacy. Based on the safety and efficacy results from Study AGLU01602, efficacy was found to be similar between the 20 mg/kg and 40 mg/kg every other week doses, and the safety concerns, particulary for immunogenicity and infusion reactions, were less in the 20 mg/kg dose group as compared to the 40 mg/kg dose group. Thus, the recommended dose of Myozyme is 20 mg/kg every other week.

1.3.5 Drug-Drug Interactions

No drug-drug interactions were explored in the Myozyme clinical development program.

1.3.6 Special Populations

Pompe disease is a rare, autosomal recessive, inherited, lysosomal storage disease that is estimated to occur with an incidence of 1/300,000 to 1/40,000. The entire Myozyme clinical development program has been conducted in Pompe disease patients only. Pompe disease is classified by the age at onset of clinical signs and symptoms of Pompe disease (infantile-onset, childhood/juvenile-onset, and adult-onset), and the majority of patients treated in the Myozyme clinical progam for whom efficacy and safety data were submitted to the application were in the infantile-onset population. Response to treatment with Myozyme appears to vary considerably by Pompe disease age classification, which is the subject of this review and will be discussed in greater detail in the body of this review. No data were available in geriatric patients (≥65 years of age), as Pompe disease predominantly affects a younger patient population.

Males and females were nearly equally studied in the clinical development program, and although the number of patients studied was small, male and female patients do not appear to respond differently to Myozyme. As Pompe disease occurs worldwide, patients from the United States, Asia, the Middle East, Europe, and South American have been included in clinical studies and EAPs; however, insufficient information exists to determine a difference in response to Myozyme treatment by ethnic origin.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Recombinant human acid α-glucosidase (alglucosidase alfa, rhGAA) is the investigational agent studied in this application, and the Sponsor (Genzyme) intends to market rhGAA under the trade name Myozyme®. Endogenous acid α-glucosidase (GAA) is a lysosomal hydrolase 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. Deficient activity of acid α-glucosidase results in intralysosomal accumulation of glycogen. Myozyme is a new molecular entity (NME) being proposed as an enzyme replacement therapy (ERT) for the treatment of Pompe disease (Glycogen Storage Disease II, GSD II, acid maltase deficiency, glycogenosis type II), an inherited disorder of glycogen metabolism resulting from absent or deficient activity of acid α-glucosidase. Myozyme is produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells.

2.2 Currently Available Treatment for Indications

There are no available treatments known to impact the survival or progression of Pompe disease. Current treatment involves supportive care, and management of manifestations of the disease and its complications (e.g., assistive devices, nutritional therapy, respiratory support).

2.3 Availability of Proposed Active Ingredient in the United States

Acid α-glucosidase is not a currently marketed product in the United States (US). Prior to the PDUFA action date of 28-April-2006, Myzoyme is only available in the US under Investigational New Drug (IND) #10780.

2.4 Important Issues With Pharmacologically Related Products

Acid α-glucosidase has previously been investigated in the US (and in other countries) in 2 other formulations: 1) rhGAA derived from the milk of transgenic animals (Pharming), and 2) CHO cell-derived rhGAA (Synpac) under INDs —— respectively. These products are no longer being investigated, and patients previously treated with these formulations have been transitioned to treatment with Myozyme. The Pharming and Synpac formulations of rhGAA had been administered to small numbers of Pompe disease patients only, and clinical experience with these products is limited. Preliminary data from these studies have suggested that ERT with rhGAA may be beneficial in Pompe disease patients; however, given the small number of patients treated with these formulations, no determination on the clinical activity of these formulations relative to the Myozyme formulation can be made. In regard to the safety of the Pharming and Synpac formulations, both products appear to be highly immunogenic, particularly the Pharming formulation, which lead to the development of the Myozyme as a potentially less antigenic form of rhGAA.

2.5 Presubmission Regulatory Activity

Myozyme has been studied under IND 10780. Myozyme was granted Orphan Drug Designation on 19-August-1997, and Fast Track Designation on 13-February-2003. This biologics licensing application (BLA) was submitted under STN 125141/0, and was granted priority review status as a proposed treatment for Pompe disease.

The infantile-onset form of Pompe disease is a uniformly and rapidly fatal (usually by 18 months of age) disease for which no established treatments are known to impact survival or progression of disease. The Agency and the Sponsor have had ongoing and extensive discussions regarding the clinical development program for Myozyme (and the previous formulations of rhGAA) for about the past ten years with the purpose of assisting in the development of treatments for this patient population. Notable issues relevant to the review of this application that have been identified in these discussions between the Agency and the Sponsor include (source of information includes documentation contained in the IND and BLA files for Myozyme, and as summarized in a consultation by Marc Walton, M.D., Ph.D., CDER):

- Agreement was reached between the Agency and the Sponsor that an historical control was to be used for the pivotal study in the infantile-onset Pompe disease population (Study AGLU01602), which was to include infantile-onset Pompe disease patients with symptom onset at or prior to the age of six months, as a placebo-control was considered unethical in this clinical situation. Given the constraints of an historical comparison, mortality was selected as the most reliable outcome measure. Concern remained that advances in adjunctive therapy, such as ventilatory support, could alter the course of the disease (e.g., prolong survival). That is, knowing that infants were for the first time receiving a treatment that theoretically could alter the disease course may have resulted in a greater willingness to apply mechanical ventilatory support to the AGLU01602 study population. Thus, it was decided that invasive ventilator-free survival in the AGLU01602 population was to be compared to survival in the historical cohort.

- In 2002, Genzyme conducted a worldwide, retrospective chart review of patients with infantile-onset Pompe disease at several clinical centers. Data were collected to assess the certainty of diagnosis, the onset of clinically evident disease, the nature of the impairments leading to the diagnosis, major management modalities, and the age of death of the patients. The data in this retrospective chart review were formally collected and submitted to the application as Study AGLU-004-00: Historical Control Group Study, entitled "Epidemiologic study of the natural history of infantile Pompe disease".

- A subset of patients was selected from the historical control dataset based on the eligibility criteria in AGLU01602, so that the historical comparator population was as comparable as possible to the patients enrolled in AGLU01602. The results of this historical data collection, and identification of the matched-subset altered the prior impressions of the disease course. It had previously been thought that no infantile-onset Pompe disease infant survived past 12 months of age; however, data from the historical data collection disclosed that patients matched to the population selected for study in

AGLU01602 showed survival in at least a small percentage of patients (approximately 20%) past 12 months, with near universal mortality in this population seen at 18 months of age. Thus, survival to 18 months was selected as the endpoint at which patients would not have survived in absence of intervention.

- The Division was unwilling to stipulate to the adequacy of an historical control for Study AGLU1702 as the Pompe disease population represented in this study (patients with age at onset of signs and symptoms of Pompe disease at or prior to 12 months of age) had increased heterogeneity of outcomes compared to the AGLU01602 study population.

- Pompe disease encompasses a wide range of phenotypes that differ in the age of onset, extent of organ involvement, and rate of progression to death. Childhood/juvenile- and adult-onset Pompe disease is characterized by a more slowly progressive myopathy relative to the infantile-onset variant, broad heterogeneity in the course of the disease, and a virtual absent of the cardiomyopathy. The important differences in the juvenile- and adult-onset disease presentation and progression relative to the infantile-onset variant make this population a distinctly different population for study. As juvenile- and adult-onset Pompe disease patients' survival is measured in decades, extrapolation of survival data in the infantile-onset Pompe disease population to the treatment of juvenile- and adult-onset Pompe disease patients is not possible. To this end, the Agency reached additional agreement with the Sponsor on the clinical development of Myozyme in the juvenile- and adult-onset Pompe disease population to include the following:
    - A prospective, 12-month observational study in juvenile- and adult-onset Pompe disease (AGLU02303) has been conducted (initiated March 2004) to assist in better characterizing the clinical presentation and progression of juvenile- and adult-onset Pompe disease, and to assist in the design of a juvenile- and adult-onset Pompe disease clinical trial.
    - A randomized, double-blind, placebo-controlled, 52-week, safety and effeicacy study of Myozyme in the treatment of juvenile- and adult-onset Pompe disease patients has been initiated (August 2005), enrollment has been completed (March 2006) and the study is ongoing. This study is designed to support an indication for the treatment of juvenile- and adult-onset Pompe disease patients with Myozyme.

2.6 Other Relevant Background Information

Myozyme received a marketing authorization approval in the European Union from the European Agency for the Evaluation of Medical Products (European Medicines Agency, EMEA) on 03-April-2006. The indication states:

"Myozyme is indicated for long-term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of Pompe disease (acid α-glucosidase deficiency).

The benefits of Myozyme in patients with late-onset Pompe disease have not been established."

Background information on Pompe Disease important to this application is summarized as follows:

Pompe disease[1] (glycogen storage disease type II, GSD II, glycogenosis type II, acid maltase deficiency) is an autosomal recessive, inherited disorder of glycogen metabolism resulting from absent or deficient activity of the lysosomal hydrolase acid α-glucosidase (GAA). Acid α-glucosidase catalyses the hydrolysis of α-1,4- and α-1,6-glucosidic linkages in lysosomes, leading to the complete hydrolysis of glycogen to glucose. GAA deficiency results in intralysosomal accumulation of glycogen in numerous tissues, but is most marked in cardiac and skeletal muscle, and in hepatic tissues of infants, and is limited to skeletal muscle (and is of a lesser magnitude relative to the infantile-onset form) in the juvenile- and adult-onset forms. In contrast to the other glycogen storage disorders, no defect in the glycogen degradation pathway is associated with Pompe disease, as the major site of glycogen metabolism is within the cytoplasm. Estimates of the incidence of Pompe disease in western nations ranges from 1/300,000 to 1/40,000, and may vary in different ethnic groups and for the different clinical forms. Heterozygous carriers are considered healthy.

Pompe disease encompasses a wide range of phenotypes, all of which include varying degrees of myopathy, but differ in the age of onset, extent of organ involvement, and rate of progression to death. The classic infantile-onset disease is the most severe, with clinical findings of cardiomegaly, hypotonia, hepatomegaly, and death due to cardiorespiratory failure usually before the age of 2 years. The adult-onset form of the disease is at the other extreme, and is typically a slowly progressive, proximal myopathy with onset as late as the second to sixth decade of life, and involves only skeletal muscle. Between the two extremes is a heterogeneous group of presentations (childhood/juvenile-onset), usually without cardiac involvement, and with a progressive course of myopathy, including major impairment of respiratory function. Death in all forms of the disease usually results from respiratory failure.

Infantile-onset Pompe disease is most commonly defined as age of onset of clinical signs and symptoms of Pompe disease by six months of age or younger (but also has been defined as age of onset up to 12 months). Infantile-onset Pompe disease is further sub-divided into the classic infantile-onset form, including patients with signs and symptoms of Pompe disease at six months of age or younger AND cardiac hypertophy, and the muscular-variant infantile-onset form, including patients with signs and symptoms of Pompe disease at six months of age or younger, but without cardiac involvement. The classic infantile-onset form of Pompe disease is the most severe form of Pompe disease, and typically presents within the first few months of life with marked cardiomegaly, hyptonia, rapidly progressive weakness, macroglossia, and less marked hepatomegaly. There is generalized glycogen deposition predominantly in cardiac, skeletal, and smooth muscle, liver, renal tubular epithelium, and the central nervous system (CNS). Mental development is grossly normal, although due to the early death of patients, the natural progression of mental development is unknown. The course of classic infantile-onset Pompe disease is rapidly progressive with death usually before 1 to 2 years of life due to cardiorespiratory failure.

Childhood/juvenile-onset Pompe disease is most commonly defined as age of onset of signs and symptoms of Pompe disease after the age of six to 12 months and by the age of 16 years, and

adult-onset is defined as symptom onset after 16 years. Juvenile- and adult-onset Pompe disease is characterized by a slowly progressive muscle weakness, and there is an absence of cardiac involvement. Symptoms may begin in the first decade of life, but may be mild and patients may not come to medical attention until the second to sixth decade of life. In most patients, proximal muscle and truncal involvement are the presenting symptoms, and there is greater involvement of the lower than the upper limbs. The muscle involvement may be patchy, and not all muscles in the same area are equally affected. In some patients, however, the respiratory muscle involvement may predominate and patients may present with respiratory failure. Death in either presentation is usually due to respiratory failure.

The clinical diagnosis is confirmed by virtual absence (infantile-onset) or markedly reduced activity (juvenile- and adult-onset) of GAA in muscle biopsies and cultured fibroblasts. Pompe disease is genetically heterogeneous with missense, nonsense, and splice-site mutations, partial deletions, and insertions described in the relatively small number of patients analyzed. A few mutations have been described that are common in certain ethnic groups.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

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 summary at the time of this review, but two notable issues identified by Dr. Mills include:

- Due to unresolved manufacturing issues for the 2000 liter (l) scale product that appear to have an impact on the pharmacokinetics and, possibly, on the toxicity of the product, consideration of the 2000 l product for approval was withdrawn by the Sponsor, and approval is being recommended for the 160 l scale product only (for which clinical safety data are available).
- The recommendation for a number of post-marketing commitments (PMCs) to be performed after Myozyme approval was made (please see approval letter for a listing of these PMCs).

3.2 Animal Pharmacology/Toxicology

The preclinical data have been extensively reviewed by the Animal Pharmacology Reviewer (Barbara J. Wilcox, Ph.D.). Please see the pharmacology/toxicology review and evaluation for a complete review of the preclinical data. Notable findings from Dr. Wilcox's review include:

- The preclinical data were found to be supportive of approval for Myozyme for the infantile-onset patient population.
- Additional reproductive toxicology studies with Myozyme are recommended.
- Similar to comments from the Product Reviewer, due to unresolved manufacturing issues for the 2000 l scale product, approval is recommended only for the 160 l scale product.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

This application includes clinical efficacy or outcomes measures from ten Genzyme-sponsored clinical studies and expanded access programs (EAPs), in which all patients received treatment with open-label Myozyme. Five clinical studies and EAPs were conducted in infantile-onset Pompe disease patients, and five studies and EAPs were conducted in juvenile- and adult-onset Pompe disease patients. Safety information was submitted from the same ten clinical studies and EAPs as for efficacy, with additional, limited information obtained from an ongoing, double-blind, placebo-controlled, safety and efficacy study in juvenile- and adult-onset Pompe disease (Study AGLU02704). Supportive data were also provided from clinical studies and EAPs conducted using the Pharming and Synpac formulations of rhGAA, although these data were of limited utility in defining the effect and safety of treatment with Myozyme. A retrospective, international, observation, natural history study was also conducted in infantile-onset Pompe disease patients for the purpose of better characterizing the natural course of infantile-onset Pompe disease. Subpopulations were selected from this natural history study and were used as historical reference comparison populations for Studies AGLU01602 and AGLU01702 instead of concurrent or placebo controls. The results of this natural history study were also included in this application.

4.2 Tables of Clinical Studies

The clinical studies and expanded access programs performed in support of the Myozyme clinical development program, including completed and ongoing studies, are summarized in the following table:

Table 1: Myozyme Clinical Development Program

Study	Description
Infantile-Onset Studies	
AGLU-004-00, n=168 (rhGAA-exposed n=0)	Obervational, retrospective, chart review of 168 infantile-onset Pompe disease patients conducted between February and November 2002. This natural history study was conducted for the purpose of better characterizing the natural course of infantile-onset disease. No patient received treatment with rhGAA. Reference populations were selected from this study for use as the historical controls in Studies1602 & 1702.
AGLU01602 (Study 1602), n=18	Multicenter, international, randomized (to dose), open-label (OL), historical-control, PK, PD, safety, and efficacy study of Myozyme 20 or 40 mg/kg qow in 18 classic infantile-onset Pompe disease patients ages ≤7 months at the time of first infusion, with cardiac hypertrophy, and who were not receiving ventilatory support at study entry (conducted from 26-May-2003 to 15-June-2005).
AGLU01702 (Study 1702), n=21	Multicenter, international, non-randomized, historical-control, PK, PD, safety, and efficacy study of Myozyme 20 mg/kg qow in 21 Pompe disease patients ages ≥3 to 3.5 years at time of first infusion. Patients may have been receiving ventilatory support at study entry. Interim data only (to Week 52 for most patients) were submitted to the application (conducted 17-March-2003 to ongoing)
AGLU02203, n=5	OL, uncontrolled, US expanded-access, safety and efficacy study of Myozyme 20 mg/kg qow in 5 infantile-onset Pompe disease patients at an advanced stage of disease progression (29-December-2003 to ongoing). Patients had a mean age of 10.3 years at study entry (range 7-16 years). The objective was to provide Myozyme treatment to these patients.
AGLU02003, n=7	OL, extension, safety and efficacy study of Myozyme (10 mg/kg every week, or 20, 30, or 40 mg/kg qow) in 7 infantile-onset patients who had previous received treatment with other rhGAA formulations (Synpac or Pharming) (10-April-2003 to ongoing). Patients were a mean age of 22 months at first rhGAA treatment (range 2 to 73 months), and 41 months at first Myozyme treatment (range 24 to 76 months).
AGLU1205-02, Amendments 4 & 5, n=1	OL, extension study of Myozyme 20-40 mg/kg qow in a single infantile-onset Pompe disease patient (age 3 months at first rhGAA infusion and 41 months at first Myozyme infusion) who had previously received other rhGAA formulations (Synpac and Pharming) for 3 years under INDs — , (AGLU1205-02 conducted from 12-June-2003 to ongoing).
Juvenile and Adult-Onset Studies	
AGLU02804, n=5	OL, uncontrolled, non-randomized, single-center, 26-week, PK, safety, and efficacy study of Myozyme 20 mg/kg qow to 5 patients with juvenile-onset Pompe disease. Patients were ages 6 to 15 years (median 12.7 years) at baseline, with symptom onset at ages 1 to 12 years. All patients could ambulate 10 m at baseline, and patients on invasive ventilation at baseline were excluded.
AGLU02503, n=3	OL, European, expanded access, safety and efficacy program of Myozyme 20 mg/kg qow in 3 patients with clinically advance juvenile-onset Pompe disease (04-November-2003 to ongoing). Four patients were enrolled, and 3 received treatment. Patients were ages 9, 17 and 19 years at study entry, and had onset of signs and symptoms of Pompe disease at >12 months to ≤21 years. The objective of the study was to provide acces to treatment with Myozyme to these patients.
AGLU02103, n=1	OL, extension, safety and efficacy study of Myozyme 30 mg/kg qow in 1 juvenile-onset Pompe disease patient who had previously received 3.7 years of Pharming and Synpac rhGAA formulations under INDs — AGLU02103 conducted from 11-Apr-2003 to ongoing). The patient was age 16 years at first rhGAA treatment, and age 20 years at first Myozyme treatment.
AGLU02704 (LOTS) (ongoing, limited data available)	Multicenter, international, randomized, double-blind, placebo-controlled, 52-week, PK, safety, and efficacy study of Myozyme in about 80 juvenile- and adult-onset Pompe disease patients. First patient was enrolled August 2005, enrollment was completed March 2006, and study completion is anticipated in March 2007.
AGLU02303, (rhGAA-exposed n=0)	Mulitcenter, internation, prospective, 12-month, observational/natural history study initiated March 2004, intended to better characterize the clinical presentation of juvenile and adult-onset Pompe disease, to assist in determining clinical efficacy endpoints for the planned placebo-controlled study AGLU02704.
Expanded Access Programs	
International EAP	An expanded access program conducted outside the US providing Myozyme to patients of any age with Pompe disease. 54 patients have been enrolled as of 08-March-2005.
AGLU02603 (US EAP)	Ongoing, OL, expanded access study in the US for severely affected patients with Pompe disease who do not meet the clinical eligibility criteria for enrollment in an ongoing study of Myozyme.

4.3 Review Strategy

The most important study submitted to this application was Study AGLU01602. Study AGLU01602 was a multicenter, international, open-label, 52-week, safety and efficacy study performed in 18 patients with classic infantile-onset Pompe disease, and the recommendation for approval of Myozyme as a treatment for Pompe disease is based entirely on the ventilator-free survival benefit seen with Myozyme treatment in this pivotal study. The comprehensive safety and efficacy data submitted to the application for Study AGLU01602 permitted substantive clinical review.

Study AGLU01702 was the largest study submitted in support of the Myozyme application, and was conducted in 21 infantile-onset Pompe disease patients. Study AGLU01702 is an ongoing, multicenter, international, non-randomized, open-label, 104-week, safety and efficacy study, and the comprehensive safety and efficacy outcomes information available for this study also permitted substantive clinical review. Interim results only for Study AGLU01702, up to Week 52 for most patients, were submitted for review.

Analyses of studies AGLU01602 and AGLU01702 were emphasized in this review, and comprehensive reviews of these studies are summarized in the Appendix section under the Individual Study Reports. The data submitted for the three remaining studies and expanded access programs (EAPs) conducted in the infantile-onset population were of lesser importance to the review, as they contained limited safety and outcomes assessments.

Information on safety and outcomes measures for 24 juvenile- and adult-onset Pompe disease patients was available for review in the application. The data submitted to the application for Study AGLU02804 were the only data in the the juvenile- and adult-onset population that were amenable to detailed review. Study AGLU02804 was an open-label, nonrandomized, uncontrolled, single-center, 26-week, safety and efficacy study conducted in five juvenile-onset Pompe disease patients; however, as this was an open-label, uncontrolled study and the endpoints were highly subjective (e.g., six-minute walk test [6MWT] is highly dependent on patient effort), the results of this study were of limited utility in determining a treatment effect of Myozyme in this patient population. The information on the remaining 19 juvenile- and adult-onset patients from EAPs was submitted to the application in the form of narratives. The patient population in these EAPs was extremely diverse, and the length of treatment, doses of Myozyme administered, safety and outcomes assessments measured, and the scope of information provided in the narratives were highly variable, and highly subjective. Thus, these data were of limited utility in defining either a treatment effect or a safety profile of Myozyme administration in the juvenile- and adult-onset population.

Thus, a comprehensive review of the efficacy and safety results for the Myozyme clinical development program will focus on about 44 patients, 39 of whom were infantile-onset patients, and the additional safety and outcomes information available for review in the remaining approximately 40 additional patients will be considered in lesser detail.

4.4 Data Quality and Integrity

Several problems and concerns with this application were noted, and are listed as follows (including, but not limited to):

- There were numerous errors, omissions, and incomplete data noted in the datasets, making many of the endpoint results unreliable. For example, the datasets for the growth parameters (particularly for length and head circumference) in Studies AGLU01602 and, especially, AGLU1702 contained numerous instances of implausible results, such as patients appearing to lose, then gain length or head circumference from visit to visit. Similar problems with implausible results were seen to a lesser extent in the cardiac parameter datasets. The overall result of these obvious errors was to call into question the reliability of the data submitted to the entire application. However, as ventilator-free survival was an easily measured and verifiable outcome measure, it was felt that the primary endpoint result for the pivotal study AGLU01602 was likely reliable, and considered to be accurate.

- Basic information necessary for the review of the application was missing from the original application. This included such information as documentation of the timing of all screening and baseline procedures, and the signing of the Informed Consent Form for all patients; detailed descriptions of procedures performed (e.g., randomization, developmental testing) and techniques (e.g., blinding of study personnel) used in the studies; large amounts of safety and efficacy data for Study AGLU1702 (e.g., safety data collected after 03-September-2004, efficacy data on six of 21 patients after Week 12, and data for the Leiter-R cognitive development test); data on juvenile- and adult-onset patients in support of the proposed indication (e.g., information on a total of four of these patients had been submitted to the original application, with information in the remaining 20 patients, predominantly in the form of narratives, submitted late in the review cycle in Amendments 002 and 007, in November and December 2005, respectively); and a large number of product-related issues (e.g., validation assay requests), among others. This resulted in three Information Request (IR) letters being sent from the Division to the Sponsor during the review cycle, requesting information in about 80 questions. Receipt of responses to these questions in December 2005 and January 2006 resulted in a major amendment to the application, and a three-month extension to the PDUFA goal date. As some of the information was submitted very late in the review cycle, the remaining time available did not permit a thorough review of all the information submitted.

- The construct of the application was confusing. There were twelve separate submissions to the application during the review cycle, the data were poorly organized, and the Sponsor did not effectively integrate the existing data submitted during the entire review cycle. For example, safety data were scattered throughout the submission, there was no integrated safety summary that encompassed the entire safety experience submitted to the application, important information was frequently located in multiple pieces in appendices, and either not noted or not clearly displayed within the body of the reviews, summaries or individual study reports. This resulted in difficulty for the reviewers in

navigating through the application, locating information critical to the review of this submission, and comprehensively summarizing the existing data. The twelve separate submissions (original and 11 amendments) to this application are summarized in the following table:

Table 2: BLA 125141/0, Original and Amendment Summary

Amendment	Date Received	Description
000	29-July-2005	Original submission. Note: 1) Study 1602 (pivotal) contained 26-week interim data only, and 2) original submission contained information on 4 late-onset patients only (AGLU02103, n=1 and AGLU02503, n=3)
001	01-Sept-2005	Study 1602 final data (52-week) for primary endpoint, and major endpoints of growth, motor function (AIMS, Pompe PEDI) and cognitive function (BSID-II). Safety data (SAEs only) through 15-June-2005 cutoff for studies 1602, 1702, 2203, 2003, 2103, 1205-02, 2603, 2503 and the international EAP, and immunogenicity data from studies 1602 and 1702 through 15-June-2005.
002	02-Nov-2005	Abridged Clinical Study Reports (CSR) for Study 1602 incorporating updates from Amendment 001, and information on 13 late-onset Pompe disease patients from: 1) AGLU02804 (n=5) final CSR, and 2) narratives on 8 patients from EAP AGLU02503 (n=2), AGLU2103 (n=1), AGLU02103 (updated from Amendment 000, n=1), AGLU02503 (updated for 2 of 3 patients from Amendment 000, n=2), and International EAP (n=5)
003	02-Nov-2005	Administrative correspondence: copies of information submitted to DSI
004	15-Nov-2005	Electronic datasets for Study AGLU02804 (CSR only submitted in Amendment 002)
005	05-Dec-2005	4-month safety update to BLA
006	16-Dec-2005	Response to request for information, clinical and CMC. Clinical information included new efficacy information for Study 1602: ventilator status, description of norms for motor and cognitive function, randomization dates, updated KM plots, and randomization scheme. Safety information included DSMB charter.
007	21-Dec-2005	Response to request for information. Study 1702 efficacy data for remaining 6 patients through Week 52.(no electronic datasets), and information (narratives only) for an additional 10 late-onset patients
008	06-Jan-2005	Response to request for information, CMC and clinical. Clinical information included responses to questions 1-11, 13-34, 69-70 and 72-73 of IR letter #1, all questions in IR letter #2. Also included resubmission of proposed indication for labeling and justification.
009	17-Jan-2006	Request for type A meeting. Question list included.
010	19-Jan-2006	Response to request for information. Responses to question 12 and 71, and updated responses to questions 70 and 72 from IR letter #1.
011	15-Feb-2006	Response to request for information. Clinical protocol for AGLU02403, extension study to Study AGLU01602.

Missing, incomplete, and unorganized safety data resulted in a worrisome safety signal for hypersensitivity being noted late in the review cycle after a serious, related hypersensitivity reaction was submitted as an expedited report to the Myozyme IND. Receipt of this expedited report resulted in a request by the Division to the Sponsor for the Sponsor to query their pharmacovigilence database for similar events. This query resulted in the uncovering of numerous hypersensitivity reactions, some of which were life-threatening, and some of which had not been previously reported as serious events in either the Myozyme IND or the BLA. In discussions with the Sponsor, the Sponsor stated that not all of these events were submitted as serious events to the IND, nor the BLA, as they were considered to be expected events as they were listed in the

Investigator's Brochure. These discussions resulted in a clarification on reporting procedures to be followed for this application.

- Define files were, at times, unhelpful, did not adequately explain the dataset fields, and contained errors, limiting their utility.

- Electronic datasets were not submitted for a number of outcomes measures considered important to the review of this application (e.g., z-scores and percentiles for growth data), resulting in manual review and compilation of some data by the reviewers.

The Division of Scientific Investigations (DSI) performed 2 clinical site audits for this application, including: 1) Dr. Byrne (Shands Hospital), Gainesville, Florida (Site #81 in AGLU01602), and 2) Dr. Kishnani (Duke University), Durham, North Carolina (Site #1 in AGLU01602). These sites were selected for inspection because of their high enrollment, geographic location, and . —— The overall observation noted by the DSI Inspector (Jose Javier Taverez, M.S.) for the two clinical sites was that "there was sufficient documentation to assure that all audited patients did exist, fulfilled the eligibility criteria, received the assigned study medication, and had their primary efficacy endpoint captured as specified in the protocol. No underreporting of adverse events noted (*sic*). Overall data... appear acceptable for use in support of BLA 125141."

4.5 Compliance with Good Clinical Practices

The sponsor stated that studies AGLU01602, AGLU01702, and AGLU02804 were carried out in accordance with Good Clinical Practice (GCP) regulations. The remaining studies and EAPs were not conducted as GCP studies.

4.6 Financial Disclosures

Financial disclosures were included in the submission. For Studies AGLU01602 and AGLU01702, notable findings were:

1. —— ias a financial interest in the outcome of the study. —— —— —— research grants and fellowship funding. These payments do not reflect monies paid directly to —— however. It was also disclosed that Dr. —— accepted payments (honoraria) from Genzyme totaling $5,000.
2. The —— , Dr. —— reported acceptance of honoraria and laboratory support grants of more than $40,000 from Genzyme.

5 CLINICAL PHARMACOLOGY

The clinical pharmacology data have been extensively reviewed by the Clinical Pharmacology and Biopharmaceutics Reviewer (Anil Rajpal, M.D.); please see the Clinical Pharmacology and

Biopharmaceutics review for the completed review of these data. Dr. Rajpal's findings for the pharmacokinetic (PK) and pharmacodynamic (PD) data are noted, briefly, as follows:

5.1 Pharmacokinetics

The pharmacokinetic (PK) parameters for Myozyme after a single infusion were assessed in 13 patients from AGLU01602, ages 1 to 7 months, in the 20 mg/kg and 40 mg/kg dose groups. Systemic exposure was noted to be approximately dose proportional between the 20 and 40 mg/kg doses. No accumulation was noted when PK parameters were measured at Week 12, with similar results having been obtained for these parameters. The PK results for the 13 patients from Study AGLU01602 after a single infusion are summarized in the following table:

Table 3: Study AGLU01602, Myozyme PK Parameters After a Single Infusion

	Dose Group	
	20 mg/kg	**40 mg/kg**
n=	5	8
PK Parameter		
Cmax (mcg/mL)	262 ± 31	276 ± 64
AUC_∞ (mcg-hr/mL)	811 ± 141	1781 ± 520
CL (mL/hr/mL)	25 ± 4	24 ± 7
Vss (mL/kg)	96 ± 16	119 ± 28
$t_{½}$ (hr)	2.3 ± 0.4	2.9 ± 0.5

The PK results obtained in 14 patients in Study AGLU01702, ages 6 months to 3.5 years, at a dose of 20 mg/kg were similar to those observed in the 20 mg/kg dose group in the AGLU01602 study. Nineteen of 21 patients who received treatment with Myozyme, and had PK and antibody titer data available at Week 12, developed antibodies to alglucosidase alfa. Five patients with antibody titers ≥12,800 at Week 12 had an average increase in clearance (CL) of 50% (range 5% to 90%) from Week 1 at Week 12.

5.2 Pharmacodynamics

Pharmacodynamic (PD) measures were evaluated by comparing skeletal muscle GAA activity and skeletal muscle glycogen content (by biochemical and histomorphometric methods) at baseline, and at Weeks 12 and 52. Plasma and urine oligosaccharides were also collected. In general, the skeletal muscle glycogen content analyses, and the plasma and urine oligosaccharide measures did not show a consistent correlation with clinical outcome, and should be considered as exploratory at this time.

5.3 Exposure-Response Relationships

Doses of Myozyme administered in the Myozyme clinical development program ranged from 10 mg/kg every other week to 40 mg/kg every week by intravenous infusion. Most patients in the Myozyme clinical development program received treatment with Myozyme at a dose of 20 mg/kg every other week. The next most frequently administered dose was 40 mg/kg every other week. Information available on patients receiving doses of Myozyme less than 20 mg/kg and greater than 40 mg/kg every other week was extremely limited, and was not of sufficient detail to provide any assessment of safety or efficacy. Based on the safety and efficacy results from

Study AGLU01602, efficacy was found to be similar between the 20 mg/kg and 40 mg/kg every other week doses, and the safety concerns, particulary for immunogenicity and infusion reactions, were less in the 20 mg/kg dose group as compared to the 40 mg/kg dose group. It is noted, however, that each dose group in the AGLU01602 study contained only nine patients, and it is possible that a difference in efficacy between the doses exists, but was unable to be determined.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The Sponsor is proposing that Myozyme receive the following indication:

The data submitted to the Myozyme application is only supportive of an indication for use in patients with infantile-onset Pompe disease, in whom a ventilator-free survival benefit has been demonstrated. Adequate and well-controlled studies have not been completed in the juvenile- and adult-onset population, and the risk/benefit profile of Myozyme in the juvenile- and adult-onset population has not been described. Therefore, the Division is proposing the following indication:

"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."

6.1.1 Methods

This application includes clinical efficacy or outcomes measures from ten clinical studies and expanded access programs (EAPs), in which all patients received treatment with open-label Myozyme. The entire Myozyme clinical program was conducted in Pompe disease patients, and given the rarity of this disease, the entire Myozyme-exposed population in this application was small. Comprehensive efficacy and safety data that permitted substantive review were available in about 44 patients, 39 of whom were infantile-onset patients. There was additional safety and outcomes information available for review in about 40 additional patients; however, this information was of limited utility in defining either the effects of Myozyme treatment or the safety of Myozyme administration, and will be considered in lesser detail.

Five clinical studies and EAPs were performed in approximately 52 infantile-onset Pompe disease patients, with comprehensive safety and efficacy data permitting substantive review

available in 39 patients in Studies AGLU01602 and AGLU01702. Analyses of studies AGLU01602 and AGLU01702 were emphasized in this review, and comprehensive reviews of these studies are summarized in the Appendix section under the Individual Study Reports.

The most important study submitted to this application was Study AGLU01602, an open-label, historical-control, 52-week, safety and efficacy study performed in 18 classic infantile-onset Pompe disease patients. The data submitted to the application from this study were analyzed for the purpose of making a determination on the effectiveness of Myozyme for the proposed indication.

Study AGLU01702 was the largest study submitted to the Myozyme application (conducted in 21 infantile-onset Pompe disease patients). Study AGLU01702 is an ongoing, non-randomized, open-label, 104-week, safety and efficacy study, and interim results only, up to Week 52 for most patients, were submitted for review. These data also were analyzed for the purpose of making a determination on the effectiveness of Myozyme for the proposed indication. However, it is noted that although comparisons were made in this study to an historical reference population, it was recognized by the Division that determining anything less than a dramatic treatment effect in this population would be difficult due to the highly heterogeneous presentation and progression of the disease in this Pompe disease age group, and as there was no concurrent control.

The data submitted for the three remaining studies and EAPs conducted in the infantile-onset population were of lesser importance to the review, as they contained limited safety and outcomes assessments, and will be considered in lesser detail. Studies conducted in the infantile-onset population (including the natural history study) are listed in the following table:

Table 4: Myozyme Clinical Development Program, Infantile-Onset Studies

Study AGLU-	Population	Description
004-00	Infantile-onset n=168	Obervational, retrospective, chart review of 168 infantile-onset Pompe disease patients conducted between February and November 2002. This study included data obtained using a retrospective chart review of 168 untreated patients diagnosed with infantile-onset Pompe disease with the purpose of better characterizing the natural course of infantile-onset Pompe disease. No patient received treatment with rhGAA. Reference populations were selected from this study for use as the historical controls in StudiesAGLU01602 and AGLU01702.
01602	Classic infantile-onset, n=18	Multicenter, international, randomized (to dose), open-label (OL), historical-control, PK, PD, safety, and efficacy study of Myozyme 20 or 40 mg/kg qow in 18 classic infantile-onset Pompe disease patients ages ≤7 months at the time of first infusion, with cardiac hypertrophy, and who were not receiving ventilatory support at study entry (conducted from 26-May-2003 to 15-June-2005).
01702	Infantile- and childhood/juvenile-onset (age at onset <12 months), n=21	Multicenter, international, non-randomized, historical-control, PK, PD, safety, and efficacy study of Myozyme 20 mg/kg qow in 21 Pompe disease patients ages ≥3 to 3.5 years at time of first infusion. Patients may have been receiving ventilatory support at study entry. Interim data only (to Week 52 for most patients) were submitted to the application (conducted 17-March-2003 to ongoing)
02203	Infantile-onset (probable muscular variant and classic forms, age at onset ≤6 months) n=5	OL, uncontrolled, US expanded-access, safety and efficacy study of Myozyme 20 mg/kg qow in 5 infantile-onset Pompe disease patients at an advanced stage of disease progression (29-December-2003 to ongoing). Patients had a mean age of 10.3 years at study entry (range 7-16 years). The objective was to provide Myozyme treatment to these patients.
02003	Infantile-onset n=7	OL, extension, safety and efficacy study of Myozyme (10 mg/kg every week, or 20, 30, or 40 mg/kg qow) in 7 infantile-onset patients who had previous received treatment with other rhGAA formulations (Synpac or Pharming) (10-April-2003 to ongoing). Patients were a mean age of 22 months at first rhGAA treatment (range 2 to 73 months), and 41 months at first Myozyme treatment (range 24 to 76 months).
1205-02	Infantile-onset, n=1	OL, extension study of Myozyme 20-40 mg/kg qow in a single infantile-onset Pompe disease patient (age 3 months at first rhGAA infusion and 41 months at first Myozyme infusion) who had previously received other rhGAA formulations (Synpac and Pharming) for 3 years under INDs — AGLU1205-02 conducted from 12-June-2003 to ongoing).
Total	**n=52**	

Five studies and EAPs were conducted in juvenile- and adult-onset Pompe disease patients, and information on 24 of these patients was available for review. The data submitted for Study AGLU02804, an open-label, nonrandomized, uncontrolled, 26-week, safety and efficacy study, were the only data in the juvenile- and adult-onset population that were amenable to detailed review; however, as this study was open-label and uncontrolled, and the outcomes measures were highly subjective (e.g. 6MWT is highly dependent on patient effort), no reasonable assessment of the effect of Myozyme treatment on juvenile- and adult-onset Pompe disease patients could be made from these data. The information on the remaining 19 juvenile- and adult-onset patients from EAPs was submitted to the application in the form of narratives. The patient population in these EAPs was extremely diverse, and the length of treatment, doses of Myozyme administered, safety and outcomes assessments measured, and the scope of information provided in the narratives were highly variable, and highly subjective. Thus, these data were of limited utility in defining either a treatment effect or a safety profile of Myozyme administration in the

juvenile- and adult-onset population, and were considered in less detail. Studies conducted in the juvenile- and adult-onset population are listed in the following table:

Table 5: Myozyme Clinical Development Program, Juvenile/Childhood- and Adult-Onset Studies

Study	Population	Description
AGLU02804	Juvenile-onset (age range 1-6 yrs), n=5	OL, uncontrolled, non-randomized, single-center, 26-week, PK, safety, and efficacy study of Myozyme 20 mg/kg qow to 5 patients with juvenile-onset Pompe disease. Patients were ages 6 to 15 years (median 12.7 years) at baseline, with symptom onset at ages 1 to 12 years. All patients could ambulate 10 m at baseline, and patients on invasive ventilation at baseline were excluded.
AGLU02503	Juvenile-onset (age range at symptom onset 1-3 yrs), n=3	OL, European, expanded access, safety and efficacy program of Myozyme 20 mg/kg qow in 3 patients with clinically advance juvenile-onset Pompe disease (04-November-2003 to ongoing). Four patients were enrolled, and 3 received treatment. Patients were ages 9, 17 and 19 years at study entry, and had onset of signs and symptoms of Pompe disease at >12 months to ≤21 years. The objective of the study was to provide acces to treatment with Myozyme to these patients.
AGLU02103	Juvenile-onset (age 11 yrs), n=1	OL, extension, safety and efficacy study of Myozyme 30 mg/kg qow in 1 juvenile-onset Pompe disease patient who had previously received 3.7 years of Pharming and Synpac rhGAA formulations under IND[redacted], (AGLU02103 conducted from 11-Apr-2003 to ongoing). The patient was age 16 years at first rhGAA treatment, and age 20 years at first Myozyme treatment.
International EAP	Infantile-, juvenile- and adult-onset (1 patient age at symptom onset 6 months c/w infantile-onset muscular variant, remaining 13 patients, juvenile-onset, age range 2-35 yrs), n=13	An expanded access program conducted outside the US providing Myozyme to patients of any age (infantile-, juvenile- and adult-onset) with Pompe disease. 54 patients have been enrolled as of 08-March-2005.
AGLU02603 (US EAP)	Juvenile- and adult-onset (ages 2 and 21 yrs), n=2	Ongoing, OL, expanded access study in the US for severely affected patients with Pompe disease who do not meet the clinical eligibility criteria for enrollment in an ongoing study of Myozyme.
AGLU02704 (LOTS)	Limited safety data available only	Multicenter, international, randomized, double-blind, placebo-controlled, 52-week, PK, safety, and efficacy study of Myozyme in about 80 juvenile- and adult-onset Pompe disease patients. First patient was enrolled August 2005, enrollment was completed March 2006, and study completion is anticipated in March 2007.
Total	**n=24**	

Thus, a comprehensive review of the efficacy and safety results for the Myozyme clinical development program will focus on about 44 patients, 39 of whom were infantile-onset patients, and the additional safety and outcomes information available for review in the remaining approximately 40 additional patients will be considered in lesser detail.

6.1.2 General Discussion of Endpoints

The pivotal study in this application is Study AGLU01602, and the entire decision for approval of this application was based on the primary endpoint of ventilator-free survival from Study AGLU01602. Relevant issues with the primary endpoint are discussed, as follows:

The primary efficacy endpoint in the pivotal study AGLU01602 was the Kaplan-Meier estimate of the proportion of patients who were alive and free of invasive ventilator support at 18 months

of age with survival measured as time from birth for patients treated with rhGAA with both dose groups combined using all data through 52 weeks after the last patient was randomized to treatment. This was compared to the proportion of survivors at 18 months of age in an untreated historical cohort. The primary endpoint was considered to have been met if there was no overlap between the two-sided 95% CI for the proportion of rhGAA treated patients alive and free of invasive ventilation at 18 months of age and the 95% CI for 18 months survival of untreated patients in the historical control subgroup. Patients who were alive but had not yet reached 18 months of age were right censored. Invasive ventilator-free survival was defined as 1) the patient was ventilator-free for a 14-day period bracketing the target time point, or 2) the investigator determined that the patient's ventilator use was due to secondary causes only (e.g., aspiration pneumonia) at the target time point and the patient was followed for up to an additional 30 days. If during this additional 30 days the patient became ventilator-free for at least 14 consecutive days, the patient was considered to be ventilator free.

Exploratory analyses for the primary endpoint included estimates of ventilator-free survival time from the date of first symptoms, date of diagnosis, and date of study treatment initiation. Sensitivity analyses for survival rates in the historical control subgroup included:
1) comparisons of the rhGAA-treated group survival rate to survival rates from the historical control subgroup subsets in which patients who died prior to three, four, five, and six months of age were removed from the total sample size of 62; 2) assessment of whether the survival inferences were dependent on the age at first rhGAA infusion using a subset of the historical control subgroup selected based on the median age at first infusion of rhGAA, and after rhGAA-treated patients were partitioned into two groups based on their age at first rhGAA infusion (less than or greater than median age); and 3) with exclusion of patients with congenital abnormalities or clinically significant disease status recorded as "unknown" from the control group.

Comparison to an historical control was accepted by the Division as infantile-onset Pompe disease is a uniformly fatal disease for which there are no established treatments, and placebo treatment was considered unethical in this clinical situation. Given the constraints of an historical comparison, mortality was selected as the most reliable outcome measure. As there was concern that the use of ventilatory support could alter the course of the disease (e.g., prolong survival), and as the clinical situation in the Study AGLU01602 was different than in the historical control setting (i.e., in the clinical study, parents and caregivers knew that infants were receiving a potentially beneficial treatment, and the willingness to apply mechanical ventilatory support to patients may have been greater than in the historical control setting where no potentially beneficial treatments existed), it was decided that invasive ventilator-free survival in the AGLU01602 population was to be compared to survival in the historical cohort. Near universal mortality was noted in the historical control population at 18 months of age, thus, ventilator-free survival at 18 months was selected as the endpoint, as this was the timepoint at which patients would not have survived in the absence of intervention.

The Statistical Reviewer (Lisa Kammerman, Ph.D.) noted that major statistical issues existed for the analyses performed in Study AGLU01602 (please see the Statistical Review and Evaluation by Dr. Kammerman for a detailed discussion of these issues), including:

1. Inappropriate use of the Kaplan-Meier methodogy, where the survival analysis started at the date of birth, instead of at the more appropriate time of randomization in Study AGLU01602. Quantification of the treatment difference between the Study AGLU01602 population and the historical control group was almost impossible because of this, as date of randomization did not exist in the historical control group.
2. A potential selection bias existed in this study, as patients in AGLU01602 had to survive long enough to start treatment, whereas that condition did not apply to the historical control subgroup. This selection bias likely favored the treated patients. However, this selection bias was minimal when 18-month survival was evaluated as almost no patients survived in the historical control group at 18 months of age.
3. Improved outcomes over time were noted in the historical control group, likely due to more aggressive therapy and the better availability of therapies in later years. This likely favored treated patients as they were born in later years as compared to the historical control patients.

Overall, despite these limitations, the data suggest improved outcomes among patients treatment with Myozyme when visually compared with the natural history of patients who go untreated. However, quantification of this difference is almost impossible, and it was recommended by Dr. Kammerman that Kaplan-Meier graphs not be displayed in labeling, as a survival difference between the two groups was likely over-estimated in favor of treated patients.

6.1.3 Study Design

Two of the clinical studies submitted to the application underwent detailed review: AGLU01602 and AGLU01702 (Studies AGLU01602 and AGLU01702 are also described in the Appendix section in the Individual Study Reports. Please refer to the Individual Study Reports for more detailed discussions of these studies). The historical comparator groups for Studies AGLU01602 and AGLU01702 were selected from the historical control population identified in Study AGLU-004-00, and the study design for AGLU-004-00 will also be described here.

The study design for AGLU-004-00 is described as follows:

AGLU-004-00 was a multi-national, multi-center historical cohort study designed to characterize the natural history of disease progression in untreated patients with infantile-onset Pompe disease. Historical data were derived from a retrospective review of patient medical records. Sites participating in the study were identified by a questionnaire, and included sites in North America, Europe, Israel, and Taiwan. These sites were searched for cases of Pompe disease, living or dead, who had not been treated with exogenous enzyme therapy. To be enrolled in the study, patients were required to have a clinical diagnosis of infantile-onset Pompe disease defined as documented GAA enzyme deficiency or GAA gene mutations, AND onset of symptoms by 12 months of age corrected for gestation. Data collection included demographics, survival, disease chronology, physical examination data, laboratory data, and treatment data including ventilator use.

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 therapy. Most patients identified were born after 1985 (151 of 168 cases). Overall survival in the natural history study was poor, with a median survival of 8.7 months; however, nearly one quarter of patients survived to one year, and a small percentage (about 7%) lived past two years, with prolonged survival documented to 73.4 months in one patient.

For comparison to the AGLU01602 population, a subset of 62 patients was selected from within the 168 patients in the AGLU-004-00 cohort based on screening criteria adapted from Study AGLU01602. This subgroup is known as the historical control subgroup, and was designed to select a control population that most closely matched the study population entered into Study AGLU01602. The inclusion criteria for the historical control subgroup included age at first symptoms less than or equal to 26 weeks of age, age at confirmed diagnosis less than or equal to 26 weeks of age, and presence of cardiomyopathy by 26 weeks of age (LVMI $\geq$65 g/m^2). Exclusion criteria included any known ventilator use between zero and six months of age, documented major congenital abnormality, and clinically significant disease other than Pompe disease. Survival in the historical control subgroup was poor. Of the 61 patients with a known date of death, one 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 can provide the certainty of comparison as, for example, a placebo-control group, it appears that survival in the historical control subgroup at 18 months of age provides a reasonable comparator for ventilator-free survival in Study AGLU01602 treatment group.

For comparison to the AGLU01702 poulation, two reference populations were selected from within the AGLU-004-00 cohort. An Historical Reference Subgroup (n=86) was selected from AGLU-004-00 using screening criteria adapted from the AGLU01702 eligibility criteria, whereby AGLU-004-00 patients were excluded from the Historical Reference Subgroup if they had a GAA activity >2% of mean of the normal range (patients without GAA levels available for assessment were not excluded), died, or were lost to follow-up at less than or equal to six months of age, had an LVMI less than 65 g/m^2 at age less than or equal to 12 months or had an LVMI less than or equal to 79 g/m^2 at age greater than 12 months, had symptoms of congestive heart failure AND an EF less than 40%, had a major congenital abnormality, or had clinically significant disease other than Pompe disease. For additional comparison, an Historical Reference Subset (n =15) was also selected from the Historical Reference Subgroup, whereby patients who died before the median age at which the Study 1702 population received their first infusion (15 months of age) were excluded.

The study designs for AGLU01602 and AGLU01702 are described as follows:

Study AGLU01602 was a multicenter (n=7), multinational, open-label, randomized (to dose), dose-ranging, safety, efficacy, pharmacodynamic (PD) and pharmacokinetic (PK) study of rhGAA in the treatment of 18 patients with infantile-onset Pompe disease. Eligible patients were randomized 1:1 to receive an intravenous (IV) infusion of rhGAA 20 mg/kg or 40 mg/kg every other week (qow) for 52 weeks. Patients were eligible for the study if they had a definitive diagnosis of Pompe disease defined as a deficiency in GAA activity, onset of clinical signs of

Pompe disease before the age of six months and cardiac hypertrophy, and if they were less than or equal to six months of age at first infusion. The primary efficacy endpoint for the study was the proportion of patients who were alive and free of invasive ventilator support at 18 months of age, as compared to an historical control subgroup of similar age and disease severity. Major efficacy endpoints included changes from baseline at Week 52 in measures of cardiac status (LVMI, EF), physical growth (length, weight, and head circumference), and achievement of motor and mental developmental milestones assessed by Alberta Infant Motor Scale (AIMS), Bayley Scales of Infant Development II (BSID-II), and Pompe Pediatric Evaluation of Disability Inventory (PEDI) testing. As infantile-onset Pompe disease is a uniformly fatal disease for which there are no established treatments, no placebo treatment was administered, and an historical cohort was used as the control group.

Study AGLU01702 is an ongoing, multicenter (n=6), multinational, open-label, non-randomized, safety, efficacy, PD and PK study of rhGAA in the treatment of 21 patients with infantile-onset Pompe disease. Eligible patients were to receive IV infusions of rhGAA 20 mg/kg qow for 52 weeks followed by a 52-week maintenance phase at the same dose. Patients were eligible for the study if they were more than six months and less than or equal to 36 months of age at the time of first infusion, and had a diagnosis of Pompe disease defined as a deficiency in GAA activity, onset of clinical signs consistent with Pompe disease by 12 months of age, and cardiac hypertrophy. The primary efficacy endpoint was the proportion of patients alive over the course of treatment. Secondary efficacy endpoints included the effect of treatment on respiratory function, cardiac status, motor development, cognitive development, and physical growth. This study had no concurrent control, and no placebo treatment was administered. Comparison to an historical control reference population was provided. Interim efficacy and safety data through Week 52 only for this study were submitted to the BLA. Although the initial 52 weeks of the study have been completed, the 52-week maintenance phase is ongoing at the time the application was submitted, and final results for the entire 104 weeks of the study are not yet available. The last patient received her first dose of rhGAA on 28-May-2004; thus, the study is expected to be completed on or about 28-May-2006.

The remaining studies and expanded access programs submitted to this application were considered in lesser detail. The study designs for these studies and programs are described as follows:

The remaining infantile-onset Pompe disease studies and EAPs were:

- Study AGLU02203 is an ongoing, open-label, expanded access, safety and efficacy study of Myozyme 20 mg/kg qow conducted in the US in five infantile-onset Pompe disease patients at an advanced stage of disease progression. Patients had a mean age of 10.3 years at study entry (range 7-16 years). All patients enrolled in this study had documented GAA deficiency and one of the following criteria: 1) cardiac hypertrophy, 2) was receiving invasive- or noninvasive-venitlatory support, or 3) had severe motor delay. The objective of the study was to provide ERT with Myozyme to these patients, as they did not meet the clinical characteristics for inclusion in other Myozyme studies, and as there was no alternative treatment available to them.

- Study AGLU02003 is an open-label, international, long-term, safety and efficacy, extension study of Myozyme (10 mg/kg per week, or 20, 30, or 40 mg/kg qow) administration to seven infantile-onset patients who were previously enrolled in clinical trials of ERT with other formulations of rhGAA (Pharming and Synpac). Patients had a mean age of 22 months at first rhGAA treatment (range 2 to 73 months), and 41 months, (range 24 to 76 months) at first Myozyme treatment. At the time of transition to Myozyme, two patients were receiving invasive-ventilatory support, and one patient was receiving noninvasive-ventilatory support. The objective of the study was to monitor the long-term safety and outcomes of rhGAA treatment in these patients.

- Study AGLU1205-02, Amendments 4 & 5, is an ongoing, open-label, extension study of Myozyme 20 to 40 mg/kg qow administration to a single infantile-onset Pompe disease patient, who had previously received rhGAA (Synpac and Pharming formulations) for three years under INDs — This patient was age 3 months at first rhGAA infusion and 41 months at first Myozyme infusion. The patient required invasive-ventilatory support at age 39 months (while on Synpac rhGAA) and continued to require invasive-ventilatory support at the time of first Myozyme infusion.

Juvenile- and adult-onset Pompe disease patients were treated in five separate studies and EAPs. All of the studies and programs in juvenile- and adult-onset patients were considered in lesser detail. The study designs for these studies and expanded access programs are described as follows (more detailed information on these 24 patients is described in the Appendix section, under Individual Study Reports, Juvenile- and Adult-Onset Pompe Disease Summary):

- Study AGLU02804 was an open-label, nonrandomized, uncontrolled, single-center, 26-week, safety and efficacy study of five juvenile-onset Pompe disease patients ages 6 to 15 years at study entry (median age 12.7 years), with onset of first symptoms at ages 1 to 12 years. All patients were able to ambulate at least 10 meters (m) at baseline, and patients on invasive ventilation at baseline were excluded. All patients received Myozyme 20 mg/kg qow for 26 weeks. The primary efficacy measures were changes from baseline at Week 26 in distance walked in six minutes (six-minute walk test, 6MWT), and pulmonary function test (PFT) parameters.

- The remaining 19 patients were treated in four different studies and expanded access programs, and the information was submitted predominantly as narratives. The study designs for these studies and programs are described as follows.

    - Study AGLU02503 is an ongoing, open-label, European expanded access program of Myozyme 20 mg/kg qow in the treatment of severely affected juvenile-onset Pompe disease patients. Four patients were enrolled in the EAP, but only three patients received treatment with rhGAA (one patient died prior to receiving any treatment). All patients enrolled in the EAP had documented signs or symptoms of Pompe disease at age greater than 12 months, were 21 years of age or younger at study entry, had documented GAA deficiency, and were severely affected (non-ambulatory and needing assisted ventilation). The initial

report submitted in the original submission to the application contained information on the first 26-weeks of treatment in these patients. A 52-week update was received in Amendment 002 for two of the patients (one patient died at Week 20).

- Study AGLU02103 is an ongoing, open-label, extension, safety and efficacy study of Myozyme 30 mg/kg qow in a single juvenile-onset patient, who had previously received 3.7 years of rhGAA treatment (Pharming and Synpac formulations) under INDs
- International EAP is an ongoing EAP conducted outside the US, which provides Myozyme to patients with infantile-, juvenile- and adult-onset Pompe disease. Fifty-four patients have been enrolled in this EAP as of 08-March-2005, and narratives for 14 of these patients were submitted to the application from this EAP, including 13 juvenile-onset patients and one muscular variant infantile-onset patient (IW).
- AGLU02603 (US EAP) is an ongoing, open-label, expanded access program conducted in the US for severely affected patients with juvenile- and adult-onset Pompe disease, who did not meet the clinical eligibility criteria for enrollment in an ongoing study of Myozyme. The first patient was enrolled December 2004. Narratives on two patients were submitted to the application from this EAP.

6.1.4 Efficacy Findings

Detailed reviews of the efficacy results for Studies AGLU01602 and AGLU01702 were performed and are summarized in the Appendix section in the Individual Study Reports. Please refer to the Individual Study Reports for more detailed discussions of these results.

The key efficacy findings from Studies AGLU01602 and AGLU01702 are summarized as follows:

6.1.4.1 Study AGLU01602: Ventilator-Free Survival at Week 52

The primary efficacy endpoint in Study AGLU01602 was the proportion of patients alive and free of invasive ventilation using Kaplan-Meier methodology as compared to survival in the Historical Control Subgroup at 18 months of age. The results show that there was a clear invasive ventilator-free survival advantage at 18 months of age seen in the rhGAA-treated patients as compared to survival in the Historical Control Subgroup. At the 18-month milestone, 15 of 18 (83%) rhGAA-treated patients were alive and free of invasive ventilatory-support, as compared to one of 61 surviving patients (2%) in the historical control. The overall results for the primary endpoint at the 52-Week milestone at the 15-June-2005 and 15-September-2005 updates are summarized in the following table:

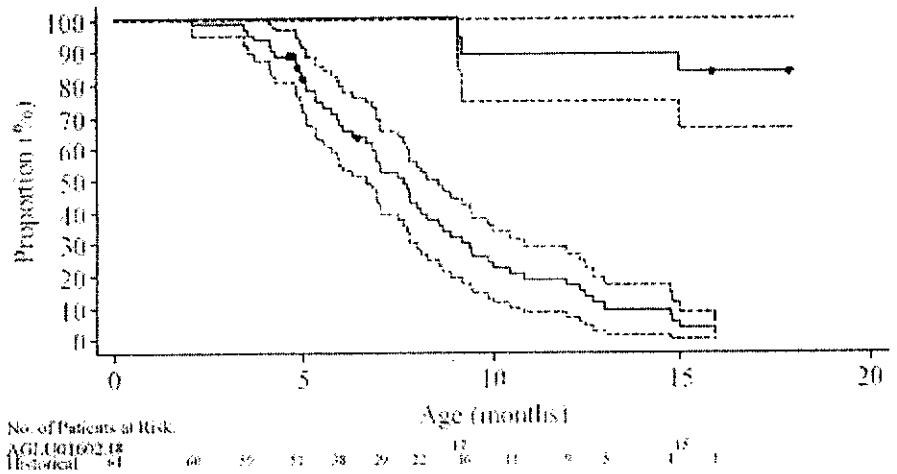
Table 6: Study 1602, Primary Endpoint of Ventilator-Free Survival, 52-Week Results

Dose Group	Study 1602 n =	Patients Alive & VF*, n (%)	Patients Meeting Primary Endpoint, n (%)	Patients Censored, n =	Proportion Estimate & 95% CI**	Historical Control n =	Patients Alive, n (%)	Proportion Estimate & 95% CI#
As of 15-June-2005 Update								
Overall, n =	18	13 (72)	3 (17)	2	83 (66, 100)	61	1 (2)	2 (0, 6)
20 mg/kg, n =	9	8 (89)	1 (11)	0	89 (68, 100)	-	-	-
40 mg/kg, n =	9	7 (78)	2 (22)	2	78 (51, 100)	-	-	-
As of 15-September-2005 Update								
Overall, n =	18	15 (83)	3 (17)	0	83 (59, 96)	61	1 (2)	2 (0, 6)
20 mg/kg, n =	9	8 (89)	1 (11)	0	89 (52, 100)	-	-	
40 mg/kg, n =	9	7 (78)	2 (22)	0	78 (40, 97)	-	-	

*VF= ventilator free
**Proportions and CI from Kaplan-Meier analysis of time to invasive ventilation or death for 15-June-2005 update, exact CI for 15-September 2005 update
#Proportions from Kaplan-Meier analysis of time to death.

The Kaplan-Meier curve for the time to invasive ventilation or death at the 18-month milestone (as of 15-June-2005 cutoff, two patients censored) is represented graphically in the following figure (electronically copied and reproduced from the Sponsor's submission). The lower line on the graph is the survival rate estimates curve for the Historical Control Subgroup with 95% CI surrounding it. The top line is the invasive ventilator-free survival rate estimate curve for Study AGLU01602 patients, with 95% CI surrounding it. It is noted that the analysis was the more conservative criterion of non-overlapping 95% CIs, and not the statistical significance of the comparison of 18-month survival rates.

Figure 1: Kaplan-Meier Plot of Time to Invasive Ventilation or Death from Date of Birth through 18-Month Milestone Compared to Historical Control Subgroup Survival



Exploratory and sensitivity analyses showed no obvious differences between the two rhGAA dose groups for invasive ventilator-free survival, nor were there differences in invasive

ventilator-free survival noted depending on age at diagnosis, first infusion, or first symptoms in rhGAA-treated patients. A selection bias in favor of patients enrolled in AGLU01602 was seen at the 12-month milestone (AGLU01602 patients had to survive long enough to start treatment, whereas that condition did not apply to the historical control subgroup) when an analysis for survival at the 12-month milestone was performed for age at death in the historical control eliminating patients who died at ages less than six months from the survival rate proportion estimate. This selection bias was minimal at the 18-month milestone (as only one patient in the Historical Control Subgroup survived to 18 months of age), showing a clear treatment effect for invasive ventilator-free survival at 18 months of age in rhGAA-treated patients.

6.1.4.2 Study AGLU01702: Survival at Week 52

The primary efficacy endpoint in Study AGLU01702 was the proportion of patients alive at Week 52. The results show that 16 of the 21 treated patients (76%) were alive at the Week 52 milestone, and at the Week 26 milestone, 17 of 21 patients were alive (81%). Five patients died during the 52-week treatment period at ages 8, 9, 12, 14 and 17 months. Sixteen patients remained alive at the Week 52 milestone, ranging in age from 16 to 56 months. The overall results are summarized in the following table.

Table 7: Study 1702, Patients Alive at Weeks 26 and 52

Patients, n =	21	95% CI
Duration of Treatment		
26 weeks, n (%)	17 (81)	58, 95
52 weeks, n (%)	16 (76)	53, 92

A comparison of age at death in an Historical Control Subgroup (n=86) and Subset (n=15), comprised of patients who were similar to the treated population in age and disease severity, showed that the age range at death in these historical control reference groups was broad, and overlapped with the outcomes in the treated population. Survival was additionally analyzed by the Sponsor by age at first infusion (inclusive of the first 15 patients enrolled only), and compared to the Historical Reference Subgroup (n=86) where patients were divided into three reference subsets by age (age <12 months at first infusion, >12 months at first infusion, and all patients). The results showed that survival depended on age at first infusion, with patients who survived to an age greater than 12 months prior to first infusion tending to have a longer survival compared to patients treated at an age of 12 months or younger. Kaplan-Meier estimates of conditional 52-week survival rate vs. survival rates seen in the first 15 patients enrolled in Study 1702 divided by age at first infusion are summarized from the Sponsor's study report in the following table.

Table 8: Study 1702, Analysis of Survival by Age at First Infusion as Compared to Historical Reference Subgroup

	Study 1702		Historical Reference Subgroup	
Age Category at 1st Infusion	Median Age at 1st Infusion (mos)	Actual 52-Week Survival Rate, n (%) [95%CI]	n =	Kaplan-Meier Estimate of Conditional 52-Week Survival Rate % [95% CI]
≤12 months, n = 6	8.1	3 (50%) [12%, 88%]	60	16% [6%, 26%]
>12 months, n = 9	18.1	8 (89%) [52%, 100%]	11	46% [16%, 75%]
All Patients, n = 15	15.0	11 (73%) [45%, 92%]	16	38% [14%, 61%]

An evaluation of respiratory status at baseline and Week 52 was also performed, and showed that at baseline, 16 of 21 patients were free of invasive ventilator support, including two patients on noninvasive ventilation, and five patients on invasive ventilatory support. For the five patients who were receiving invasive ventilator support at baseline, one died and four remained on invasive ventilation throughout the study. For the 16 patients not on invasive ventilatory support at baseline, ten remained free of ventilatory support, four died, and two required invasive ventilation. Thus, at Week 52, seven patients had a worsening status, including five patients who died, and two patients not on invasive ventilatory support at baseline who became invasive-ventilator dependent. A trend was noted in that patients with worsening status tended to have younger ages at diagnosis and at first infusion than patients who had no change in status.

Interpretation of the results for Study AGLU01702 was further complicated by the broadening of the study population through violations of the entry criteria, which allowed for a much more diverse study population (including both more severely-affected patients and patients with more attenuated disease) to be included in the study than originally intended, as historically it has been shown that even small increments in age at diagnosis can result in much longer survival in untreated patients. Discerning anything less than a dramatic treatment effect in this Pompe disease population would have been difficult in any case, due to the highly heterogeneous persentation and progression of the disease in this Pompe disease age group, but the additional difficulty resulting from the broadening of the treatment population through protocol violations made the likelihood of discerning a treatment effect in this study even less probable.

Thus, the overall results for Study AGLU01702 show that survival (and the outcome of worsening status of respiratory failure or death) overlaps with the outcomes in the historical reference groups, and appears to be at least partially dependent on the patients' ages at first infusion. These results are consistent with the known historical results in Pompe disease, where younger patients (i.e., those with more rapidly progressive disease, who come to medical attention at a younger age) tend to have a poorer prognosis. Therefore, due to the highly heterogeneous rate of progression to death in this Pompe disease patient population, and as there was no concurrent control group for the study, it was not possible to determine whether survival in AGLU01702 was due to a treatment effect with rhGAA in this population, or if the findings were consistent with the natural progression of the underlying disease.

6.1.4.3 Major Efficacy Endpoints

6.1.4.3.1 Cardiac Parameters

In both the AGLU01602 and AGLU01702 studies, the evaluation of cardiac parameters included repeated measurements of LVMI, LVM Z-scores, and EF by echocardiography.

In Study AGLU01602, the cardiac parameter results were notable for decreases in LVMI and LVM Z-scores in all patients from baseline at Week 52, consistent with the PD effect of rhGAA on cardiac muscle; however, there was no clear correlation by individual patient with decreases in LVMI and changes in EF, nor was there a clear correlation with the changes in the cardiac parameters and clinical outcome assessed by invasive ventilator-free survival, motor

development, or the development of cardiac Adverse Events (AEs) consistent with cardiac failure. The review of AEs consistent with cardiac failure was notable for only five post-baseline AEs in five patients, and as the signs and symptoms of cardiac and respiratory failure overlap in this patient population and as there were no historical control cardiac failure data available for comparison, no clear clinical effect on cardiac function can be discerned from rhGAA-treatment. Thus, the relevance of the PD effect of rhGAA treatment on cardiac function in these patients is unknown, and no clear clinical effect of rhGAA treatment on cardiac function could be definitively determined from the available data.

In Study AGLU01702, the results for LVMI showed that, overall, there was a mean decrease in LVMI from baseline to Week 52. In the 18 patients with LVMI results at baseline and at least one post-baseline visit, 13 patients had decreases in LVMI, four had no change in LVMI, and one patient had an increase in LVMI at Week 52 (or last available visit). The results for the LVM Z-scores were similar to the results for LVMI. The EF results showed highly variable results, with changes in EF ranging from -31% to +40%, with eleven patients having an increase in EF, and ten patients having a decrease in EF at the last available study visit. There did not appear to be an association between change from baseline in EF and patient outcome; however, an EF of <40% at baseline, or the development of signs and symptoms of cardiac failure at anytime during the study (from screening through last available visit) tended to be associated with a poor outcome (e.g., ventilator dependence or death). Thus, although a pharmacodynamic effect of rhGAA treatment was seen in this study by decreasing LVMI and LVM Z-score, there was no clear benefit on cardiac or clinical outcome seen with rhGAA treatment. Obvious errors were also noted in some of the cardiac parameter results, and the cardiac results are to be interpreted with caution.

6.1.4.3.2 Physical Growth Parameters

Physical growth was assessed through repeated measurements of body weight, length, and head circumference.

In Study AGLU1602, the growth data were notable for numerous missing and inconsistent datapoints, making interpretation of the data unreliable. Despite these limitations, however, weight, length, and head circumference increased in all patients throughout the study. Age-matched comparisons for weight and length showed that almost all patients were within two SD of the mean for normals at Week 52. No data on weight for height assessments and relation to method of feeding and calorie intake were presented, however, limiting the utility of the results. Head circumference data showed two patients with relative microencephaly at Week 52, and it is unclear if increasing head size for most patients during the study was attributable to catch-up or to central nervous system (CNS) glycogen accumulation similar to that found in other storage disorders. Thus, the overall effects of rhGAA treatment on physical growth are unclear, and it is recommended that follow-up trials for infants, including standardized measurements and analysis of growth in relationship to feeding and nutritional status, and weight for height be determined, and that longer term follow-up of head size be performed.

In Study AGLU01702, numerous irregularities in the data were noted. This was especially true for length and head circumference, where there were numerous missing datapoints and obvious

errors throughout the dataset. Of the 20 of 21 patients with baseline and at least one post-baseline result for length, eight patients had one (or more) clearly erroneous measurement(s). For head circumference, six patients had at least one clearly erroneous measurement. Due to the large number of errors, it was felt that the growth measurements data were unreliable and no conclusions will be drawn or inferred from the growth results.

6.1.4.3.3 Motor Development Assessments

In Study AGLU1602, the results for motor development were assessed using the AIMS and Pompe PEDI assessment tools. These results were notable in that the majority of patients treated with rhGAA experienced clinically meaningful gains in motor developmental milestones. Results from historical controls and from the medical literature show that few motor milestones are achieved in untreated patients and these few milestones are lost with disease progression. However, it is additionally noted that the majority of patients remained significantly delayed compared to normal age-matched peers and further follow-up is warranted to demonstrate persistence or catch-up with normal age-matched peers. Five patients by the AIMS test and four patients by the Pompe PEDI failed to achieve new motor milestones at anytime during the study, all of whom required ventilatory support during continued treatment and follow-up. Two patients who had initially showed the achievement of new motor milestones on the AIMS and Pompe PEDI tests (walking or weight bearing) had almost complete loss of these motor milestones later in the study and became ventilator dependent during continued treatment and follow-up. This coincided with the development of markedly elevated antibody titers and suggests interference from antibody with clinical response.

In Study AGLU01702, motor development was assessed using the AIMS, Pompe PEDI, and PDMS-2 tests. The results were consistent across the three tests evaluated, although interpretation of these test results was limited somewhat by missing data, especially in the sicker patients. Overall, the results appear to show that about half of the patients had modest gains in gross motor function (i.e., predominantly proximal, lower extremity muscle strength and function), but these patients were delayed compared to non-disabled, same-age peers. The other half of patients had little to no meaningful gains (or regression) in gross motor function. Gains (or preservation) in fine motor function (i.e. predominantly distal, upper extremity muscle function) were more evident, with most patients demonstrating gains in fine motor function that in some cases, approached age-matched norms. These motor development results are not surprising as in Pompe disease, proximal muscle weakness typically presents first and is more pronounced than distal muscle weakness, and lower limbs (and truncal musculature) are more affected than upper limbs. It is not known, however, if the fine motor gains (or preservation) in these patients was the results of treatment with rhGAA as these findings are consistent with the natural progression of the underlying disease. It was additionally noted that patient outcome tended to be associated with gross motor gains and function, but not with fine motor gains and function. That is, patients with higher gross motor scores tended to do better (by the outcome of death or ventilatory-support) than did patients with little or no gains and lower gross motor scores. No obvious correlation with fine-motor scores and outcomes was seen.

6.1.4.3.4 Cognitive Development Assessments

Cognitive development was assessed using the BSID-II assessment tool in both studies. In both Study AGLU01602 and Study AGLU01702, cognitive development results from the BSID-II test were encouraging, with most patients demonstrating increases in BSID-II scores from baseline at Week 52, and with most patients having scores within the normal or mildly delayed ranges as compared to same-age, normally developing peers. Longer-term follow-up of all of these patients is warranted, however, as these results are not predictive of future cognitive development (e.g., school-age function).

6.1.4.4 Additional Results

6.1.4.4.1 Study AGLU02804

Key efficacy measures in this Study AGLU02804 were the six-minute walk test (6MWT) and pulmonary function tests (PFTs). The 6MWT was performed twice for each patient, once at a "Comfortable Speed" and another time at a "Faster Speed". The results show that distance walked was largely dependent on patient effort and underscores the subjective nature of these results. The results are otherwise uninterpretable in an open-label study. The results are summarized in the following table.

Table 9: Study 2804 Results of the 6MWT

Overall, the results from this study were found to be highly subjective, and were uninterpretable. Further study in the juvenile- and adult-onset patient population in blinded, controlled trials is needed.

6.1.4.4.2 International Expanded Access Program: Patient

Patient — results were submitted in the form of a narrative, and are summarized as follows:

Patient — (The Netherlands) is a 19 year old male who presented with symptoms of Pompe disease at age six months when the patient experienced feeding difficulties. Motor milestones were delayed, and the patient was able to stand at age two years and walk without support at age 2.5 years. Pompe disease was diagnosed at age 2.5 years by fibroblast assay. The patient was wheelchair dependent from the age of nine and was unable to walk or stand, but was able to move his legs. At baseline (prior to any rhGAA treatment), cardiac status was normal and pulmonary function was within normal limits for age. ERT with Pharming (transgenic rabbit milk) rhGAA formulation was started in September 1999 at the age of 11 years at 10 mg/kg/week, then 20 mg/kg/week at Week 29. In July 2002, the patient transitioned to Myozyme (after 144 weeks of treatment with the Pharming preparation). After the start of rhGAA treatment, the patient had a dramatic improvement in muscle strength and function. After 72 weeks of treatment, he could rise from a chair and walk ten steps. He underwent an Achilles tendon release procedure at 75 weeks of treatment, and muscle strength and function continued to improve thereafter. After two years of treatment, he was able to walk short distances, and in the following years was able to run, ride a bike and play soccer.

This patient's profile most closely fits that of the muscular-variant infantile-onset form (age at onset by six months of age and cardiac sparing). The patient's dramatic response to treatment

with rhGAA (Pharming formulation) that was maintained on Myozyme is compelling and noteworthy.

6.1.4.4.3 Additional Expanded Access Narratives

The information from the narratives in the 19 remaining juvenile- and adult-onset patients (those patients not enrolled in Study AGLU02804), for whom information was submitted to the application are summarized as follows:

- 18/19 patients were ventilator-dependent at baseline, and 18/19 were wheelchair dependent at baseline, consistent with advanced stage of disease.
- All information for these patients was submitted as narratives.
- Wide range of treatment lengths was reported (20 weeks to 8 years).
- Quality of the information was, for the most part, exceedingly poor. Details were few, at times contradictory, and in at least one case, the narrative was illegible.
- One patient had a definite response to treatment (Patient — see above), and this patient's clinical history was most consistent with the muscular variant infantile-onset form of Pompe disease.
- No ventilator dependent patient was shown to have been able to discontinue ventilatory support. However, five patients were reported to have decreased the numbers of hours per day on ventilator support (ranging from a decreased requirement of 3 to 10 hours per day). No objective data were submitted to support this, and in some cases, narratives had conflicting information.
- Remaining patients had few objective signs of change.

All of these patients are summarized in more detail in the Appendix section, in the Individual Study Reports, Juvenile- and Adult-onset Pompe Disease Summary. Please refer to this section for more detailed information.

6.1.5 Clinical Microbiology

Not applicable.

6.1.6 Efficacy Conclusions

The efficacy results from the Myozyme clinical program provided substantial evidence of a benefit of treatment with Myozyme in the infantile-onset Pompe disease patient population. Evidence of a treatment benefit was demonstrated in Study AGLU01602, where treatment of infantile-onset Pompe disease patients with Myozyme at or prior to the age of seven months resulted in an invasive ventilator-free survival benefit at 18 months of age as compared to an untreated historical control of similar age and disease severity. Clinically meaningful gains in motor function were also demonstrated in these patients, although the majority of these patients were substantially delayed compared to same-age, non-disabled peers. It is not known if these results are sustained, especially in patients developing elevated anti-rhGAA antibody titers, and longer-term follow-up of these patients is needed.

No substantial evidence of a treatment effect of Myozyme in the Study AGLU01702 patient population could be determined, and the results of the 52-week interim analysis for Study AGLU01702 failed to definitely establish the efficacy of Myozyme in patients ages three months to 3.5 years at first infusion. Discerning anything less than a dramatic treatment effect in this Pompe disease population would have been difficult due to the highly heterogeneous presentation and progression of the disease in this Pompe disease age group, and the study results, not surprisingly, overlapped with the outcomes in an historical control reference population similar in age and disease severity. Interpretation of this study was additionally complicated by the lack of a concurrent control group, a large number of protocol violators by study entry criteria, and the poor quality of the data for several of the endpoints. Secondary endpoints of respiratory and motor function also were consistent with anecdotal and medical literature reports of the expected progression of the disease in this patient population. That is, patients with worsening status (e.g., death or ventilator dependence) tended to be younger than patients with stable status during the study, consistent with a more rapidly progressive disease course in patients with first symptoms and diagnosis at younger ages. Motor development showed modest gains in gross motor function in approximately half of the patients in the study, and most patients showed gains in fine motor function. This result is consistent with the earlier presentation and progression of proximal, lower extremity (and truncal) motor involvement and the relative sparing of distal motor function earlier in the course of the disease. These findings make it extremely difficult to determine whether there was a treatment effect with rhGAA in this population, or if the findings were due to the natural progression of the underlying disease. Longer-term treatment with rhGAA in this population is needed.

Outcomes measures in the remaining clinical studies and expanded access programs were of limited utility in determining the effect of Myozyme in Pompe disease. These results tended to be highly subjective with few objectively or consistently collected outcomes measures available for review. It is especially noted that there was a lack of objective data submitted in the juvenile- and adult-onset patient population, as there have been no adequate and well-controlled studies completed to date in this population. Thus, no assessment of the effect of Myozyme treatment on juvenile- and adult-onset Pompe disease patients is possible at this time.

Extrapolation of treatment effect from the most severely affected infantile-onset Pompe disease patients to the juvenile- and adult-onset Pompe disease patient population is not felt to be appropriate. The regulations for extrapolation of data from adult patients to pediatric patients state that extrapolation is possible when the course of the disease and the effects of the drug are sufficiently similar. While extrapolation in the reverse direction, from younger to older patients can be considered, the courses of disease are not the same in the infantile-onset, and juvenile- and adult-onset patients. For example, survival in juvenile- and adult-onset patients is typically measured in decades, not months as for infantile-onset patients, cardiac hypertrophy is not described in juvenile- and adult-onset patients, glycogen storage in skeletal muscle is patchy in older patients, and there is extreme heterogeneity of clinical presentation and progression of disease in juvenile- and adult-onset patients. These differences have also lead to substantial differences in study design being necessary for the juvenile- and adult-onset patients as compared to the infantile-onset patients. Thus, the data obtained in the ongoing Study

AGLU02704 (LOTS) will be essentital in establishing efficacy (and safety) in the juvenile- and adult-onset Pompe disease patient population.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

This application includes clinical safety information from ten Genzyme-sponsored clinical studies and expanded access programs (EAPs), in which all patients received treatment with open-label Myozyme. There were no placebo-controls used in any of these studies. Five clinical studies and EAPs were conducted in infantile-onset Pompe disease patients, and five studies and EAPs were conducted in juvenile- and adult-onset Pompe disease patients. Additional, limited information was obtained from an ongoing, double-blind, placebo-controlled, safety and efficacy study in juvenile- and adult-onset Pompe disease (Study AGLU02704, LOTS). These additional data consisted of isolated MedWatch reports submitted by the Sponsor to the Agency for serious, expedited Adverse Events (AEs), and for reports on hypersensitivity and infusion reactions that were submitted to the application at the request of the Division.

The most comprehensive safety data submitted to the application were the safety data collected in the two largest, GCP-compliant studies conducted in infantile-onset patients in support of this application: Studies AGLU01602 and AGLU01702. Safety data in these two 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 oversight (among others). Study AGLU02804 was also a GCP study subject to the same requirements as studies AGLU01602 and AGLU01702; however, this study was small (n=5) and of limited duration, resulting in a more limited safety database for the juvenile- and adult-onset patients.

The remaining studies were non-GCP studies and expanded access programs, in which safety data were collected predominantly through spontaneous reporting of Serious Adverse Events (SAEs), and, for the most part, the available safety data did not permit detailed review. These studies and programs do not allow for as complete a safety profile to be described as in the GCP studies, and these data were of limited utility.

In addition, the true Myozyme-exposure in the entire Myozyme clinical development program is unclear to this Reviewer. Full safety information was submitted to the application for 44 patients participating in GCP studies, including:

- AGLU01602, n=18
- AGLU01702, n=21
- AGLU02804, n=5

More limited information from non-GCP studies and programs was submitted in an additional 17 patients, including:

- AGLU02203, n=5
- AGLU02003, n=7
- AGLU1205-02, n=1
- AGLU02503, n=3
- AGLU02103, n=1

Reviewer comment: the 61 patients noted above include the 56 patients included in the 4-month safety summary submitted to the application plus the five additional patients from Study AGLU02804 submitted to the application in November 2005.

Additional information, predominantly in the form of SAE reporting, was submitted for an unknown number of Myozyme-exposed patients treated in other expanded access programs, and it is not known if the complete safety experience available for Myozyme has been submitted to the application for review.

The review of the safety data was additionally limited by:

- No comprehensive or integrated safety summary that encompassed all of the safety data submitted to this application was performed by the Sponsor. As safety data were submitted in pieces in the multiple submissions to this application, locating, reviewing and integrating all of the safety information contained in this application was extremely difficult. For example, most of the SAEs submitted to the application were reported as narratives that were located in multiple places scattered throughout the submission, with no comprehensive listing or summary located anywhere in the application. Thus, important safety information was, in effect, obscured by the presentation of the data in the application.
- A large amount of safety information from Study AGLU01702 was never submitted to the application. Safety data up to Week 52 of treatment was submitted for most patients in this study; however, many patients had Myozyme-exposure up to 2 years, but this extended safety experience was never included in the application.
- A worrisome safety signal for hypersensitivity was noted late in the review cycle after a serious, related hypersensitivity reaction was submitted as an expeditied report to the Myozyme IND. Receipt of this expedited report resulted in a request by the Division to the Sponsor for the Sponsor to query their pharmacovigilence database for similar events. This query resulted in the uncovering of numerous hypersensitivity reactions, some of which were life-threatening, and some of which had not been previously reported as serious events to either the Myozyme IND or the BLA. In discussions with the Sponsor, the Sponsor stated that not all of these events were submitted as serious events to the IND, nor the BLA, as they were considered to be expected events as they were listed in the Investigator's Brochure. These discussions resulted in a clarification on reporting procedures to be followed for this application. As these reactions were identified and reported late in the review cycle (April 2006), there was insufficient time available to

thoroughly assess and review this safety signal. Until that work can be completed, it is appropriate to remain cautious about the safety of this product, and to label the product in a conservative manner until more can be learned about the extent of the problem.

- As patients participating in these studies have considerable underlying disease-related morbidity, and as there was no placebo-control in any of the studies (with the exception of AGLU2704, for which there is limited information), the identification of drug-related toxicities is challenging.

Safety information available from Studies AGLU01602 and AGLU01702 was amenable to pooling. Thus, pooled results for these two studies will be summarized and presented for most of the safety sections (below). Safety data for Studies AGLU01602 and AGLU01702 were also analyzed in detail by individual study (please see the Appendix section, Individual Study Reports for a more detailed discussion of the individual study safety results). Additional information from the other studies and programs will be summarized where available and as appropriate.

7.1.1 Deaths

Deaths as of a safety cut-off date of 08-March-2005 were summarized in the 4-month safety summary submitted to the application on 05-December-2005 (Amendment 005). These deaths occurred in the 56 patients included in the 4-month safety summary from Studies AGLU- 01602, -01702, -02203, -02003, -1205-02, -02503, and -02103, and additional deaths (from an unknown number of Myzoyme-exposed patients) were also reported from the Pharmacovigilance dabtabase from the International expanded access program (EAP), also to a cut-off date of 08-March-2005.

There were 14 deaths listed in the 4-month safety update: ten deaths were reported in 56 Myozyme-exposed patients, and four additional deaths were reported from the International EAP (overall denominator is not known). One additional death was known to have occurred in approximately September 2005 (personal communication with the Sponsor): Patient 303 died after completing participation in Study AGLU01602 and transitioning to an EAP. For these 15 patients, causes of death were predominantly due to complications of underlying disease, including cardiac and respiratory failure/arrest, and infection. One additional death was noted in a patient in Study AGLU01702 (Patient 401), who died of ventricular fibrillation/cardiac arrest after induction of general anesthesia for central venous catheter placement during the study Screening/Baseline period (study-related procedure). This patient was never treated with Myozyme.

These 16 deaths are listed in the following table:

Table 11: Deaths

Study	Patient	Age at First Infusion (mos)	Age at Death (mos)	Estimated Exposure (mos)	Cause of Death	Attribution
1602	305	6	20	14	Desaturation and bradycardia	Not Related
1602*	303*	7	32	25	Multiorgan failure/septicemia	Not Related
1702**	401**	Never treated	9	None	Ventricular fibrillation/Cardiac arrest	Not related
1702	405	13	17	4	Cardiorespiratory arrest	Not Related
1702	407	8	12	4	Cardiorespiratory arrest	Not Related
1702	409	6	8	2	Arrhythmia, actue heart failure, actue pulmonary edema	Not Related
1702	412	8	14	6	Arrythmia	Not Related
1702	419	9	9	<1	Cardiac arrest	Not Related
2003	203	8	34	26	Respiratory failure	Not Related
2003	206	3	32	29	Cardiac arrest	Not Related
2503	9301	20	20	<1	Cardiorespiratory arrest	Not Related
2203	747	7	10	3	Respiratory failure	Not Related
Int'l EAP	60-729	7	9	2	Cardiorespiratory failure	Not Related
Int'l EAP	99-702	10	14	4	Cardiac arrest	Not Related
Int'l EAP	102-716	8	15	7	Respiratory failure	Not Related
Int'l EAP	129-749	29	32	3	Cardiac failure	Not Related

*Patient died after completing study AGLU01602 and after transition to an expanded access program
**Patient died in Screening/baseline period during general anesthesia for central venous catheter placement (study procedure related)

7.1.2 Other Serious Adverse Events

Serious Adverse Events that occurred in the infantile-onset studies AGLU01602 and AGLU01702 were pooled by this Reviewer. Pooling was performed by combining all treatment-emergent SAEs (occurring on or after Day 0, day of first Myozyme administration) from:

1. Study AGLU01602, safety information to a cut-off date of 15-June-2005, after all patients had completed at least 52 weeks of Myozyme (dataset Amendment 002 aex_1.xpt); and
2. Study AGLU01702, safety information to, at latest, the cut-off date of 09-December-2005, inclusive of the Week 52 visit (or last visit for patients who died) for all patients (dataset Amendment 008 aex_1.xpt).

The results showed 35 of 39 patients reported at least one SAE during the studies. SAEs tended to reflect the underlying disease (e.g., respiratory and infectious terms) or treatment intervention complications (e.g., catheter-related infection). The most commonly reported SAE was pneumonia, reported by 16 of 39 patients (41%) in the pooled population, followed by respiratory failure (31%) and respiratory distress (26%). The types and frequencies of SAEs reported were also similar in both studies when considered individually (not shown). Other significant serious adverse events, including infusion associated reactions, hypersensitivity and infusion-related reactions, cardiac arrhythmias, and acute cardiorespiratory failure are discussed in Section 7.1.3.3 Other significant adverse events (please refer to this section for a more detailed discussion of these events). The most commonly reported SAEs (reported by ≥2 patients) are listed in the following table.

Table 12: Pooled SAEs, Studies AGLU01602 and AGLU01702, Most Common (Reported by ≥2 Patients)

Treated patients, n =	SAE Incidence Rates 39
SOC AE Preferred Term	**n (%)**
Cardiac disorders	
Cardiorespiratory arrest	4 (10)
Bradycardia	3 (8)
Arrhythmia	2 (5)
Cardiomyopathy	2 (5)
Gastrointestinal disorders	
Vomiting	3 (8)
Diarrhea	2 (5)
Gastroesophageal reflux disease	2 (5)
Upper gastrointestinal hemorrhage	2 (5)
General disorders and administration site conditions	
Pyrexia	5 (13)
Infections and infestations	
Pneumonia	16 (41)
Catheter related infection	8 (21)
Respiratory syncytial virus infection	6 (15)
Gastroenteritis	5 (13)
Bronchiolitis	4 (10)
Viral infection	4 (10)
Bacteremia	2 (5)
Bronchitis	2 (5)
Influenza	2 (5)
Nasopharyngitis	2 (5)
Ear Infection	2 (5)
Otitis media	2 (5)
Respiratory tract infection	2 (5)
Tracheitis	2 (5)
Upper respiratory tract infection	2 (5)
Injury, poisoning and procedural complications	
Fracture, femur	3 (8)
Investigations	
Ejection fraction decreased	3 (8)
Oxygen saturation decreased	3 (8)
Respiratory, thoracic and mediastinal disorders	
Respiratory failure	12 (31)
Respiratory distress	10 (26)
Pneumonia aspiration	4 (10)
Asthma	3 (8)
Atelectasis	2 (5)
Bronchospasm	2 (5)
Cough	2 (5)
Dyspnea	2 (5)
Hypoxia	2 (5)
Pulmonary edema	2 (5)
Respiratory arrest	2 (5)
Skin and subcutaneous tissue disorders	
Urticaria	2 (5)

As patients in Study AGLU01602 were randomized equally to treatment with Myozyme 20 mg/kg or 40 mg/kg, SAE incidence rates could also be compared by dose group. There were no

obvious differences in SAE incidence rates occurring in either dose group. The results for the most commonly reported SAEs (by ≥2 patients) by dose group for Study AGLU01602 are summarized in the following table.

Table 13: Study 1602, Most Commonly Reported SAEs (reported by ≥2 patients)

	SAE Incidence Rates		
	All	20 mg/kg	40 mg/kg
Treated Patients, n =	18	9	9
SOC			
AE Preferred Term	n (%)	n (%)	n (%)
Cardiac disorders			
Bradycardia	2 (11)	1 (11)	1 (11)
Gastrointestinal disorders			
Upper gastrointestinal hemorrhage	2 (11)	2 (22)	0
General disorders and administration site conditions			
Pyrexia	2 (11)	1 (11)	1 (11)
Infections and infestations			
Pneumonia	8 (44)	4 (44)	4 (44)
Catheter related infection	5 (28)	1 (11)	4 (44)
Respiratory syncytial virus infection	5 (28)	2 (22)	3 (33)
Bronchiolitis	4 (22)	2 (22)	2 (22)
Gastroenteritis	4 (22)	1 (11)	3 (33)
Viral infection	4 (22)	3 (33)	1 (11)
Nasopharyngitis	2 (11)	0	2 (22)
Ear Infection	2 (11)	0	2 (22)
Otitis media	2 (11)	1 (11)	1 (11)
Respiratory tract infection	2 (11)	1 (11)	1 (11)
Injury, poisoning and procedural complications			
Fracture, femur	2 (11)	1 (11)	1 (11)
Investigations			
Ejection fraction decreased	2 (11)	1 (11)	1 (11)
Oxygen saturation decreased	2 (11)	1 (11)	1 (11)
Respiratory, thoracic and mediastinal disorders			
Respiratory failure	7 (39)	3 (33)	4 (44)
Pneumonia aspiration	4 (22)	3 (33)	1 (11)
Respiratory distress	4 (22)	2 (22)	2 (22)
Asthma	2 (11)	1 (11)	1 (11)
Atelectasis	2 (11)	1 (11)	1 (11)

7.1.3 Dropouts and Other Significant Adverse Events

There were no discontinuations for Adverse Events (AEs) in AGLU01602 and AGLU01702, other than for patient deaths (one patient died prior to study completion in study AGLU01602, and six patients died prior to study completion in Study AGLU01702 – see Deaths section above). This Reviewer is aware of four patients who were discontinued from Myozyme treatment in clinical studies and EAPs. Two adult patients were discontinued from Study AGLU02704 (LOTS), one adult patient was discontinued from Study AGLU02603 (US EAP), and one infantile-onset patient was discontinued from Study AGLU02203 (International EAP). These patients are:

- Patient 16709/ — 32 year old female participating in LOTS;
- Patient 90701 — 61 year old male participating in LOTS;
- Patient 075-831 — 46 year old female participating in US EAP; and
- Patient 44-730/ — 10-month old female participating in AGLU02203 (EAP)

7.1.3.1 Overall profile of dropouts

Three of the patients who dropped out were adult patients, and one was an infantile-onset patient. Limited information is available on any of these patients, other than age and gender, which was abstracted from the MedWatch forms or narratives associated with the Adverse Events (AEs). These patients included three females and one male, ranging in age from 10 months to 61 years (10 months, 32 years, 46 years, and 61 years).

7.1.3.2 Adverse events associated with dropouts

All four patients who were withdrawn were withdrawn due to Adverse Events (AEs), all of which were likely hypersensitivity or infusion-related reactions. These AEs included: anaphylactic reaction, angioedema, likely anaphylactic/hypersensitivity reaction (hypotension, flushing, tachycardia, rigors), and recurrent infusion/hypersensitivity reactions (episodes of desaturation, cyanosis, rash, fever, hypotension, and other AEs) in the face of continuing clinical decline. All of these reactions occurred during or immediately after Myozyme infusion.

Patient 075-831 — he 46 year old female participating in the US EAP, was noted by the Sponsor to have withdrawn consent; however, the Agency initially received notification of this patient's discontinuation from a third party (not from the Sponsor), and the patient's own description of her reason for discontinuing participation was due to the AE she experienced during infusion, and her concerns about the risks of continued treatment with Myozyme. Patient 44-730 — the 10-month old who experienced recurrent hypersensitivity/infusion-related reactions to Myozyme was also noted by the Sponsor to have been voluntarily withdrawn; however, this patient experienced multiple, recurrent, severe (some of which were life-threatening) reactions to Myozyme, all the while experiencing continued decline in her clinical condition. It is inconceivable that the decision to withdraw this patient (by the patient's parents) was not influenced by the negative clinical course associated with Myozyme treatment.

The AEs leading to discontinuation in these four patients are briefly summarized as follows:

Patient 16709 — anaphylactic reaction (pruritus, rash, chest tightness, throat tightness, headache, nausea, flushing, wheezing, tachycardia) that occurred during infusion of the second Myozyme administration. The patient experienced hives during her first infusion. Laboratory testing was notable for positive IgE to rhGAA (retested sample, first testing was negative), elevated serum tryptase, and complement activation.

Patient 90701/ — angioedema (tongue edema, dysphagia, chest tightness) 20 minutes after completion of the second Myozyme infusion. IgE, serum tryptase and complement activation testing were all negative.

Patient 075-831 — hypotension, tachycardia, flushing, warm sensation, nausea, rigors, and pallor during fifth Myozyme infusion. IgE and serum tryptase testing were negative, and complement activation was positive.

Patient 44-730/ — recurrent episodes of hypotension, oxygen desaturation, cyanosis, tachycardia, rash, fever, pyrexia, bradycardia, hypotension, tachypnea, edema, and other AEs beginning at the fourth Myozyme infusion and experienced at multiple infusions thereafter. This patient also had continued clinical decline including generalized hypotonia and invasive ventilator dependency, and was discontinued from Myozyme treatment (treated from 05-August-2004 to 26-February-2005).

7.1.3.3 Other significant adverse events

7.1.3.3.1 Infusion Associated Reactions

Infusion associated reactions (IARs) were defined by the Sponsor as those AEs occurring on the day of infusion from the onset of the infusion up to and including the two-hour observation period AND were assessed by the Investigator as being at least possibly related to rhGAA treatment. IARs occurring in the infantile-onset studies AGLU01602 and AGLU01702 studies were pooled by this Reviewer (AGLU01602 Amendment 002 aex_1.xpt + AGLU01702 Amendment 008 aex_1.xpt).

The results showed that there were a total of 203 IARs reported by 20 of 39 patients (51%), and 165 of these IARs were reported by nine of these patients. The most commonly reported IARs were rash and pyrexia, reported by 9 of 39 patients (23%) each. All IARs reported in the pooled studies are listed in the following table.

Table 14: Pooled IARs, Studies AGLU01602 and AGLU01702

Treated patients, n =	IAR Incidence Rates 39	#s of IARs by Term
SOC AE Preferred Term	**n (%)**	
Cardiac disorders		
Tachycardia	4 (10)	7
Cyanosis	2 (5)	3
Gastrointestinal disorders		
Vomiting	3 (8)	8
Retching	2 (5)	7
Gastroesophageal reflux disease	1 (3)	1
General disorders and administration site conditions		
Pyrexia	9 (23)	25
Rigors	2 (5)	3
Infusion site reaction	1 (3)	1
Lethargy	1 (3)	1
Injury, poisoning and procedural complications		
Hypothermia	1 (3)	1
Investigations		
Oxygen saturation decreased	6 (15)	20
Blood pressure increased	2 (5)	2
Blood pressure decreased	1 (3)	1
Body temperature increased	1 (3)	1
Heart rate decreased	1 (3)	2
Heart rate increased	1 (3)	1
Respiratory rate increased	1 (3)	1
Nervous system disorders		
Tremor	2 (5)	3
Psychiatric disorders		
Agitation	2 (5)	4
Irritability	2 (5)	2
Restlessness	1 (3)	1
Respiratory, thoracic and mediastinal disorders		
Cough	5 (13)	17
Tachypnea	5 (13)	8
Bronchospasm	1 (3)	1
Rales	1 (3)	1
Skin and subcutaneous tissue disorders		
Rash	9 (23)	32
Urticaria	6 (15)	23
Pruritus	2 (5)	2
Edema periorbital	1 (3)	1
Hyperhidrosis	1 (3)	1
Livedo reticularis	1 (3)	1
Palmar erythemia	1 (3)	1
Vascular disorders		
Flushing	6 (15)	12
Hypertension	2 (5)	3
Pallor	2 (5)	3
Hypotension	1 (3)	2

As patients in Study AGLU01602 were randomized equally to treatment with Myozyme 20 mg/kg or 40 mg/kg, IAR incidence rates and numbers of IARs reported could also be compared by dose group. This comparison was notable in that IARs were more commonly reported in the

40 mg/kg group, with 123 of the 164 IARs reported in Study AGLU01602 having occurred in the 40 mg/kg group as compared to 41 IARs in the 20 mg/kg group. With the exception of the term oxygen saturation decreased, all of the IAR terms were reported more frequently in the 40 mg/kg group, and 20 of the 28 IAR terms were reported exclusively in the 40 mg/kg group. The most frequently reported IARs for all patients were pyrexia and rash (7 patients and 23 and 24 reports, respectively, each), followed by urticaria (5 patients, 22 reports). All IARs reported in Study AGLU01602 by incidence and by numbers of IARs reported are summarized in the following table.

Table 15: Study AGLU01602 Amendment 002, All IARs

	IAR Incidence Rates			Numbers of IARs Reported by Term		
	All	20 mg/kg	40 mg/kg	All	20 mg/kg	40 mg/kg
Treated Patients, n =	**18**	**9**	**9**			
SOC **AE Preferred Term**	**n (%)**	**n (%)**	**n (%)**			
Cardiac disorders						
Tachycardia	3 (17)	0	3 (33)	6	0	6
Cyanosis	2 (11)	0	2 (22)	3	0	3
Gastrointestinal disorders						
Vomiting	3 (17)	1 (11)	2 (22)	8	2	6
Retching	2 (11)	1 (11)	1 (11)	7	4	3
Gastroesophageal reflux disease	1 (6)	0	1 (11)	1	0	1
General disorders and administration site conditions						
Pyrexia	7 (39)	3 (33)	4 (44)	23	6	17
Rigors	2 (11)	0	2 (22)	3	0	3
Infusion site reaction	1 (6)	0	1 (11)	1	0	1
Injury, poisoning and procedural complications						
Hypothermia	1 (6)	0	1 (11)	1	0	1
Investigations						
Oxygen saturation decreased	4 (22)	2 (22)	2 (22)	18	13	5
Blood pressure decreased	1 (6)	0	1 (11)	1	0	1
Body temperature increased	1 (6)	0	1 (11)	1	0	1
Heart rate decreased	1 (6)	0	1 (11)	2	0	2
Nervous system disorders						
Tremor	1 (6)	0	1 (11)	2	0	2
Psychiatric disorders						
Irritability	2 (11)	0	2 (22)	2	0	2
Agitation	1 (6)	0	1 (11)	3	0	3
Restlessness	1 (6)	0	1 (11)	1	0	1
Respiratory, thoracic and mediastinal disorders						
Cough	3 (17)	1 (11)	2 (22)	14	3	11
Tachypnea	3 (17)	0	3 (33)	6	0	6
Rales	1 (6)	0	1 (11)	1	0	1
Skin and subcutaneous tissue disorders						
Rash	7 (39)	2 (22)	5 (56)	24	8	16
Urticaria	5 (28)	3 (33)	2 (22)	22	5	17
Livedo reticularis	1 (6)	0	1 (11)	1	0	1
Palmar erythemia	1 (6)	0	1 (11)	1	0	1
Pruritus	1 (6)	0	1 (11)	1	0	1
Vascular disorders						
Flushing	2 (11)	0	2 (22)	4	0	4
Hypertension	2 (11)	0	2 (22)	3	0	3
Hypotension	1 (6)	0	1 (11)	2	0	2
Pallor	1 (6)	0	1 (11)	2	0	2
Total				**164**	**41**	**123**

7.1.3.3.2 Hypersensitivity and Infusion-Related Reactions

A safety signal for severe hypersensitivity reactions during Myozyme infusion was noted late in the review cycle. Some of these hypersensitivity reactions have been life-threatening. Hypersensitivity reactions included anaphylactic shock (cyanosis, hypoxia, hypotension, and bronchoconstriction, requiring unspecified life support measures), anaphylactic and anaphylactoid reactions (IgE and non-IgE mediated), angioedema, and numerous cases of infusion reactions associated with two of the three organ systems of cardiac, respiratory and skin (consistent with anaphylaxis/hypersensitivity). Hypersensitivity reactions have occurred in infantile- through adult-onset patients, have lead to the discontinuation of at least three adult patients from clinical studies and expanded access programs (and possibly one infantile-onset patient from an expanded access program), and appear to have occurred in about 15% of patients treated in clinical trials with Myozyme to date.

Recognition of this signal lead to a request by the Division to the Sponsor to query their pharmacovigilence database for similar cases. As these reactions were identified and reported late in the review cycle (April 2006), and as the frequency, incidence, and magnitude of this problem is still being defined, there was insufficient time available to thoroughly assess and review this safety signal. Until this work can be completed, it is appropriate to remain cautious about the safety of this product, and to label the product in a conservative manner until more can be learned about the extent of the problem. However, as this safety signal is noteworthy, it is recommended that a warning for serious and severe hypersensitivity reactions, including life-threatening reactions and including a boxed warning, appear prominently in the product labeling.

7.1.3.3.3 Cardiac Arrhythmia

Cardiac arrhythmias associated with the use of general anesthesia have been observed during the rhGAA clinical program in several infantile-onset Pompe disease patients with underlying cardiac hypertrophy. These arrhythmias have included ventricular fibrillation, ventricular tachycardia, and bradycardia, and have resulted in cardiac arrest or death, or have required cardiac resuscitation or defibrillation in some patients.
Specific examples of these cardiac arrhythmias include the following from Studies AGLU01602 and AGLU01702:

In Study AGLU01602, at least four patients were noted to have experienced cardiac arrhythmia AEs with general anesthesia, some of which were for study-related procedures (e.g., muscle biopsy or central venous catheter placement). Two of these cardiac arrhythmia AEs were noted to have occurred in the Screening/Baseline period during study-related procedures, but prior to rhGAA administration. One patient experienced bradycardia during muscle biopsy and central line placement after receiving propofol, and one patient experienced ventricular fibrillation during muscle biopsy after receiving nitrous oxide and sevoflurane. Two additional patients were noted to have experienced cardiac arrhythmias after receiving general anesthesia during or shortly after completing the study. One patient experienced "arrhythmia" during bronchoscopy and stomaplasty after receiving ketamine, sevoflurane and succinylcholine, and another patient experienced ventricular tachycardia, ventricular fibrillation, and cardiac arrest during intubation after receiving succinylcholine, fentanyl, and etomidate.

In Study AGLU01702, cardiac arrhythmia AEs were noted to have occurred in two patients during the Screening/Baseline period and at Day 1 during the study, after administration of general anesthesia for study-related procedures. One patient experienced ventricular fibrillation resulting in cardiac arrest and death during induction of anesthesia for the baseline muscle biopsy procedure prior to receiving any treatment with rhGAA. The other patient was noted to experience bradycardia and hypotension during anesthesia for surgical procedures during the study.

The cardiac arrhythmia events associated with anesthesia use during Studies AGLU01602 and AGLU01702 are summarized in the following table.

Table 16: Study 1602, Cardiac Arrhythmias Associated with Anesthesia

Patient	AE Preferred Term	Time of Occurence
AGLU01602		
315	Bradycardia	Study day -21
319	Ventricular fibrillation	Study day -1
306	Arrhythmia	14 days post-last infusion
313	Ventricular tachycardia, ventricular fibrillation, cardiac arrest	7 days post-last infusion
AGLU1702		
401	Cardiac arrest	6 days post-signing ICF
401	Ventricular fibrillation	6 days post-signing ICF
413	Bradycardia during anaesthesia for surgical procedures	Study day 1
413	Hypotension during anaesthesia for surgical procedures	Study day 1

These events and similar events in the infantile-onset Pompe disease population in other studies and expanded access programs lead to a revision of the Investigator's Brochure and heightened awareness and training for the Investigators regarding the use of anesthetic agents in the infantile-onset Pompe disease population. Infantile-onset Pompe disease patients are at increased risk of experiencing cardiac complications during general anesthesia due to the underlying cardiac hypertrophy found in these patients. As the majority of infantile-onset patients will require central venous catheter placement for chronic Myozyme administration, the placement of a prominent warning regarding the use of general anesthesia for this procedure in the product labeling is appropriate.

7.1.3.3.4 Acute Cardiorespiratory Failure

Acute cardiorespiratory failure was observed in one infantile-onset Pompe disease patient with underlying cardiac hypertrophy after infusion of Myozyme. This patient (Patient 829-007 —) is a 3 month old male enrolled in the International EAP, who developed acute cardiac failure, worsening hypertrophic cardiomyopathy, respiratory failure requiring intubation, and intensive care unit (ICU) admission and inotropic support approximately 10 hours after his first Myozyme infusion. This event was felt likely to have been secondary to fluid overload in setting of cardiac hypertrophy. As infantile-onset patients with underlying cardiac hypertrophy are at risk of cardiac decompensation with the infusion of fluid/protein volumes, including Myozyme treatment, the placement of a prominent warning for this event in the product labeling is appropriate.

7.1.3.3.5 Hearing Loss

Hearing loss at Screening/Baseline and during treatment was reported in many patients in the rhGAA clinical development program, including infantile-, juvenile- and adult-onset patients in clinical trials and in expanded access programs. Hearing loss was described as hypoacousis, sensorineural, mixed, and conductive in these patients, and it was additionally noted that middle ear effusions were present in many patients, which complicated the interpretions of the results.

Hearing loss has been described in the medical literature as associated with Pompe disease, possibly secondary to glycogen deposition in the cochlea. Hearing loss has also been reported in other lysosomal storage diseases. It appears likely that the hearing loss reported in this study is secondary to underlying disease and not to treatment with rhGAA, although it is not possible at this time to determine whether rhGAA treatment modifies the progression or development of hearing loss in this patient population. It is recommended, therefore, that longer-term follow-up of hearing be performed in patients receiving rhGAA.

7.1.4 Other Search Strategies

No other search strategies were performed.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

For Studies AGLU01602, AGLU01702, and AGLU02804, the safety population included all enrolled patients who received at least one dose of Myozyme. Safety assessments included physical examinations (including vital signs), laboratory tests (chemistry, hematology and urinalysis), anti-rhGAA IgG antibody testing, ECGs, and AE assessments. AEs were recorded from the time of study entry (signing of the Informed Consent) and at each study visit for the duration of the study. The other assessments were collected at baseline/screening and at intervals throughout the study (see the Appendix section in the Individual Study Reports for a listing of study visits and procedures by individual study). Clinically significant worsening from screening in physical examinations, vital signs, and laboratory evaluations were documented as AEs. The anti-rhGAA antibody results were not listed as AEs, and were analyzed separately (see section 7.1.10 Immunogenicity).

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

AEs were coded by System Organ Class (SOC) and AE preferred term by the Sponsor 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. As the number of patients in the Myozyme clinical development program was small, and as AEs from only 39 patients were proposed for inclusion in the Adverse Reactions section of the product labeling, the AE preferred terms were revised by this Reviewer

(with agreement from the Sponsor), so that AE terms were clustered together to allow for a more meaningful description of the AE profile of Myozyme. For example, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, and others, were all coded to the AE preferred term of rash.

7.1.5.3 Incidence of common adverse events

Incidence rates of common AEs reported in Studies AGLU01602, AGLU01702 and AGLU02804 were analyzed from the AE datasets for each study (aex_1.xpt). Multiple datasets were submitted to the application for the AGLU01602 and AGLU01702, and the most recent datasets (Amendment 002 for AGLU01602 and Amendment 008 for AGLU01702) were used for the safety analysis as these were the most complete. The AE datasets for AGLU01602 and AGLU01702 were pooled by this Reviewer to increase the sensitivity of AE signal detection. Treatment-emergent AEs (including those AEs that occurred on or after Day 0, day of first Myozyme administration) were summarized. Recurrent or continuing AEs were counted only once, and AE incidence rates were calculated using all patients who received at least one dose of study medication as the denominator. AEs occurring during the screening/baseline period were reviewed and only notable AEs occurring during this time period are noted in this review (i.e., cardiac arrhythmias associated with the use of general anesthesia are discussed in section 7.1.3.3 Other significant adverse events).

7.1.5.4 Common adverse event tables

The most common AEs (AEs occurring in ≥20% of patients) from the pooled safety analysis for Studies AGLU01602 and AGLU01702 are summarized in the following table:

Table 17: Pooled AEs, Most Common, AGLU01602, Amendment 002 + AGLU01702, Amendment 008

Patients, n =	Patients Reporting 39
SOC **AE Preferred Term**	**n (%)**
Blood and lymphatic system disorders	**17 (44)**
Anemia	12 (31)
Cardiac disorders	**24 (62)**
Tachycardia	9 (23)
Bradycardia	8 (21)
Gastrointestinal disorders	**32 (82)**
Diarrhea	24 (62)
Vomiting	19 (49)
Gastroesophageal reflux disease	10 (26)
Constipation	9 (23)
General disorders and administration site conditions	**38 (97)**
Pyrexia	36 (92)
Infections and infestations	**37 (95)**
Pneumonia	18 (46)
Otitis media	17 (44)
Upper respiratory tract infection	17 (44)
Gastroenteritis	16 (41)
Pharyngitis	14 (36)
Ear infection	13 (33)
Oral candidiasis	12 (31)
Catheter related infection	11 (28)
Bronchiolitis	9 (23)
Nasopharyngitis	9 (23)
Injury, poisoning and procedural complications	**20 (51)**
Post procedural pain	10 (26)
Investigations	**28 (72)**
Oxygen saturation decreased	16 (41)
Respiratory, thoracic and mediastinal disorders	**38 (97)**
Cough	18 (46)
Respiratory distress	13 (33)
Respiratory failure	12 (31)
Rhinorrhea	11 (28)
Tachypnea	9 (23)
Bronchospasm	8 (21)
Skin and subcutaneous tissue disorders	**33 (85)**
Rash	24 (62)
Dermatitis diaper	14 (36)
Urticaria	8 (21)
Vascular disorders	**14 (36)**
Flushing	8 (21)

All AEs occurring in Study AGLU02804 are summarized by AE preferred term in the following table:

Table 18: AGLU02804, All AEs

	AE Incidence Rates	Numbers of AEs Reported
Treated Patients, n =	5	
Patients Reported any AE, n (%)	5 (100)	
AE Preferred Term	n (%)	
Headache	3 (60)	4
Pharyngitis	3 (60)	3
Abdominal pain upper	2 (40)	5
Malaise	2 (40)	2
Rhinitis	2 (40)	2
Allergic rhinitis	1 (20)	1
Diarrhea	1 (20)	1
Excoriation	1 (20)	1
Gastroenteritis	1 (20)	1
Keloid scar	1 (20)	1
Molluscum contagiosum	1 (20)	1
Otalgia	1 (20)	1
Pediculus capitus	1 (20)	1
Pyrexia	1 (20)	1
Respiratory tract infection	1 (20)	1
Sinusitis	1 (20)	3
Traffic accident	1 (20)	1
Upper respiratory tract infection	1 (20)	1
Visual acuity decreased	1 (20)	1
Wheezing	1 (20)	1

7.1.6 Less Common Adverse Events

Due to the small size of the Myozyme-exposed population in the Myozyme clinical program, the large number of disease-related AEs, and as there was no placebo-control data available for comparison, no meaningful analysis of less common AEs could be performed. Less common AEs for which a safety signal was detected by surveillance of expedited safety reports submitted during the review cycle have been discussed (above) and included in Section 7.1.3.3 Other significant adverse events (please refer to this section for more detailed information).

7.1.7 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 AGL0U1602, AGLU01702, and AGLU02804 individual study reports. Clinically significant worsening in any laboratory parameter was documented as an AE, and these AEs have been considered in the overall review of AEs. Laboratory parameters were also reviewed by individual clinical trial, and no notable, relevant, or remarkable findings for changes in any laboratory parameters were seen; however, there was insufficient time available in the review period to thoroughly review these data.

7.1.8 Vital Signs

Vital signs were perfomed according to the study schedules outlined in the study visits and procedures section of the AGL0U1602, AGLU01702, and AGLU02804 individual study reports. Clinically 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 Myozyme infusion, and are additionally noted in the IARs, hypersensitivity and infusion-related reactions sections (e.g., hypotension). Please refer to section 7.1.3.3 Other significant adverse reactions above for a more detailed discussion of these 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.

7.1.9 Electrocardiograms (ECGs)

Changes in ECGs were evaluated as part of the efficacy evaluations in Studies AGLU01602 and AGLU01702, as cardiac hypertrophy and other cardiac-related AEs (e.g., cardiac failure and arrhythmias) are clinical findings in infantile-onset Pompe disease. Please refer to the Integrated Review of Efficacy for a discussion of the cardiac findings.

No other notable, relevant, or remarkable findings for changes in ECGs were seen; however, there was insufficient time available in the review period to thoroughly review these data beyond the data previously discussed in the efficacy section.

7.1.10 Immunogenicity

Serum samples for anti-rhGAA IgG antibody testing were obtained pre-infusion and at intervals during the AGLU01602 and AGLU01702 studies. Anti-rhGAA antibody was assessed using ELISA and confirmed by radioimmunoprecipitation (RIP), and all immunological testing was performed by Genzyme. Immunogenicity data for Studies AGLU01602 and AGLU01702 have been analyzed in detail in the individual study reports (please refer to the Appendix Individual Study Reports for a more detailed discussion of the immunogenicity results for these individual studies). Antibody data were also collected from all patients participating in Study AGLU02804. Antibody data were not collected in any meaningful way (if at all) in the remaining Myozyme-treted patients in clinical studies and programs.

The majority of patients (34 of 38 patients with available results; 89%) in Studies AGLU01602 and AGLU01702 tested positive for IgG antibodies to rhGAA, and most of these patients developed detectable antibody by Week 12 of treatment. Some patients showed decreases in antibody titers throughout the duration of the study, but many patients did not, and these patients showed sustained elevations or increases throughout the study. Patients positive for anti-rhGAA IgG antibody were also more likely to develop infusion associated reactions (IARs) to Myozyme administration (see section 7.1.3.3. Other significant adverse events for additional information).

The immunogenicity findings for Studies AGLU01602 and AGLU01702 are notable for the following:

In Study AGLU01602:

- More patients in the 40 mg/kg group were found to have high antibody titers than patients in the 20 mg/kg group.
- Mutations that placed patients at high risk for antibody formation included those mutations that resulting in an absent protein, such as nonsense and frameshift mutations. Patients with lower risk mutations (mutations where low levels of protein are found), such as missense mutations, had a lower risk of antibody formation.
- A concerning signal was seen in patients with high-risk mutations and high anti-rhGAA IgG antibody titers. Patients with high-risk mutations and high antibody titers were more likely to have poor clinical outcomes than patients with lower risk mutations and lower antibody titers. This was particularly concerning in two patients who initially achieved gains in motor scores, then later lost those motor milestones coincident with rising and markedly elevated antibody titers (one of these two patients died). These results suggested interference of antibody with the clinical effect of Myozyme.

In Study AGLU01702:

- A similar association with high-risk mutations and antibody formation was seen in this study as was seen in Study AGLU01602
- Patients with higher antibody titers also tended to have poorer outcomes, but this was a less consistent finding than for Study AGLU1602

In Study AGLU02804, four of five patients developed anti-rhGAA IgG antibodies, but the antibody titers did not tend to be as elevated as in Studies AGLU01602 and AGLU01702 (peak titers 800 in one patient in Study AGLU02804). There were no reported IARs in this study.

Thus, in infantile-onset patients, about 90% of treated patients developed anti-rhGAA antibodies, usually by Week 12 of treatment. Antibody titers tended to be high and to remain elevated throughout treatment, and patients with high-risk mutations tended to develop higher antibody titers than patients with lower risk mutations. Patients with high antibody titers tended to have poorer outcomes, and in at least two patients, deteriorating clinical status coincided with rising and markedly elevated antibody titers. Further follow-up of immunogenicity data with Myozyme treatment, and exploration of immune tolerance and prevention regimens (in high-risk patients) are, therefore, recommended.

7.1.11 Human Carcinogenicity

No animal or human carcinogenicity studies have been conducted to date with Myozyme.

7.1.12 Special Safety Studies

No special safety studies were conducted.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There are no withdrawal phenonmena or abuse potential issues identified with Myozyme.

7.1.14 Human Reproduction and Pregnancy Data

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

7.1.15 Assessment of Effect on Growth

Growth was assessed as an efficacy endpoint in Studies AGLU01602 and AGLU01702. Please refer to the Integrated Review of Efficacy for a discussion of the growth assessment results.

7.1.16 Overdose Experience

All patients in the Myozyme clinical program were treated with doses ranging from 10 mg/kg every other week to 40 mg/kg every week. There are no reports of overdose with Myozyme.

7.1.17 Postmarketing Experience

Myozyme is not a marketed product, and there is no postmarketing experience with Myozyme.

7.2 Adequacy of Patient Exposure and Safety Assessments

The Sponsor provided primary source data with data collected from Genzyme-sponsored clinical trials. No secondary sources were used.

The Myozyme clinical development program, patient exposure, and assessments are described in detail in the following sections: 1) Section 4 Data Sources, Review Strategy, and Data Integrity (including subsections 4.1 Sources of Clinical Data, 4.2 Tables of Clinical Studies, and 4.3 Review Strategy); 2) Section 6 Integrated Review of Efficacy (including subsections 6.1.1 Methods and 6.1.3 Study Design); and 3) Section 7 Integrated Review of Safety (including subsection 7.1 Methods and Findings). Please refer to these sections for additional information.

The entire Myozyme clinical program was conducted in Pompe disease patients, and given the rarity of this disease, the entire Myozyme-exposed population, for whom data were submitted to this application, was small. This application includes clinical safety information from ten Genzyme-sponsored clinical studies and expanded access programs (EAPs), in which all patients received treatment with open-label Myozyme. There were no placebo-controls used in any of these studies. Five clinical studies and EAPs were conducted in infantile-onset Pompe disease patients, and five studies and EAPs were conducted in juvenile- and adult-onset Pompe disease patients. Additional, limited information was obtained from an ongoing, double-blind, placebo-controlled, safety and efficacy study in juvenile- and adult-onset Pompe disease (Study AGLU02704, LOTS). These additional data consisted of isolated MedWatch reports submitted by the Sponsor to the Agency for serious, expedited Adverse Events (AEs), and for reports on hypersensitivity and infusion reactions that were submitted to the application at the request of the Division.

The total patient exposure to Myozyme is unclear to this Reviewer, and is estimated to be about 280 patients (per personal communication with the Sponsor). For most of these patients, no safety data are available (other than a small number of expedited safety reports submitted during the review cycle) as these patients are being treated in ongoing clinical studies and expanded access programs, for which safety data were not available during the review cycle.

Thus, the product labeling for Myozyme will rely mainly on safety results available in 39 infantile-onset patients from Studies AGLU01602 and AGLU1702, with Myozyme exposure ranging from one week to 106 weeks of Myozyme treatment. Limited safety experience in five juvenile-onset patients was described in Study AGLU02804, with Myozyme exposure up to 26 weeks of treatment. Information on the remaining patients that is to appear in the product labeling was from a small number of expedited safety reports, and only those for which concerning safety signals were noted are to appear in the product labeling.

In the opinion of this Reviewer, the safety experience of Myozyme in the juvenile- and adult-onset Pompe disease population was not felt to have been adequately described in the data contained in this application, and further study in the juvenile- and adult-onset population is recommended.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The safety results from the Myozyme clinical development program are notable for the following safety signals and concerns that are to appear prominently in the product labeling:

1. A safety signal for severe hypersensitivity reactions during Myozyme infusion was noted late in the review cycle. Some of these hypersensitivity reactions have been life-threatening. Hypersensitivity reactions included anaphylactic shock (cyanosis, hypoxia, hypotension, and bronchoconstriction, requiring unspecified life support measures), anaphylactic and anaphylactoid reactions (IgE and non-IgE mediated), angioedema, and numerous cases of infusion reactions associated with two of the three organ systems of cardiac, respiratory and skin (consistent with anaphylaxis/hypersensitivity). Recognition of this signal lead to a request by the Division to the Sponsor to query their pharmacovigilence database for similar cases, and the frequency, incidence, and magnitude of this problem is still being defined. However, hypersensitivity reactions have occurred in infantile- through adult-onset patients, have lead to the discontinuation of at least three adult patients from Study AGLU02704 (LOTS protocol in juvenile- and adult-onset Pompe disease) and AGLU02603 (US expanded access protocol), and appear to have occurred in about 15% of patients treated in clinical trials with Myozyme to date. This safety signal is noteworthy, and it is recommended that a boxed warning appear in the product labeling.
2. One case of acute cardiorespiratory failure requiring intubation and inotropic support has been observed in an infantile-onset Pompe disease patient with underlying cardiac hypertrophy, possibly associated with fluid overload.

3. Multiple instances of cardiac arrhythmia and sudden cardiac death during general anesthesia for central venous catheter placement (needed for Myozyme infusion) have occurred in infantile-onset patients, who are at risk for arrhythmia due to underlying cardiac hypertrophy. These arrhythmias included ventricular tachycardia, ventricular fibrillation, bradycardia, and cardiac arrest, and required intervention such as cardiac defibrillation.

Safety results are otherwise summarized as follows:

5. Deaths reported in clinical studies and expanded access programs were predominantly due to underlying disease, and included respiratory and cardiac failure, cardiac arrest, and infectious causes.
6. Adverse Events (AEs) were frequently reported in clinical studies, and tended to reflect underlying disease or were AEs commonly seen with enzyme/protein infusions (e.g., allergic and hypersensitivity reactions, and AEs such as pyrexia). Serious Adverse Events (SAEs) also tended to be consistent with underlying disease (e.g., respiratory and infectious SAEs), or treatment intervention complications (e.g., catheter-related complications). The most commonly reported SAEs in clinical studies (pooled results of AGLU01602 and AGLU01702, n=39) were pneumonia, respiratory failure, respiratory syncytial virus infection, and catheter-related infection.
7. Infusion reactions were common. Pooled results from AGLU01602 and AGLU01702 showed that 51% of patients treated with Myozyme experienced infusion reactions, some of which were severe, such as oxygen desaturation, pyrexia, urticaria, hypotension, and wheezing/bronchospasm, among others.
8. Hearing loss at Screening/Baseline and during treatment was reported in many patients in the rhGAA clinical development program, including infantile-, juvenile- and adult-onset patients in clinical trials and in expanded access programs. Hearing loss was described as hypoacousis, sensorineural, mixed, and conductive in these patients, and it was additionally noted that middle ear effusions were present in many patients, which complicated the interpretions of the results. Hearing loss has been described in the medical literature as associated with Pompe disease, possibly secondary to glycogen deposition in the cochlea. Hearing loss has also been reported in other lysosomal storage diseases. It appears likely that the hearing loss reported in this study is secondary to underlying disease and not to treatment with rhGAA, although it is not possible at this time to determine whether rhGAA treatment modifies the progression or development of hearing loss in this patient population. It is recommended, therefore, that longer-term follow-up of hearing be performed in patients receiving rhGAA.

In summary, safety results from clinical trials with Myozyme have shown a concerning safety signal for the risk of hypersensitivity reactions in all age groups, some of which have been life-threatening and have lead to the discontinuation of patients from clinical trials, and for cardiac complications (cardiac failure and arrthymia) in infantile-onset patients. In infantile-onset Pompe disease, this risk appears to be acceptable given the risk of the underlying disease and the nearly universal progression to death by 18 months of age in untreated patients, and with a clear ventilator-free survival benefit having been demonstrated with Myozyme treatment. The

risk/benefit profile of Myozyme in the juvenile- and adult-onset Pompe disease patient population has not been defined. Thus, given the known risks of treatment with Myozyme, and the lack of any evidence of a treatment benefit available at this time, the treatment of patients with juvenile- and adult-onset Pompe disease with Myozyme outside of a clinical trial or other monitored clinical program cannot be recommended.

7.4 General Methodology

Please see section 7.1 for a disussion of the methodoly used in the review of safety.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Doses of Myozyme ranged from 10 mg/kg every other week to 40 mg/kg every week by intravenous infusion. Most patients in the Myozyme clinical development program received treatment with Myozyme in a dose of 20 mg/kg every other week. The next most frequently administered dose was 40 mg/kg every other week. Information available on patients receiving doses of Myozyme less than 20 mg/kg and greater than 40 mg/kg every other week was extremely limited, and was not of sufficient detail to provide any assessment of safety or efficacy. Based on the safety and efficacy results from Study AGLU01602, efficacy was found to be similar between the 20 mg/kg and 40 mg/kg every other week doses, and the safety concerns, particulary for immunogenicity and infusion reactions, were less in the 20 mg/kg dose group as compared to the 40 mg/kg dose group. Thus, the recommended dose of Myozyme is 20 mg/kg every other week.

8.2 Drug-Drug Interactions

No drug-drug interactions were explored in the Myozyme clinical development program.

8.3 Special Populations

Pompe disease is a rare, autosomal recessive, inherited, lysosomal storage disease that is estimated to occur with an incidence of 1/300,000 to 1/40,000. The entire Myozyme clinical development program has been conducted in Pompe disease patients only. Pompe disease is classified by the age at onset of clinical signs and symptoms of Pompe disease (infantile-onset, childhood/juvenile-onset, and adult-onset), and the majority of patients treated in the Myozyme clinical progam for whom efficacy and safety data were submitted to the application were in the infantile-onset population. Response to treatment with Myozyme appears to vary considerably by Pompe disease age classification, which is the subject of this review and will be discussed in greater detail in the body of this review. No data were available in geriatric patients (≥65 years of age), as Pompe disease predominantly affects a younger patient population.

Males and females were nearly equally studied in the clinical development program, and although the number of patients studied was small, male and female patients do not appear to respond differently to Myozyme. As Pompe disease occurs worldwide, patients from the United

States, Asia, the Middle East, Europe, and South American have been included in clinical studies and EAPs; however, insufficient information exists to determine a difference in response to Myozyme treatment by ethnic origin.

8.4 Pediatrics

Pompe disease predominantly affects a younger patient population, and the majority of patients studied, who had data submitted to the application, were in the infantile-onset Pompe disease population. Childhood/juvenile-onset Pompe disease patients (age of onset >1 to 16 years) have not been adequately studied to date, and the risk/benefit profile of Myozyme in these patients has not been described.

8.5 Advisory Committee Meeting

No Advisory Committee Meeting was convened to discuss this application.

8.6 Postmarketing Risk Management Plan

None warranted at the present time.

9 OVERALL ASSESSMENT

9.1 Conclusions

The efficacy results from the Myozyme clinical program provided substantial evidence of a benefit of treatment with Myozyme in the infantile-onset Pompe disease patient population. Evidence of a treatment benefit was demonstrated in Study AGLU01602, where treatment of infantile-onset Pompe disease patients with Myozyme at or prior to the age of seven months resulted in an invasive ventilator-free survival benefit at 18 months of age as compared to an untreated historical control of similar age and disease severity. Clinically meaningful gains in motor function were also demonstrated in these patients, although the majority of these patients were substantially delayed compared to same-age, non-disabled peers. It is not known if these results are sustained, especially in patients developing elevated anti-rhGAA antibody titers, and longer-term follow-up of these patients is needed.

No substantial evidence of a treatment effect of Myozyme in the Study AGLU01702 patient population could be determined, and the results of the 52-week interim analysis for Study AGLU01702 failed to definitely establish the efficacy of Myozyme in patients ages three months to 3.5 years at first infusion. Discerning anything less than a dramatic treatment effect in this Pompe disease population would have been difficult due to the highly heterogeneous presentation and progression of the disease in this Pompe disease age group, and the study results, not surprisingly, overlapped with the outcomes in an historical control reference population similar in age and disease severity. Interpretation of this study was additionally complicated by the lack of a concurrent control group, a large number of protocol violators by study entry criteria, and the poor quality of the data for several of the endpoints. Secondary endpoints of respiratory and motor function also were consistent with anecdotal and medical

literature reports of the expected progression of the disease in this patient population. That is, patients with worsening status (e.g., death or ventilator dependence) tended to be younger than patients with stable status during the study, consistent with a more rapidly progressive disease course in patients with first symptoms and diagnosis at younger ages. Motor development showed modest gains in gross motor function in approximately half of the patients in the study, and most patients showed gains in fine motor function. This result is consistent with the earlier presentation and progression of proximal, lower extremity (and truncal) motor involvement and the relative sparing of distal motor function earlier in the course of the disease. These findings make it extremely difficult to determine whether there was a treatment effect with rhGAA in this population, or if the findings were due to the natural progression of the underlying disease. Longer-term treatment with rhGAA in this population is needed.

Outcomes measures in the remaining clinical studies and expanded access programs were of limited utility in determining the effect of Myozyme in Pompe disease. These results tended to be highly subjective with few objectively or consistently collected outcomes measures available for review. It is especially noted that there was a lack of objective data submitted in the juvenile- and adult-onset patient population, as there have been no adequate and well-controlled studies completed to date in this population. Thus, no assessment of the effect of Myozyme treatment on juvenile- and adult-onset Pompe disease patients is possible at this time.

Extrapolation of treatment effect from the most severely affected infantile-onset Pompe disease patients to the juvenile- and adult-onset Pompe disease patient population is not felt to be appropriate. The regulations for extrapolation of data from adult patients to pediatric patients state that extrapolation is possible when the course of the disease and the effects of the drug are sufficiently similar. While extrapolation in the reverse direction, from younger to older patients can be considered, the courses of disease are not the same in the infantile-onset, and juvenile- and adult-onset patients. For example, survival in juvenile- and adult-onset patients is typically measured in decades, not months as for infantile-onset patients, cardiac hypertrophy is not described in juvenile- and adult-onset patients, glycogen storage in skeletal muscle is patchy in older patients, and there is extreme heterogeneity of clinical presentation and progression of disease in juvenile- and adult-onset patients. These differences have also lead to substantial differences in study design being necessary for the juvenile- and adult-onset patients as compared to the infantile-onset patients. Thus, the data obtained in the ongoing Study AGLU02704 (LOTS) will be essentital in establishing efficacy (and safety) in the juvenile- and adult-onset Pompe disease patient population.

The safety results from the Myozyme clinical development program are notable for the following safety signals and concerns that are to appear prominently in the product labeling:

1. A safety signal for severe hypersensitivity reactions during Myozyme infusion was noted late in the review cycle. Some of these hypersensitivity reactions have been life-threatening. Hypersensitivity reactions included anaphylactic shock (cyanosis, hypoxia, hypotension, and bronchoconstriction, requiring unspecified life support measures), anaphylactic and anaphylactoid reactions (IgE and non-IgE mediated), angioedema, and numerous cases of infusion reactions associated with two of the three organ systems of

cardiac, respiratory and skin (consistent with anaphylaxis/hypersensitivity). This safety signal is noteworthy, and it is recommended that a boxed warning appear in the product labeling.

2. One case of acute cardiorespiratory failure requiring intubation and inotropic support has been observed in an infantile-onset Pompe disease patient with underlying cardiac hypertrophy, possibly associated with fluid overload.
3. Multiple instances of cardiac arrhythmia and sudden cardiac death during general anesthesia for central venous catheter placement (needed for Myozyme infusion) have occurred in infantile-onset patients, who are at risk for arrhythmia due to underlying cardiac hypertrophy. These arrhythmias included ventricular tachycardia, ventricular fibrillation, bradycardia, and cardiac arrest, and required intervention such as cardiac defibrillation.

Safety results are otherwise summarized as follows:

4. Deaths reported in clinical studies and expanded access programs were predominantly due to underlying disease, and included respiratory and cardiac failure, cardiac arrest, and infectious causes.
5. Adverse Events (AEs) were frequently reported in clinical studies, and tended to reflect underlying disease or were AEs commonly seen with enzyme/protein infusions (e.g., allergic and hypersensitivity reactions, and AEs such as pyrexia). Serious Adverse Events (SAEs) also tended to be consistent with underlying disease (e.g., respiratory and infectious SAEs), or treatment intervention complications (e.g., catheter-related complications). The most commonly reported SAEs in clinical studies (pooled results of AGLU01602 and AGLU01702, n=39) were pneumonia, respiratory failure, respiratory syncytial virus infection, and catheter-related infection.
6. Infusion reactions were common. Pooled results from AGLU01602 and AGLU01702 showed that 51% of patients treated with Myozyme experienced infusion reactions, some of which were severe, such as oxygen desaturation, pyrexia, urticaria, hypotension, and wheezing/bronchospasm, among others.
7. Hearing loss at Screening/Baseline and during treatment was reported in many patients in the rhGAA clinical development program, including infantile-, juvenile- and adult-onset patients in clinical trials and in expanded access programs. It appears likely that the hearing loss reported in this study is secondary to underlying disease and not to treatment with rhGAA, although it is not possible at this time to determine whether rhGAA treatment modifies the progression or development of hearing loss in this patient population. It is recommended, therefore, that longer-term follow-up of hearing be performed in patients receiving rhGAA.

In summary, safety results from clinical trials with Myozyme have shown a concerning safety signal for the risk of hypersensitivity reactions in all age groups, some of which have been life-threatening and have lead to the discontinuation of patients from clinical trials, and for cardiac complications (cardiac failure and arrthymia) in infantile-onset patients. In infantile-onset Pompe disease, this risk appears to be acceptable given the risk of the underlying disease and the nearly universal progression to death by 18 months of age in untreated patients, and with a clear

ventilator-free survival benefit having been demonstrated with Myozyme treatment. The risk/benefit profile of Myozyme in the juvenile- and adult-onset Pompe disease patient population has not been defined. Thus, given the known risks of treatment with Myozyme, and the lack of any evidence of a treatment benefit available at this time, the treatment of patients with juvenile- and adult-onset Pompe disease with Myozyme outside of a clinical trial or other monitored clinical program cannot be recommended.

9.2 Recommendation on Regulatory Action

Recommend approving this application with revision to the proposed label.

It is recommended that Myozyme's treatment indication be restricted to patients with infantile-onset Pompe disease. A ventilator-free survival benefit with Myozyme treatment was demonstrated in a clinical study (AGLU01602) that was limited to the youngest, most severely affected Pompe disease patient population. In AGLU01602, a ventilator-free survival benefit at age 18 months was seen in infantile-onset Pompe disease patients who received their first dose of Myozyme prior to the age of seven months, who had cardiac hypertrophy, and who did not require ventilatory support at study entry, as compared to an untreated, historical-control cohort that was similar in age and disease severity.

No therapeutic benefit of Myozyme has been demonstrated in any other Pompe disease patient population, and no adequate and well-controlled studies with Myozyme in the treatment of patients with juvenile- and adult-onset Pompe disease have been completed.

Safety results from clinical trials with Myozyme have shown a concerning safety signal for the risk of hypersensitivity reactions, some of which have been life-threatening and have lead to the discontinuation of patients from clinical trials. In infantile-onset Pompe disease, this risk appears to be acceptable given the risk of the underlying disease and the nearly universal progression to death by 18 months of age in untreated patients, and with a clear ventilator-free survival benefit having been demonstrated with Myozyme treatment. The risk/benefit profile of Myozyme in the juvenile- and adult-onset Pompe disease patient population has not been defined. Thus, given the known risks of treatment with Myozyme, and the lack of any evidence of a treatment benefit available at this time, the treatment of patients with juvenile- and adult-onset Pompe disease with Myozyme outside of a clinical trial or other monitored clinical program cannot be recommended.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

None warranted at the present time.

9.3.2 Required Phase 4 Commitments

The recommended indication for Myozyme is limited by the narrow scope of the clinical data submitted in support of this application, and a number of clinical areas need to be addressed by

post-marketing commitments. It is recommended that Myozyme undergo further clinical evaluation and study in:

- The juvenile- and adult-onset Pompe disease patient population.
- A broader infantile-onset Pompe disease population than was defined by AGLU01602, to include final data from clinical study AGLU01702 (up to 104 weeks of Myozyme treatment). Study AGLU01702 included infantile-onset Pompe disease patients ages 3 months to 3.5 years at time of first dose of Myozyme, who may have been on ventilatory support at study entry.
- The growth and development of infantile-onset Pompe disease patients over time.
- Pompe disease patients of any age failing treatment. This is to include poor responders with and without high anti-rhGAA IgG antibody titers.
- The long-term evaluation of Myozyme treatment in a Pompe disease registry.
- Evaluation of sub-populations of Pompe disease patients, including pregnant or lactating females exposed to Myozyme, and ventilator-dependent patients of any age, as clinical status in these patients will need to be followed over many years. These patients may be followed in sub-studies as part of the registry.

Therefore, the following clinical post-marketing actions are recommended:

1. Completion of the juvenile- and adult-onset onset Pompe disease study AGLU02704, entitled "A randomized, double-blind, multicenter, multinational, placebo-controlled study of the safety, efficacy and pharmacokinetics of Myozyme, recombinant human acid alpha-glucosidase (rhGAA), treatment in patients with late-onset Pompe disease" (LOTS). Enrollment in this study has been completed, the study is ongoing, and the study is expected to be completed in March 2007.

2. Conduct and completion of study AGLU03206, the 52-week extension study to LOTS (AGLU02704) in juvenile- and adult-onset Pompe disease patients, entitled "An open-label extension study of patients with late-onset Pompe disease who were previously enrolled in protocol AGLU02704" (this is a draft title supplied by the sponsor). Patient accrual is expected to be completed by March 31, 2007, and the study completed by March 31, 2008.

3. Completion of study AGLU01702, entitled "An open-label, multicenter, multinational study of the safety, efficacy, pharmacokinetics, and pharmacodynamics of recombinant human acid alpha-glucosidase (rhGAA) treatment in patients >6 months and ≤36 months old with infantile-onset Pompe disease (Glycogen Storage Disease Type II)." This study is ongoing, and is expected to be completed by June 12, 2006.

4. Design and implementation of a long-term registry that will be established to obtain long-term clinical status information in patients of all ages with Pompe disease who are being treated with alglucosidase alfa. Information will be collected on patient demographics, specifics of treatment with alglucosidase alfa, clinical status, ventilatory status, motor

assessments, adverse events, assessment of immunogenicity, and potential effects of antibody formation. In patients who are less than one year of age at the start of treatment, information is to be collected on cognitive status, and auditory and visual screening assessments. This registry will be designed so that detailed clinical status information is collected at registry entry and on a 6- to 12-month basis for at least 15 years. Two sub-studies within the registry are to be performed: one sub-study that will evaluate the effect of alglucosidase alfa on pregnancy and lactation, and one sub-study that will collect information on the clinical status of patients on ventilatory support at the time of entry into the registry. The registry data will be analyzed at yearly intervals and submitted in annual reports to the Myozyme IND (#10780). The registry is expected to be initiated by January 31, 2007, and run through January 31, 2022.

5. Design and implementation of an infantile-onset Pompe disease study to assess growth and development with treatment with alglucosidase alfa, in patients who are less than one year of age at study entry. This study is to include blinded assessments of growth (including recumbent length, height, weight, and head circumference), cognitive (language and cognition) and motor (fine and gross motor) development (scales to be used are to be prospectively agreed upon), auditory and visual screening, neuro-imaging, and antibody assessments at 6- to 12-month intervals over a 10-year period. This study is expected to be implemented by January 31, 2007.

6. Design and implementation of 1) an immune tolerance protocol in Pompe disease patients who have significant antibody titers, or the presence of neutralizing antibody, and are failing treatment; and 2) the design and implementation of a preventive immune tolerance protocol in Pompe disease patients at high risk of development of significant immune responses to Myozyme.

Design and implementation of a dose- and dose-interval exploration study in patients with poor responses to treatment, regardless of antibody status. This study is to include patients in the infantile-, juvenile-, and adult-onset patient populations.

9.3.3 Other Phase 4 Requests

None recommended at the present time.

9.4 Labeling Review

The product labeling has been extensively discussed with the Sponsor, and agreement was reached between the Sponsor and the Division on the proposed labeling for Myozyme. Please see the finalized labeling for Myozyme that has been approved for this application.

9.5 Comments to Applicant

It is the recommendation of this Reviewer that the Sponsor receive the following:

1. A letter stating that the biologics license application for Myozyme has been approved. This Reviewer additionally recommends that Myzoyme's use be restricted to infantile-onset Pompe disease patients.

2. Notification that additional clinical post-marketing commitments are recommended, including further clinical evaluation and study in:
   a. The juvenile- and adult-onset Pompe disease patient population.
   b. A broader infantile-onset Pompe disease population than was defined by AGLU01602, to include final data from clinical study AGLU01702 (up to 104 weeks of Myozyme treatment). Study AGLU01702 included infantile-onset Pompe disease patients ages 3 months to 3.5 years at time of first dose of Myozyme, who may have been on ventilatory support at study entry.
   c. The growth and development of infantile-onset Pompe disease patients over time.
   d. Pompe disease patients of any age failing treatment. This is to include poor responders with and without high anti-rhGAA IgG antibody titers.
   e. The long-term evaluation of Myozyme treatment in a Pompe disease registry.
   f. Evaluation of sub-populations of Pompe disease patients, including pregnant or lactating females exposed to Myozyme, and ventilator-dependent patients of any age, as clinical status in these patients will need to be followed over many years. These patients may be followed in sub-studies as part of the registry.

The language to be used for these post-marketing commitments is listed in Section 9.3.2 Required Phase 4 Commitments (please refer to Section 9.3.2 above).

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Study AGLU01602 (Study 1602)

10.1.1.1 Study Design

Study AGLU01602 (Study 1602) was a multicenter (n=7), multinational, open-label, randomized (to dose), dose-ranging, safety, efficacy, pharmacodynamic (PD) and pharmacokinetic (PK) study of alglucosidase alfa (rhGAA) in the treatment of 18 patients with infantile-onset Pompe disease. Eligible patients were randomized 1:1 to receive an intravenous (IV) infusion of rhGAA 20 mg/kg or 40 mg/kg every other week (qow) for 52 weeks. Patients were eligible for the study if they had a definitive diagnosis of Pompe disease defined as a deficiency in GAA activity, onset of clinical signs of Pompe disease before the age of six months and cardiac hypertrophy, and if they were less than or equal to six months of age at first infusion. The primary efficacy endpoint for the study was the proportion of patients who were alive and free of invasive ventilator support at 18 months of age, as compared to an historical control subgroup. Major efficacy endpoints included changes from baseline at Week 52 in measures of cardiac status (left ventricular mass index [LVMI]), physical growth (length and weight), and achievement of motor and mental developmental milestones assessed by Alberta Infant Motor Scale (AIMS), Bayley Scales of Infant Development II (BSID-II), and Pompe Pediatric Evaluation of Disability Inventory (PEDI) testing. As infantile-onset Pompe disease is a uniformly fatal disease for which there are no established treatments, no placebo treatment was administered, and an historical cohort was used as the control group.

The first patient received his first dose of rhGAA on 26-May-2003 and the last patient received her first dose of rhGAA on 03-June-2004. The cutoff date for the interim analysis, after all patients had received 26 weeks of rhGAA treatment, was 24-November-2005, and the final visit cutoff date, after the last patient completed her 52-week visit, was 15-June-2006.

10.1.1.2 Study Objectives

The objectives of the study were to evaluate the safety, efficacy (ventilator-free survival compared to historical control), PK and PD of two doses (20 mg/kg and 40 mg/kg qow) of rhGAA in the treatment of patients with infantile-onset Pompe disease after 52 weeks of treatment.

10.1.1.3 Eligibility Criteria

To be eligible for the study, patients must have been age less than or equal to six months of age (26 weeks and 0 days corrected for gestational age) at the time of the first dose of rhGAA, and have had a diagnosis of infantile-onset Pompe disease defined as onset of clinical symptoms of Pompe disease at less than six months of age, deficient GAA activity (<5-10% normal range [depending on the laboratory used] by peripheral blood mononuclear cell [PBMC] or ≤1% normal range by cultured skin fibroblast assay), and cardiac hypertrophy (LVMI ≥65 g/m^2 by echocardiography). Patients were excluded if they had:

1. The presence of respiratory insufficiency defined as O_2 saturation <90% on room air (RA) by pulse oximetry (pulse ox), or venous partial pressure of carbon dioxide (PCO_2) >55 mmHg on RA or arterial PCO_2 >40 mmHg on RA, or any ventilation use (invasive or non-invasive) at the time of enrollment;
2. The presence of a major congenital abnormality;
3. The presence of clinically significant organic disease (excluding Pompe disease related symptoms) that, in the opinion of the Investigator, would potentially decrease survival or preclude participation in the study; or
4. Had received enzyme replacement therapy (ERT) with GAA from any source.

10.1.1.4 Concomitant Medications

No concomitant medications were prohibited from use during the study, other than the exclusion criterion for prior use of ERT with GAA, and the use of all medications was at the discretion of the treating physician. There were no routine prophylactic concomitant medications recommended or prescribed for use during the study or prior to the administration of rhGAA.

10.1.1.5 Study Visits and Procedures

All patients required placement of a permanent, indwelling, central intravenous catheter to receive ongoing study treatments. The study visits and procedures are summarized below in the following tables. All study assessments had a ±14 day window unless otherwise noted.

Table A1-1: Study 1602, Study Visits and Procedures, Screening through Week 26

			Day	Week												
	Screen	Baseline	0	2	4	6	8	10	12	14	16	18	20	22	24	26
Procedure																
Informed consent	X															
Medical history	X															
Head MRI	X															
Blood for GAA activity in PBMC	X															
Skin biopsy for GAA activity	X	X														
Skin biopsy for CRIM status		X														
Blood spot collection		X														
ACE marker allele status		X														
Venous blood gas	X															
Pulse ox (RA)	X															
GAA gene mutation analysis			X													
Chest xray		X														X
Central venous catheter placement		X														
Muscle biopsy		X							X							
Plasma oligosaccharide levels		X			X				X							X
Urine oligosaccharide levels		X			X				X							X
Hearing test		X														X
Physical exam	X	X	X		X		X		X							X
Echocardiogram	X	X			X		X		X							X
ECG		X			X		X		X							X
Safety labs (heme & chem)		X			X		X		X							X
Urinalysis		X			X		X		X		X		X		X	
Nutritional analysis		X							X							X
Anti-rhGAA antibody (IgG)			X		X		X		X		X		X		X	
PK			X						X							
AIMS		X			X		X		X							X
PDMS-2		X														X
Motor development milestones assessment		X			X		X		X							X
PEDI and Pompe PEDI		X			X		X		X							X
Modified BSID-II		X							X							X
Weight		X	X		X		X		X		X		X		X	
VS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
RhGAA infusion			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ventilator use	← Continuous monitoring →															
AE assessment	← Continuous monitoring →															
Conmeds/therapy monitoring	← Continuous monitoring →															
FU contact	X															

Table A1-2: Study 1602, Study Visits and Procedures, Weeks 28 through 52 (end-of-study)

	Week												
	28	30	32	34	36	38	40	42	44	46	48	50	52
Procedure													
Chest xray													X
Muscle biopsy													X
Plasma oligosaccharide levels						X							X
Urine oligosaccharide levels						X							X
Hearing test													X
Physical exam						X							X
Echocardiogram						X							X
ECG						X							X
Safety labs (heme & chem)						X							X
Urinalysis	X		X		X		X		X		X		X
Nutritional analysis						X							X
Anti-rhGAA antibody (IgG)						X							X
AIMS						X							X
Motor development milestones assessment						X							X
PEDI and Pompe PEDI						X							X
Modified BSID-II						X							X
Weight	X		X		X		X		X		X		X
VS	X	X	X	X	X	X	X	X	X	X	X	X	X
RhGAA infusion	X	X	X	X	X	X	X	X	X	X	X	X	X
Ventilator use	← Continuous monitoring →												
AE assessment	← Continuous monitoring →												
Conmeds/therapy monitoring	← Continuous monitoring →												
FU contact							X						

10.1.1.6 Randomization and Controls

Patients were randomized 1:1 to rhGAA 20 mg/kg or 40 mg/kg qow using a simple central randomization (without stratifying by study site) using blocks of two. As infantile-onset Pompe disease is uniformly and rapidly (usually by 18 months of age) fatal, there are no established treatments known to impact the survival or progression of infantile-onset Pompe disease, and preliminary information from studies with rhGAA derived from the milk of transgenic animals (Pharming) and CHO cell-derived rhGAA (Synpac) have suggested that ERT with GAA may be beneficial in Pompe disease patients, a placebo control was considered unethical, and all patients received active treatment with rhGAA (Genzyme formulation). An historical infantile-onset Pompe disease cohort was used as the control population in this study.

Study 1602 was an open-label study and no blinding of patients, families, or study personnel was performed, with the exception of: 1) the central cardiologist who read ECGs and echocardiograms was blinded to patient and study timepoint for the first year, but not blinded thereafter; and 2) the pathologist evaluating the tissue samples for the histopathological, biochemical and gene expression analyses was blinded to patient and sequence.

10.1.1.7 Study Medication Dose Selection, Dispensing, and Compliance

RhGAA was supplied to the study sites as a lyophilized product that was reconstituted in sterile water, then further diluted into a fixed total volume of 0.9% NaCl for injection by the site pharmacist prior to infusion (volumes depended on patient weight and dose; see study Pharmacy Manual for details). RhGAA infusions were administered in a step-wise manner, beginning with a slow initial rate (1 mg/kg/hr), with gradual increases every 30 minutes to a maximum rate of infusion of 7 mg/kg/hr (infusion rate could be increased by 2 mg/kg/hr every 30 minutes as tolerated, with doses typically administered over approximately four hours). The patient's dose of rhGAA could be reduced at any time if the patient experienced severe or intolerable reactions; however, no dose adjustments were reported during the study. As all study drug treatments were administered by study personnel, study medication monitoring and recording was under the control of the investigative staff, and all missed or incomplete infusions were documented.

10.1.1.8 Efficacy and Endpoint Measures

Data to the cutoff date of 15-June-2005 (after all patients had received 52 weeks of rhGAA treatment and all but three patients had reached 18 months of age) were analyzed for the study. The study endpoints were:

10.1.1.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint was the Kaplan-Meier estimate of proportion of patients who were alive and free of invasive ventilator support at 18 months of age with survival measured as time from birth for patients treated with rhGAA with both dose groups combined using all data through 52 weeks after the last patient was randomized to treatment. This was compared to the proportion of survivors at 18 months of age in an untreated historical cohort. The primary endpoint was considered to have been met if there was no overlap between the two-sided 95% CI for the proportion of rhGAA treated patients alive and free of invasive ventilation at 18 months of age and the 95% CI for 18 months survival of untreated patients in the historical control subgroup. Patients who were alive but had not yet reached 18 months of age were right censored. Invasive ventilator-free survival was defined as 1) the patient was ventilator-free for a 14-day period bracketing the target time point, or 2) the investigator determined that the patient's ventilator use was due to secondary causes only (e.g., aspiration pneumonia) at the target time point and the patient was followed for up to an additional 30 days. If during this additional 30 days the patient became ventilator-free for at least 14 consecutive days, the patient was considered to be ventilator free.

Additional analyses included the proportion of patients alive and free of invasive ventilator support at 12 months of age (both dose groups combined) as compared with the historical control subgroup at 12 months of age. Exploratory analyses included estimates of ventilator-free survival time from the date of first symptoms, date of diagnosis and date of study treatment initiation. Sensitivity analyses for survival rates in the historical control subgroup included: 1) comparisons of the rhGAA-treated group survival rate to survival rates from the historical control subgroup subsets in which patients who died prior to three, four, five, and six months of age were removed from the total sample size of 62; 2) assessment of whether the survival

inferences were dependent on the age at first rhGAA infusion using a subset of the historical control subgroup selected based on the median age at first infusion of rhGAA, and after rhGAA-treated patients were partitioned into two groups based on their age at first rhGAA infusion (less than or greater than median age); and 3) with exclusion of patients with congenital abnormalities or clinically significant disease status recorded as "unknown" from the control group.

10.1.1.8.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints were:

- Proportion of patients treated with rhGAA alive and free of any ventilatory support (i.e., not limited to invasive support) at 18 months of age measured from birth. Additional analysis included proportion alive and free of any ventilatory support at 12 months of age by dose group.
- Cardiac status as measured by LVMI and LVM Z-score change from baseline to Week 52;
- Physical growth (length and weight) change from baseline to Week 52.

10.1.1.8.3 Tertiary Efficacy Endpoints

Tertiary efficacy endpoints were:

- Proportion of patients alive at 18 months of age. Additional analysis included survival distribution by dose group and proportion of patients alive at 12 months of age;
- Proportion of patients with signs or symptoms of cardiac failure at Week 52;
- Total AIMS raw scores change from baseline to Week 52;
- Number of motor milestones achieved at Week 52;
- BSID-II Mental Development Index (MDI) change from baseline to Week 52;
- Pompe PEDI raw scores change from baseline to Week 52;
- Hours on ventilation from baseline to Week 52; and
- Change from baseline to Week 52 in urinary and plasma oligosaccharides

10.1.1.8.4 Exploratory Variables

Exploratory variables included:

- Circulating reactive immune material (CRIM) status
- Angiotensin converting enzyme (ACE) marker allele status
- Gene expression
- GAA gene mutation

10.1.1.8.5 Safety Assessments

Safety was assessed by: types and incidence of Adverse Events (AEs); discontinuations due to AEs; drug-related, serious and severe AEs; changes from baseline in physical exams (including vital signs); clinical laboratory assessments including clinical chemistry, hematology, urinalysis, and anti-rhGAA IgG antibody titers; and ECG assessments. Other safety variables included: circulating immune complex detection (as indicated), inhibitory antibody formation in patients testing positive for IgG, anti-rhGAA IgE antibodies, serum tryptase, and complement activation (as indicated).

10.1.1.8.6 PK and PD Measures

PK (plasma rhGAA levels) was assessed at Day 0, Week 12 and Week 52. PD was assessed by comparing skeletal muscle GAA activity and glycogen content at baseline, and at Week 12 and Week 52.

10.1.1.9 Additional Statistical Considerations

An historical cohort was used as the control population in this study. The data for the historical control population were collected in a natural history study: Study AGLU-004-00 "Epidemiologic study of the natural history of infantile Pompe disease". Data for the natural history study were retrospectively collected from review of medical charts identified in an international cohort of 168 patients with infantile-onset Pompe disease who did not receive treatment. These patients had documented GAA deficiency and onset of symptoms by the age of 12 months. A subset of 62 patients was then selected from within the AGLU-004-00 cohort based on screening criteria adapted from Study 1602. This subgroup is known as the historical control subgroup and was designed to select a control population that most closely matched the study population entered into Study 1602. The inclusion criteria for the historical control subgroup included age at first symptoms less than or equal to 26 weeks of age, age at confirmed diagnosis less than or equal to 26 week of age, and presence of cardiomyopathy by 26 weeks of age (LVMI $\geq$65 g/m^2). Exclusion criteria included any known ventilator use between zero and six months of age, documented major congenital abnormality, and clinically significant disease, other than Pompe disease. Although no historical comparison can provide the certainty of comparison as, for example, a placebo-control group, it appears that survival in the historical control subgroup provides a reasonable control group for ventilator-free survival in the Study 1602 treatment group for comparison at the 18 month timepoint.

10.1.1.10 Protocol Amendments

There were five protocol amendments to Protocol AGLU01602. No patients were enrolled under the original protocol dated 25-September-2002. The protocol amendments are briefly described as follows:

Amendment 1, dated 12-March-2003: Two patients were enrolled and began treatment under this amendment. Changes included: specified that the central cardiologist would be blinded to patient and study time point, added that investigators would remain blinded to the results of efficacy, PK and PD variables, extended primary efficacy analysis to include the survival probability and corresponding 95% CI at 12 and 18 months, and other minor changes were noted.

Amendment 2, dated 20-August-2003: Two patients were enrolled and began treatment under this amendment. Changes included: modified the length of the study to 52 weeks of treatment, modified the primary efficacy endpoint to survival from birth at 18 months of age for patients treated with rhGAA for 52 weeks as compared to an historical cohort, modified secondary objectives to include ventilator-free survival, added arterial pCO_2 >40 mmHg on RA to exclusion criteria, and other minor changes.

Amendment 3, dated 23-September-2003: One patient was enrolled and began treatment under this amendment. This amendment included minor changes.

Amendment 4, dated 08-October-2003: Ten patients were enrolled and began treatment under this amendment. Changes included: eliminated adaptive randomization based on ACE marker allele status (in actuality, all patients were randomized by simple randomization procedures) and other minor changes.

Amendment 5, dated 18-May-2004: Three patients were enrolled and began treatment under this amendment. Changes included: 1) change to primary efficacy variable such that primary efficacy would be measured by the Kaplan-Meier estimate of the proportion of patients treated with rhGAA who were alive and free of invasive ventilator support at 18 months of age as compared to an historical cohort. The survival probability and corresponding 95% two-sided CI would be estimated at 18 months of age for patients treated with rhGAA until 52 weeks after the last patient was randomized to treatment; 2) Changes to secondary efficacy endpoints would be measured by evaluating the effect of treatment on time to ventilator dependence or death from birth at 12 months of age. Time to any ventilatory support or death, LVMI and physical growth were also added as secondary efficacy variables; 3) Changes to tertiary efficacy variables such that efficacy would be measured by the Kaplan-Meier estimator of the proportion of patients alive at 18 months of age, signs and symptoms of cardiac failure at Week 52, motor development, maintenance of cognitive function, change in functional status, change in levels of oligosaccharides in urine and plasma, and time on any ventilation baseline to Week 52, added infusion visits and assessments after Week 52 to continue study until 52 weeks after the last patient had been randomized to treatment, and other minor changes.

10.1.1.11 Study Conduct

The sponsor noted that the study was conducted under ICH/GCP guidelines.

Financial disclosures were included in the submission, and notable findings include the following:

1. Dr. [redacted] noted payments from the sponsor (honoraria) totaling $5,000, and t[redacted]. The time period is from 2003 through Q2 2005. The investigator notes that payments to [redacted] do not reflect monies paid directly to the investigator.
2. Dr. [redacted] reported $500 in honoraria, and $40,000 in [redacted] laboratory support grants for 2003 through Q2 2005.

A Data Safety Monitoring Board (DSMB), comprised of three physicians (later added a fourth) knowledgeable about Pompe disease and who had no direct relationship with the study provided medical and ethical guidance related to the conduct of the study. The DSMB assembled quarterly to review adverse events (AEs), serious AEs (SAEs), laboratory listings and for other safety related reasons (please see DSMB charter for additional information). An independent Allergic Reaction Review Board (ARRB) was also established, which was consulted on an *ad hoc* basis to review reports of moderate or severe infusion-associated reactions (IARs) and provide guidance on IAR management.

A central cardiologist read all echocardiograms and ECGs, and a central physical therapist scored all motor and cognitive assessments. Three branches of a central laboratory (one each in Europe, the US, and Australia) were used for standard safety laboratory analyses. GAA activity in peripheral blood mononuclear cells (PBMC) was conducted in one of three laboratories (in the US, Taiwan or France), GAA activity in skin fibroblasts was conducted at Duke University Medical Center in North Carolina, and pathology, histochemical, pharmacokinetic, immunologic, GAA mutational analyses, CRIM status, ACE marker allele status, and gene expression analysis were conducted in Genzyme specialty laboratories in Framingham, Massachusetts.

10.1.1.12 Study Results

Efficacy and safety data for Study 1602 were received in multiple submissions. The sponsor conducted an interim analysis after all patients had completed 26 weeks of treatment, and the 26-week interim analysis of the efficacy and safety data was submitted as the original submission. Per agreement with the sponsor, 52-week updates to the primary endpoint and major secondary endpoints (AIMS, Pompe PEDI, BSID-II and growth) were submitted as Amendment 001 to the BLA (received 01-September-2005). The sponsor later submitted updates for all the endpoints in the study to on 02-November-2005 (Amendment 002). An update to the safety data with data through 31-October-2005 was submitted in the 4-month safety update on 05-December-2005 (Amendment 005). An additional update for the primary endpoint was obtained with a cutoff of 15-September-2005 after all patients except one had completed the study and reached 18 months of age (Patient 319 had not yet reached 18 months of age, but had met the primary endpoint), which showed essentially no change from the 15-June-2005 update. Thus, efficacy data in the study to the cutoff date of 15-June-2005, after all patients had received 52 weeks of rhGAA treatment, and safety data collected up to 31-October-2005 (4-month safety update) were available for all endpoints in the study and will be included in this review.

10.1.1.12.1 Patient Population

Nineteen (19) patients were enrolled in Study 1602 and 18 patients received treatment with rhGAA. The first dose of rhGAA was administered to the first patient on 26-May-2003 and the last patient enrolled received her first dose of rhGAA on 03-June-2003. The last patient randomized underwent her Week 26 visit on 24-November-2004 and her Week 52 visit on 15-June-2005. There was one patient who was enrolled but not treated with rhGAA (Patient 304). This patient required invasive ventilation during the baseline period (exclusion criterion). Five days after the informed consent was signed, this patient developed respiratory decompensation and requiring intubation and mechanical ventilation. This patient had undergone some

screening/baseline study-related procedures, but no invasive procedures (i.e., no central line placement or muscle biopsy – personal communication with sponsor). The patient was discontinued from the study and enrolled in an expanded access study. The remaining 18 patients completed the 52 weeks of the study, and there were no discontinuations. The following table summarizes patient ages and length of treatment at the 26-week and 52-week data cut-off timepoints.

Table A1-3: Study 1602, Summary of RhGAA Administration and Cutoff Dates

Patient	Treatment Group (mg/kg)	Age at 1st Infusion* (mos)	Age at Interim Analysis Cutoff (mos)	Age at 26-Week Milestone (mos)	Age at 15-June-2005 Cutoff (mos)	Age at 52-Week Milestone (mos)
301	40	4.8	18.4	12.0	29.7	18.0
302	20	5.6	18.0	12.0	28.6	18.0
303	40	6.1	18.2	12.0	28.1	18.0
305	20	5.0	18.1	12.0	**	18.0
306	20	5.8	18.1	12.0	26.4	18.0
307	40	6.0	18.3	12.0	26.2	18.0
308	40	4.3	12.1	12.0	23.1	18.0
309	20	4.8	12.2	12.0	23.7	18.0
310	20	5.7	18.5	12.0	24.4	18.0
311	40	6.1	18.3	12.0	25.2	18.0
312	20	5.1	12.1	12.0	21.2	18.0
313	40	1.8	12.4	12.0	18.5	18.0
314	20	1.9	12.0	12.0	18.0	18.0
315	40	1.2	7.3	7.3	15.9	15.9
316	20	5.5	13.4	12.0	20.3	18.0
317	40	5.6	12.3	9.2	18.8	18.0
318	40	5.4	11.3	11.3	17.9	17.9
319	20	1.8	7.8	7.8	14.4	14.4

*Corrected for gestational age (adjusted to full-term gestational age of 40 weeks if <40 weeks of gestation)
**Patient died at age 19.8 months

There were eight screen failures for the study, who did not qualify for the following reasons: three patients did not have Pompe disease, were heterozygous, or baseline GAA was too high, two patients died prior to completing screening procedures, two patients' parents refused to consent to the trial, one patient had a congenital abnormality, and one patient was on respiratory support (later enrolled in Study 1702).

There were eleven international clinical sites participating in the study, and patients were enrolled at seven of these eleven sites. Enrollment by clinical site is summarized in the following table.

Table A1-4: Study 1602, Enrollment by Site

Site ID #	Site (Investigator)	# of Patients Enrolled	Patients Enrolled at Site
01	Durham, NC, USA (Duke Univ. Med. Ctr, PI: P. Kishnani)	3	307, 309, 311
02	Lyon, France (Pediatrique Hôpital Debrousse, PI : M. Nicolino)	3	301, 308, 318
21	Cincinnati, OH, USA (Cincinnati Children's Hosp. Med. Ctr, PI: N. Leslie)	1	316
52	Taipei, Taiwan, ROC (Natl. Taiwan Univ. Hosp., PI: WL HWu)	4	304*, 305, 306, 310
60	Haifa, Israel (Rambam Med. Ctr, PI: H. Mandel)	3	302, 303, 315
81	Gainesville, FL, USA (Shands Hosp. Univ. FL, PI: B. Byrne)	3	313, 317, 319
83	Manchester, UK (Royal Manchester Hosp, PI: JE Wraith)	2	312, 314
Total, n =	**7 sites**	**19**	

*Withdrawn prior to receiving rhGAA

Randomization to treatment by study site is summarized in the table below. As patients were randomized centrally in blocks of two, patients by dose were not balanced at each site.

Table A1-5: Randomization to Treatment Group by Site

Site	01	02	21	52	60	81	83
All Patients, n =	3	3	1	3*	3	3	2
20 mg/kg, n =	1	0	1	3	1	1	2
40 mg/kg, n =	2	3	0	0	2	2	0

*excluding Patient 304

At the end of the study after the last patient had completed 52 weeks of treatment(15-June-2005), 17 of 18 were living (Patient 305 died at age 19.8 months of age after completing the 18-month milestone, but while the study was ongoing), and of those 17 patients, 16 were enrolled in the extension study AGLU02403. The remaining patient (Patient 303) was enrolled in an expanded access protocol. Thus, all 17 patients were continued on rhGAA.

10.1.1.12.2 Demographics

Baseline demographics showed that 11 of the 18 treated patients (61%) were male, and seven were Caucasian (39%). One patient was diagnosed with Pompe disease prenatally, and in the remaining patients, the diagnosis was made between 0.2 to 6.8 months of age (median 4.3 months). Age at first symptoms ranged from 0 to 5.4 months (median 1.0 month), and corrected age (for gestational age) at first infusion ranged from 1.2 to 6.1 months (median 5.3 months). Baseline demographics were similar between the two dose groups, with the exception of a minor imbalance by gender with more males being randomized to the 40 mg/kg dose group. Baseline demographic data were also similar to baseline data in the Historical Control Subgroup, which had a median age at first symptoms of 1.9 months and median age at diagnosis of 4.1 months. Baseline demographic data for patients enrolled in Study 1602 and the Historical Control Subgroup are summarized in the following table.

Note: in the Study 1602 dataset, for patients with no age of first symptoms noted, imputed age of first symptoms was date of diagnosis. If date of diagnosis/first symptoms not known (e.g., month noted but no date) then patient was assigned the 15th of that month.

Table A1-6: Study 1602 and Historical Control Subgroup, Demographic Data

	Study 1602			Historical Control Subgroup
		Treatment Group		
	All	20 mg/kg	40 mg/kg	All
ITT Population, n =	18	9	9	62
Demographic				
Gender				
Male, n (%)	11 (61)	4 (44)	7 (78)	28 (45)
Female, n (%)	7 (39)	5 (56)	2 (22)	34 (55)
Race				
Caucasian, n (%)	7 (39)	3 (33)	4 (44)	31 (50)
Black, n (%)	4 (22)	1 (11)	3 (33)	4 (6)
Asian, n (%)	3 (17)	3 (33)	0	18 (29)
Hispanic, n (%)	2 (11)	1 (11)	1 (11)	1 (2)
Other, n (%)	2 (11)	1 (11)	1 (11)	8 (13)
Age at First Symptoms (mos)				
Mean	1.6	1.7	1.5	1.9
Median	1.0	1.5	0.4	1.9
Min, max	0, 5.4	0, 5.4	0, 4.3	0, 5.9
Age at Postnatal Diagnosis (mos)				
Mean	3.6	4.0	3.3	3.6
Median	4.3	4.7	4.2	4.1
Min, max	0.2, 6.8	0.7, 6.2	0.2, 6.8	Prenatal, 6.6
Chronologic Age at 1st Infusion (mos)				NA
Mean	5.1	5.1	5.1	
Median	5.6	5.7	5.4	
Min, max	1.2, 7.3	1.9, 7	1.2, 7.3	
Corrected Age at 1st Infusion (mos)				NA
Mean	4.6	4.6	4.6	
Median	5.3	5.1	5.4	
Min, max	1.2, 6.1	1.8, 5.8	1.2, 6.1	

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Study 1602 demographic data by individual patient are summarized in the following table.

Table A1-7: Study 1602, Demographic Data by Individual Patient

Patient	Treatment Group (mg/kg)	Gender	Race	Chronologic Age at 1st Infusion (mos)	Corrected* Age at 1st Infusion (mos)	Chronologic Age at Symptom Onset (mos)	Chronologic Age at Diagnosis (mos)
301	40	M	Caucasian	5.0	4.8	0	0.7
302	20	M	Caucasian	7.0	5.6	0	4.7
303	40	F	Caucasian	7.0	6.1	2.4	4.9
305	20	F	Asian	5.7	5.0	2.6	4.0
306	20	M	Asian	5.9	5.8	1.5	4.8
307	40	M	Black	6.9	6.0	4.2	4.2
308	40	M	Other (Turkish)	4.3	4.3	0	1.7
309	20	F	Hispanic	5.3	4.8	0.2	5.0
310	20	M	Asian	6.4	5.7	5.4	6.2
311	40	M	Hispanic	7.3	6.1	2.2	6.8
312	20	F	Caucasian	5.1	5.1	2.5	2.9
313	40	F	Black	2.3	1.8	0.4	0.7
314	20	M	Other (Ecuadorian)	1.9	1.9	0	0.7
315	40	M	Caucasian	1.2	1.2	0.2	0.2
316	20	F	Black	6.9	5.5	3	6.0
317	40	M	Black	6.2	5.6	0.1	6.0
318	40	M	Caucasian	5.4	5.4	4.3	4.5
319	20	F	Caucasian	2.1	1.8	0	1.9

*Corrected for gestational age

10.1.1.12.3 Concomitant Medications

Approximately 700 different concomitant medications (conmeds) were administered during the study for a wide range of conditions and indications, and all 18 patients used multiple conmeds during the study. The most commonly recorded indications for conmed use included infection, respiratory problems, acute illness (e.g., diarrhea, fever, URI), anesthesia for procedures (e.g., biopsies) and vaccinations. The most commonly prescribed medications were antibiotics and anesthetic and analgesic agents (including local and system anesthetic agents, sedatives, and analgesics such as acetaminophen). Medications were additionally specifically classified as "premedication" by the sponsor. Nine of 18 patients required premedication during the study beginning at Day 0 through end of study, which required administration at from three to 40 study visits per patient. Medications used for premedication included: antihistamines (dexchlorpheniramine, promethazine, diphenhydramine) in eight patients, glucocorticosteroids (solumedrol, prednisone, prednisolone, hydrocortisone) in six patients, antipyretics (acetaminophen, ibuprofen) in three patients, and antiemetic agents in one patient (ondansetron). Premedication conmed usage is summarized in the following table.

Table A1-8: Study 1602, Concomitant Medications "Premedications" Administered

Patient	Dose Group	Premedication Administrations (At # of Visits)	Comments
301	40	5 (3)	Week 32 through 36, including solumedrol & dexchlorpheniramine
303	40	103 (40)	Weeks 2 through 86, including promethazine & hydrocortisone
305	20	9 (9)	Weeks 44 through 60, including diphenhydramine
306	20	5 (5)	Weeks 82 through 90, including ibuprofen
310	20	19 (11)	Weeks 58 through 78, including diphenhydramine & solumedrol,
313	40	43 (34)	Weeks 2 through 70, including diphenhydramine, acetaminophen, & ibuprofen
318	40	42 (20)	Week 16 through 54, including solumedrol & dexchlorpheniramine
317	40	25 (16)	Weeks 2 through 54, including diphenhydramine & solumedrol
319	20	59 (22)	Day 0 through Week 52, including acetaminophen, diphenhydramine, ondansetron, prednisone, & prednisolone

10.1.1.12.4 Compliance with Study Medication

Study medication was administered at the clinical sites; thus, study medication administration and compliance was largely under the control of study personnel. Compliance with study medication was very high. Fourteen (14) of 18 patients received 100% of study medication. One patient had a dose daly at Week 34 (308), and one patient received all doses except for one partial dose (Patient 312 received a partial infusion at Week 12 due to IV problems). Two patients missed more than one infusion, including: 1) Patient 316, who missed the Week 36 dose due to illness, and received a partial dose at Week 10 due to nursing error; and 2) Patient 303 who missed five doses due to illness or AEs, and had three partial doses due to AEs. Study medication compliance is summarized in the following table.

Table A1-9: Study 1602, Compliance with Study Medication

Patient	Dose Group	Weeks in Study	Complete Doses Received (%)	Comments
301	40	Through Week 106	54/54 (100)	
302	20	Through Week 94	48/48 (100)	
303	40	Through Week 86	36/44 (81)	5 missed doses: received <5 mL at Weeks 2 and 38 due to AEs, missed Weeks 70, 72 and 82 due to illness. 3 partial doses (Weeks 20, 22 and 78) due to AEs, IARs, and infusion reactions
305	20	Through Week 60	31/31 (100)	
306	20	Through Week 90	46/46 (100)	
307	40	Through Week 84	43/43 (100)	
308	40	Through Week 82	42/42 (100)	Week 34 infusion given at Week 35 (venous access problems)
309	20	Through Week 80	41/41 (100)	
310	20	Through Week 78	40/40 (100)	
311	40	Through Week 78	40/40 (100)	
312	20	Through Week 70	35/36 (97)	Partial dose at Week 12 due to IV problem
313	40	Through Week 70	36/36 (100)	
314	20	Through Week 70	36/36 (100)	
315	40	Through Week 64	33/33 (100)	
316	20	Through Week 58	27/29 (93)	Missed dose at Week 36 due to illness. Partial dose at Week 10 due to nursing error
317	40	Through Week 54	28/28 (100)	
318	40	Through Week 54	28/28 (100)	

319	20	Through Week 52	27/27 (100)

10.1.1.12.5 Protocol Deviations and Violations

Protocol deviations were noted to be frequent, and predominantly consisted 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) Two patients (Patients 303 and 311) were 6.1 months of age after correction for gestational age at first infusion (protocol required patients to be less than or equal to six months plus zero days of age). Exceptions for entry of these patients into the study were granted by the Medical Monitor.
2) Patient 303 underwent randomization prior to Informed Consent having been signed (Randomized 29-August-2003, Informed Consent signed 02-September-2003)
3) Patient 316 did not have updated Informed Consent Form signed prior to protocol procedures being performed.
4) Patient 302 underwent AIMS, PDMS, Pompe PEDI, BSID and motor milestone assessment prior to the Informed Consent having been signed.
5) Patient 310 had parental samples for GAA mutation analysis drawn prior to Informed Consent having been obtained.
6) Patients 313's and 319's parents were inadvertently given the Parental Genotyping Informed Consent for Study 1702 to sign rather than for Study 1602 (forms are identical other than protocol title and number)
7) DSI inspector of Site 81 (Gainesville site) noted that the three patients entered at site 81 (311, 317 and 319) did not have weight information entered correctly (mean weight only entered, protocol states that three separate weights were to be obtained and the average of three weights used for study drug dose calculation). It is unclear if three weights were obtained and if the appropriate dose was given to these three patients (noted on protocol deviation log that Patient 319 had measurements performed only once each at Week 38). It is noted that all three of these patients required mechanical ventilation at 18.9, 9.2 and 9.1 months of age, respectively.
8) Patient 307 received rhGAA intended for Study AGLU02203 instead of Study 1602 rhGAA due to insufficient supply of Study 1602 rhGAA. The AGLU02203 rhGAA was manufactured using the 2000 L manufacturing process.

It is unlikely that these protocol violations resulted in meaningful changes to the overall results of the study, particularly the primary endpoint results.

10.1.1.12.6 Primary Efficacy Endpoint

The primary efficacy endpoint was the proportion of patients alive and free of invasive ventilation using Kaplan-Meier methodology as compared to survival in the Historical Control Subgroup at 18 months of age. For the primary analysis, time to event is measured from date of birth. The results show that overall, three patients met the primary endpoint of invasive-ventilation as of 18 months of age. No patient died Two patients were censored as they had not yet reached 18 months of age; however, neither one of these patients had reached a primary endpoint as of 15-June-2005. An update to patient status as of 15-September-2005 after all

patients but one had reached 18 months of age showed no change in status for any patient (Patient 319 was less than 18 months of age, but had met the primary endpoint of invasive ventilator support). A comparison to the Historical Control Subgroup showed that of the 61 patients in the Historical Control Subgroup for whom an age of death is known (total 62 patients in subgroup), one of the 61 patients (2%) survived beyond 18 months of age. Median age from birth to first ventilatory support or death in the Historical Control Subgroup was 7.0 months (95% CI 6.5, 8.3). The results show a significant difference between rhGAA-treated patients and untreated patients in the Historical Control Subgroup, with treated patients showing a survival and ventilator-free survival advantage. The sponsor pooled the results of the two treatment groups, but no obvious differences in the primary endpoint between the dose groups are seen, with one patient in the 20 mg/kg group and two patients in the 40 mg/kg group requiring invasive ventilatory support. The overall results for the primary endpoint at the 52-Week milestone at the 15-June-2005 and 15-September-2005 updates are summarized in the following table (summarized from sponsor's submission):

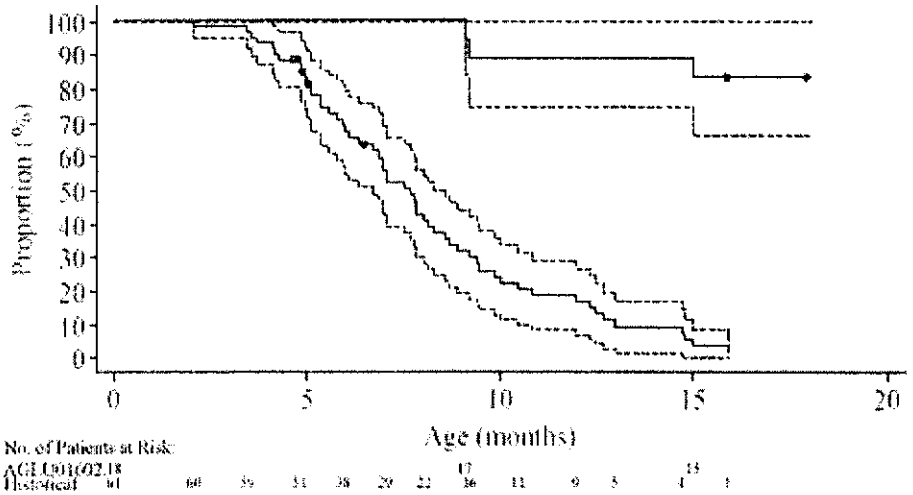
Table A1-10: Study 1602, Primary Endpoint of Ventilator-Free Survival, 52-Week Results

Dose Group	Study 1602					Historical Control		
	n =	Patients Alive & VF*, n (%)	Patients Meeting Primary Endpoint, n (%)	Patients Censored, n =	Proportion Estimate & 95% CI**	n =	Patients Alive, n (%)	Proportion Estimate & 95% CI#
As of 15-June-2005 Update								
Overall, n =	18	13 (72)	3 (17)	2	83 (66, 100)	61	1 (2)	2 (0, 6)
20 mg/kg, n =	9	8 (89)	1 (11)	0	89 (68, 100)	-	-	-
40 mg/kg, n =	9	7 (78)	2 (22)	2	78 (51, 100)	-	-	-
As of 15-September-2005 Update								
Overall, n =	18	15 (83)	3 (17)	0	83 (59, 96)	61	1 (2)	2 (0, 6)
20 mg/kg, n =	9	8 (89)	1 (11)	0	89 (52, 100)	-	-	
40 mg/kg, n =	9	7 (78)	2 (22)	0	78 (40, 97)	-	-	

*VF= ventilator free
**Proportions and CI from Kaplan-Meier analysis of time to invasive ventilation or death for 15-June-2005 update, exact CI for 15-Sept-2005 update
#Proportions from Kaplan-Meier analysis of time to death.

The Kaplan-Meier curve for the time to invasive ventilation or death at the 18 month milestone (as of 15-June-2005 cutoff, two patients censored) is represented graphically in the following figure (electronically copied and reproduced from the sponsor's submission). The lower line on the graph is the survival rate estimates curve for the Historical Control Subgroup with 95% CI surrounding it. The top line is the ventilator-free survival rate estimate curve for Study 1602 patients, with 95% CI surrounding it. It is noted that the analysis was the more conservative criterion of non-overlapping 95% CIs, and not the statistical significance of the comparison of 18-month survival rates.

Figure A1-1: Kaplan-Meier Plot of Time to Invasive Ventilation or Death from Date of Birth through 18-Month Milestone Compared to Historical Control Subgroup Survival



Patient status at the 52-week milestone (15-June-2005) is also summarized by individual patient in the following table.

Table A1-11: Study 1602, Status of Individual Patients at 52-Week Milestone, Updated with 15-September-2005 Results

Patient	Treatment Group (mg/kg)	Age*at 1st Infusion (mos)	Age* at week milestone (mos)	RhGAA exposure at 52-week milestone (mos)	Status at 52-week milestone (mos)	Age*at start of invasive ventilation (mos)
301	40	5.0	18.0	10.0	Invasive	15.0
302	20	7.0	18.0	11.0	Alive & VF	-
303	40	7.0	18.0	11.0	Alive & VF	-
305	20	5.7	18.0	12.3	Noninvasive	(12.0)
306	20	5.9	18.0	12.1	Noninvasive	(13.7)
307	40	6.9	18.0	11.1	Alive & VF	-
308	40	4.3	18.0	7.8	Alive & VF	-
309	20	5.3	18.0	6.9	Alive & VF	-
310	20	6.4	18.0	11.6	Alive & VF	-
311	40	7.3	18.0	10.7	Alive & VF	-
312	20	5.1	18.0	7.0	Alive & VF	-
313	40	2.3	18.0	10.1	Noninvasive	(14.9)
314	20	1.9	18.0	10.1	Alive & VF	-
315	40	1.2	15.9	6.1	Alive & VF	-
316	20	6.9	18.0	6.4	Alive & VF	-
317	40	6.2	18.0	3.0	Invasive	9.2
318	40	5.4	17.9		Alive & VF	-
319	20	2.1	14.4	5.7	Invasive	9.1

*Age not adjusted for age at gestation. Ages in ( ) represent age at start of noninvasive ventilation.
**VF = invasive ventilator-free

Patients were entered into the study at different times, and had varying lengths of treatment and ages at the 52-week milestone. As all patients continued to be followed, the status of all patients at the 15-June-2005 and 15-September-2005 cutoffs was known. The results for all patients as of

the 15-June-2005 cutoff showed that patient ages ranged from 14.4 to 29.7 months of age, and total length of treatment with rhGAA ranged from 12.3 to 24.7 months. Seven of the 18 treated patients had reached the primary endpoint of invasive ventilation, and one of these seven patients had died. The median age at invasive-ventilation or death is not yet known. These results also show that for the three patients on noninvasive ventilation at 18 months of age (Patients 305, 306, 313), all three patients subsequently required invasive-ventilation. The 15-September-2005 update showed no change in ventilator status for any patient; however, Patient 303 was noted to have died in after completing Study 1602 and being enrolled in an expanded access program (personal communication with the sponsor). The status of all patients as of 15-June-2005 is summarized in the following table.

Table A1-12: Study 1602, Status of Individual Patients as of 15-June-2005

Patient	Treatment Group (mg/kg)	Age* at 1st Infusion (mos)	RhGAA exposure at 15-Jun-05 or time of death (mos)	Age* at 15-Jun-05 (mos)	Status as of 15-Jun-05	Age* at start of invasive ventilation (mos)	Age* at death (mos)
301	40	5.0	24.7	29.7	Invasive	15.0	-
302	20	7.0	21.6	28.6	None	-	-
303	40	7.0	21.1	28.1	Invasive	24.5	-
305	20	5.7	14.0	-	Invasive/died	19.4	19.8
306	20	5.9	20.5	26.4	Invasive	19.7	-
307	40	6.9	19.2	26.2	None	-	-
308	40	4.3	18.8	23.1	None	-	-
309	20	5.3	18.4	23.7	None	-	-
310	20	6.4	17.9	24.4	None	-	-
311	40	7.3	18.0	25.2	None	-	-
312	20	5.1	16.1	21.2	None	-	-
313	40	2.3	16.2	18.5	Invasive	18.5	-
314	20	1.9	16.1	18.0	None	-	-
315	40	1.2	14.7	15.9	None	-	-
316	20	6.9	13.4	20.3	None	-	-
317	40	6.2	12.6	18.8	Invasive	9.2	-
318	40	5.4	12.5	17.9	None	-	-
319	20	2.1	12.3	14.4	Invasive	9.1	-

*Chronologic age not adjusted for age at gestation

10.1.1.12.6.1 Additional Primary Endpoint Analyses

Additional and exploratory analyses of the primary endpoint were performed. The endpoint of patients alive and free of invasive ventilator support at 12 months of age showed that two patients, one patient in each of the two dose groups, had met the primary endpoint at the 12-month milestone (89% invasive ventilator-free survival). Both of these patients (Patients 317 and 319) were receiving invasive ventilation, and no patient had died. On comparison to the Historical Control Subgroup, nine of 61 patients were alive at 12 months of age (15% survival); however, the comparison of the treatment group in Study 1602 to the Historical Control Subgroup is subjectto selection bias and the results are less reliable than for the 18-month endpoint comparison (see sensitivity analyses below). The results overall and by individual patient are summarized in the following tables.

TableA1-13 : Study 1602, Additional Primary Endpoint Analysis, 12-Month Milestone

Dose Group	Study 1602				Historical Control		
	n =	Patients Alive & VF, n (%)	Patients meeting Primary Endpoint, n (%)	Proportion Estimate & 95% CI	n =	Patients Alive, n (%)	Proportion Estimate & 95% CI
Overall, n =	18	16 (89)	2 (11)	89 (74, 100)	61	9 (15)	17 (7, 27)
20 mg/kg, n =	9	8 (89)	1 (11)	89 (68, 100)	-	-	
40 mg/kg, n =	9	8 (89)	1 (11)	89 (68, 100)	-	-	

Patient status at the 26-week milestone (15-June-2005) is also summarized by individual patient in the following table.

Table A1-14: Study 1602, Status of Individual Patients at 26-Week Milestone, Updated Results as of 15-June-2005

Patient	Treatment Group (mg/kg)	Age*at 1st Infusion (mos)	Age* at 26-week milestone (mos)	RhGAA exposure at 26-week milestone (mos)	Status at 26-week milestone	Age*at start of invasive ventilation (mos)
301	40	5.0	12.0	7.0	Noninvasive	(12.0)
302	20	7.0	12.0	5.0	Alive & VF	-
303	40	7.0	12.0	5.0	Alive & VF	-
305	20	5.7	12.0	6.3	Noninvasive	(12.0)
306	20	5.9	12.0	6.1	Alive & VF	-
307	40	6.9	12.0	5.1	Alive & VF	-
308	40	4.3	12.0	7.7	Alive & VF	-
309	20	5.3	12.0	6.7	Alive & VF	-
310	20	6.4	12.0	5.6	Alive & VF	-
311	40	7.3	12.0	4.7	Alive & VF	-
312	20	5.1	12.0	6.9	Alive & VF	-
313	40	2.3	12.0	9.7	Alive & VF	-
314	20	1.9	12.0	10.1	Alive & VF	-
315	40	1.2	12.0	10.8	Alive & VF	-
316	20	6.9	12.0	5.1	Alive & VF	-
317	40	6.2	12.0	5.8	Invasive	9.2
318	40	5.4	12.0	6.6	Alive & VF	-
319	20	2.1	12.0	9.9	Invasive	9.1

*Age not adjusted for age at gestation
**VF = invasive ventilator-free. Age at onset of noninvasive ventilation appears in ( ).

Exploratory evaluations by date of first symptoms, date of diagnosis, date of study treatment initiation, length of rhGAA treatment, and dose group assignment, revealed no obvious differences in any of these parameters between patients who required invasive-ventilation or died during study treatment and those who remained alive and ventilator-free. It is noted, however, that for patients requiring invasive ventilation, the median age at the start of invasive ventilation was 18.5 months, and eight of the eleven patients who were alive and free of invasive ventilation were less than 18.5 months of age as of the last patient status update (15-September-2005). It is not known if these younger patients will develop respiratory failure as they age. Patients by invasive-ventilation status are summarized in the following table.

Table A1-15: Patients by Invasive-Ventilation Status (last date noted 15-Sept-05)

Patient	Dose (mg/kg)	Age at First Symptoms (mos)	Age at Diagnosis (mos)	Age at First Infusion (mos)	Age at Start of Invasive Ventilation (mos)	RhGAA Exposure (mos)	Age at Cut-off (mos)
Patients Requiring Invasive Ventilation							
301	40	0	0.7	5.0	15.0	24.7	32.7
303	40	2.4	4.9	7.0	24.5	21.1	31.3
305	20	2.6	4.0	5.7	19.4/19.8*	14.0**	-
306	20	1.5	4.8	5.9	19.7	20.5	29.4
313	40	0.4	0.7	2.3	18.5	16.2	21.5
317	40	0.1	6.0	6.2	9.2	12.6	21.8
319	20	0	1.9	2.1	9.1	12.3	17.4
Mean	-	1.0	3.3	4.9	16.6	17.3	25.7
Median	-	0.4	4.0	5.7	18.5	16.2	25.6
Min, max	-	0, 2.6	0.7, 6.0	2.1, 7.0	9.1, 24.5	14.0, 24.7	17.4, 32.7
Patients Not Requiring Invasive Ventilation							
302	20	0	4.7	7.0	-	21.6	31.6
307	40	4.2	4.2	6.9	-	19.2	29.2
308	40	0	1.7	4.3	-	18.8	26.1
309	20	0.2	5.0	5.3	-	18.4	26.7
310	20	5.4	6.2	6.4	-	17.9	27.4
311	40	2.2	6.8	7.3	-	18.0	28.2
312	20	2.5	2.9	5.1	-	16.1	24.2
314	20	0	0.7	1.9	-	16.1	21.0
315	40	0.2	0.2	1.2	-	14.7	18.9
316	20	3.0	6.0	6.9	-	13.4	23.3
318	40	4.3	4.5	5.4	-	12.5	20.9
Mean	-	2.0	3.9	5.2	-	17.0	25.2
Median	-	2.2	4.5	5.4	-	17.9	26.1
Min, max	-	0, 5.4	0.2, 6.8	1.2, 7.0	-	12.5, 21.6	18.9, 31.6

*age at death
** exposure at time of death

10.1.1.12.6.2 Sensitivity Analyses of Primary Endpoint

To control for selection bias whereby "healthier" patients who survived to at least six months of age were included and "sicker" patients who died at a younger age (i.e, less than six months of age) were excluded from Study 1602, sensitivity analyses were performed by the sponsor. In these analyses, the proportion of rhGAA-treated patients in Study 1602 who were alive and free of invasive ventilation at 12 and 18 months of age were compared to survival rates from the Historical Control Subgroup in which patients who died prior to three, four, five, or six months of age were removed. The 12- and 18-month survival rates for the rhGAA-treated patients remained higher than the survival estimates for each of these analyses, with non-overlapping confidence intervals. It is noted, however, that in the 12-month survival analyses, the proportion estimates for survival increases in the Historical Control Subgroup steadily increased as the younger aged patients were excluded, suggesting that the 12-month comparison was susceptible to selection bias. This trend is completely eliminated when 18-month survival is evaluated as almost no patients survive in the Historical Control Subgroup at 18 months. Thus, ventilator-free survival at 18 months appears to be a more robust assessment vs. the historical control for

discerning an rhGAA-treatment effect. The sponsor's results are summarized in the following table (from the sponsor's abridged final report).

Table A1-16: Study 1602, Sensitivity Analyses, Primary Endpoint

Study 1602 Invasive Ventilator-Free Survival			Historical Control Subgroup Survival		
Age	**n =**	**Proportion estimate (95% CI)**	**Age Milestone Subset**	**n =**	**Proportion estimate (95% CI)**
12 Months	18	89 (74, 100)	All patients	61	17 (7, 27)
			3 months	60	17 (7, 27)
			4 months	57	18 (7, 29)
			5 months	45	21 (9, 33)
			6 months	37	25 (11, 39)
18 Months	18	83 (66, 100)	All patients	61	2 (0, 6)
			3 months	60	2 (0, 6)
			4 months	57	2 (0, 6)
			5 months	45	2 (0, 7)
			6 months	37	3 (0, 8)

10.1.1.12.7 Secondary Efficacy Endpoints

10.1.1.12.7.1 Alive and Free of Ventilatory Support

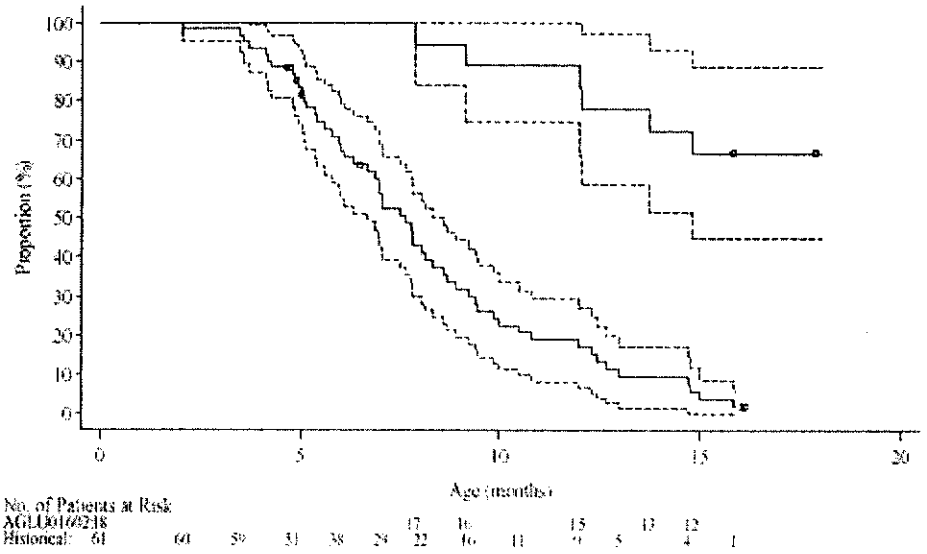
The proportion of patients who were alive and free of any ventilatory support at 12- and 18-months of age was assessed. Ventilatory support was defined as any invasive or noninvasive form of ventilatory support. Ventilator use in planned surgical or protocol-related procedures, if the total duration of ventilatory support was less than three days, was not counted as an event. Patients were considered to be free of any ventilation at the 12- or 18-month milestones if they were free of any ventilation for the 14-day period bracketing this date or, if they required ventilator support at the target time point (for secondary causes only) and were able to come off of ventilatory support for at least 14 consecutive days during a 30-day follow-up period. Overall, the results show that at the 18-month milestone (52 weeks updated to reflect known status of patients as of 15-September-2005), twelve patients (six in each dose group) were alive and free of any ventilatory support, three patients required invasive ventilation, and three patients required noninvasive ventilatory support. At the 12-month milestone, four patients (two patients in each dose group) required any ventilatory support: two each invasive and noninvasive ventilatory support. Patients alive and free of any ventilatory support at the 12- and 18-month milestones are summarized in the following table:

Table A1-17: 1602, Patients Alive and Free of Any Ventilatory Support at 12- and 18-Month Milestones

	All	40 mg Group	20 mg Group	Proportion Estimate
Treated Patients, n =	18	9	9	**& 95% CI**
12-Month Milestone				
Alive and Free of Any Ventilatory Support, n =	14	7	7	80 (60, 100)
Died, n =	0	0	0	
On Ventilatory Support	4	2	2	
Invasive	2	1	1	
Non-invasive	2	1	1	
18-Month Milestone				
Alive and Free of Any Ventilatory Support, n =	12	6	6	67 (45, 88)
Died, n =	0	0	0	
On Ventilatory Support	6	3	3	
Invasive	3	2	1	
Non-invasive	3	1	2	

The results by individual patient are also represented graphically in the following figure (electronically copied and reproduced from the sponsor's submission):

Figure A1-2: Study 1602, Any Ventilator-Free Survival vs. Historical Control Subgroup Survival



Overall, the results for any ventilator-free survival (invasive or noninvasive) as compared to survival in the Historical Control Subgroup at Week 52 showed a survival advantage in favor of rhGAA-treated patients, which is consistent with the results of an invasive-ventilator free survival advantage in the rhGAA-treated patients as compared to the Historical Control Subgroup at Week 52 (primary endpoint).

10.1.1.12.7.2 Cardiac Parameters

Cardiac parameters were assessed by echocardiography, focusing primarily on left ventricular mass (LVM), LVMI, and ejection fraction (EF), which were assessed at baseline and at Weeks 4,

8, 12, 26, 38 and 52. Cardiac hypertrophy (referred to as cardiomyopathy by the sponsor) was defined as an LVM greater than two standard deviations (SDs) from the mean for age-matched normals. All patients had cardiac hypertrophy at baseline (entry criterion for the study). Fifteen of 18 patients had LVMI and LVM Z-scores at baseline (missing Patients 302, 303 and 318). The results show that all patients had a decrease in LVMI throughout the course of the study. LVMI progressively decreased from a mean at baseline of 193 g/m^2 to a mean of 87 g/m^2 at Week 52 (mean change from baseline -118 g/m^2). LVM Z-scores decreased from a mean of 7.1 (approximately 7 SD above the mean) at baseline to a mean of 3.3 at Week 52 (mean decrease in Z-score of -4.3 at Week 52). The LVM Z-scores ranged from a minimum of 0.7 to a maximum of 6.3 at Week 52, which is consistent with LVM ranging from the normal range to some patients continuing to have massively increased LVM compared to normals. The EF results showed a small mean increase in EF from a mean at baseline of 51% to 55% at Week 52. Mean EF results initially showed decreases through Week 12, with subsequent smaller increases at Weeks 26, 38 and 52. The cardiac parameter results through Week 52 are summarized in the following table:

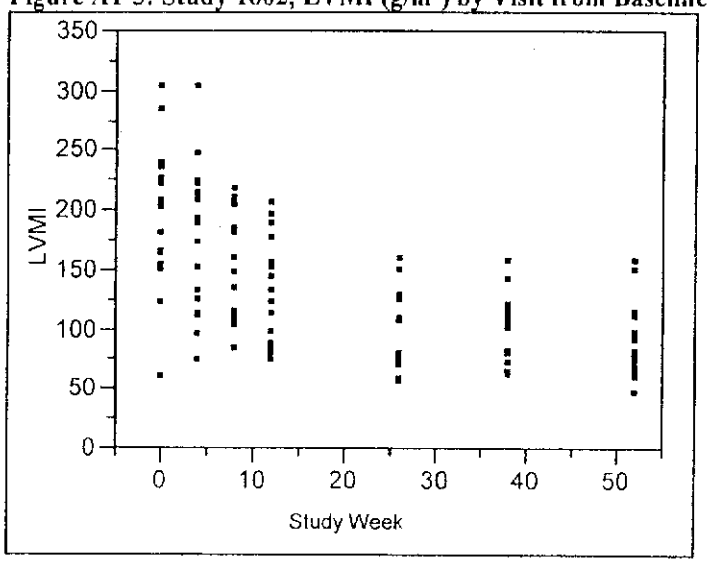
Table A1-18: Study 1602, Cardiac Parameters Baseline through Week 52

	Baseline	Week 4	Week 8	Week 12	Week 26	Week 38	Week 52
Parameter							
LVMI (g/m^2), n =	15	16	16	16	14	12	15
Mean	193	172	147	130	98	100	87
Median	202	180	140	126	92	103	77
Range	59, 302	73, 302	83, 217	72, 205	56, 158	61, 156	45, 157
ΔLVMI*(g/m^2), n =	-	14	13	13	12	11	14
Mean	-	-26	-59	-70	-110	-112	-118
Median	-	-27	-55	-78	-102	-100	-119
Range	-	-75, +44	-120, 0	-116, -26	-178, -43	-182, -46	-193, -45
LVM Z-Score, n =	15	16	16	16	14	12	15
Mean	7.1	6.6	6.0	5.3	4.0	4.1	3.3
Median	7.6	7.0	6.0	5.4	3.9	4.4	3.1
Range	2.6, 9.3	3.0, 9.3	3.8, 7.8	3.0, 7.5	2.1, 6.4	2.1, 6.3	0.7, 6.3
ΔZ-Score*, n =	-	14	13	13	12	12	14
Mean	-	-0.7	-1.6	-2.0	-3.6	-3.6	-4.3
Median	-	-0.6	-1.8	-1.8	-3.7	-3.7	-4.8
Range	-	-2.3, +0.8	-3.0, -0.1	-3.1, -0.9	-5.5, -1.2	-5.8, -1.3	-5.8, -1.3
Ejection Fraction, n =	16	16	17	16	15	13	18
Mean	51	44	42	44	55	53	55
Median	50	43	42	44	57	53	56
Range	25, 76	27, 64	22, 69	27, 60	21, 74	33, 71	24, 76
ΔEF*, n =	-	15	15	14	13	12	16
Mean	-	-7	-11	-7	+1	+6	+2
Median	-	-3	-9	-8	-8	+5	+9
Range	-	-24, +11	-38, +10	-30, +10	-14, +26	-29, +23	-40, +40

*Change from Baseline

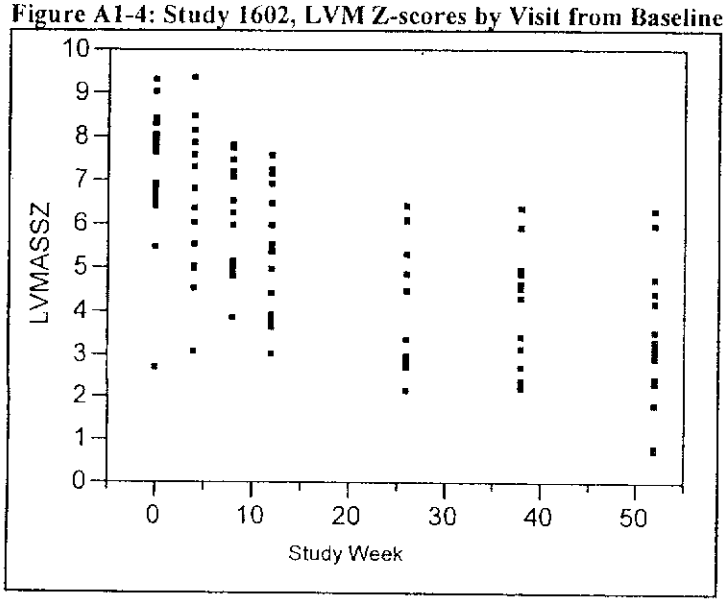
The results for LVMI by study visit from baseline to Week 52 are represented graphically in the following figure:

Figure A1-3: Study 1602, LVMI (g/m^2) by Visit from Baseline to Week 52



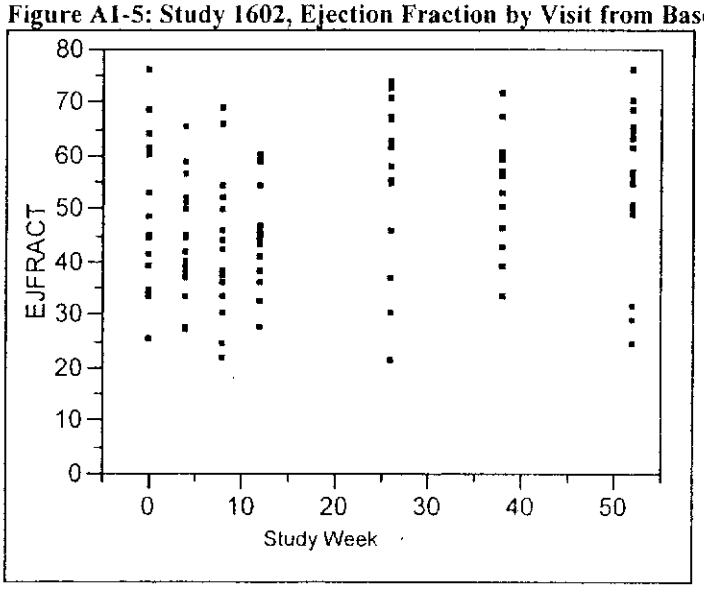
The results for LVM Z-scores by study visit from baseline to Week 52 are represented graphically in the following figure:

Figure A1-4: Study 1602, LVM Z-scores by Visit from Baseline to Week 52



The results for ejection fraction by study visit from baseline to Week 52 are represented graphically in the following figure:

Figure A1-5: Study 1602, Ejection Fraction by Visit from Baseline to Week 52



Cardiac status was also assessed by the proportion of patients with signs or symptoms of cardiac failure through Week 52 of the study (tertiary endpoint). There were two patients (Patients 309 and 314) who had signs or symptoms compatible with cardiac failure at baseline. By Week 52, four patients (Patients 303, 306, 313 and 314; Patient 314 had cardiac failure AE at Day 1 only) had AEs reported that were compatible with or could be indicative of cardiac failure. However, it is noted from a clinical standpoint that there is overlap in the signs and symptoms of cardiac failure with respiratory failure in this patient population, and as there were no historical control data available for comparison, no conclusions can be drawn from these cardiac failure results. It is additionally noted that three of the patients listed below (Patients 303, 306 and 313) also developed respiratory failure requiring invasive ventilation at some time during the study. AEs reported during the study that are compatible with cardiac failure are summarized in the following table:

Table A1-19: Study 1602, Cardiac AEs Compatible with Signs or Symptoms of Cardiac Failure

Patient	SOC	AE Preferred Term	Verbatim AE Term	Days after 1st Infusion
303	Cardiac disorders	Hypertrophic obstructive cardiomyopathy	Left ventricular outflow obstruction	580
303	Cardiac disorders	Hypertrophic obstructive cardiomyopathy	LV obstruction	492
306	Cardiac disorders	Diastolic dysfunction	Diastolic dysfunction	411
313	Cardiac disorders	Cardiac failure	Worsening heart function	485
314	Cardiac disorders	Cardiac failure	Poor cardiac function	1

Overall, the cardiac parameter results showed decreases in LVMI and LVM Z-scores for all patients from baseline at Week 52 that are consistent with the pharmacodynamic (PD) effect of ERT with rhGAA; however, there was no clear correlation by individual patient with decreases in LVMI and changes in EF, nor was there a clear correlation with the changes in the cardiac parameters and clinical outcome assessed by invasive ventilator-free survival, motor

development, or the development of cardiac AEs consistent with cardiac failure. Thus, the relevance of the PD effect of rhGAA treatment on cardiac function is unknown, and no clear clinical effect of rhGAA treatment on cardiac function could be definitively determined from the available data.

10.1.1.12.7.3 Physical Growth

Growth was assessed through repeated measurements of body weight and length, and head circumference. Growth data were expressed as standardized age- and gender-matched percentiles and Z-scores with reference to the Center for Disease Control/National Center for Health Statistics (CDC/NCHS) growth charts (Note: CDC/NCHS charts are scaled for a US populations and patients in this study are an international cohort). The quality of data supplied by the sponsor for physical growth is poor contained obvious errors in some patients that were noted on review of the data, such as decreases in lengths and head sizes from prior time points, and missing datapoints were frequent for many patients.

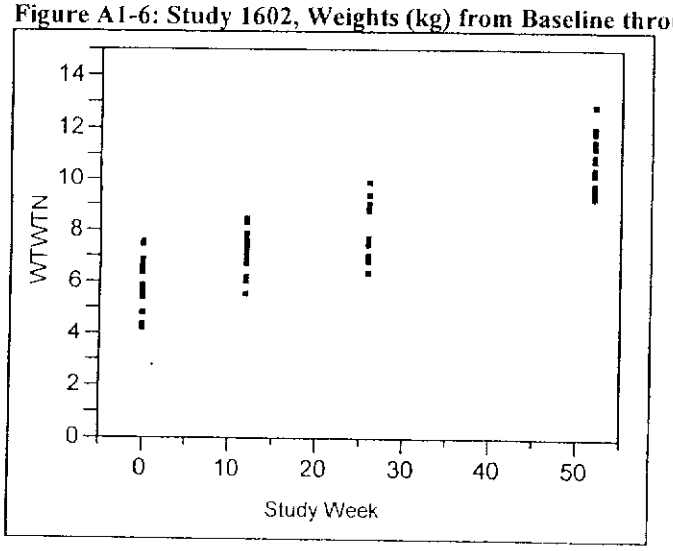
Despite limitations in data quality, the results show that all patients had increases in length, weight and head circumference from baseline through Week 52. For weight at baseline, mean Z-score was -1.4 (-3.3 to +0.8). At Week 52, weight mean Z-score increased to -0.6 (-2.2 to +0.8) consistent with improved weight gain approaching norms for age (all but two patients were within two SD of mean for age at Week 52). For length, mean Z-score at baseline was -0.3 (-3.0 to +2.5) and at Week 52 was +0.5 (-2.7 to +3.4), with all but three patients within two SD of mean for age (one patient was less than -2, and two patients were more than +2). Head circumference at baseline showed a mean Z-score of -1.2 at baseline (-4.8 to +0.1), and at Week 52 mean Z-score increased to -0.7 (-2.6 to +0.9), with all but three patients within two SD of the mean for age (three patients were less than-2, and no patient was greater than +2). The overall study results for growth parameters from baseline through Week 52 are summarized in the following table (a summary of growth parameters by individual patient is located in the subappendix):

Table A1-20: Study 1602, Growth Parameters

	Baseline	Week 12	Week 26	Week 52
Parameter				
Weight (kg), n =	18	18	18	18
Mean	5.9	7.1	8.4	10.6
Median	5.7	7.1	8.7	10.6
Min, max	4.1, 7.5	5.5, 8.4	6.3, 9.8	9.2, 12.8
Weight Z-score, n =	18	18	18	18
Mean	-1.4	-1.5	-1.3	-0.6
Median	-1.7	-1.6	-1.3	-0.5
Min, max	-3.3, +0.8	-4.2, +0.9	-4.5, +0.1	-2.2, +0.8
Length (cm), n =	16	17	17	15
Mean	63	67	74	82
Median	63	69	75	82
Min, max	53, 76	63, 76	66, 80	74, 91
Length Z-score, n =	16	17	17	15
Mean	-0.3	+0.2	+0.1	+0.5
Median	-0.3	0	+0.5	+0.5
Min, max	-3.0, +2.5	-2.5, +2.1	-3.9, +1.6	-2.7, +3.4
Head Circumference (cm), n =	14	17	16	15
Mean	41	42	44	46
Median	41	43	45	47
Min, max	36, 44	39, 46	42, 47	43, 49
Head Circumference Z-score, n =	16	17	16	15
Mean	-1.2	-1.4	-1.0	-0.7
Median	-1.0	-1.1	-0.9	-0.5
Min, max	-4.8, +0.1	-4.4, +0.2	-3.2, +0.4	-2.6, +0.9

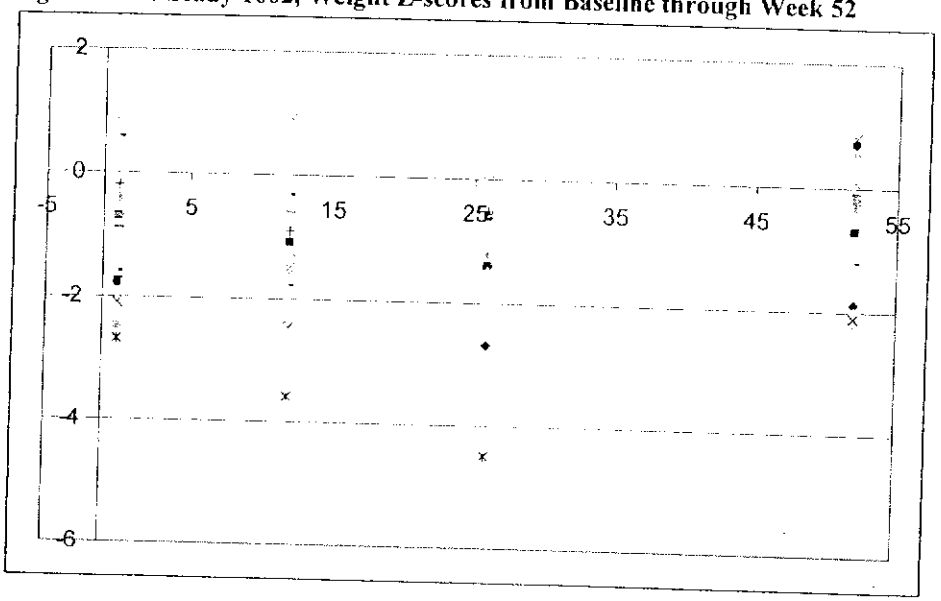
Weights from baseline to Week 52 are represented graphically in the following figure:

Figure A1-6: Study 1602, Weights (kg) from Baseline through Week 52



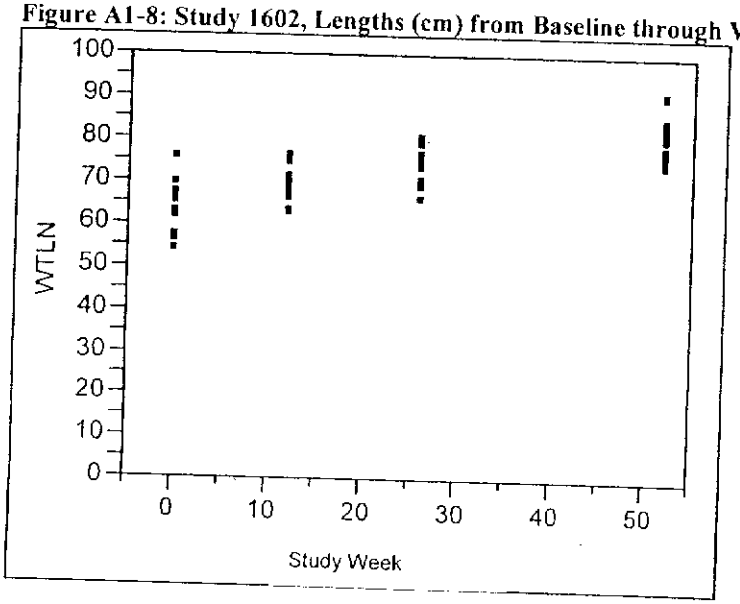
Weight mean Z-scores from baseline to Week 52 are represented graphically in the following figure:

Figure A1-7: Study 1602, Weight Z-scores from Baseline through Week 52



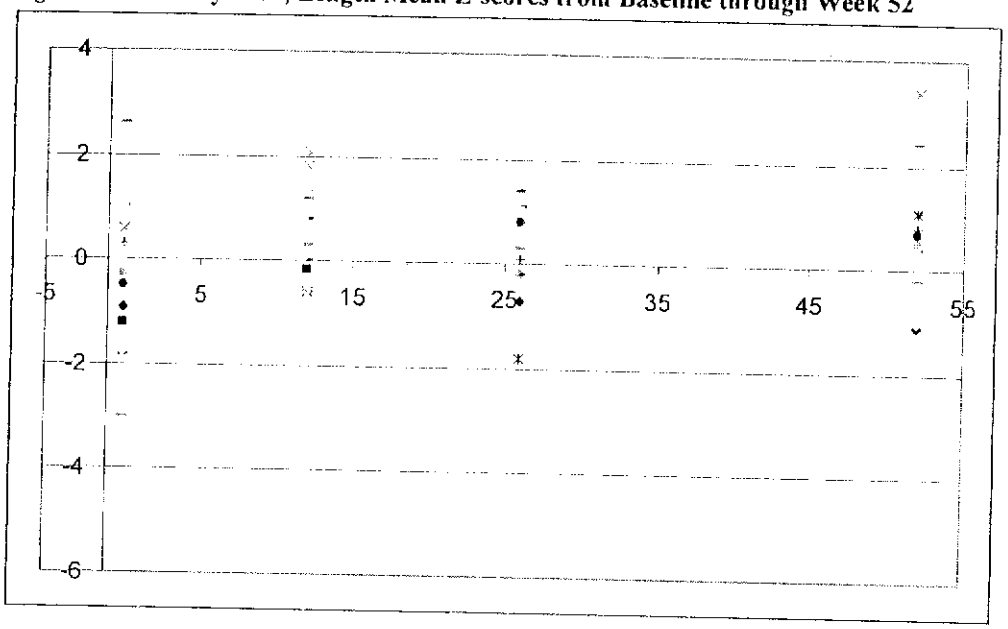
Lengths from baseline to Week 52 are represented graphically in the following figure:

Figure A1-8: Study 1602, Lengths (cm) from Baseline through Week 52



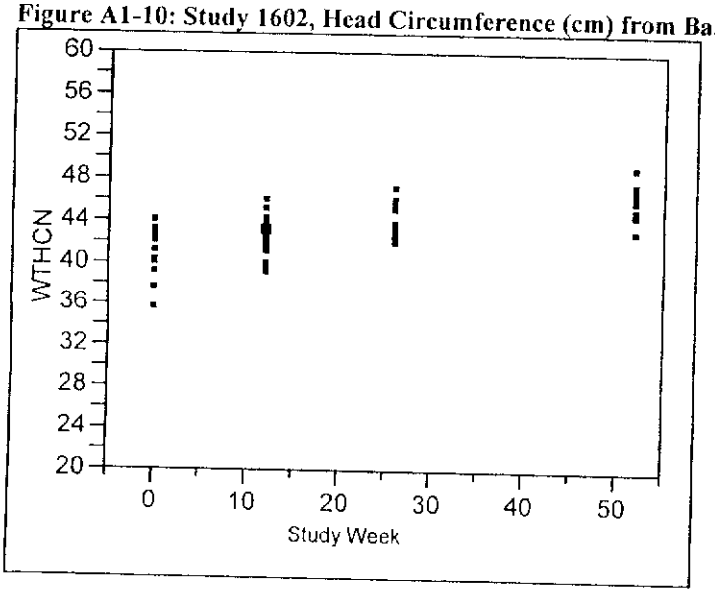
Length mean Z-scores from baseline to Week 52 are represented graphically in the following figure:

FigureA1-9: Study 1602, Length Mean Z-scores from Baseline through Week 52



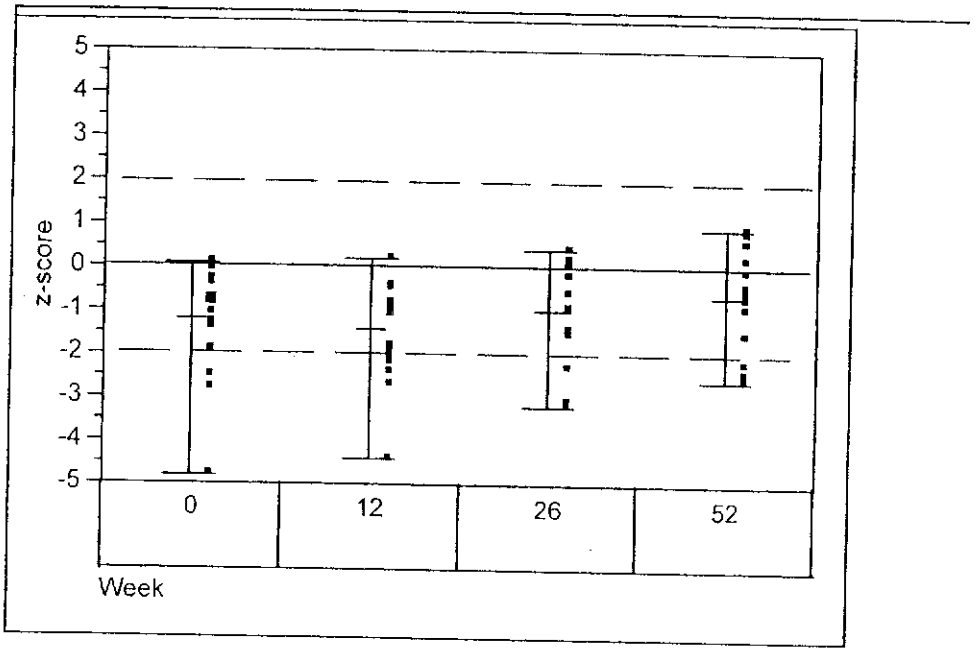
Head circumferences from baseline to Week 52 are represented graphically in the following figure:

Figure A1-10: Study 1602, Head Circumference (cm) from Baseline through Week 52



Head circumference mean Z-scores from baseline to Week 52 are represented graphically in the following:

Figure A1-11: Study 1602, Head Circumference Mean Z-scores from Baseline through Week 52



A consultation from the Division of Pediatric Drug Development was requested by the Division on the growth assessments used in this study, and the following comments are noted (for a complete review by the Pediatric consultant, please see Medical Officer Consult, by Hari Sachs, M.D., FAAP):

- Data from the Historical Cohort (n=168) suggest that median weight-, height- and head-circumference percentiles at birth were only slightly smaller than average, but final measurements indicate that the weight and head circumference measurements were less than the tenth percentile (interpretation of these data is limited as the methodology utilized to measure these growth parameters was not specified and measurements for each patient were not available for review). Feeding difficulties and failure-to-thrive were present in greater than 50% of patients and greater than 75% of patients received nutritional support, but whether or not feeding difficulties were present is not known in approximately 30% of the historical cohort limiting the usefulness of these data.
- Limitations in Study 1602 data were noted (errors, missing data and reference to US population norms only).
- Presentation of weight for length to assess relative failure to thrive, and analysis regarding method of feeding and calorie intake were recommended by the Pediatric Consultant, but were not available for Study 1602.
- Head circumference results noted two patients (Patients 311 and 317) with relative microencephaly (small head sizes disproportionately small compared with length). Relative microencephaly is of significance due to the association between developmental

delay and microencephaly. Increasing head size was also noted by the Pediatric Consultant as possibly being of concern as this may represent either catch up growth or CNS glycogen accumulation similar to that found in other storage disorders.

The overall conclusion was that effects on growth are unclear, as growth was not correlated with feeding method, gestational age or nutritional status. There were missing data and errors in length and head size measurements noted. It was recommended that follow-up trials for infants should included standardized measurements and analysis of growth in relationship to feeding method and nutritional status, and weight for height data should be presented. This Reviewer is in agreement with the findings and recommendations of the Pediatric Consultant, and although the growth data appear to show encouraging trends in growth, further study is warranted based on the limitations in the data as noted above.

10.1.1.12.8 Tertiary Efficacy Endpoints

(An overall assessment of the motor and cognitive development findings for the AIMS, Pompe PEDI and BSID-II tests is provided after the BSID-II summary.)

10.1.1.12.8.1 Alberta Infant Motor Scale (AIMS) Performance Scores at Week 52

The AIMS is a widely used observational measure of infant motor performance that assesses motor maturation of the infant from term (40 weeks gestational age) through the age of independent walking (approximately 18 months of age). AIMS describes the motor development sequence according to the development of postural control relative to the various postural positions: prone, supine, sitting and standing (maximum scores prone 21, supine 9, sit 12 and stand 16). Observations are scored (maximum 58 points for raw score), and the raw score is converted into an age-equivalent score (the age at which 50% of healthy peers achieved such score, indicating the developmental age at which the patient is performing). The following is a listing of the scored motor development milestones from the AIMS test (discrete milestones grouped in four categories: supine, floor mobility (prone), sitting, standing/walking, which are roughly hierarchical in terms of difficulty within each category but do not reflect a developmental sequence). At each assessment, the patient's score was equal to the total number of milestones achieved (table electronically copied and reproduced from the sponsor's submission):

Figure A1-12: AIMS Motor.Development Milestones

Positions		Milestone Description
Supine Or Supported Supine		Turns Head Side To Side To Look At Parent
		Grasps Small Object
		Reaches Up Or Out To Grasp Small Object
		Brings Hands Together In Midline
		Transfers Small Object Hand To Hand
Floor Mobility		Rolls Prone To Supine Position
		Rolls Supine To Prone Position
Sitting	Supported Sitting	Holds Head Upright With Body Supported In Chair Or By Person
		Holds Head Steady While Attending To An Activity-trunk Supported
		Grasps Small Object
		Reaches Up Or Out To Grasp Small Object
		Brings Hands Together In Midline-supported Sitting
		Transfers Small Object Hand To Hand
	Independent Sitting	Sits Independently-propped Without Independent Head Control
		Sits Independently-holds Head Steady To Attend To Activity
		Grasps Small Object
		Reaches Up Or Out To Grasp Small Object
		Brings Hands Together In Midline-independent Sitting
		Transfers Small Object Hand To Hand
	Sitting Transitions	Pulls To Sit Without Head Lag
		Transitions From Floor Into Sitting Independently
Standing and Walking		Bears Weight Through Lower Extremities
		Walks With Hands Held
		Pulls To Stand Independently
		Walks Independently
		Walks While Carrying Object
		Goes Up Stairs With Assistance (rail, hand[s] held, assistive device)
		Goes Up Stairs Independently

The results show that at baseline all patients except one (Patient 302) had motor scores less than the 50th percentile for age (11 of whom had percentile scores less than or equal to the first percentile). By Week 52, 13 patients showed varying degrees of increases in motor raw scores (achieved new motor milestones). Seven of these 13 patients demonstrated motor development in the greater than or equal to the 50th percentile for age (raw scores 55-58 out of a possible 58). The remaining six patients had percentile scores ranging from less than the first to ninth percentile for age (raw scores 16-51) demonstrating progress in these patients in motor develop, albeit delayed for age. Five patients (301, 305, 306, 317 and 319) failed to achieve new motor milestones as demonstrated by the AIMS test, with little to no increases (or regression) in the AIMS raw score. It is noted that all five of these patients required invasive or noninvasive ventilation at the 52-week milestone (as did Patient 313, raw score 51, ninth percentile, who required noninvasive ventilation). Historical control comparisons were not provided for the AIMS results, nor for any of the motor or developmental assessments performed as part of this

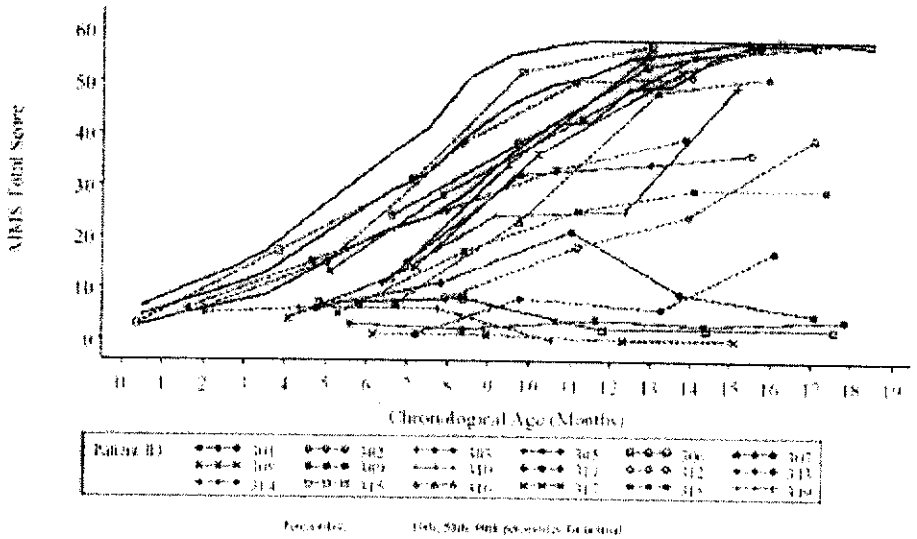
study. However, as infantile-onset Pompe disease is a progressive disorder, and loss of motor milestones with increasing age is noted to be characteristic of disease progression, gains in motor milestones would not be expected in any untreated patient. The AIMS results at baseline and Week 52 by individual patient are summarized in the following table (a complete listing of AIMS results by individual patient is located in the subappendix).

Table A1-21: Study 1602, AIMS Motor Performance Scores from Baseline to Week 52

Patient	Week	Chronologic Age (mos)	Raw Score (58)	Age Equivalent Score (mos)	Percentile Score	Status
301	Baseline	4.8	6	1.1	<1	
	52	17.1	5	0.8	<1	Invasive
302	Baseline	6.6	24	6.0	66	
	52	18.9	58	≥14	≥50	A & VF
303	Baseline	7.0	15	4.0	2	
	52	19.4	55	13	≥50	A & VF
305	Baseline	5.6	3	<0.5	<1	
	52	17.8	4	<0.5	<1	Noninvasive
306	Baseline	5.8	7	1.4	<1	
	52	17.6	2	<0.5	<1	Noninvasive
307	Baseline	6.6	12	3.3	1	
	52	18.9	58	≥14	≥50	A & VF
308	Baseline	4.1	4	<1	<1	
	52	16.2	58	≥14	≥50	A & VF
309	Baseline	5.1	13	3.6	7	
	52	17.1	57	≥14	≥50	A & VF
310	Baseline	6.4	11	3.0	<1	
	52	18.4	47	9.9	<1	A & VF
311	Baseline	7.2	1	<0.5	<1	
	52	19.2	16	4.2	<1	A & VF
312	Baseline	4.8	7	1.3	<1	
	52	17.0	39	8.4	<1	A & VF
313	Baseline	2.0	6	1.0	16	
	52	14.0	51	11.4	9	Noninvasive
314	Baseline	1.6	6	1.0	25	
	52	13.8	39	8.4	<1	A & VF
315	Baseline	0.4	3	0.5	14	
	52	13.0	57	≥14	65	A & VF
316	Baseline	6.7	7	1.4	<1	
	52	18.9	57	≥14	≥50	A & VF
317	Baseline	6.2	1	0.5	<1	
	52	18.7	0	<0.5	<1	Invasive
318	Baseline	5.3	5	0.8	<1	
	52	17.3	29	6.7	<1	A & VF
319	Baseline	2.0	5	0.8	7	
	26	7.7	6	1.0	<1	Invasive
	52	Not available	Not available	Not available	Not available	

The AIMS results are also represented graphically in the following figure (electronically copied and reproduced from the sponsor's submission):

Figure A1-13: AIMS Motor Performance Age-Equivalent Scores from Baseline to Week 52



10.1.1.12.8.2 Pompe PEDI Evaluation of Disability Inventory

The PEDI[2] is a standardized instrument developed to assess the functional capabilities of children six months to seven and a half years of age. Functional skills (performed independently) and caregiver assistance skills (performed with assistance) are assessed in three contents domains: self-care (e.g., feeding, grooming bathing, dressing), mobility (e.g., chair or bed transfer, locomotion), and social function (e.g., comprehension, expression). Higher scores indicate better performance and increased independence. The PEDI is administered as a parental report questionnaire.

The Pompe PEDI[3] is a standardized, modified version of the PEDI specifically designed for patients with Pompe disease. Since Pompe disease primarily impacts motor function, the PEDI mobility and self-care functional skill scales were modified for the Pompe PEDI by adding items that reflected the types of functional skills and deficits noted in children with Pompe disease, and new items were 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). The Pompe PEDI was administered as a telephone interview questionnaire and parent-reported items were scored as "capable" or "unable". Raw scores are transformed to normative and scaled scores. Normative scores are available for children up to seven years of age to describe how a child is performing compared to same-aged peers without a disability. Scaled scores are reported on a 0-100 continuum used to represent functional skills achieved (the higher the score, the more skills the child can perform). The mobility scales has four levels (by scaled score): limited movement (0-30) for patients who are not yet mobile, incipient mobility (30-50) for patients who use powered wheelchairs or have floor mobility/weight bearing, basic self mobility (50-70) for patients manually driving a wheelchair or walking with crutches, and advanced skill movement

(70-100) for patients who are self-mobile and can participate in sports. Self care scores also have four levels of function: object use (0-30) describing patients who can use their hands and fingers but not shoulder, incipient self-care (30-50) for patients who exhibit improved fine motor and proximal control and can assist caregivers, basic person care (50-70) for patients who can bathe, dress, and perform personal hygiene on their own with minimal assistance, and advanced self care (70-100) describing patients who can perform toileting, tying shoes, grooming hair and managing personal hygiene. For the Pompe PEDI, 50% of non-disabled 18-month olds will score a 48 for mobility (range 38-60 for the 3rd to 97th percentiles).

The results for the mobility scores showed that at baseline, 13 of 18 patients had normative scores less than 50 (ranging from 16 to 47) and five patients had scores greater than 50 (ranging from 52-64). At Week 52, two patients had normative scores greater than 50, and 16 patients had scores less than 50 (less than 10 to 49), six of whom had scores less than 10, indicating substantial motor developmental delay compared to non-disabled peers. By scaled scores, which show the child's motor development compared to the same child's previous scores and allowing an assessment of the same child over time, four patients (301, 305, 306 and 317) showed essentially no increases in scaled score (or a decrease), and 14 patients showed mobility score gains from baseline to Week 52 of varying amounts. Higher scaled scores were associated with a better outcome. Of the six patients requiring invasive or noninvasive ventilation, five of these patients had scaled scores less than 20 at Week 52 (301, 305, 306, 317 and 319), which shows a strong association of low mobility scaled scores and eventual ventilator dependence (the sixth patient requiring noninvasive ventilatory support [Patient 313] had a scaled score of 41). There were no obvious differences in the results by treatment group. The results for the self-care score were similar to the mobility scores.

By comparison with typically-developing 18-month olds (scaled score range 38-60 for the 3rd to 97th percentiles), nine of 18 Study 1602 patients scored less than the third percentile for mobility and 15 of 18 scored less than the third percentile for self-care, showing substantial motor developmental delays compared to same-age peers. However, similar to the AIMS results, no increases in motor milestones as demonstrated by the Pompe PEDI would have been expected in any untreated infantile-onset patient. The Pompe PEDI mobility and self-care scores by individual patient are summarized in the following tables and are represented graphically in the following figures (with thanks to Ellis Unger, M.D., Ph.D., CDER) (a complete listing of Pompe PEDI scores is located in the subappendix).

Table A1-23: Study 1602, Pompe PEDI Scores, Mobility Scores

Patient/ Dose Group	Week	Chron Age (Mos)	Mobility Scores Raw	Scaled (SE)	Normative Std	Status
301	Baseline	4.8	2	8.1 (3.0)	34	
40 mg	52	17.1	1	4.5 (3.6)	<10	Invasive
302	Baseline	6.6	15	26.7 (1.5)	62	
20 mg	52	18.9	86	54.8 (1.0)	51	A & VF
303	Baseline	7.0	9	21.0 (1.9)	16	
40 mg	52	19.4	65	48.7 (0.9)	37	A & VF
305	Baseline	5.6	6	16.8 (2.2)	47	
20 mg	52	17.6	6	16.8 (2.2)	<10	Noninvasive
306	Baseline	5.8	9	21 (1.9)	54	
20 mg	52	17.6	3	10.8 (2.7)	<10	Noninvasive
307	Baseline	6.6	9	21.0 (1.9)	54	
40 mg	52	18.9	72	50.7 (0.9)	41	A & VF
308	Baseline	4.1	3	10.8 (2.7)	38	
40 mg	52	16.2	53	44.9 (1.0)	45	A & VF
309	Baseline	5.1	9	21.0 (1.9)	54	
20 mg	52	17.1	64	48.4 (0.9)	52	A & VF
310	Baseline	6.4	12	24.2 (1.7)	23	
20 mg	52	18.4	51	44.2 (1.0)	26	A & VF
311	Baseline	7.2	4	13.1 (2.5)	42	
40 mg	52	19.2	18	28.8 (1.4)	<10	A & VF
312	Baseline	4.8	6	16.8 (2.2)	47	
20 mg	52	17.0	27	34.0 (1.3)	23	A & VF
313	Baseline	2.0	2	8.1 (3)	34	
40 mg	52	14.0	42	40.9 (1.1)	37	Noninvasive
314	Baseline	1.6	1	4.5 (3.6)	29	
20 mg	52	13.8	28	34.6 (1.2)	24	A & VF
315	Baseline	0.4	0	0 (5.8)	22	
40 mg	52	13.0	60	47.2 (1.0)	49	A & VF
316	Baseline	6.7	8	19.8 (2.0)	52	
20 mg	52	18.9	80	53.0 (0.9)	47	A & VF
317	Baseline	6.2	2	8.1 (3)	<10	
40 mg	52	18.7	3	10.8 (2.7)	<10	Invasive
318	Baseline	5.3	3	10.8 (2.7)	38	
40 mg	52	17.3	29	35.1 (1.2)	25	A & VF
319	Baseline	2.0	0	0 (5.6)	22	
20 mg	52	14.4	6	16.8 (2.2)	<10	Invasive

Table A1-24: Study 1602, Pompe PEDI Scores, Self-Care Scores

Patient/ Dose Group	Week	Chron Age (Mos)	Self-Care Raw	Self-Care Scaled (SE)	Self-Care Normative Std	Status
301	Baseline	4.8	5	18.8 (2.8)	58	
40 mg	52	17.1	7	23.1 (2.5)	11	Invasive
302	Baseline	6.6	8	25.0 (2.5)	71	
20 mg	52	18.9	46	53.0 (1.2)	54	A & VF
303	Baseline	7.0	10	28.7 (2.4)	31	
40 mg	52	19.4	25	42.4 (1.4)	30	A & VF
305	Baseline	5.6	5	18.8 (2.8)	58	
20 mg	52	17.6	6	21.0 (2.6)	<10	Noninvasive
306	Baseline	5.8	3	12.7 (3.5)	46	
20 mg	52	17.6	3	12.7 (3.5)	<10	Noninvasive
307	Baseline	6.6	10	26.7 (2.4)	79	
40 mg	52	18.9	33	46.7 (1.3)	40	A & VF
308	Baseline	4.1	1	4.9 (4.0)	30	
40 mg	52	16.2	35	47.7 (1.3)	58	A & VF
309	Baseline	5.1	6	21.0 (2.6)	63	
20 mg	52	17.1	30	45.2 (1.3)	53	A & VF
310	Baseline	6.4	8	25.0 (2.5)	21	
20 mg	52	18.4	31	45.7 (1.3)	38	A & VF
311	Baseline	7.2	9	26.8 (2.5)	75	
40 mg	52	19.2	25	42.4 (1.4)	30	A & VF
312	Baseline	4.8	6	21.0 (2.6)	63	
20 mg	52	17.0	32	46.2 (1.3)	55	A & VF
313	Baseline	2.0	6	21.0 (2.6)	63	
40 mg	52	14.0	23	41.2 (1.4)	46	Noninvasive
314	Baseline	1.6	2	9.0 (3.5)	38	
20 mg	52	13.8	19	38.6 (1.5)	41	A & VF
315	Baseline	0.4	0	0 (6.3)	19	
40 mg	52	13.0	25	42.4 (1.4)	48	A & VF
316	Baseline	6.7	10	28.7 (2.4)	79	
20 mg	52	18.9	48	53.9 (1.2)	56	A & VF
317	Baseline	6.2	3	12.7 (3.5)	<10	
40 mg	52	18.7	7	23.1 (2.5)	<10	Invasive
318	Baseline	5.3	6	21.0 (2.6)	63	
40 mg	52	17.3	23	41.2 (1.4)	46	A & VF
319	Baseline	2.0	2	9.0 (3.5)	38	
20 mg	52	Not avail	11	30.3 (2.3)	25	Invasive

Figure A1-14: Study 1602, Pompe PEDI Mobility Scores, 20 mg/kg = black line, 40 mg/kg = dotted gray line

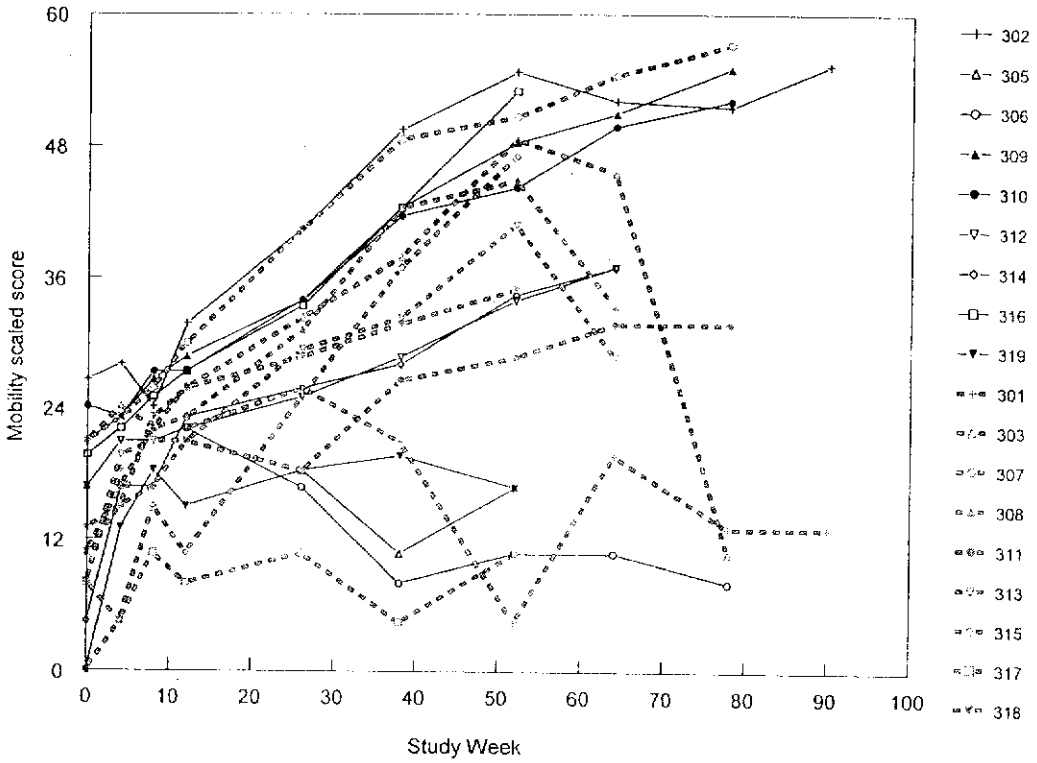
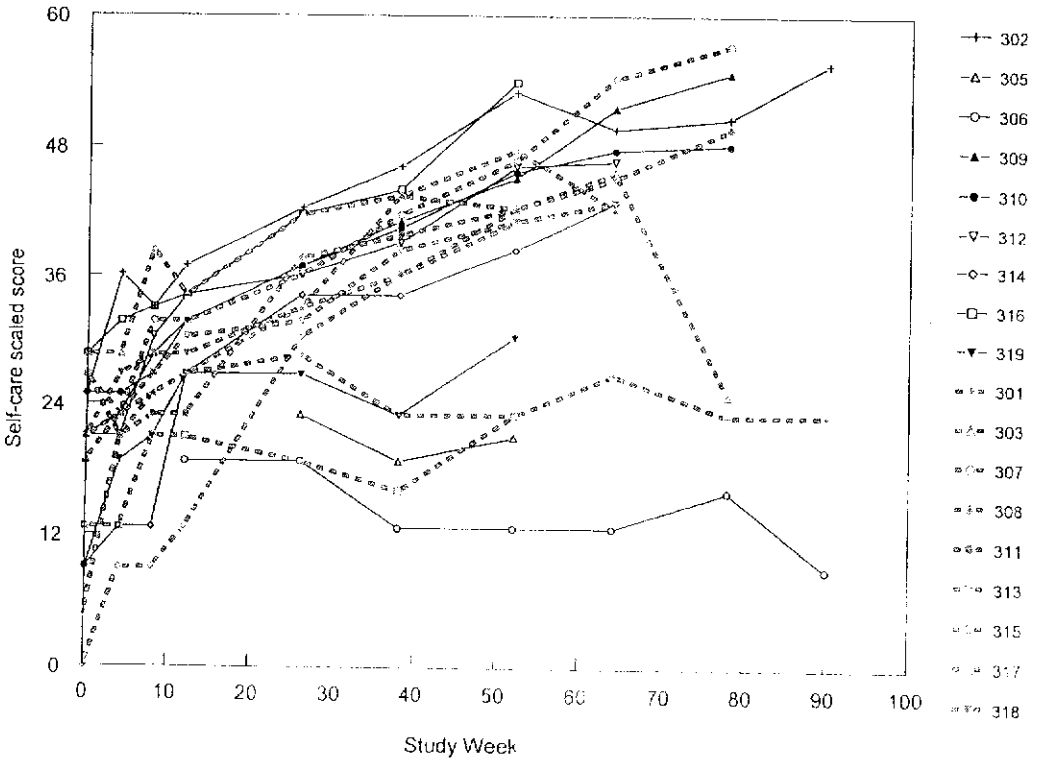


Figure A1-15: Study 1602, Pompe PEDI Self-Care Scores, 20 mg/kg = black line, 40 mg/kg = dotted gray line

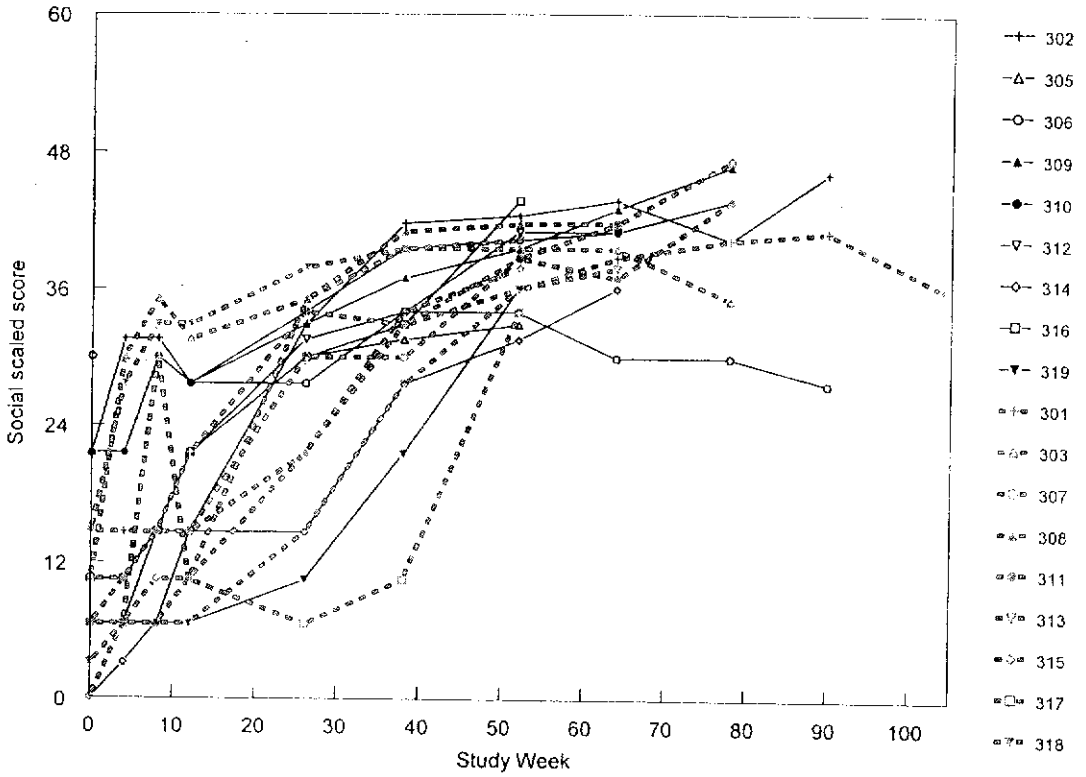


The Pompe PEDI social function scores assessed skills such as comprehension and expression. At baseline for almost all patients, normative scores could not be obtained due to the young age of the patients. At Week 52 by normative scores, four patients scored greater than 50, 13 patients scored 27 to 48, and one patient scored 13. By scaled scores, all 18 patients showed increases from baseline to Week 52 (intra-patient comparison). There was no obvious correlation between a patient's motor or self-care scores and the social score, nor was there an obvious correlation between social score and eventual ventilator dependence. The Pompe PEDI social function scaled scores by individual patient are summarized in the following table and are represented graphically in the following figure (with thanks to Ellis Unger, M.D., Ph.D., CDER) (a complete listing of social function scores is located in the subappendix).

Table A1-25: Study 1602, Pompe PEDI Scores, Social Function Scores

Patient/ Dose Group	Week	Chron Age (Mos)	Social Function Scores			Status
			Raw	Scaled (SE)	Normative Std	
301	Baseline	4.8	4	14.7 (3.2)	NA	
40 mg	52	17.1	12	36.1 (1.5)	45	Invasive
302	Baseline	6.6	5	21.6 (5.5)	NA	
20 mg	52	18.9	20	42.5 (1.3)	37	A & VF
303	Baseline	7.0	3	10.5 (3.2)	29	
40 mg	52	19.4	16	39.6 (1.4)	29	A & VF
305	Baseline	5.6	5	21.6 (5.5)	NA	
20 mg	52	17.6	9	32.9 (1.7)	41	Noninvasive
306	Baseline	5.8	7	30.0 (2.1)	NA	
20 mg	52	17.6	10	34.0 (1.6)	43	Noninvasive
307	Baseline	6.6	3	10.5 (3.2)	NA	
40 mg	52	18.9	15	38.8 (1.4)	27	A & VF
308	Baseline	4.1	2	6.6 (2.9)	NA	
40 mg	52	16.2	19	41.8 (1.3)	53	A & VF
309	Baseline	5.1	3	10.5 (3.2)	NA	
20 mg	52	17.1	16	39.6 (1.4)	50	A & VF
310	Baseline	6.4	5	21.6 (5.5)	43	
20 mg	52	18.4	17	40.4 (1.3)	31	A & VF
311	Baseline	7.2	2	6.6 (2.9)	NA	
40 mg	52	19.2	15	38.8 (1.4)	27	A & VF
312	Baseline	4.8	2	6.6 (2.9)	NA	
20 mg	52	17.0	18	41.1 (1.3)	53	A & VF
313	Baseline	2.0	1	3.1 (3.1)	NA	
40 mg	52	14.0	12	36.1 (1.5)	45	Noninvasive
314	Baseline	1.6	0	0 (NA)	NA	
20 mg	52	13.8	8	31.6 (1.8)	39	A & VF
315	Baseline	0.4	0	0 (NA)	NA	
40 mg	52	13.0	14	37.9 (1.5)	48	A & VF
316	Baseline	6.7	3	10.5 (3.2)	NA	
20 mg	52	18.9	22	43.8 (1.2)	41	A & VF
317	Baseline	6.2	2	6.6 (2.9)	24	
40 mg	52	18.7	10	34 (1.6)	13	Invasive
318	Baseline	5.3	4	14.7 (3.2)	NA	
40 mg	52	17.3	17	40.4 (1.3)	51	A & VF
319	Baseline	2.0	2	6.6 (2.9)	NA	
20 mg	52	Not avail	12	36.1 (1.5)	45	Invasive

Figure A1-16: Study 1602, Pompe PEDI Social Scores, 20 mg/kg = black line, 40 mg/kg = dotted gray line



10.1.1.12.8.3 Bayley Scales of Infant Development II (BSID-II)

The Modified Bayley Scales of Infant Development (BSID-II) is used to assess cognitive, language, and personal/social development in children from one through 42 months of age. The mental age-equivalent score is used to determine the age level at which a child is functioning, regardless of chronological age, while the mental development index (MDI) score is used to compare a child's performance to that of same-age normally developing peers. MDIs within normal limits (WNL) range from 85-114, mildly delayed performance range from 70-84, and significantly delayed are less than or equal to 69. The BSID-II was not intended to be administered to seriously ill children, or children with severe motor impairment, as test assessments require cooperation with the examiner and some of the test assessments in young children require some motor abilities (e.g, pointing to and picking up objects). Thus, for the seriously ill or severely motor impaired children in this study (e.g., those ventilatory dependent), the results may not necessarily accurately reflect the child's mental development.

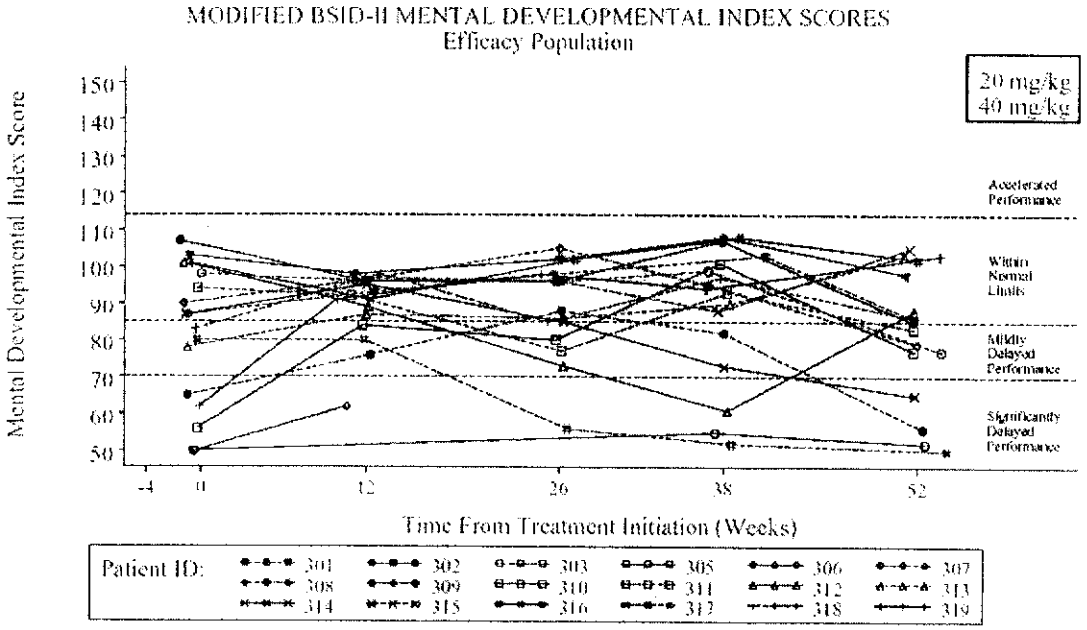
The results show that 17 of 18 patients had increases in their total raw score from baseline at Week 52 (Patient 306 had a decrease in score). At baseline, compared to same-age normally developing peers (MDI), nine of 17 tested patients scored in the normal range, three showed mild delays, and five showed significant delays. At Week 52, nine of 18 patients scored in the normal range, four showed mild delays, and five showed significant delays. Of the five patients showing

significant delays at Week 52, four patients were on ventilation and had motor developmental delays on the AIMS and Pompe PEDI assessments. The long-term cognitive develop in infantile-onset Pompe disease is not known, as historically, almost all of these infants have not survived beyond age 18 months. The BSID-II results in this study are also not predictive of future cognitive development (e.g., school-age function). The BSID-II results at baseline and Week 52 for individual patients is summarized in the following table (complete listing is located in the subappendix) and represented graphically in the following figure (figure electronically copied and reproduced from the sponsor's submission).

Table A1-26: Study 1602, BSID-II Scores

Patient/ Dose Group	Week	Total Raw Score	Chron Age (Mos)	Age Equiv (Mos)	MDI	Outcome
301 40 mg	Baseline	38	4.8	3	65	Invasive
	52	82	17.1	11	56	
302 20 mg	Baseline	59	6.6	6	107	A & VF
	52	109	18.9	17	85	
303 40 mg	Baseline	62	7.0	6	98	A & VF
	52	101	19.4	15	77	
305 20 mg	Baseline	11	5.6	<1	<50	Noninvasive
	52	76	17.8	9	52	
306 20 mg	Baseline	34	5.8	3	<50	Noninvasive
	52	Not available				
	64	25	20.3	2	<50	
307 40 mg	Baseline	58	6.6	5	90	A & VF
	52	106	18.9	16	79	
308 40 mg	Baseline	38	4.1	3	87	A & VF
	52	96	16.2	14	86	
309 20 mg	Baseline	57	5.1	5	103	A & VF
	52	107	17.1	17	107	
310 20 mg	Baseline	41	6.4	4	56	A & VF
	52	101	18.4	15	77	
311 40 mg	Baseline	60	7.2	5	94	A & VF
	52	104	19.2	16	83	
312 20 mg	Baseline	45	4.8	4	101	A & VF
	52	102	17	16	88	
313 40 mg	Baseline	17	2.0	1	78	Noninvasive
	52	96	14	14	103	
314 20 mg	Baseline	8	1.6	<1	87	A & VF
	52	78	13.8	10	65	
315 40 mg	Baseline	0	0.4	<1	Not done	A & VF
	52	93	13	13	105	
316 20 mg	Baseline	56	6.7	5	101	A & VF
	52	109	18.9	17	102	
317 40 mg	Baseline	53	6.2	5	80	Invasive
	52	76	18.7	9	<50	
318 40 mg	Baseline	47	5.3	4	83	A & VF
	52	101	17.3	15	86	
319 20 mg	Baseline	9	2.0	<1	62	Invasive
	52	96	14.4	14	103	

Figure A1-17: Study 1602, BSID-II MDI Scores from Baseline through Week 52



Consultations regarding the validity of the motor and developmental assessments (AIMS, Pompe PEDI and BSID-II) were requested from the Division of Pediatric Drug Development (Hari Sachs, M.D., FAAP) and from the Division of Neurology Products (Marc Walton, M.D., Ph.D.). The pediatric consultant noted the following:

- The three scales are appropriate and compliment each other. The BSID-II and AIMS are norm-referenced instruments intended to identify children at risk for developmental delay at various ages. The PEDI is intended to examine changes in functional performance for a particular patient. The AIMS identifies the highest motor ability achieved, while the PEDI examines how the infants and toddlers interact with their environment. The BSID-II tracks motor and cognitive status. The evaluation of infants was additionally noted to be challenging, as infants may demonstrate fluctuating developmental patterns.
- The majority of patients treated with rhGAA experienced clinically meaningful gains in developmental milestones; however, the majority of patients remained significantly delayed compared to normal age-matched peers. Further follow-up is warranted to demonstrate persistence or "catch-up" with normal age-matched peers.
- Results from the historical cohort showed that greater than 75% of patients had no developmental milestones documented. In a few (less than 20) patients, milestones were documented, and no patient maintained the ability to stand, walk, run or climb steps. The AIMS and PEDI were not administered to any patients, and the BSID-II was administered to only one. Further review of the literature suggests that few motor milestones are achieved and the few milestones gained are lost with disease progression.

- The scales may need additional validation in the ethnic groups under study, as ethnic differences have been noted in some assessments, and at the ages studied, none of the scales are predictive of later function and ability.
- The AIMS and BSID-II are unlikely to be useful for patients with the other Pompe variants as they have developmental ceilings of 18 months and 3.5 years, respectively.

The neurology consultant noted the following:

- The assessments (AIMS, Pompe PEDI and BSID-II) were not intended as "validated" outcome tools to support a claim of efficacy, and were intended for descriptive purposes. As the majority of the study patients have survived to ages not previously observed for patients with infantile-onset Pompe disease, these assessments were intended to assist in the assessment of the quality of life for these infants.
- There is no significant amount of data available on patients with infantile-onset Pompe disease with the AIMS, Pompe PEDI and BSID-II tools from which to form a comparison. To the end of forming a comprehensive assessment to the functional abilities of these infants, however, then the tools selected appear to be reasonable. These tools' sensitivity to various functions, however, may have a different neurological basis in these infants than in the infants for whom there exists extensive prior experience. Therefore, the interpretation of the meaning of the specific components of these assessments should be done with caution.
- Even with enzyme treatment these patients remain severely impaired and do not approach the median of normal infant level of function. These patients should be followed over time as they continue to receive ERT.

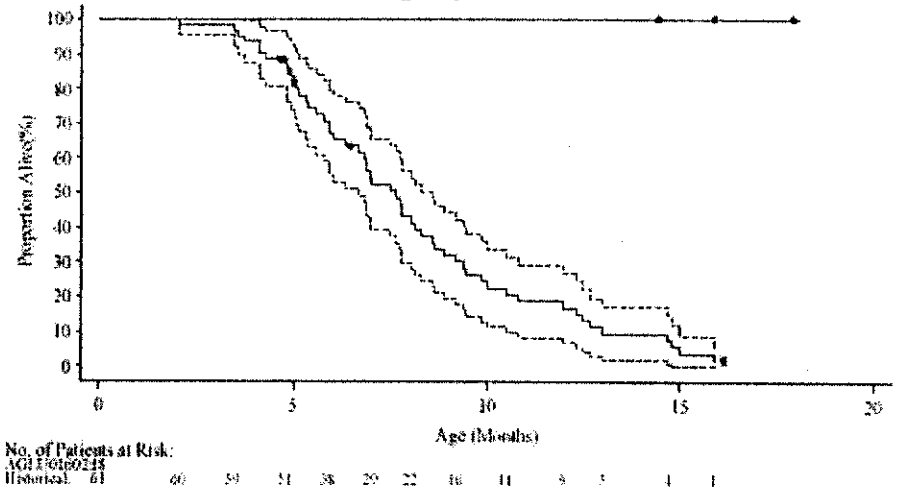
Thus, overall, the motor development assessments were notable for the majority of patients treated with rhGAA demonstrating clinically meaningful gains in motor function by the AIMS and Pompe PEDI tests. Most patients remained significantly delayed compared to normal age-matched peers, however, and further follow-up of motor development is warranted. Durability of response is also of concern as two patients who initially demonstrated gains in motor function had an almost complete loss of these milestones later in the study (Patients 313 and 303), both of whom later required invasive ventilatory support, and one of whom died (Patient 303). The loss of motor milestones coincided with the development of markedly elevated anti-rhGAA IgG antibody titers, suggesting interference from antibody with clinical response. Mental developmental results from the BSID-II test were encouraging, with most patients demonstrating increases in BSID-II scores from baseline at Week 52, and with most patients having scores within the normal or mildly delayed ranges as compared to same-age normally developing peers. Longer-term follow-up of these patients is warranted, however, as these results are not predictive of future cognitive development (e.g., school-age function).

10.1.1.12.9 Other Endpoints

10.1.1.12.9.1 Survival at 12 and 18 Months of Age

The proportion of patients alive at 12 and 18 months of age was estimated and compared to survival probability in the historical control subgroup. Eighteen of 18 patients in Study 1602 survived to 12 and 18 months of age. In contrast, using data from the historical control subgroup, of the 61 patients included in the subgroup for whom date of death was known, nine of 61 (15%) survived beyond 12 months of age and one of 61 (2%) survived beyond 18 months of age. Median age at death was 7.5 months in the Historical Control Subgroup, and median age of death in the Study 1602 population has not been reached (two patients have died as of late-September 2005: Patient 305 at age 19.8 months and Patient 303 at age approximately 32 months). The results are represented graphically in the following figure (electronically copied and reproduced from the sponsor's submission).

Figure A1-18: Study 1602, Kaplan-Meier Estimate of Time to Death from Date of Birth as Compared to Survival in the Historical Control Subgroup



Although comparison with the historical control shows a survival advantage in rhGAA-treated patients, a comparison between the historical control and Study 1602 patients was never intended to provide a valid comparison between the two patient groups. Data from the historical control show that only a small number of patients were ever placed on ventilatory support, indicating that respiratory failure was often a pre-terminal event. It is noted that there was no potentially life-saving treatment available for patients in the historical control (i.e., no ERT available), and this fact may have influenced decision making as to initiating ventilatory support (that is, parents may not have opted for ventilatory support in the historical control population given the lack of a potentially efficacious treatment available at that time). This is contrasted with the fact that as of 15-September-2005, seven patients in Study 1602 had been placed on invasive ventilatory support. As these Study 1602 patients developed ventilatory failure, the ventilatory support is thought to be life-prolonging treatment, thereby affecting the survival outcome measure in the Study 1602 study population. Thus, ventilator-free survival in Study 1602 vs. survival in the Historical Control Subgroup is a more valid comparison that is consistent with the treatment

approach taken with the historical control patients, and the comparison of survival results is noted here for completeness only.

10.1.1.12.9.2 Hours on Ventilation

Hours on ventilation (both invasive and non-invasive) were assessed by the sponsor from baseline to Week 52, and did not include ventilator use in planned surgical or protocol-related procedures, or if the total duration of ventilatory support was less than three days. In the opinion of this Reviewer, this is not a meaningful analysis. No meaningful comparison can be made to the historical control subgroup because of a lack of data in the subgroup, and because in almost all cases for the patients in Study 1602 who required any ventilatory support, these patients required long-term ventilatory support and the actual number of hours of ventilation was not important to the interpretation of the data. For patients in Study 1602 as of the 15-June-2005 data cutoff, a total of 9 of 18 patients required any ventilatory support, including:

- Seven patients (301, 303, 304, 305, 306, 313, 317 and 319) were receiving long-term invasive ventilatory support. Most of these patients required several periods of invasive or noninvasive ventilatory support of varying lengths of time, and then eventually required long-term invasive ventilatory support from which they were unable to be discontinued for the duration of Study 1602. In most of these patients, periods of noninvasive ventilation predicted eventual transition to invasive ventilatory support.
- Patient 311 required 15 days of non-invasive ventilation (BIPAP) at age 7.5 months for influenza, and did not require ventilatory support thereafter.
- Patient 309 required one day of invasive ventilatory support for a procedure, and did not require ventilatory support thereafter.
- At the 18-month milestone, three patients (17%) required invasive ventilation

In contrast, in the historical control subgroup, a history of ventilator support was reported in six of 62 patients (10%), no use of ventilator support at any time was reported in 31 patients (50%) and was unknown in 25 patients (40%). The median age at which ventilator support was first instituted for the six patients with available data was 7.7 months. There were a total of nine ventilator episodes in these six patients, which were required primarily for "advancement of the disease". In the three of the six patients who required ventilator assistance in whom data were available, first ventilator support lasted a median of one day and was likely a peri-terminal event. The reasons for stopping support were not documented.

10.1.1.12.10 Exploratory Variables

10.1.1.12.10.1 CRIM and ACE Marker Allele Status

Circulating Reactive Immune Material (CRIM) status was determined from a skin fibroblast assay in all patients. A patient was considered to be CRIM positive if the presence of any bands corresponding to the apparent molecular weight of major protein forms of GAA were detected in samples on Western blot assay (including 110, 95, 76 or 70 kDa forms). Angiotensin-converting enzyme (ACE) marker allele status was determined by polymerase chain reaction (PCR) amplification of genomic DNA. ACE is encoded in the DCP-1 gene, and polymorphisms consist of the absence (deletion, D allele) or presence (insertion, I allele) of a 287-base pair DNA Alu

fragment located within intron 16 of the DCP-1 gene. The D allele may encourage the growth of type II muscle fibers (anaerobic metabolism) while the I allele may encourage the growth of type I muscle fibers (oxidative metabolism). Fifteen of 18 patients were CRIM positive, and three patients (303, 313, and 319) were CRIM negative at baseline. These results were notable in that the three patients who were CRIM negative at baseline all required invasive ventilation at some point in the study. The ACE marker results showed that three of 18 patients had no results available, four patients were I/I, three patients were D/D and eight patients were I/D. There was no obvious correlation between ACE marker allele status and outcome. The results are summarized in the following table.

Table A1-27: Study 1602, Baseline CRIM and ACE Marker Allele Status

Patient	Dose	CRIM Status	ACE Marker Allele	Outcome
301	40	Positive	I/D	Invasive
302	20	Positive	I/D	None
303	40	Negative	NA	Invasive
305	20	Positive	I/D	Invasive/died
306	20	Positive	D/D	Invasive
307	40	Positive	I/D	None
308	40	Positive	I/I	None
309	20	Positive	I/I	None
310	20	Positive	I/I	None
311	40	Positive	I/D	None
312	20	Positive	NA	None
313	40	Negative	I/D	Invasive
314	20	Positive	I/I	None
315	40	Positive	D/D	None
316	20	Positive	I/D	None
317	40	Positive	NA	Invasive
318	40	Positive	I/D	None
319	20	Negative	D/D	Invasive

NA = Not available

10.1.1.12.10.2 Gene expression GAA Gene Mutational Analysis

The GAA mutational analysis was notable in that of the 14 of 18 patients with mutational analysis results, all 14 had different mutations, and most were compound heterozygotes. An analysis by GAA mutation was, therefore, not possible. Only three of 18 patients had detectable GAA activity on baseline muscle biopsy results (lower limit of quantification [LLQ] of the assay was 3.0 nmol/hr/g wet tissue). No normal values for GAA activity in muscle biopsy specimens were provided, and according to the sponsor (personal communication) no normal ranges for GAA activity in muscle biopsy specimens are currently known. The results are summarized in the following table.

Table A1-28: Study 1602, GAA Mutational Analysis

Patient	Maternal Allele	Maternal Allele: Class of Mutation	Paternal Allele	Paternal Allele : Class of Mutation	Baseline GAA Activity
301	(Del exon 18) c.2481+102_2646+31del p.Gly828_Asn882del	Inframe deletion	c.437delT p.Met146ArgfsX7	Frameshift	<3.0
302	c.1064T>C p.Leu355Pro	Missense	c.1064T>C p.Leu355Pro	Missense	8.8
303	N/A	N/A	N/A	N/A	<3.0
305	N/A	N/A	N/A	N/A	<3.0
306	c.872T>C p.Leu291Pro	Missense	c.872T>C p.Leu291Pro	Missense	8.5
307	c.1710C>G p.Asn570Lys	Missense	c.2560C>T p.Arg854X	Nonsense	<3.0
308	c.1465G>A p.Asp489Asn	Missense	c.40_47delGCCGTCTG p.Ala14ArgfsX18	frameshift	<3.0
309	c.1802C>T p.Ser601Leu; c.1726G>A p.Gly726Ser; c.2065G>A p.Glu689Lys	Missense	c.1099T>C p.Trp367Arg	Missense	4.6
310	c.1935C>A p.Asp645Glu; c.1726G>A p.Gly726Ser; c.2065G>A p.Glu689Lys	Missense	c.1194(IVS7)+2T>C	Splice site mutation	<3.0
311	c.2297A>C p.Tyr766Ser	Missense	c.2297A>C p.Tyr766Ser	Missense	<3.0
312	N/A	N/A	N/A	N/A	<3.0
313	c.2560C>T p.Arg854X	Nonsense	c.2560C>T p.Arg854X	Nonsense	<3.0
314	c.2741_2742delAG; c.2743_2746dupCAGG p.Gln914ProfsX30	Frameshift	c.2741_2742delAG; c.2743_2746dupCAGG p.Gln914ProfsX30	Frameshift	<3.0
315	c.1210G>A p.Asp404Asn	Missense	c.1064T>C p.Leu355Pro	Missense	<3.0
316	c.2560C>T p.Arg854X	Nonsense	c.1979G>A p.Arg660His	Missense	<3.0
317	N/A	N/A	N/A	N/A	<3.0
318	(Del exon 18) c.2481+102_2646+31del p.Gly828_Asn882del	Inframe deletion	(Del exon 18) c.2481+102_2646+31del p.Gly828_Asn882del	Inframe deletion	<3.0
319	c.1754(IVS12)+1G>A	Splice site mutation	c.722_723delTT p.Phe241CysfsX88	frameshift	<3.0

10.1.1.12.11 Immunogenicity

Serum samples for anti-rhGAA antibody testing were obtained pre-infusion, at 4-week intervals for the first 26 weeks, then at Weeks 38 and 52, and at 12-week intervals thereafter. All immunological testing was performed by Genzyme. Anti-rhGAA antibody was assessed using ELISA and confirmed by radioimmunoprecipitation (RIP).

The results show that 16 of 18 patients (eight of nine patients in each dose group) developed anti-rhGAA antibody at anytime during the study. One patient (Patient 303) had detectable antibody at Baseline, ten patients had detectable antibody beginning at Week 4, four patients at Week 8, one patient at Week 12, and one patient at Week 64. Antibody titers ranged from 0 to 409,600, and more patients in the 40 mg/kg group (seven of nine) had antibody titers >1,000 (arbitrarily selected as cutpoint) than patients in the 20 mg/kg group (four of nine). None of the 16 patients with any detectable anti-rhGAA antibody during the study became antibody negative. Some patients showed decreases in antibody titer throughout the duration of the study, but many

patients did not, and these patients showed sustained elevations or increases throughout the study. Individual patient antibody titers are summarized in the following table:

Table A1-29: Study 1602, Antibody Titers

20 mg/kg	Patient Number								
Week	302	305	306	309	310	312	314	316	319
0	0	0	0	0	0	0	0	0	0
4	400	100	0	0	0	-	100	0	800
8	3200	800	0	100	400	-	3200	100	3200
12	12800	3200	0	200	400	-	6400	100	12800
16	12800	3200	0	200	400	-	12800	100	12800
20	6400	6400	0	200	400	-	6400	100	-
24	6400	3200	0	200	400	-	12800	100	51200
38	1600	400	0	200	400	0	6400	400	25600
52	400	200	0	100	400	-	6400	100	-
64	200	-	200	100	400	-	3200	-	-
78	200	-	200	400	400	-	-	-	-
90		-	200	-	-	-	-	-	-
104		-	-	-	-	-	-	-	-
40 mg/kg									
Week	**301**	**303**	**307**	**308**	**311**	**313**	**315**	**317**	**318**
0	0	100	0	0	0	0	0	0	0
4	400	800	-	-	1600	6400	-	12800	800
8	3200	3200	3200	-	6400	25600	-	12800	12800
12	25600	6400	1600	200	6400	25600	-	25600	51200
16	12800	12800	800	200	6400	51200	-	0	25600
20	12800	51200	800	400	6400	0	-	51200	51200
24	25600	25600	800	200	25600	102400	0	25600	25600
38	51200	204800	400	200	12800	204800	0	204800	25600
52	25600	204800	200	200	3200	163840	0	102400	51200
64	51200	409600	400	200	1600	163840	0	-	-
78	25600	409600	400	100	1600	-	-	-	-
90	102400	-	-	-	-	-	-	-	-
104	51200	-	-	-	-	-	-	-	-

Value of "0" corresponded to an ELISA within normal range (WNR) or a negative RIP, and no dilutions were performed. Samples with readings of above normal range (ANR) on ELISA or positive RIP underwent dilution.

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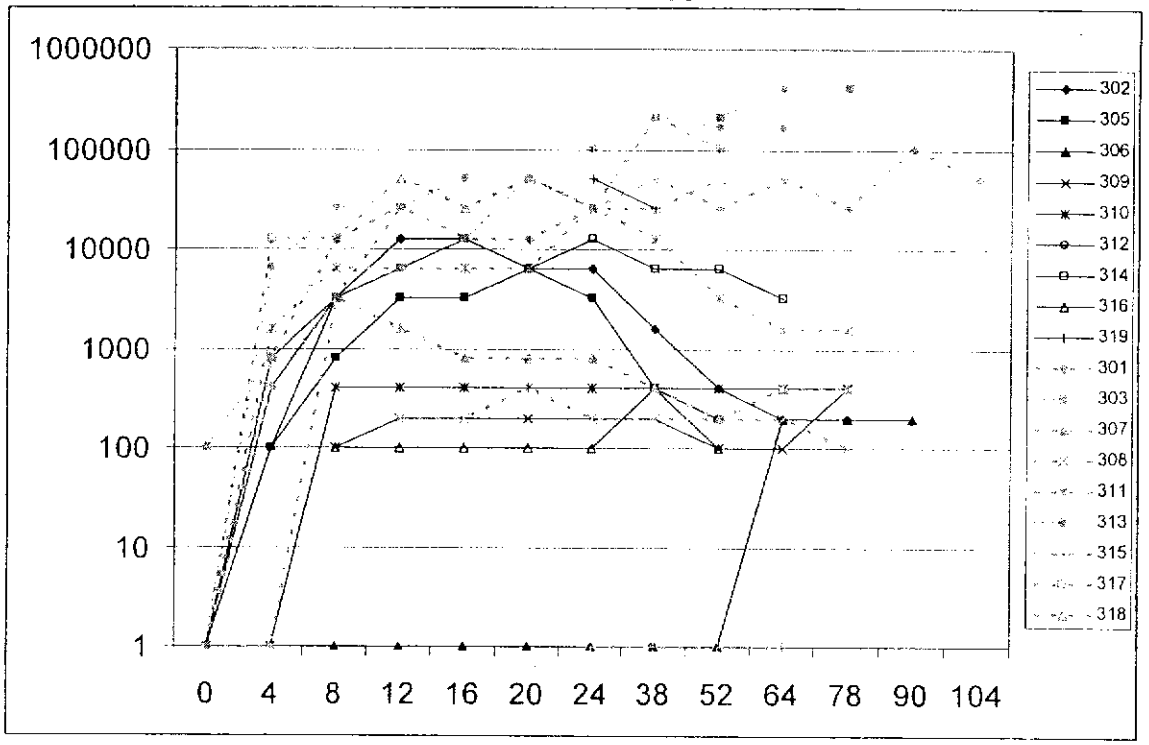
Antibody titers by individual patient are also represented graphically in the following figure (logarithmic scale):

Figure A1-19: Study 1602, Antibody Titers (log scale, zero values entered as 1) gray dashed line = 40 mg/kg and solid black line = 20 mg/kg patients



Immunogenicity was further explored by correlating antibody titers with the primary endpoint and motor development milestones. The results are notable for the following:

- Mutations that place the patient at high risk for antibody formation include those resulting in an absent protein, such as nonsense and frameshift mutations, and lower risk mutations where low levels of protein are found would include missense mutations. For the seven patients with poor outcomes (invasive ventilation or death), three patients did not have mutation information available (303, 305, 317), three patients (301, 313, 319) had high risk mutations in both alleles (deletion, frameshift, nonsense or splice site mutations) and one patient (306) had two missense mutations. Patient 303 (mutation unknown) was low-level antibody positive at baseline, and three patients (303, 313, 319) were also CRIM negative at baseline. In patients with better outcomes (did not reach primary endpoint), one patient (312) did not have mutation information available, two patients (314, 318) had high-risk mutations in both alleles (frameshift and inframe deletion mutations), and the remaining eight patients had lower-risk mutations in at least one allele (missense).
- In general, patients with poor outcomes tended to have higher peak antibody titers, with five of seven patients with poor outcomes having a peak titer >50,000 compared with one patient with a better outcome with titers >50,000.

- Two patients (303, 313) initially made substantial progress in motor development by both the AIMS and Pompe PEDI assessments. Both patients had loss of most motor milestones and became ventilator dependent later in the study. Loss of motor milestones and ventilator dependence coincided with peak antibody titers that were markedly elevated. This result is concerning, as the development of antibody associated with clinical deterioration may suggest interference from antibody with the clinical response. As many patients in this study have sustained or increasing antibody titers, many of whom have markedly elevated titers, following these patients over time to correlate antibody titers/immune response with sustained or lost milestones and overall outcome is essential.

The immunogenicity results by individual patient are summarized in the following table.

Table A1-30: Study 1602, Antibody Analysis/Exploration

Patient	Maternal/Paternal Alleles: Mutation Class	CRIM Status	Peak Titers	Outcome	Comments
301	Inframe deletion/ Frameshift	Positive	102,400	Invasive	Minimal progress in motor development on AIMS and Pompe PEDI
303	NA/NA	Negative	409,600	Invasive/died*	Initially made substantial progress in motor development on Pompe PEDI and AIMS ("walker") until approx. Week 64, then lost most milestones. Had rising antibody titers throughout study to peak at Weeks 64 and 78.
305	NA/NA	Positive	6,400	Invasive/died	Minimal progress in motor development on AIMS and Pompe PEDI
306	Missense/Missense	Positive	200	Invasive	Minimal progress in motor development on AIMS and Pompe PEDI
313	Nonsense/Nonsense	Negative	204,800	Invasive	Initially made good progress in motor development on Pompe PEDI and AIMS ("stander") until approx. Week 52, then lost most milestones. Had rising antibody titers throughout study to peak at Weeks 38, but remained markedly elevated (163,840) through Weeks 52 and 64.
317	NA/NA	Positive	204,800	Invasive	Minimal progress in motor development on AIMS and Pompe PEDI
319	Splice site/Frameshift	Negative	51,200	Invasive	Minimal progress in motor development on AIMS and Pompe PEDI
302	Missense/Missense	Positive	12,800	A & VF	Achieved independent ambulation ("walker") on AIMS test and substantial gains on Pompe PEDI
307	Missense/Nonsense	Positive	3,200	A & VF	Achieved independent ambulation ("walker") on AIMS test and substantial gains on Pompe PEDI
308	Missense/Frameshift	Positive	400	A & VF	Achieved independent ambulation ("walker") on AIMS test and substantial gains on Pompe PEDI
309	Missense/Missense	Positive	400	A & VF	Achieved independent ambulation ("walker") on AIMS test and substantial gains on Pompe PEDI
310	Missense/Splice site	Positive	400	A & VF	Good progress by motor milestones ("stander") on AIMS test and Pompe PEDI
311	Missense/Missense	Positive	25,600	A & VF	Modest motor gains (sit independently, unable to weight bear on legs) on AIMS and Pompe PEDI
312	NA/NA	Positive	0	A & VF	Modest motor gains (sit independently, unable to weight bear on legs) on AIMS and Pompe PEDI
314	Frameshift/Frameshift	Positive	12,800	A & VF	Good progress by motor milestones ("stander") on AIMS test and Pompe PEDI
315	Missense/Missense	Positive	0	A & VF	Achieved independent ambulation ("walker") on AIMS test and substantial gains on Pompe PEDI
316	Nonsense/Missense	Positive	400	A & VF	Achieved independent ambulation ("walker") on AIMS test and substantial gains on Pompe PEDI
318	Inframe deletion/ Inframe deletion	Positive	51,200	A & VF	Modest motor gains (sit independently, unable to weight bear on legs) on AIMS and Pompe PEDI

*died at approximately 32 months of age after completion of study and transition to expanded access program

10.1.1.12.12 Pharmacokinetic (PK) and Pharmacodynamic (PD) Measures

The PK and PD results have been reviewed in detail by the Clinical Pharmacology Reviewer (see review by Anil Rajpal, M.D.), and will be treated briefly here. Plasma rhGAA PK parameters were calculated for each patient at baseline and Week 12. The PK results showed that there were few notable differences in PK characteristics between the two dose groups, other than differences in AUC (1.9 times higher in 40 mg/kg group than 20 mg/kg) and C_{max} (1.5 times higher in 40 mg/kg than 20 mg/kg group), which are related to concentration of rhGAA present in plasma. The PK parameters are summarized as follows:

Table A1-31: Study 1602, Plasma PK Parameters

Parameter	Day 0	Week 12
C_{max}, ng/mL		
20 mg/kg	1,609,10 ±27,598	195,540 ±73,190
40 mg/kg	271,253 ±61,251	256,096 ±50,920
AUC, ng*h/mL		
20 mg/kg	937,896 ±199,381	1,017,118 ± 262,278
40 mg/kg	1,883,581 ±407,002	1,861,479 ± 407,002
α-half-life, hrs	0.57 ± .081	0.59 ± .065
β-half-life, hrs	2.71 ± .58	2.80 ± .57
Clearance,		
mL/hr	133 ± 41	154 ± 51
mL/hr/kg	22.1 ± 4.2	21.8 ± 5.4
Vl		
mL	264 ± 87	308 ± 91
mL/kg	43.5 ± 8.4	43.5 ± 8.4
Vss		
mL	404 ± 116	469 ± 100
mL/kg	66.9 ± 10.3	67.0 ± 9.8

Pharmacodynamic (PD) measures were evaluated by comparing skeletal muscle GAA activity and skeletal muscle glycogen content (by biochemical and histomorphometric methods) at baseline and Weeks 12 and 52. Plasma and urine oligosaccharides were also collected. Please see the Clinical Pharmacology review for a complete discussion of these findings. In general, however, the skeletal muscle glycogen content analyses and the plasma and urine oligosaccharide measures did not show a consistent correlation with clinical outcome and should be considered as exploratory at this time.

10.1.1.13 Efficacy Summary

The efficacy results from Study 1602 show the following:

1. For the primary endpoint of proportion of patients alive and free of invasive ventilation at 18 months of age, there was a clear ventilator-free survival advantage at 18 months seen in the rhGAA-treated patients as compared to survival in the Historical Control Subgroup. At the 18-month milestone, 15 of 18 (83%) rhGAA-treated patients were alive and ventilator free, as compared to one of 61 surviving patients (2%) in the historical control. Exploratory and sensitivity analyses showed no obvious differences between the two rhGAA dose groups for ventilator-free survival, nor were there differences in survival noted depending on age at diagnosis, first infusion or first symptoms in rhGAA-treated patients. A selection bias in favor of patients enrolled in Study 1602 was seen, however, when an analysis controlling for age at death in the historical control (eliminating patients who died at ages less than six months from the survival rate proportion estimate) for survival at the 12-month milestone was performed. This selection bias was minimal at the 18-month milestone (as only one patient in the Historical Control Subgroup survived to 18 months of age), showing a clear treatment effect for ventilator-free survival at 18 months of age in rhGAA-treated patients.

2. Evaluation of cardiac parameters, including LVMI, LVM Z-scores and EF were notable for decreases in LVMI and LVM Z-scores in all patients through Week 52, consistent with the PD effect of rhGAA on cardiac muscle. Mean EF showed only a small mean increase from baseline at Week 52, however, and the clinical relevance of the PD effect of rhGAA on cardiac function is unknown. The review of AEs consistent with cardiac failure was notable for only five post-baseline AEs in five patients. As the signs and symptoms of cardiac and respiratory failure overlap in this patient population and as there were no historical control cardiac failure data available for comparison, no clear clinical effect on cardiac function can be discerned from rhGAA-treatment.

3. Physical growth was assessed through repeated measurements of body weight and length, and head circumference. These data were notable for numerous missing and inconsistent datapoints, making interpretation of the data unreliable. Despite these limitations, however, weight, length, and head circumference increased in all patients throughout the study. Age-matched comparisons for weight and length showed that almost all patients were within two SD of the mean for normals at Week 52. No data on weight for height assessments and relation to method of feeding and calorie intake were presented, however, limiting the utility of the results. Head circumference data showed two patients with relative microencephaly at Week 52, and it is unclear if increasing head size for most patients during the study was attributable to catch-up or to CNS glycogen accumulation similar to that found in other storage disorders. Thus, the overall effects of rhGAA treatment on physical growth are unclear, and it is recommended that follow-up trials for infants, including standardized measurements and analysis of growth in

relationship to feeding and nutritional status and weight for height be determined, and that longer term follow-up of head size be performed.

4. Motor and mental development were assessed using the AIMS, Pompe PEDI, and BSID-II assessment tools (these assessments were noted to be appropriate and complimentary by Pediatric and Neurology consultants to the Division). These results were notable in that the majority of patients treated with rhGAA experienced clinically meaningful gains in developmental milestones. Results from historical controls and from the medical literature show that few motor milestones are achieved in untreated patients and these few milestones are lost with disease progression. However, it is additionally noted that the majority of patients remained significantly delayed compared to normal age-matched peers and further follow-up is warranted to demonstrate persistence or catch-up with normal age-matched peers. Five patients by the AIMS test and four patients by the Pompe PEDI failed to achieve new motor milestones at anytime during the study, all of whom required ventilatory support during continued treatment and follow-up. Two patients who had initially showed the achievement of new motor milestones on the AIMS and Pompe PEDI tests (walking or weight bearing) had almost complete loss of these motor milestones later in the study and became ventilator dependent during continued treatment and follow-up. This coincided with the development of markedly elevated antibody titers and suggests interference from antibody with clinical response. Mental developmental results from the BSID-II test were encouraging, with most patients demonstrating increases in BSID-II scores from baseline at Week 52, and with most patients having scores within the normal or mildly delayed ranges as compared to same-age normally developing peers. Longer-term follow-up of these patients is warranted, however, as these results are not predictive of future cognitive development (e.g., school-age function).

5. Immunogenicity data showed that 16 of 18 patients (89%) developed anti-rhGAA antibody at anytime during the study (15 of 16 patients by Week 12 and 16 of 16 patients by Week 64). Antibody titers were very high (maximum 409,600), and were greater than 6,400 (arbitrarily selected as "high" cutpoint) in ten of 16 antibody positive patients at anytime during the study. More patients in the 40 mg/kg dose group developed "high" titers than in the 20 mg/kg group. Although some patients had decreasing antibody titers over time, many patients continued to show sustained or increasing antibody titers throughout the study. A concerning signal was seen in patients with high-risk mutations (frameshift or deletion mutations and absent or near-absent endogenous protein) and high anti-rhGAA IgG antibody titers. Patients with high-risk mutations and high antibody titers were more likely to have poor clinical outcomes than patients lower risk mutations and lower antibody titers. Two patients with high antibody titers had losses of motor gains that also coincided with rising and elevated antibody titers. As the number of patients in this study was small, no definite conclusions can be made from these results; however, the results are concerning and further follow-up and evaluation of the effect of immunogenicity on patient outcome is warranted.

Thus, the treatment of infantile-onset Pompe disease patients with rhGAA at or prior to the age of seven months results in an invasive ventilator-free survival benefit at 18 months of age as compared to an Historical Control Subgroup. The long-term growth and development of these patients is unknown, however, and it is unclear if the results are sustained, especially in patients developing elevated anti-rhGAA antibody titers. Long-term follow-up and additional study in these patients is warranted.

10.1.1.14 Review of Safety

Safety was assessed by types and incidence of Adverse Events (AEs), discontinuations due to AEs, and drug-related, serious and severe AEs, and changes from baseline in physical exams (including vital signs), clinical laboratory assessments including clinical chemistry, hematology, urinalysis, and anti-GAA antibody IgG titers, and ECG assessments. Other safety variables included: circulating immune complex detection (as indicated), inhibitory antibody formation in patients testing positive for IgG, anti-rhGAA IgE antibodies, serum tryptase and complement activation (as indicated). Safety data are available up until the cutoff date of 15-June-2005 (after all patients had completed the Week 52 visit) for all patients in Study 1602.

10.1.1.14.1 Exposure

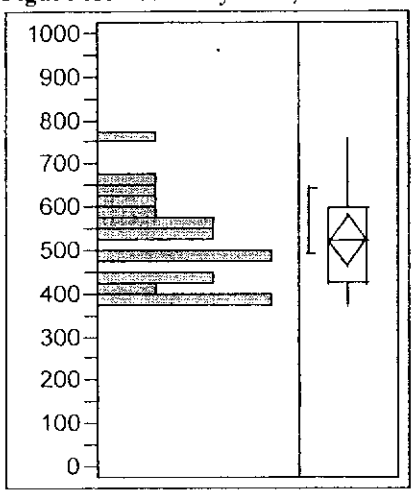
As of the safety data cutoff date of 15-June-2005, patient exposure to rhGAA ranged from 52 to 106 weeks of treatment (375 to 751 days) of qow infusions (27 to 54 infusions). Exposure overall and by individual patient is represented graphically in the following figure and summarized in the following table.

Table A1-32: Study 1602, Exposure to rhGAA

Patient	Weeks in Study	Days in Study	Infusions Received
301	106	751	54
302	94	657	48
303	86	642	36*
305	60	427	31
306	90	623	46
307	84	585	43
308	82	572	42
309	80	560	41
310	78	545	40
311	78	546	40
312	70	489	35**
313	70	492	36
314	70	489	36
315	64	447	33
316	58	407	27#
317	54	382	28
318	54	380	28
319	52	375	27
Mean	74	521	37
Median	74	518	36
Min, Max	52, 106	375, 751	27, 54

*Missed 5 doses and received 3 partial doses. **Received 1 partial dose. #Missed one dose and received 1 partial dose

Figure A1-20: Study 1602, Patient Exposure (Days) to rhGAA



10.1.1.14.2 Adverse Events

Adverse Events (AEs) were collected from the signing of Informed Consent through study completion; however, unless otherwise noted, only treatment-emergent AEs, defined as those that started following initiation of study medication (Day 0, day of first infusion) through study completion are included here. Recurrent or continuing AEs were counted only once (unless otherwise specified). AE incidence rates were calculated using all patients who received at least one dose of study medication as the denominator (n=18). All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), and are presented by AE Preferred Term. AEs were tabulated and analyzed using the aex_1.xpt dataset in Amendment 002 of the submission, which (per personal communication with the sponsor) represents the complete AE dataset for Study 1602 through the Week 52 visit for the last patient enrolled (15-June-2005).

There were 75 AEs captured in the database that had their onset prior to the date of first infusion (screening/baseline period), or for which no AE start date was noted (including three AEs experienced by Patient 304 who never received rhGAA). These screening/baseline AEs were notable for two cardiac arrhythmia AEs that occurred during study-related procedures, but prior to rhGAA exposure (these cardiac arrhythmia AEs are discussed in greater detail in the Other Adverse Events section below). The Screening/Baseline AEs were otherwise noted to be consistent with underlying disease and will not be further discussed.

Review of the treatment-emergent AEs showed that there were large numbers (>1100 AE reports) and types (>240 different preferred terms) of AEs were reported during the study, and all 18 patients reported multiple AEs. Individual patients reported from 19 to 157 AEs (11 to 68 different AE terms) per patient, and there was a numerically greater number of AEs reported in the 40 mg/kg group (approximately 660 AEs) than in the 20 mg/kg group (approximately 470 AEs). There were no deaths up to the 52-week milestone, although two patients died during continued follow-up and treatment (see Deaths section below). There were no discontinuations

during the study due to AEs or for any other reason, and all patients completed 52 weeks of study treatment.

AEs were reported most commonly in the Infections and Infestations, and Respiratory, Thoracic, and Mediastinal Disorders System Organ Classes (SOCs). In general, reported AEs tended to reflect the underlying disease (e.g., respiratory and infectious AEs), or were AEs commonly seen with enzyme/protein infusions (e.g., rash, fever/pyrexia). By AE Preferred Term, the rates of AEs reported were highest for pyrexia (18 of 18 patients reporting, 100%), rash (13, 72%), otitis media (12, 67%), and gastroenteritis (11, 61%). The most commonly reported AEs (by incidence rates) are summarized in the following table (cutoff arbitrarily selected as ≥5 or >25% of patients reporting, for a complete list of the incidence of all AEs reported during the study, please refer to the subappendix.)

Table A1-33: Study 1602 Amendment 002, Most Commonly Reported AEs (Reported by ≥5 Patients)

Treated Patients, n =	All 18	20 mg/kg 9	40 mg/kg 9
SOC			
AE Preferred Term	**n (%)**	**n (%)**	**n (%)**
Blood and lymphatic system disorders			
Anemia	10 (56)	5 (56)	5 (56)
Cardiac disorders			
Tachycardia	6 (33)	2 (22)	4 (44)
Ear and labyrinth disorders			
Hypoacusis	5 (28)	2 (22)	3 (33)
Eye disorders			
Conjunctivitis	5 (28)	2 (22)	3 (33)
Gastrointestinal disorders			
Diarrhea	10 (56)	6 (67)	4 (44)
Vomiting	10 (56)	4 (44)	6 (67)
Gastroesophageal reflux disease	5 (28)	2 (22)	3 (33)
General disorders and administration site conditions			
Pyrexia	18 (100)	9 (50)	9 (50)
Infections and infestations			
Otitis media	12 (67)	5 (56)	7 (78)
Gastroenteritis	11 (61)	4 (44)	7 (78)
Pharyngitis	9 (50)	4 (44)	5 (56)
Pneumonia	9 (50)	5 (56)	4 (44)
Upper respiratory tract infection	9 (50)	6 (67)	3 (33)
Catheter related infection	8 (44)	3 (33)	5 (56)
Ear infection	7 (39)	2 (22)	5 (56)
Nasopharyngitis	6 (33)	2 (22)	4 (44)
Viral infection	6 (33)	3 (33)	3 (33)
Bronchiolitis	5 (28)	3 (33)	2 (22)
Oral candidiasis	5 (28)	3 (33)	2 (22)
Respiratory syncytial virus infection	5 (28)	2 (22)	3 (33)
Investigations			
Oxygen saturation decreased	9 (50)	4 (44)	5 (56)
Respiratory, thoracic and mediastinal disorders			
Cough	9 (50)	3 (33)	6 (67)
Respiratory failure	7 (39)	3 (33)	4 (44)
Rhinorrhea	6 (33)	2 (22)	4 (44)
Tachypnea	6 (33)	1 (11)	5 (56)
Respiratory distress	5 (28)	2 (22)	3 (33)
Upper respiratory tract congestion	5 (28)	2 (22)	3 (33)
Skin and subcutaneous tissue disorders			
Rash	13 (72)	6 (67)	7
Dermatitis diaper	6 (33)	3 (33)	3 (33)
Urticaria	6 (33)	4 (44)	2 (22)
Eczema	5 (28)	3 (33)	2 (22)

10.1.1.14.3 Deaths

Two of the 18 patients in the study were known to have died during continued follow-up and treatment after receiving more than 52 weeks of treatment. One patient (305) died at age 19.8

months due to underlying disease/respiratory failure after having received approximately 14 months of treatment with rhGAA. This patient required invasive ventilatory support after approximately 13 months of rhGAA treatment, and the cause of death was reported as death due to desaturation and bradycardia while hospitalized for respiratory distress and pneumonia. Another patient (303) died at approximately 32 months of age after completing the study and while enrolled in an expanded access program (personal communication with the sponsor) after having received approximately 25 months of rhGAA treatment. The cause of death was reported as multiorgan failure and septicemia. This patient became invasive ventilator dependent at 24.5 months of age after receiving treatment with rhGAA for approximately 17 months.

10.1.1.14.4 Infusion Associated Reactions (IARs)

Infusion Associated Reactions (IARs) were defined by the sponsor as those AEs occurring on the day of infusion from the onset of the infusion up to and including the two-hour observation period AND were assessed by the Investigator as being at least possibly related to rhGAA treatment. By this definition, a total of 164 IARs, including 28 different AE preferred terms were reported in 11 patients. IARs were more commonly reported in the 40 mg/kg group, with 123 of the 164 IARs reported compared to 41 IARs in the 20 mg/kg group. With the exception of the term oxygen saturation decreased, all of the IAR terms were reported more frequently in the 40 mg/kg group, and 20 of the 28 IAR terms were reported exclusively in the 40 mg/kg group. The most frequently reported IARs for all patients were pyrexia and rash (7 patients and 23 and 24 reports, respectively, each), followed by urticaria (5 patients, 22 reports). All reported IARs by incidence and by numbers of IARs reported are summarized in the following table.

Table A1-34: Study 1602 Amendment 002, All IARs

	IAR Incidence Rates			Numbers of IARs Reported by Term		
	All	20 mg/kg	40 mg/kg	All	20 mg/kg	40 mg/kg
Treated Patients, n =	**18**	**9**	**9**			
SOC **AE Preferred Term**	**n (%)**	**n (%)**	**n (%)**			
Cardiac disorders						
Tachycardia	3 (17)	0	3 (33)	6	0	6
Cyanosis	2 (11)	0	2 (22)	3	0	3
Gastrointestinal disorders						
Vomiting	3 (17)	1 (11)	2 (22)	8	2	6
Retching	2 (11)	1 (11)	1 (11)	7	4	3
Gastroesophageal reflux disease	1 (6)	0	1 (11)	1	0	1
General disorders and administration site conditions						
Pyrexia	7 (39)	3 (33)	4 (44)	23	6	17
Rigors	2 (11)	0	2 (22)	3	0	3
Infusion site reaction	1 (6)	0	1 (11)	1	0	1
Injury, poisoning and procedural complications						
Hypothermia	1 (6)	0	1 (11)	1	0	1
Investigations						
Oxygen saturation decreased	4 (22)	2 (22)	2 (22)	18	13	5
Blood pressure decreased	1 (6)	0	1 (11)	1	0	1
Body temperature increased	1 (6)	0	1 (11)	1	0	1
Heart rate decreased	1 (6)	0	1 (11)	2	0	2
Nervous system disorders						
Tremor	1 (6)	0	1 (11)	2	0	2
Psychiatric disorders						
Irritability	2 (11)	0	2 (22)	2	0	2
Agitation	1 (6)	0	1 (11)	3	0	3
Restlessness	1 (6)	0	1 (11)	1	0	1
Respiratory, thoracic and mediastinal disorders						
Cough	3 (17)	1 (11)	2 (22)	14	3	11
Tachypnea	3 (17)	0	3 (33)	6	0	6
Rales	1 (6)	0	1 (11)	1	0	1
Skin and subcutaneous tissue disorders						
Rash	7 (39)	2 (22)	5 (56)	24	8	16
Urticaria	5 (28)	3 (33)	2 (22)	22	5	17
Livedo reticularis	1 (6)	0	1 (11)	1	0	1
Palmar erythemia	1 (6)	0	1 (11)	1	0	1
Pruritus	1 (6)	0	1 (11)	1	0	1
Vascular disorders						
Flushing	2 (11)	0	2 (22)	4	0	4
Hypertension	2 (11)	0	2 (22)	3	0	3
Hypotension	1 (6)	0	1 (11)	2	0	2
Pallor	1 (6)	0	1 (11)	2	0	2
Total				**164**	**41**	**123**

IARs were also evaluated by individual patient. One hundred (100) of the 164 IARs were reported in two patients: Patient 318 (40 mg) experienced 53 IARs, and Patient 303 (40 mg)

experienced 43 IARs. All patients except one with high antibody titers (high arbitrarily designated as >6,400) experienced IARs, and no patient (n=2) with antibody titers of 0 reported an IAR. IARs by individual patient are summarized in the following table.

Table A1-35: Number of IARs Reported by Patient

Patient	Dose	# of IARs	IAR Terms	Peak Ab Titers	Study Outcome
301	40	4	Rash (2), hypothermia (1), tachycardia (1)	102,400	Invasive
302	20	2	Pyrexia (1), urticaria (1)	12,800	None
303	40	43	Pyrexia (10), rash (10), urticaria (4), cough (2), cyanosis (2), hypertension (2), rigors (2), tachycardia (2), vomiting (2), flushing (1), infusion site reaction (1), irritability (1), pruritus (1), rales (1), restlessness (1), tachypnea (1)	409,600	Invasive
305	20	4	Pyrexia (2), rash (1), urticaria (1)	6,400	Invasive/died
306	20	3	Pyrexia (3)	200	Invasive
307	40	0	-	3,200	None
308	40	0	-	400	None
309	20	0	-	400	None
310	20	14	Rash (7), cough (3), urticaria (3), oxygen saturation decreased (1)	400	None
311	40	4	Rash (2), pyrexia (1), body temperature increased (1)	25,600	None
312	20	0	-	0	None
313	40	7	Pyrexia (4), tachypnea (2), blood pressure decreased (1)	204,800	Invasive
314	20	0	-	12,800	None
315	40	0	-	0	None
316	20	0	-	400	None
317	40	8	Oxygen saturation decreased (4), heart rate decreased (2), irritability (1), rash (1)	204,800	Invasive
318	40	57	Urticaria (13), cough (9), vomiting (4), agitation (3), flushing (3), retching (3), tachycardia (3), tachypnea (3), hypotension (2), pallor (2), pyrexia (2), tremor (2), cyanosis (1), gastroesophageal reflux disease (1), hypertension (1), livedo reticularis (1), oxygen saturation decreased (1), palmar erythema (1), rash (1), rigors (1)	51,200	None
319	20	18	Oxygen saturation decreased (12), retching (4), vomiting (2)	51,200	Invasive

10.1.1.14.5 Serious Adverse Events (SAEs)

A total of 172 Serious Adverse Events (SAEs), including 72 different preferred terms were reported by 17 of 18 patients in the study (only Patient 316 in 20 mg/kg dose group did not report an SAE). SAEs tended to reflect the underlying disease (e.g., respiratory and infectious terms) or treatment intervention complications (e.g., catheter related infection). By incidence rates, specific SAEs were about as commonly reported in the 20 mg/kg group as in the 40 mg/kg group. There was a numerically similar number of SAEs reported in each dose group (20 mg/kg group reported 87 SAEs and 40 mg/kg group reported 85 SAEs). The most commonly reported (by ≥2 patients) SAE terms were: pneumonia (8 patients), respiratory failure (7), catheter related infection and respiratory syncytial virus infection (5 each), and bronchiolitis, gastroenteritis, aspiration pneumonia, respiratory distress and viral infection (4 each). Pneumonia, respiratory failure, aspiration pneumonia, and catheter related infection were also the most numerically commonly reported SAEs during the study. The most commonly reported SAEs by incidence

and by numbers of reported SAEs are summarized in the following table (for a complete listing of all SAEs reported during the study, please refer to the subappendix).

Table A1-36: Study 1602, Most Commonly Reported SAEs (reported by ≥2 patients)

	SAE Incidence Rates			Numbers of SAEs Reported by Term		
	All	20 mg/kg	40 mg/kg	All	20 mg/kg	40 mg/kg
Treated Patients, n =	**18**	**9**	**9**			
SOC						
AE Preferred Term	**n (%)**	**n (%)**	**n (%)**			
Cardiac disorders						
Bradycardia	2 (11)	1 (11)	1 (11)	2	1	1
Gastrointestinal disorders						
Upper gastrointestinal hemorrhage	2 (11)	2 (22)	0	5	5	0
General disorders and administration site conditions						
Pyrexia	2 (11)	1 (11)	1 (11)	2	1	1
Infections and infestations						
Pneumonia	8 (44)	4 (44)	4 (44)	21	16	5
Catheter related infection	5 (28)	1 (11)	4 (44)	7	2	5
Respiratory syncytial virus infection	5 (28)	2 (22)	3 (33)	5	2	3
Bronchiolitis	4 (22)	2 (22)	2 (22)	5	2	3
Gastroenteritis	4 (22)	1 (11)	3 (33)	4	1	3
Viral infection	4 (22)	3 (33)	1 (11)	4	3	1
Nasopharyngitis	2 (11)	0	2 (22)	4	0	4
Otitis	2 (11)	0	2 (22)	2	0	2
Otitis media	2 (11)	1 (11)	1 (11)	3	1	2
Respiratory tract infection	2 (11)	1 (11)	1 (11)	2	1	1
Injury, poisoning and procedural complications						
Fracture femur	2 (11)	1 (11)	1 (11)	2	1	1
Investigations						
Ejection fraction decreased	2 (11)	1 (11)	1 (11)	2	1	1
Oxygen saturation decreased	2 (11)	1 (11)	1 (11)	2	1	1
Respiratory, thoracic and mediastinal disorders						
Respiratory failure	7 (39)	3 (33)	4 (44)	15	8	7
Pneumonia aspiration	4 (22)	3 (33)	1 (11)	12	11	1
Respiratory distress	4 (22)	2 (22)	2 (22)	5	2	3
Asthma	2 (11)	1 (11)	1 (11)	2	1	1
Atelectasis	2 (11)	1 (11)	1 (11)	2	1	1
Total				**172**	**87**	**85**

The number of SAEs reported by individual patient ranged from zero to 32, and as expected, the patients with the poorest outcomes (those requiring ventilatory support) had the largest numbers of SAEs. SAEs by individual patient are summarized in the following table:

Table A1-37: Number of SAEs Reported by Patient

Patient	Dose	# of SAEs	SAE Terms	Study Outcome
301	40	17	Fracture (4), bronchiolitis (2), pneumonia (2), respiratory failure (2), atelectasis (1), bradycardia (1), cough (1), gastroenteritis (1), gastroesophageal reflux disease (1), oxygen saturation decreased (1), pyrexia (1)	Invasive
302	20	6	Asthma (1), gastroenteritis (1), pneumonia (1), pyrexia (1), tonsillitis (1), viral infection (1)	None
303	40	16	Myopathy (3), urticaria (2), aspiration pneumonia (1), catheter related infection (1), hypertrophic obstructive cardiomyopathy (1), hypokinesia (1), leukodystrophy (1), rales (1), pneumonia (1), respiratory failure (1), septic shock (1), supraventricular arrhythmia (1), ventricular hypertrophy (1)	Invasive
305	20	22	Pneumonia (7), respiratory failure (4), catheter related infection (2), sputum retention (2), aspiration pneumonia (1), bradycardia (1), oxygen saturation decreased (1), pneumothorax (1), respiratory acidosis (1), upper gastrointestinal hemorrhage (1), vocal cord paresis (1)	Invasive/died
306	20	32	Aspiration pneumonia (8), pneumonia (7), upper gastrointestinal hemorrhage (4), respiratory failure (3), arrhythmia (1), bronchiolitis (1), electrolyte imbalance (1), esophageal erosion (1), gastritis erosive (1), hypotension (1), injury asphyxiation (1), localized infection (1), otitis media (1), upper respiratory tract infection (1)	Invasive
307	40	1	Pneumonia (1)	None
308	40	4	Nasopharyngitis (2), diarrhea (1), vomiting (1)	None
309	20	3	Dental caries (1), ejection fraction decreased (1), respiratory syncytial virus infection (1)	None
310	20	6	Supraventricular tachycardia (4), Arrhythmia nodal (1), atrial tachycardia (1)	None
311	40	17	Bronchospasm (3), catheter related complication (2), catheter related infection (2), bacteremia (1), ejection fraction decreased (1), gastroenteritis (1), influenza (1), lymphadenopathy (1), middle ear effusion (1), respiratory distress (1), respiratory syncytial virus infection (1), superior vena cava occlusion (1), ventricular extrasystoles (1)	None
312	20	6	Dysphagia (2), bronchiolitis (1), pneumonia (1), syncope (1), viral infection (1)	None
313	40	6	Respiratory distress (2), catheter related infection (1), otitis (1), pulmonary edema (1), respiratory failure (1)	Invasive
314	20	2	Respiratory distress (1), respiratory syncytial virus infection (1)	None
315	40	5	Asthma (1), catheter related infection (1), pneumonia (1), respiratory syncytial virus infection (1), viral infection (1)	None
316	20	0	-	None
317	40	10	Respiratory failure (3), otitis media (2), heart rate decreased (1), gastritis viral (1), respiratory tract infection (1), tracheitis (1), urinary tract infection (1)	Invasive
318	40	9	Bronchitis (2), nasopharyngitis (2), bronchiolitis (1), gastroenteritis (1), otitis (1), rash (1), respiratory syncytial virus infections (1),	None
319	20	10	Aspiration pneumonia (2), atelectasis (1), cardiorespiratory arrest (1), dyspnea (1), fracture (1), respiratory distress (1), respiratory failure (1), respiratory tract infection (1), viral infection (1)	Invasive

10.1.1.14.6 Other Adverse Events: Cardiac Arrhythmias and Hearing Loss

Two cardiac arrhythmia AEs were noted to have occurred in the Screening/Baseline period during study-related procedures, but prior to rhGAA administration. One patient (315)

experienced bradycardia during muscle biopsy and central line placement after receiving propofol, and one patient (319) experienced ventricular fibrillation during muscle biopsy after receiving nitrous oxide and sevoflurane. Two additional patients were noted to have experienced cardiac arrhythmias after receiving anaesthesia during or shortly after completing the study. Patient 306 experienced "arrhythmia" during bronchoscopy and stomaplasty after receiving ketamine, sevoflurane and succinylcholine after approximately 80 weeks of treatment, and Patient 313 experienced ventricular tachycardia, ventricular fibrillation, and cardiac arrest during intubation after receiving succinylcholine, fentanyl, and etomidate approximately one week after completion of 70 weeks of the study.

These events and similar events in the infantile-onset Pompe disease population in other studies, including one patient death in Study 1702 (ventricular fibrillation and cardiac arrest during central line placement post-anaesthesia), lead to a revision of the Investigator's Brochure and heightened awareness and training for the Investigators regarding the use of anaesthetic agents in these patients, who are at high risk of cardiac complications likely due to underlying cardiac hypertrophy. The cardiac arrhythmia events associated with anaesthesia are summarized in the following table.

Table A1-38: Study 1602, Cardiac Arrhythmias Associated with Anaesthesia

Patient	AE Preferred Term	Days Prior to 1st Infusion
315	Bradycardia	-21
319	Ventricular fibrillation	-1
		Days Post-Last Infusion
306	Arrhythmia	14
313	Ventricular tachycardia, ventricular fibrillation, cardiac arrest	7

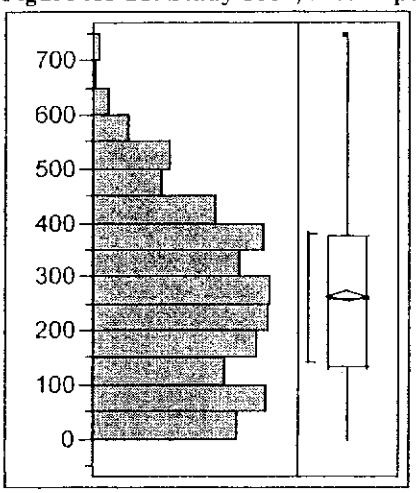
Hearing loss was reported in several patients during the study. Thirteen of 18 patients underwent hearing tests at Screening/Baseline, and of these 13 patients, five had abnormal hearing results in at least one ear. At Week 26, seven patients were noted to have abnormal hearing in at least one ear, including three patients with abnormal results at baseline, one patient with normal hearing at baseline, and three patients with no baseline hearing results. Hearing loss was described as hypoacousis, sensorineural, mixed, and conductive in these patients. It was noted that middle ear effusions were present in many patients, which complicated the interpreations of the results.

Hearing loss at Screening/Baseline and during treatment was reported in many patients in the rhGAA clinical development program, including infantile-, juvenile- and adult-onset patients in clinical trials and in expanded access programs. Hearing loss in Pompe disease has also been reported in the medical literature, and appears to be due to the underlying disease (thought to be secondary to cochlear glycogen deposition). Hearing loss has also been reported in other lysosomal storage disease. It appears likely that the hearing loss reported in this study is secondary to underlying disease and not to treatment with rhGAA, although it is not possible at this time to determine if rhGAA treatment modifies the progression or development of hearing loss in this patient population. It is recommended, therefore, that longer-term follow-up of hearing be performed in patients receiving rhGAA.

10.1.1.14.7 Adverse Events Over Time

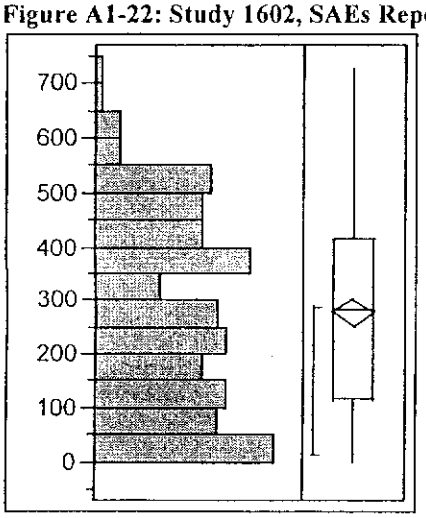
AEs were assessed over the duration of the study, and in general, the occurrence of AEs appeared to be fairly evenly distributed over time. The numbers of AEs reported by study day are represented graphically in the following figure (fewer AEs reported after approximately Day 450 is consistent with fewer patients with exposure to study treatment greater than 450 days).

Figure A1-21: Study 1602, AEs Reported Over Time (Study Day)



The SAEs reported over time showed similar results to AEs over time, with the occurrence of SAEs appearing to be fairly evenly distributed over time. The numbers of SAEs reported by study day are represented graphically in the following figure.

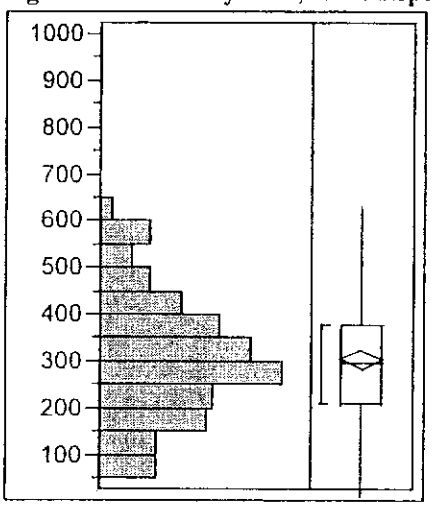
Figure A1-22: Study 1602, SAEs Reported Over Time (Study Day)



IARs over time appeared to show IARs occurring more commonly in the first year of the study. There are several possible explanations for this: 1) premedication was commonly given to patients who had previously experienced IARs; 2) patients may have developed tolerance to study medication, which is supported by some (but not all) patients showing decreases in

antibody titers over the course of the study; or 3) the patient with the largest number of IARs (Patient 318) was in the study for only 380 days. The numbers of IARs reported by study day are represented graphically in the following figure:

Figure A1-23: Study 1602, IARs Reported Over Time (Study Day)



10.1.1.14.8 Laboratory Results

In general, there were no notable patterns of clinical laboratory abnormalities seen in the study. Elevations in CK, ALT and AST were noted throughout the study, consistent with muscle damage and release of enzyme. Anemia was noted as an AE (as were low Hgb and Hct) in eleven patients (72%); however, this may have been secondary to underlying disease, frequent phlebotomy, and nutritional status of the patients. There were isolated elevations in other laboratory parmeters in individual patients, but no consistent patterns were seen that were likely to be attributable to rhGAA treatment. There were no other notable laboratory results, other than the immunogenicity results, which are summarized above.

10.1.1.15 Safety Summary

The safety results from Study 1602 show the following:

1. AEs were frequently reported in this study, and all 18 patients reported multiple AEs. This is not unexpected due to the severity of the underlying disease and the medically fragile conditions of the study patients. In general, AEs tended to reflect underlying disease (e.g., respiratory and infectious AEs), or were AEs commonly seen with enzyme/protein infusions (e.g., rash, fever/pyrexia). By AE preferred term, the most commonly reported AEs (by incidence rates) were pyrexia (100% of patients), rash (72%), otitis media (67%) and gastroenteritis (61%).

2. There were two deaths reported in the 18 patients in the study. One death occurred during the study in Patient 305, who died at age 19.8 months due to underlying disease/respiratory failure (desaturation and bradycardia while hospitalized for

respiratory distress and pneumonia) after having received approximately 14 months of rhGAA treatment. Another patient (303) died at approximately 32 months of age after completing the study and while enrolled in an expanded access program, after having received approximately 25 months of rhGAA treatment. The cause of death was reported as multiorgan failure and septicemia. No other patient discontinued participation in the study due to an AE or for any other reason.

3. IARs were reported in 11 patients, and were more commonly reported in the 40 mg/kg group than in the 20 mg/kg group. IARs were also more commonly reported in patients with antibody titers >6,400, and no IARs were reported in the two patients with antibody titers of zero. The most commonly reported IARs were pyrexia and rash (39% of patients), and urticaria (28%). Approximately two thirds of the IARs reported during the study were reported in two patients (Patients 318 and 303), both of whom were in the 40 mg/kg group and had peak antibody titers >50,000. Nine patients (50%) required premedication prior to infusions at one or more study visits, and all patients except Patient 303 were able to receive >90% of scheduled rhGAA doses. Patient 303 missed five doses and received three partial doses of rhGAA (80% of scheduled infusions) due to AEs, including IARs (Patient 303 was also noted to initially gain new developmental milestones that were later lost, coincident with rising antibody titers, and this patient eventually became ventilator dependent).

4. SAEs were reported in 17 of 18 patients, and tended to reflect underlying disease (e.g., respiratory and infectious SAEs) or treatment intervention complications (e.g., catheter related infection). The most commonly reported SAEs were pneumonia (44% of patients), respiratory failure (39%), and catheter related infection and respiratory syncytial virus infection (28% each).

5. Serious cardiac arrhythmia AEs were noted in four patients at any time during the study, and were associated with anaesthesia use for procedures. These arrhythmias included ventricular tachycardia, ventricular fibrillation, bradycardia and cardiac arrest. Similar cardiac arrhythmias have also been reported in infantile-onset Pompe disease patients in other rhGAA studies, and at least one patient in another Genzyme rhGAA study (Study 1702) experienced ventricular fibrillation, cardiac arrhythmia, and death associated with anaesthesia. Cardiac arrhythmia is felt to be due to risk of anaesthetic agents in these high-risk patients due to the underlying cardiac hypertrophy associated with infantile-onset Pompe disease, which has lead to heightened awareness and training of investigative staff for the rhGAA clinical program.

6. Hearing loss was reported in many patients in this study at Screening/Baseline and at follow-up assessments. Hearing loss has also been reported in other clinical studies and expanded access programs in the rhGAA clinical program. Hearing loss has been described in the medical literature as associated with Pompe disease, possibly secondary to glycogen deposition in the cochlea, and hearing loss has been described in other lysosomal storage diseases. It appears likely that the hearing loss reported in this study is secondary to underlying disease and not to treatment with rhGAA, although it is not

possible at this time to determine whether rhGAA treatment modifies the progression or development of hearing loss in this patient population. Longer-term follow-up of hearing in patients receiving rhGAA is recommended.

In summary, given the risk of the underlying disease and the nearly universal progression to death by 18 months of age in untreated patients with infantile-onset Pompe disease, the safety profile of rhGAA is acceptable, and all patients in Study 1602 were able to receive greater than 80% of scheduled doses of rhGAA. Safety concerns noted were either likely due to underlying disease or were similar to AEs seen with other enzyme/protein infusions.

10.1.1.16 Conclusions and Recommendations

Based on the results of Study 1602, it is the recommendation of this Reviewer that rhGAA 20 mg/kg be approved. The treatment of infantile-onset Pompe disease patients with rhGAA at or prior to the age of seven months results in a ventilator-free survival benefit at 18 months of age as compared to an Historical Control Subgroup. It is unclear if the results are sustained, however, especially in patients developing elevated anti-rhGAA antibody titers, and the long-term growth and development of these patients is unknown. The safety profile of rhGAA is found to be acceptable given the seriousness of the underlying disease. Safety concerns noted with rhGAA were either likely due to underlying disease or were similar to AEs seen with other enzyme/protein infusions. As the rhGAA 20 mg/kg and 40 mg/kg doses were found to have similar efficacy, and as the rhGAA 20 mg/kg dose was noted to have a more favorable safety profile as compared to the rhGAA 40 mg/kg dose, the rhGAA 20 mg/kg dose is the recommended dose for use in the infantile-onset Pompe disease patient population. Noteworthy safety signals that are recommended to be incorporated into product labeling include a warning regarding the use of anaesthesia in this patient population (as anaesthesia is frequently used for catheter placement, and an indwelling catheter is needed for the long-term administration of rhGAA in these patients), and warnings/precautions regarding anti-rhGAA antibody formation, infusion-associated AEs, and possible loss of enzyme effect with antibody formation.

10.1.1.17 Subappendix: Study 1602

10.1.1.17.1 Study 1602: Height and Weight by Individual Patient

Table A1-39: Study 1602, Height and Weight

Patient/ Dose Group	Week	Chron Age (Mos)	Weight			Height		
			Kg	Z-score	%ile	Cm	Z-score	%ile
301 40 mg	Baseline	4.8	5.7	-1.7	4	62	-0.9	18
	12	7.9	6.6	-2.4	1	68	-0.6	29
	26	11.1	7.6	-2.7	0	73	-0.7	25
	38	13.8	7.9	-2.9	0	75	-0.9	
	52	17.0	9.5	-1.9	3	78	-1.1	14
	64	19.7	10.5	-1.2	11	Not avail		
	78	23.0	13.0	0.4	65	95	2.6	100
	90	25.7	14.6	1.1	87	84	-1.0	15
	104	29.1	17.3	2.2	99	92	0.4	64
302 20 mg	Baseline	7.0	7.5	-0.7	23	65	-1.1	13
	12	9.7	8.4	-1.1	14	Not avail		
	26	12.9	9.0	-1.4	8	79	1.0	84
	38	15.7	9.7	-1.3	9	Not avail		
	52	18.9	10.9	-0.7	23	Not avail		
	64	21.7	11.6	-0.5	29	85	-0.2	43
	78	24.9	11.9	-0.6	26	93	1.6	95
	90	27.7	12.5	-0.5	32	Not avail		
303 40 mg	Baseline	7.0	6.4	-1.8	3	Not avail		
	12	9.7	7.3	-1.6	6	74	1.2	89
	26	13.0	9.8	0.1	55	79	1.4	92
	38	15.8	10.7	0.2	59	85	2.2	99
	52	19.3	12.0	0.6	72	Not avail		
	64	22.7	13.0	0.9	81	Not avail		
	78	26.3	13.5	0.7	76	Not avail		
305 20 mg	Baseline	5.7	5.4	-2.1	2	66	0.6	73
	12	8.4	7.0	-1.5	6	74	1.8	96
	26	11.6	8.8	-0.6	28	75	0.8	78
	38	14.4	10.1	-0.1	46	80	1.1	87
	52	17.5	11.8	0.8	77	90	3.4	100
306 20 mg	Baseline	5.8	5.5	-2.7	0	62	-2.0	3
	12	8.4	6.1	-3.6	0	69	-0.6	28
	26	11.6	6.3	-4.5	0	70	-1.8	4
	38	14.4	7.1	-4.1	0	76	-0.9	18
	52	17.8	9.3	-2.1	2	85	1.1	86
	64	20.3	9.8	-2.0	2	85	0.2	58
	78	23.6	12.8	0.1	56	90	0.8	79
	90	26.3	13.9	0.6	73	95	1.8	96
307 40 mg	Baseline	6.8	6.6	-2.0	3	67	-0.3	37
	12	9.6	8.2	-1.3	10	71	-0.6	29
	26	12.8	9.8	-0.6	28	79	0.8	78
	38	15.6	11.3	0.1	53	80	0.2	57

Table A1-39: Study 1602, Height and Weight

Patient/ Dose Group	Week	Chron Age (Mos)	Weight			Height		
			Kg	Z-score	%ile	Cm	Z-score	%ile
	52	18.8	12.8	0.7	77	85	0.7	76
	64	21.5	14.7	1.6	95	88	0.8	80
	78	24.8	14.8	1.4	91	90	1.0	83
308 40 mg	Baseline	4.3	6.9	-0.2	43	65	0.3	62
	12	7.2	7.8	-0.9	18	68	-0.8	23
	26	10.2	9.3	-0.5	31	74	0.1	55
	38	13.1	10.4	-0.3	39	75	-0.8	22
	52	16.3	11.2	-0.2	43	83	0.8	79
	64	19.4	12.2	0.2	57	84	0.2	58
	78	22.3	12.8	0.3	60	88	0.6	72
309 20 mg	Baseline	5.3	7.5	0.6	74	67	1.0	85
	12	7.9	7.6	-0.3	37	70	0.8	79
	26	11.3	8.8	-0.6	28	76	1.1	87
	38	14.0	10.0	-0.2	42	79	0.6	73
	52	17.4	10.7	-0.2	43	81	0.4	65
	64	19.9	12.7	1.1	86	82	0.2	57
	78	23.2	12.9	0.7	75	85	-0.2	44
310 20 mg	Baseline	6.3	7.4	-0.8	20	76	2.5	100
	12	9.2	8.2	-1.3	10	76	1.2	89
	26	12.4	9.8	-0.6	28	80	1.4	91
	38	15.1	10.9	-0.3	40	84	1.4	92
	52	18.4	11.5	-0.2	40	91	2.4	99
	64	21.2	13.0	0.5	70	89	1.2	88
	78	24.4	14.0	0.9	81	93	1.7	96
311 40 mg	Baseline	7.2	6.0	-3.2	0	69	-0.2	43
	12	9.7	7.8	-1.8	4	70	-0.8	20
	26	13.3	8.7	-1.9	3	75	-0.9	17
	38	16.1	9.2	-2.0	2	79	-0.4	33
	52	19.1	9.7	-2.0	2	80	-1.0	17
	64	22.0	10.4	-1.7	5	83	-0.8	20
	78	25.2	10.2	-2.2	1.3	84	-1.1	15
312 20 mg	Baseline	4.9	5.7	-1.0	16	65	1.0	84
	12	7.9	6.8	-1.3	10	71	1.3	90
	26	11.1	7.6	-2.0	3	76	1.0	84
	38	13.8	8.4	-1.6	5	78	0.8	80
	52	17.3	9.7	-1.1	13	81	0.4	65
	64	20.1	10.1	-1.2	11	83	0.1	54
313 40 mg	Baseline	2.1	4.2	-1.6	6	54	-1.9	3
	12	5.0	5.5	-1.9	3	63	-0.7	23
	26	8.3	7.0	-1.5	6	71	0.5	69
	38	11.1	8.6	-0.8	21	74	0.3	61
	52	14.3	9.2	-1.0	16	78	0.3	61
	64	17.0	9.3	-1.6	6	81	0.4	65
314 20 mg	Baseline	1.8	5.4	0.8	78	57	0.1	56
	12	4.6	7.1	0.1	53	68	1.4	92
	26	7.9	8.7	0.1	52	74	1.6	94
	38	10.7	9.9	0.1	52	79	1.7	96
	52	13.8	10.8	0.1	52	82	1.5	93

Table A1-39: Study 1602, Height and Weight

Patient/ Dose Group	Week	Chron Age (Mos)	Weight			Height		
			Kg	Z-score	%ile	Cm	Z-score	%ile
	64	16.6	11.2	-0.2	43	85	1.2	89
315 40 mg	Baseline	1.1	4.6	-0.4	34	57	0.1	56
	12	3.9	7.1	0.9	81	68	2.1	98
	26	7.2	8.7	0.1	52	Not avail		
	38	9.8	9.8	0.3	62	75	0.9	82
	52	13.1	10.4	-0.3	39	Not avail		
	64	15.9	11.1	-0.1	46	82	0.8	79
316 20 mg	Baseline	6.7	5.5	-2.5	0.6	65	-0.3	39
	12	9.9	6.7	-2.3	1	69	-0.6	28
	26	13.2	8.8	-1.2	12	75	-0.2	44
	38	15.7	9.6	-0.8	21	77	-0.1	45
	52	18.9	10.9	-0.2	44	82	0.5	69
317 40 mg	Baseline	6.2	5.6	-3.3	0	61	-3.0	0
	12	9.1	6.0	-4.2	0	66	-2.5	1
	26	12.1	6.7	-4.2	0	66	-3.9	0
	38	15.1	7.7	-3.6	0	73	-2.2	1
	52	18.3	9.3	-2.2	1	74	-2.7	0
318 40 mg	Baseline	5.4	6.2	-1.7	4	Not avail		
	12	8.1	7.4	-1.8	3	71	0	51
	26	11.3	8.7	-1.4	8	75	-0.1	44
	38	14.1	9.1	-1.7	4	78	-0.1	45
	52	17.3	10.2	-1.2	11	85	1.1	86
319 20 mg	Baseline	2.0	4.7	-0.8	21	56	-0.9	19
	12	4.5	6.0	-0.6	28	63	0.3	60
	26	7.7	7.4	-0.6	28	69	0.3	62
	38	10.6	8.1	-1.0	16	72	0.0	51
	52	14.2	10.1	-0.1	46	76	-0.2	41

10.1.1.17.2 Study 1602: Head Circumference by Individual Patient

Table A1-40: Study 1602, Head Circumference

Patient/ Dose Group	Week	Chron Age (Mos)	Head Circumference		
			Cm	Z-score	%ile
301 40 mg	Baseline	4.8	43	-0.1	45
	12	7.9	44	-0.4	33
	26	11.1	45	-0.9	17
	38	13.8	45	-1.4	8
	52	17.0	47	-0.5	31
	64	19.7	Not avail		
	78	23.0	50	1.1	86
	90	25.7	51	1.5	94
	104	29.1	52	1.6	94
302 20 mg	Baseline	7.0	44	0.1	55
	12	9.7	45	-0.4	35
	26	12.9	47	0.4	65
	38	15.7	48	0.6	71
	52	18.9	Not avail		
	64	21.7	49	0.1	55

Table A1-40: Study 1602, Head Circumference

Patient/ Dose Group	Week	Chron Age (Mos)	Head Circumference		
			Cm	Z-score	%ile
	78	24.9	49	0.1	52
	90	27.7	Not avail		
303 40 mg	Baseline	7.0	Not avail		
	12	9.7	43	-0.8	22
	26	13.0	45	-0.2	44
	38	15.8	46	0.0	51
	52	19.3	Not avail		
	64	22.7	Not avail		
	78	26.3	Not avail		
305 20 mg	Baseline	5.7	40	-1.4	7
	12	8.4	41	-2.2	2
	26	11.6	43	-1.4	8
	38	14.4	45	-0.7	26
	52	17.5	43	-2.6	1
306 20 mg	Baseline	5.8	40	-2.5	1
	12	8.4	42	-2.7	0
	26	11.6	42	-3.1	0
	38	14.4	43	-3.3	0
	52	17.8	45	-2.4	1
	64	20.3	45	-2.3	1
	78	23.6	46	-2.0	2
	90	26.3	47	-1.4	8
307 40 mg	Baseline	6.8	44	-0.4	34
	12	9.6	46	0.2	60
	26	12.8	47	0.4	65
	38	15.6	47	-0.4	36
	52	18.8	49	0.9	80
	64	21.5	50	0.9	80
	78	24.8	50	1.0	84
308 40 mg	Baseline	4.3	42	-0.8	23
	12	7.2	44	-0.8	20
	26	10.2	46	0.1	55
	38	13.1	46	-0.6	27
	52	16.3	47	-0.4	36
	64	19.4	47	-0.8	22
	78	22.3	48	-0.7	24
309 20 mg	Baseline	5.3	42	-0.3	38
	12	7.9	43	-0.5	30
	26	11.3	45	0.2	57
	38	14.0	47	0.7	77
	52	17.4	48	0.8	79
	64	19.9	47	0.4	65
	78	23.2	48	0.3	61
310 20 mg	Baseline	6.3	42	-1.4	8
	12	9.2	44	-1.1	14
	26	12.4	44	-2.3	1
	38	15.1	46	-0.8	21
	52	18.4	47	-0.7	24

Table A1-40: Study 1602, Head Circumference

Patient/ Dose Group	Week	Chron Age (Mos)	Head Circumference		
			Cm	Z-score	%ile
	64	21.2	47	-0.8	23
	78	24.4	49	0.1	52
311 40 mg	Baseline	7.2	43	-1.1	13
	12	9.7	43	-2.0	3
	26	13.3	46	-1.0	16
	38	16.1	46	-1.3	10
	52	19.1	47	-0.9	18
	64	22.0	48	-0.3	37
	78	25.2	47	-1.4	8
312 20 mg	Baseline	4.9	41	-0.3	39
	12	7.9	42	-1.0	16
	26	11.1	43	-1.5	7
	38	13.8	44	-1.2	12
	52	17.3	45	-1.5	7
	64	20.1	45	-1.4	8
313 40 mg	Baseline	2.1	36	-2.8	0
	12	5.0	40	-2.1	2
	26	8.3	42	-1.4	8
	38	11.1	44	-0.9	20
	52	14.3	45	-0.6	28
	64	17.0	44	-1.8	3
314 20 mg	Baseline	1.8	39	-0.1	45
	12	4.6	43	0.2	60
	26	7.9	45	0.2	60
	38	10.7	47	0.9	81
	52	13.8	48	0.6	71
	64	16.6	48	0.2	57
315 40 mg	Baseline	1.1	39	-0.4	33
	12	3.9	Not avail		
	26	7.2	Not avail		
	38	9.8	44	-1.2	12
	52	13.1	Not avail		
	64	15.9	Not avail		
316 20 mg	Baseline	6.7	41	-1.3	10
	12	9.9	42	-1.8	4
	26	13.2	Not avail		
	38	15.7	46	0.3	63
	52	18.9	47	-0.1	47
317 40 mg	Baseline	6.2	38	-4.8	00
	12	9.1	40	-4.4	0
	26	12.1	43	-3.2	0
	38	15.1	44	-2.6	1
	52	18.3	45	-2.2	2
318 40 mg	Baseline	5.4	Not avail		
	12	8.1	42	-2.4	1
	26	11.3	45	-0.9	17
	38	14.1	45	-2.0	2
	52	17.3	47	-0.5	31

Table A1-40: Study 1602, Head Circumference

Patient/ Dose Group	Week	Chron Age (Mos)	Head Circumference		
			Cm	Z-score	%ile
319	Baseline	2.0	37	-1.9	3
20 mg	12	4.5	39	-1.9	3
	26	7.7	43	-0.6	27
	38	10.6	43	-1.7	5
	52	14.2	46	0.2	68

10.1.1.17.3 Study 1602: Cardiac Parameters by Individual Patient

Table A1-41: Study 1602, Cardiac Parameters

Patient/ Dose	Week	Ejection Fraction	ΔEF from Baseline	LVMI	ΔLVMI from Baseline	LVM Z-score	ΔLVM Z-score from Baseline
301	0	68	0	238	0	8.4	-0.0
40 mg	4	50	-19	223	-14	8.13	-0.3
	8	49	-19	146	-92	6.2	-2.2
	12	54	-14	121	-116	5.3	-3.1
	26	55	-13	71	-167	2.9	-5.5
	38	.	.	.	.	.	.
	52	76	7	80	-157	3.3	-5.1
	64	69	0	68	-170	2.4	-6.0
	78	71	3	87	-151	3.3	-5.1
302	4	51	.	73	.	3.0	.
20 mg	8	69	.	111	.	4.9	.
	12	60	.	72	.	3.0	.
	26	62	.	.	.	.	.
	38	60	.	.	.	.	.
	52	63	.	.	.	.	.
	64	58	.	58	.	1.6	.
	78	65	.	61	.	1.9	.
	90	56	.	.	.	.	.
303	4	.	.	.	.	.	.
40 mg	8	52	.	180	.	7.0	.
	12	45	.	112	.	4.9	.
	26	74	.	75	.	2.9	.
	38	.	.	.	.	.	.
	52	70	.	.	.	.	.
305	0	53	0	302	0	9.3	-0.0
20 mg	0	.	.	.	.	.	.
	4	36	-16	302	0	9.3	0.0
	8	44	-9	181	-120	7.1	-2.2
	12	43	-10	205	-97	7.5	-1.8
	26	67	14	124	-178	5.3	-4.0
	38	57	4	119	-182	4.9	-4.4
	52	68	16	110	-192	4.4	-4.9
306	0	64	0	163	0	6.7	0.0
20 mg	4	65	1	95	-68	4.4	-2.3
	8	66	2	83	-81	3.8	-2.9
	12	58	-5	79	-85	3.6	-3.1
	26	72	8	56	-107	2.1	-4.6

Table A1-41: Study 1602, Cardiac Parameters

Patient/ Dose	Week	Ejection Fraction	ΔEF from Baseline	LVMI	ΔLVMI from Baseline	LVM Z-score	ΔLVM Z-score from Baseline
	38	59	-5	105	-59	4.6	-2.1
	52	64	1	74	-90	2.9	-3.8
	64	57	-7	77	-87	3.1	-3.6
	78	65	1	41	-122	0.1	-6.6
	90	70	6	44	-119	0.3	-6.4
307	0	25	0	283	0	9.0	-0.0
40 mg	4	28	2	221	-62	7.8	-1.2
	8	24	-1	203	-80	7.4	-1.6
	12	27	2	195	-88	7.2	-1.8
	26	45	20	128	-155	5.2	-3.8
	38	46	21	109	-174	4.5	-4.5
	52	65	40	90	-193	3.5	-5.5
	64	59	34	72	-211	2.4	-6.6
	78	67	42	42	-241	0.1	-8.9
308	0	60	0	225	0	8.0	-0.0
40 mg	4	56	-3	150	-75	6.3	-1.7
	8	42	-18	111	-114	5.0	-3.0
	12	.	.	.	.	.	.
	26	61	1	70	-155	2.8	-5.2
	38	71	12	70	-155	2.6	-5.4
	52	50	-10	66	-159	2.3	-5.7
	64	61	1	64	-162	2.1	-5.9
	78	58	-1	64	-162	2.1	-5.9
309	0	44	0	220	0	7.9	-0.0
20 mg	4	45	1	188	-32	7.2	-0.7
	8	54	10	217	-4	7.8	-0.1
	12	32	-12	143	-78	5.9	-2.0
	26	70	26	126	-953	5.2	-2.7
	38	67	23	61	-159	2.1	-5.8
	52	56	12	76	-144	2.9	-5.0
	64	60	16	60	-160	1.9	-6.0
	78	69	25	63	-157	2.0	-5.9
310	0	45	0	179	0	6.8	0.0
20 mg	4	27	-18	171	-8	6.8	-0.0
	8	46	1	.	.	.	.
	12	46	2	130	-49	5.5	-1.3
	26	37	-8	105	-74	4.4	-2.4
	38	50	5	79	-100	3.1	-3.7
	52	63	18	59	-120	1.7	-5.1
	64	58	13	56	-123	1.5	-5.3
	78	61	17	.	.	.	.
311	0	34	0	163	0	6.6	-0.0
40 mg	4	37	3	113	-50	5.0	-1.6
	8	33	-1	108	-55	4.8	-1.8
	12	44	10	83	-79	3.7	-2.9
	26	.	.	.	.	.	.
	38	50	16	63	-100	2.3	-4.3
	52	50	16	45	-118	0.8	-5.8
	64	59	24	69	-94	2.6	-4.0

Table A1-41: Study 1602, Cardiac Parameters

Patient/ Dose	Week	Ejection Fraction	ΔEF from Baseline	LVMI	ΔLVMI from Baseline	LVM Z-score	ΔLVM Z-score from Baseline
	78	63	28	69	-94	2.5	-4.1
312 20 mg	0	48	0	208	0	7.8	-0.0
	4	40	-9	212	5	7.8	-0.0
	8	36	-13	208	0	7.7	-0.1
	12	36	-13	175	-32	6.9	-0.9
	26	.	.	.	.	.	.
	38	53	4	113	-95	4.8	-3.0
	52	61	12	77	-131	3.1	-4.7
313 40 mg	0	39	0	153	0	6.5	-0.0
	4	41	3	132	-21	6.0	-0.5
	8	30	-9	103	-50	4.7	-1.8
	12	46	8	83	-70	3.9	-2.6
	26	57	19	57	-96	2.1	-4.4
	38	56	17	82	-72	3.4	-3.1
	52	49	10	96	-57	4.2	-2.3
	64	38	0	96	-57	4.1	-2.4
314 20 mg	0	76	0	149	0	6.3	0.0
	4	59	-17	109	-40	4.9	-1.4
	8	38	-38	106	-43	4.8	-1.5
	12	60	-16	87	-62	3.9	-2.4
	26	66	-10	68	-81	2.6	-3.7
	38	.	.	.	.	.	.
	52	57	-19	64	-85	2.2	-4.1
	64	.	.	.	.	.	.
315 40 mg	0	61	0	59	0	2.6	0.0
	4	.	.	.	.	.	.
	8	.	.	.	.	.	.
	12	.	.	.	.	.	.
	26	.	.	.	.	.	.
	38	.	.	.	.	.	.
	52	55	-6	.	.	.	.
316 20 mg	0	60	0	122	0	5.4	0.0
	4	39	-21	124	2	5.5	0.1
	8	42	-18	114	-8	5.1	-0.3
	12	43	-17	96	-26	4.3	-1.1
	26	45	-14	79	-43	3.3	-2.1
	52	24	-35	45	-77	0.7	-4.7
317 40 mg	0	41	0	202	0	7.6	-0.0
	4	52	11	246	44	8.4	0.8
	8	37	-4	184	-18	7.2	-0.4
	12	41	0	151	-51	6.4	-1.2
	26	30	-11	158	-44	6.4	-1.2
	38	42	1	156	-46	6.3	-1.3
	52	32	-9	157	-45	6.3	-1.3
318 40 mg	0	33	0	.	.	.	.
	4	33	-0	206	.	7.6	.
	8	22	-11	159	.	6.5	.
	12	27	-6	188	.	7.1	.
	26	21	-12	150	.	6.0	.

Table A1-41: Study 1602, Cardiac Parameters

Patient/ Dose	Week	Ejection Fraction	ΔEF from Baseline	LVMI	ΔLVMI from Baseline	LVM Z-score	ΔLVM Z-score from Baseline
	38	33	0	101	.	4.3	.
	52	56	23	113	.	4.7	.
319 20 mg	0	68	0	233	0	8.2	0.0
	4	44	-24	192	-42	7.5	-0.7
	8	37	-31	134	-100	5.9	-2.3
	12	38	-30	154	-80	6.4	-1.8
	26	55	-14	108	-125	4.8	-3.4
	38	39	-29	140	-93	5.9	-2.3
	52	29	-40	149	-85	5.9	-2.3

10.1.1.17.4 Study 1602: AIMS Scores by Individual Patient

Table A1-42: Study 1602, AIMS Scores by Category

Patient/ Dose Group	Week	Category Raw Score Prone (21)	Supine (9)	Sit (12)	Stand (16)	Total Raw Score (58)	Chron Age (Mos)	Age Equiv Score (Mos)	Percentile Score
301 40 mg	Baseline	1	4	1	0	6	4.8	1.1	<1
	12	3	6	2	0	11	7.8	3.0	<1
	26	6	8	7	0	21	11.0	5.1	<1
	38	1	6	2	0	9	13.8	2.2	<1
	52	0	4	1	0	5	17.1	0.8	<1
	64	0	5	1	0	6	20.0	1.1	
	78	0	4	1	0	5	23.3	0.8	
	90	0	0	0	0	0	25.5	<0.5	
	104	0	3	0	0	3	29.0	<0.5	
302 20 mg	Baseline	8	7	6	3	24	6.6	6.0	66
	12	14	9	12	3	38	9.7	8.3	36
	26	21	9	12	11	53	12.9	12.0	54
	38	21	9	12	15	57	15.7	≥14	≥50
	52	21	9	12	16	58	18.9	≥14	
	78	21	9	12	16	58	25.0	≥14	
303 40 mg	Baseline	5	4	4	2	15	7.0	4.0	2
	12	12	9	8	3	32	9.8	7.4	15
	26	12	8	11	3	34	13	7.8	<1
	38	9	9	11	7	36	15.5	8.1	<1
	52	21	9	12	13	55	19.4	13	
	64	21	9	12	13	55	23.1	12.9	
	78	0	0	0	1	1	26.5	<0.5	
305 20 mg	Baseline	0	2	0	1	3	5.6	<0.5	<1
	12	0	2	0	0	2	8.4	<0.5	<1
	26	0	2	1	1	4	11.6	<0.5	<1
	38	0	2	0	1	3	14.3	<0.5	<1
	52	1	2	0	1	4	17.8	<0.5	<1
306 20 mg	Baseline	0	5	1	1	7	5.8	1.4	<1
	12	1	5	1	1	8	8.4	1.8	<1
	26	0	2	0	0	2	11.8	<0.5	<1
	38	0	2	0	0	2	14.4	<0.5	<1

Table A1-42: Study 1602, AIMS Scores by Category

Patient/ Dose Group	Week	Category Raw Score Prone (21)	Supine (9)	Sit (12)	Stand (16)	Total Raw Score (58)	Chron Age (Mos)	Age Equiv Score (Mos)	Percentile Score
	52	0	2	0	0	2	17.6	<0.5	<1
	64	0	0	0	0	0	20.3	<0.5	
	78	0	0	0	0	0	23.6	<0.5	
	90	0	0	0	0	0	26.3	<0.5	
307 40 mg	Baseline	3	4	3	2	12	6.6	3.3	1
	12	11	9	0	4	34	9.5	7.7	26
	26	21	9	12	13	55	12.9	12.0	52
	38	21	9	12	16	58	15.4	≥14	≥50
	52	21	9	12	16	58	18.9	≥14	≥50
	64	21	9	12	16	58	21.8	≥14	
308 40 mg	Baseline	1	3	0	0	4	4.1	<1	<1
	12	5	7	2	0	14	7.2	3.8	<1
	26	14	8	11	3	36	10.2	8.1	3
	38	20	9	12	11	52	13.8	12	18
	52	21	9	12	16	58	16.2	≥14	≥50
309 20 mg	Baseline	3	7	1	2	13	5.1	3.6	7
	12	8	8	9	3	28	7.9	6.4	23
	26	15	9	11	8	43	11.3	9.0	13
	38	21	9	12	13	55	14.0	12.0	55
	52	21	9	12	15	57	17.1	≥14	≥50
	64	21	9	12	16	58	19.8	≥14	
310 20 mg	Baseline	3	5	1	2	11	6.4	3.0	<1
	12	9	8	4	3	24	9.1	5.7	1
	26	9	7	6	3	25	12.4	5.9	<1
	38	21	8	10	10	49	15.1	10.4	<5
	52	20	8	11	8	47	18.4	9.9	<1
	64	19	9	12	12	52	21.2	11.7	
	78	21	9	11	13	54	23.9	12.3	
311 40 mg	Baseline	0	0	1	0	1	7.2	<0.5	<1
	12	2	4	2	0	8	9.8	1.8	<1
	26	0	5	1	0	6	13.3	1.0	<1
	38	3	7	7	0	17	16.1	4.3	<5
	52	4	6	6	0	16	19.2	4.2	<1
	64	12	9	9	0	30	22.0	7.0	
	78	13	9	11	2	35	25.1	7.9	
312 20 mg	Baseline	1	4	1	1	7	4.8	1.3	<1
	12	1	5	1	1	8	7.9	1.8	<1
	26	2	7	8	1	18	11.2	4.5	<1
	38	4	9	10	1	24	13.9	5.7	<1
	52	18	8	12	1	39	17.0	8.4	<1
	64	19	9	12	1	41	20.0	8.7	
313 40 mg	Baseline	1	3	0	2	6	2.0	1.0	16
	12	4	5	5	1	15	5.0	4.0	14
	26	15	9	12	2	38	8.3	8.2	52
	38	21	9	12	8	50	11.1	11.0	49
	52	21	9	12	9	51	14.0	11.4	9
	64	12	9	11	0	32	17.2	7.4	<5
314	Baseline	2	2	1	1	6	1.6	1.0	25

Table A1-42: Study 1602, AIMS Scores by Category

Patient/ Dose Group	Week	Category Raw Score Prone (21)	Supine (9)	Sit (12)	Stand (16)	Total Raw Score (58)	Chron Age (Mos)	Age Equiv Score (Mos)	Percentile Score
20 mg	12	6	6	1	2	15	4.7	4.0	19
	26	11	8	4	2	25	8.0	5.8	10
	38	11	9	10	3	33	10.7	7.6	<1
	52	13	9	10	7	39	13.8	8.4	<1
	64	17	9	11	11	48	16.6	10.1	<5
315 40 mg	Baseline	1	1	0	1	3	0.4	0.5	14
	12	9	4	2	2	17	3.8	4.3	79
	26	9	9	10	3	31	7.1	7.2	50
	38	21	9	12	10	52	9.8	11.7	78
	52	21	9	12	15	57	13.0	≥14	65
316 20 mg	Baseline	1	4	2	0	7	6.7	1.4	<1
	12	10	7	6	0	23	9.7	5.5	<1
	26	21	9	12	6	48	13.2	10.1	26
	38	21	9	12	9	51	15.9	11.4	<1
	52	21	9	12	15	57	18.9	≥14	≥50
317 40 mg	Baseline	0	0	1	0	1	6.2	0.5	<1
	12	0	0	1	0	1	8.9	<0.5	<1
	26	0	0	0	0	0	12.3	<0.5	<1
	38	0	0	0	0	0	15.1	<0.5	<1
	52	0	0	0	0	0	18.7	<0.5	<1
318 40 mg	Baseline	0	4	1	0	5	5.3	0.8	<1
	12	3	8	5	1	17	8.4	4.3	<1
	26	7	8	9	1	25	11.2	5.9	<1
	38	9	8	11	1	29	14.1	6.7	<1
	52	10	9	9	1	29	17.3	6.7	<1
319 20 mg	Baseline	1	2	1	1	5	2.0	0.8	7
	12	1	4	1	0	6	4.3	1.0	<1
	26	1	4	1	0	6	7.7	1.0	<1
	38	0	0	0	0	0	10.5	<0.5	<1
	52						Not avail		

10.1.1.17.5 Study 1602: Pompe PEDI Scores by Individual Patient

10.1.1.17.5.1 Mobility Scores

Table A1-43: Study 1602, Pompe PEDI Scores, Mobility Scores

Patient/ Dose Group	Week	Chron Age (Mos)	Mobility Scores Raw	Scaled (SE)	Normative Std Score
301 40 mg	Baseline	4.8	2	8.1 (3.0)	34
	12	7.8	10	22.2 (1.8)	19
	26	11.0	14	25.9 (1.6)	26
	38	13.8	9	32.9 (1.7)	<10
	52	17.1	1	4.5 (3.6)	<10
	64	20.0	15	38.8 (1.4)	<10
	78	23.3	17	40.4 (1.3)	<10
	90	25.5	18	41.1 (1.3)	<10

Table A1-43: Study 1602, Pompe PEDI Scores, Mobility Scores

Patient/ Dose Group	Week	Chron Age (Mos)	Mobility Scores Raw	Mobility Scores Scaled (SE)	Normative Std Score
	104	29.0	12	36.1 (1.5)	<10
302 20 mg	Baseline	6.6	15	26.7 (1.5)	62
	12	9.7	23	31.9 (1.3)	38
	26	12.9	41	40.5 (1.1)	36
	38	15.7	68	49.5 (0.9)	54
	52	18.9	86	54.8 (1.0)	51
	64	21.9	77	52.1 (0.9)	45
	78	25.0	75	51.6 (0.9)	26
	90	27.9	88	55.4 (1.0)	37
303 40 mg	Baseline	7.0	9	21.0 (1.9)	16
	12	9.8	14	25.9 (1.6)	26
	26	13	24	32.4 (1.3)	20
	38	15.5	35	37.9 (1.2)	31
	52	19.4	65	48.7 (0.9)	37
	64	23.1	55	45.6 (1.0)	29
	78	26.5	3	10.8 (2.7)	<10
305 20 mg	Baseline	5.6	6	16.8 (2.2)	47
	12	8.4	Not done		
	26	11.6	7	18.4 (2.1)	11
	38	14.3	3	10.8 (2.7)	<10
	52	17.6	6	16.8 (2.2)	<10
306 20 mg	Baseline	5.8	9	21 (1.9)	54
	12	8.4	10	22.2 (1.8)	19
	26	11.8	6	16.8 (2.2)	<10
	38	14.4	2	8.1 (3)	<10
	52	17.6	3	10.8 (2.7)	<10
	64	20.3	3	10.8 (2.7)	<10
	78	23.6	2	8.1 (3)	<10
	90	26.3	0	0 (5.8)	<10
307 40 mg	Baseline	6.6	9	21.0 (1.9)	54
	12	9.5	20	30.1 (1.4)	35
	26	12.9	41	40.5 (1.1)	36
	38	15.4	65	48.7 (0.9)	52
	52	18.9	72	50.7 (0.9)	41
	64	21.8	85	54.5 (1.0)	50
	78	25.0	94	57.3 (1.0)	42
308 40 mg	Baseline	4.1	3	10.8 (2.7)	38
	12	7.2	11	23.2 (1.7)	21
	26	10.2	22	31.3 (1.3)	37
	38	13.8	46	42.4 (1.1)	40
	52	16.2	53	44.9 (1.0)	45
	64	18.8	26	33.5 (1.3)	<10
309 20 mg	Baseline	5.1	9	21.0 (1.9)	54
	12	7.9	18	28.8 (1.4)	32
	26	11.3	27	34.0 (1.3)	43
	38	14.0	46	42.4 (1.1)	40
	52	17.1	64	48.4 (0.9)	52
	64	19.8	73	51.0 (0.9)	42

Table A1-43: Study 1602, Pompe PEDI Scores, Mobility Scores

Patient/ Dose Group	Week	Chron Age (Mos)	Mobility Scores Raw	Scaled (SE)	Normative Std Score
	78	23.3	87	55.1 (1.0)	52
310 20 mg	Baseline	6.4	12	24.2 (1.7)	23
	12	9.1	16	27.5 (1.5)	29
	26	12.4	27	34.0 (1.3)	23
	38	15.1	44	41.7 (1.1)	39
	52	18.4	51	44.2 (1.0)	26
	64	21.2	69	49.8 (0.9)	39
	78	23.9	77	52.1 (0.9)	45
311 40 mg	Baseline	7.2	4	13.1 (2.5)	42
	12	9.8	9	21.0 (1.9)	16.2
	26	13.3	7	18.4 (2.1)	<10
	38	16.1	15	26.7 (1.5)	<10
	52	19.2	18	28.8 (1.4)	<10
	64	22.0	23	31.9 (1.3)	<10
	78	25.1	23	31.9 (1.3)	<10
312 20 mg	Baseline	4.8	6	16.8 (2.2)	47
	12	7.9	10	22.2 (1.8)	19
	26	11.2	13	25.1 (1.6)	25
	38	13.9	18	28.8 (1.4)	13
	52	17.0	27	34.0 (1.3)	23
313 40 mg	Baseline	2.0	2	8.1 (3)	34
	12	5.0	9	21.0 (1.9)	54
	26	8.3	19	29.5 (1.4)	34
	38	11.1	24	32.4 (1.3)	40
	52	14.0	42	40.9 (1.1)	37
	64	17.2	18	28.8 (1.4)	13
314 20 mg	Baseline	1.6	1	4.5 (3.6)	29
	12	4.7	11	23.2 (1.7)	57
	26	8.0	14	25.9 (1.6)	26
	38	10.7	17	28.2 (1.4)	31
	52	13.8	28	34.6 (1.2)	24
	64	16.6	33	37.0 (1.2)	29
315 40 mg	Baseline	0.4	0	0 (5.8)	22
	12	3.8	3	10.8 (2.7)	38
	26	7.1	13	25.1 (1.6)	25
	38	9.8	33	37.0 (1.2)	49
	52	13.0	60	47.2 (1.0)	49
316 20 mg	Baseline	6.7	8	19.8 (2.0)	52
	12	9.7	16	27.5 (1.5)	29
	26	13.2	26	33.5 (1.3)	42
	38	15.9	46	42.4 (1.1)	40
	52	18.9	80	53.0 (0.9)	47
317 40 mg	Baseline	6.2	2	8.1 (3)	<10
	12	8.9	2	8.1 (3)	<10
	26	12.3	3	10.8 (2.7)	<10
	38	15.1	1	4.5 (3.6)	<10
	52	18.7	3	10.8 (2.7)	<10
318	Baseline	5.3	3	10.8 (2.7)	38

Table A1-43: Study 1602, Pompe PEDI Scores, Mobility Scores

Patient/ Dose Group	Week	Chron Age (Mos)	Mobility Scores Raw	Scaled (SE)	Normative Std Score
40 mg	12	8.4	14	25.9 (1.6)	26
	26	11.2	18	28.8 (1.4)	32
	38	14.1	23	31.9 (1.3)	19
	52	17.3	29	35.1 (1.2)	25
319 20 mg	Baseline	2.0	0	0 (5.6)	22
	12	4.3	5	15.2 (2.4)	45
	26	7.7	7	18.4 (2.1)	11
	38	10.5	8	19.8 (2.0)	14
	52	14.4	6	16.8 (2.2)	<10

10.1.1.17.5.2 Self-Care Scores

Table A1-44: Study 1602, Pompe PEDI Scores, Self-Care Scores

Patient/ Dose Group	Week	Chron Age (Mos)	Self-Care Raw	Scaled (SE)	Normative Std Score
301 40 mg	Baseline	4.8	5	18.8 (2.8)	58
	12	7.8	9	26.9 (2.5)	26
	26	11.0	10	28.7 (2.4)	31
	38	13.8	7	23.1 (2.5)	11
	52	17.1	7	23.1 (2.5)	11
	64	20.0	9	26.9 (2.5)	0
	78	23.3	7	23.1 (2.5)	<10
	90	25.5	7	23.1 (2.5)	<10
	104	29.0	0	0	<10
302 20 mg	Baseline	6.6	8	25.0 (2.5)	71
	12	9.7	17	37.0 (1.6)	54
	26	12.9	25	42.4 (1.4)	48
	38	15.7	32	46.2 (1.3)	55
	52	18.9	46	53.0 (1.2)	54
	64	21.9	39	49.7 (1.2)	46
	78	25.0	41	50.6 (1.2)	37
	90	27.9	52	55.7 (1.2)	47
303 40 mg	Baseline	7.0	10	28.7 (2.4)	31
	12	9.8	14	34.2 (1.9)	47
	26	13	24	41.9 (1.4)	47
	38	15.5	27	43.6 (1.3)	50
	52	19.4	25	42.4 (1.4)	30
	64	23.1	31	45.7 (1.3)	38
	78	26.5	8	25.0 (2.5)	<10
305 20 mg	Baseline	5.6	5	18.8 (2.8)	58
	12	8.4	Not done		
	26	11.6	7	23.1 (2.5)	15
	38	14.3	5	18.8 (2.8)	<10
	52	17.6	6	21.0 (2.6)	<10
306 20 mg	Baseline	5.8	3	12.7 (3.5)	46
	12	8.4	5	18.8 (2.8)	<10

Table A1-44: Study 1602, Pompe PEDI Scores, Self-Care Scores

Patient/ Dose Group	Week	Chron Age (Mos)	Self-Care Raw	Self-Care Scaled (SE)	Normative Std Score
	26	11.8	5	18.8 (2.8)	<10
	38	14.4	3	12.7 (3.5)	<10
	52	17.6	3	12.7 (3.5)	<10
	64	20.3	3	12.7 (3.5)	<10
	78	23.6	4	16.1 (3.1)	<10
	90	26.3	2	9.0 (3.5)	<10
307 40 mg	Baseline	6.6	10	26.7 (2.4)	79
	12	9.5	12	31.8 (2.1)	40
	26	12.9	16	36.2 (1.7)	36
	38	15.4	24	41.9 (1.4)	47
	52	18.9	33	46.7 (1.3)	40
	64	21.8	49	54.3 (1.2)	57
	78	25.0	56	57.4 (1.2)	51
308 40 mg	Baseline	4.1	1	4.9 (4.0)	30
	12	7.2	9	26.9 (2.5)	26
	26	10.2	13	33.1 (2.0)	43
	38	13.8	27	43.6 (1.3)	50
	52	16.2	35	47.7 (1.3)	58
	64	18.8	25	42.4 (1.4)	30
309 20 mg	Baseline	5.1	6	21.0 (2.6)	63
	12	7.9	12	31.8 (2.1)	40
	26	11.3	17	37.0 (1.6)	54
	38	14.0	23	41.2 (1.4)	46
	52	17.1	30	45.2 (1.3)	53
	64	19.8	43	51.6 (1.2)	51
	78	23.3	50	54.8 (1.2)	58
310 20 mg	Baseline	6.4	8	25.0 (2.5)	21
	12	9.1	12	31.8 (2.1)	40
	26	12.4	17	37.0 (1.6)	38
	38	15.1	22	40.6 (1.4)	45
	52	18.4	31	45.7 (1.3)	38
	64	21.2	35	47.7 (1.3)	42
	78	23.9	36	48.2 (1.3)	43
311 40 mg	Baseline	7.2	9	26.8 (2.5)	75
	12	9.8	7	23.1 (2.5)	15
	26	13.3	18	37.8 (1.6)	39
	38	16.1	21	40.0 (1.5)	43
	52	19.2	25	42.4 (1.4)	30
	64	22.0	30	45.2 (1.3)	36
	78	25.1	39	49.7 (1.2)	36
312 20 mg	Baseline	4.8	6	21.0 (2.6)	63
	12	7.9	14	34.2 (1.9)	47
	26	11.2	16	36.2 (1.7)	52
	38	13.9	20	39.3 (1.5)	42
	52	17.0	32	46.2 (1.3)	55
313 40 mg	Baseline	2.0	6	21.0 (2.6)	63
	12	5.0	11	30.3 (2.3)	82
	26	8.3	12	31.8 (2.1)	40

Table A1-44: Study 1602, Pompe PEDI Scores, Self-Care Scores

Patient/ Dose Group	Week	Chron Age (Mos)	Self-Care Raw	Self-Care Scaled (SE)	Self-Care Normative Std Score
	38	11.1	19	38.6 (1.5)	59
	52	14.0	23	41.2 (1.4)	46
	64	17.2	26	43 (1.4)	49
314 20 mg	Baseline	1.6	2	9.0 (3.5)	38
	12	4.7	9	28.9 (2.5)	75
	26	8.0	14	34.2 (1.9)	47
	38	10.7	14	34.2 (1.9)	47
	52	13.8	19	38.6 (1.5)	41
	64	16.6	26	43 (1.4)	49
315 40 mg	Baseline	0.4	0	0 (6.3)	19
	12	3.8	3	12.7 (3.5)	46
	26	7.1	11	30.3 (2.3)	36
	38	9.8	16	36.2 (1.7)	52
	52	13.0	25	42.4 (1.4)	48
316 20 mg	Baseline	6.7	10	28.7 (2.4)	79
	12	9.7	14	34.2 (1.9)	47
	26	13.2	24	41.9 (1.4)	68
	38	15.9	28	44.1 (1.3)	51
	52	18.9	48	53.9 (1.2)	56
317 40 mg	Baseline	6.2	3	12.7 (3.5)	<10
	12	8.9	6	21.0 (2.6)	<10
	26	12.3	5	18.8 (2.8)	<10
	38	15.1	4	16.1 (3.1)	<10
	52	18.7	7	23.1 (2.5)	<10
318 40 mg	Baseline	5.3	6	21.0 (2.6)	63
	12	8.4	10	28.7 (2.4)	31
	26	11.2	13	33.1 (2.0)	43
	38	14.1	16	36.2 (1.7)	36
	52	17.3	23	41.2 (1.4)	46
319 20 mg	Baseline	2.0	2	9.0 (3.5)	38
	12	4.3	9	26.9 (2.5)	75
	26	7.7	9	26.9 (2.5)	26
	38	10.5	7	23.1 (2.5)	15
	52	Not avail	11	30.3 (2.3)	25

10.1.1.17.5.3 Social Function Scores

Table A1-45: Study 1602, Pompe PEDI Scores, Social Function Scores

Patient/ Dose Group	Week	Chron Age (Mos)	Social Function Scores Raw	Social Function Scores Scaled (SE)	Social Function Scores Normative Std Score
301 40 mg	Baseline	4.8	4	14.7 (3.2)	NA
	12	7.8	5	21.6 (5.5)	43
	26	11.0	10	34.0 (1.6)	58
	38	13.8	9	21.0 (1.9)	41
	52	17.1	12	36.1 (1.5)	45
	64	20.0	8	19.8 (2.0)	27

Table A1-45: Study 1602, Pompe PEDI Scores, Social Function Scores

Patient/ Dose Group	Week	Chron Age (Mos)	Social Function Scores		
			Raw	Scaled (SE)	Normative Std Score
	78	23.3	4	13.1 (2.5)	31
	90	25.5	4	13.1 (2.5)	17
	104	29.0	0	0	<10
302 20 mg	Baseline	6.6	5	21.6 (5.5)	NA
	12	9.7	6	27.7 (2.7)	50
	26	12.9	9	32.9 (1.7)	41
	38	15.7	19	41.8 (1.3)	53
	52	18.9	20	42.5 (1.3)	37
	64	21.9	22	43.8 (1.2)	41
	78	25.0	17	40.4 (1.3)	15
	90	27.9	26	46.2 (1.2)	32
303 40 mg	Baseline	7.0	3	10.5 (3.2)	29
	12	9.8	8	31.6 (1.8)	55
	26	13	11	35.1 (1.6)	44
	38	15.5	16	39.6 (1.4)	50
	52	19.4	16	39.6 (1.4)	29
	64	23.1	16	39.6 (1.4)	29
	78	26.5	11	35.1 (1.6)	<10
305 20 mg	Baseline	5.6	5	21.6 (5.5)	NA
	12	8.4	Not done		
	26	11.6	7	30.0 (2.1)	53
	38	14.3	8	31.6 (1.8)	39
	52	17.6	9	32.9 (1.7)	41
306 20 mg	Baseline	5.8	7	30.0 (2.1)	NA
	12	8.4	6	27.7 (2.7)	50
	26	11.8	6	27.7 (2.7)	50
	38	14.4	10	34.0 (1.6)	43
	52	17.6	10	34.0 (1.6)	43
	64	20.3	7	30 (2.1)	<10
	78	23.6	7	30 (2.1)	<10
	90	26.3	6	27.7 (2.7)	<10
307 40 mg	Baseline	6.6	3	10.5 (3.2)	NA
	12	9.5	4	14.7 (3.2)	34
	26	12.9	7	30.0 (2.1)	37
	38	15.4	7	30.0 (2.1)	37
	52	18.9	15	38.8 (1.4)	27
	64	21.8	19	41.8 (1.3)	35
	78	25.0	28	47.3 (1.2)	35
308 40 mg	Baseline	4.1	2	6.6 (2.9)	NA
	12	7.2	3	10.5 (3.2)	29
	26	10.2	11	35.1 (1.6)	59
	38	13.8	18	41.1 (1.3)	53
	52	16.2	19	41.8 (1.3)	53
	64	18.8	19	41.8 (1.3)	35
309 20 mg	Baseline	5.1	3	10.5 (3.2)	NA
	12	7.9	4	14.7 (3.2)	34
	26	11.3	9	32.9 (1.7)	56
	38	14.0	13	37 (1.5)	47

Table A1-45: Study 1602, Pompe PEDI Scores, Social Function Scores

Patient/ Dose Group	Week	Chron Age (Mos)	Social Function Scores		
			Raw	Scaled (SE)	Normative Std Score
	52	17.1	16	39.6 (1.4)	50
	64	19.8	21	43.1 (1.2)	39
	78	23.3	27	46.8 (1.2)	49
310 20 mg	Baseline	6.4	5	21.6 (5.5)	43
	12	9.1	6	27.7 (2.7)	50
	26	12.4	10	34.0 (1.6)	43
	38	15.1	16	40.0 (1.4)	50
	52	18.4	17	40.4 (1.3)	31
	64	21.2	18	41.1 (1.3)	33
	78	23.9	22	43.8 (1.2)	41
311 40 mg	Baseline	7.2	2	6.6 (2.9)	NA
	12	9.8	4	14.7 (3.2)	34
	26	13.3	5	21.6 (5.5)	25
	38	16.1	9	32.9 (1.7)	41
	52	19.2	15	38.8 (1.4)	27
	64	22.0	13	37 (1.5)	22
	78	25.1	22	43.8 (1.2)	25
312 20 mg	Baseline	4.8	2	6.6 (2.9)	NA
	12	7.9	5	21.6 (5.5)	43
	26	11.2	8	31.6 (1.8)	55
	38	13.9	10	34 (1.6)	43
	52	17.0	18	41.1 (1.3)	53
313 40 mg	Baseline	2.0	1	3.1 (3.1)	NA
	12	5.0	2	6.6 (2.9)	NA
	26	8.3	4	14.7 (3.2)	34
	38	11.1	6	27.7 (2.7)	50
	52	14.0	12	36.1 (1.5)	45
	64	17.2	14	37.9 (1.5)	48
314 20 mg	Baseline	1.6	0	0 (NA)	NA
	12	4.7	4	14.7 (3.2)	NA
	26	8.0	4	14.7 (3.2)	34
	38	10.7	6	27.7 (2.7)	50
	52	13.8	8	31.6 (1.8)	39
	64	16.6	12	36.1 (1.5)	45
315 40 mg	Baseline	0.4	0	0 (NA)	NA
	12	3.8	3	10.5 (3.2)	NA
	26	7.1	5	21.6 (5.5)	43
	38	9.8	10	34 (1.6)	58
	52	13.0	14	37.9 (1.5)	48
316 20 mg	Baseline	6.7	3	10.5 (3.2)	NA
	12	9.7	5	21.6 (5.5)	43
	26	13.2	7	30 (2.1)	37
	38	15.9	9	32.9 (1.7)	41
	52	18.9	22	43.8 (1.2)	41
317 40 mg	Baseline	6.2	2	6.6 (2.9)	24
	12	8.9	3	10.5 (3.2)	29
	26	12.3	2	6.6 (2.9)	<10
	38	15.1	3	10.5 (3.2)	<10

Table A1-45: Study 1602, Pompe PEDI Scores, Social Function Scores

Patient/ Dose Group	Week	Chron Age (Mos)	Social Function Scores		
			Raw	Scaled (SE)	Normative Std Score
	52	18.7	10	34 (1.6)	13
318 40 mg	Baseline	5.3	4	14.7 (3.2)	NA
	12	8.4	9	32.9 (1.7)	56
	26	11.2	14	37.9 (1.5)	62
	38	14.1	16	39.6 (1.4)	50
	52	17.3	17	40.4 (1.3)	51
319 20 mg	Baseline	2.0	2	6.6 (2.9)	NA
	12	4.3	2	6.6 (2.9)	NA
	26	7.7	3	10.5 (3.2)	29
	38	10.5	5	21.6 (5.5)	43
	52	Not avail	12	36.1 (1.5)	45

10.1.1.17.6 Study 1602: BSID-II Scores by Individual Patient

Table A1-46: Study 1602, BSID-II Scores

Patient/ Dose Group	Week	Total Raw Score	Chron Age (Mos)	Age Equiv (Mos)	MDI
301 40 mg	Baseline	38	4.8	3	65
	12	60	7.8	5	76
	26	78	11.0	10	88
	38	83	13.8	11	82
	52	82	17.1	11	56
	64	93	20.0	13	54
	78	97	23.3	14	<50
	90	103	25.5	16	<50
	104	55	29.0	5	<50
302 20 mg	Baseline	59	6.6	6	107
	12	73	9.7	8	96
	26	86	12.9	11	96
	38	102	15.7	16	107
	52	109	18.9	17	85
	64	116	21.9	19	78
	78	118	25.0	19	64
	90	133	27.9	24	78
303 40 mg	Baseline	62	7.0	6	98
	12	73	9.8	8	96
	26	86	13	11	96
	38	98	15.5	15	99
	52	101	19.4	15	77
	64	113	23.1	18	72
	78	104	26.5	16	50
305 20 mg	Baseline	11	5.6	<1	<50
	12	Not done			
	26	Not done			
	38	72	14.3	8	55
	52	76	17.8	9	52
306	Baseline	34	5.8	3	<50

Table A1-46: Study 1602, BSID-II Scores

Patient/ Dose Group	Week	Total Raw Score	Chron Age (Mos)	Age Equiv (Mos)	MDI
20 mg	12	53	8.4	5	62
	26	Not done			
	38	Not done			
	52	Not available			
	64	25	20.3	2	<50
	78	63	23.6	6	<50
	90	Not available			
307 40 mg	Baseline	58	6.6	5	90
	12	70	9.5	7	96
	26	89	12.9	12	105
	38	96	15.4	14	95
	52	106	18.9	16	79
	64	117	21.8	19	80
	78	130	25.0	23	88
308 40 mg	Baseline	38	4.1	3	87
	12	64	7.2	6	93
	26	78	10.2	10	98
	38	96	13.8	14	103
	52	96	16.2	14	86
	64	104	18.8	16	75
309 20 mg	Baseline	57	5.1	5	103
	12	66	7.9	7	98
	26	84	11.3	11	102
	38	98	14.0	15	108
	52	107	17.1	17	107
	64	114	19.8	18	88
	78	130	23.3	23	100
310 20 mg	Baseline	41	6.4	4	56
	12	68	9.1	7	84
	26	79	12.4	10	80
	38	99	15.1	15	101
	52	101	18.4	15	77
	64	101	21.2	15	54
	78	118	23.9	19	70
311 40 mg	Baseline	60	7.2	5	94
	12	68	9.8	7	92
	26	78	13.3	10	77
	38	95	16.1	14	93
	52	104	19.2	16	83
	64	116	22.0	19	84
	78	123	25.1	21	74
312 20 mg	Baseline	45	4.8	4	101
	12	62	7.9	6	89
	26	71	11.2	8	73
	38	76	13.9	9	61
	52	102	17	16	88
	64	105	20.0	16	70
313 40 mg	Baseline	17	2.0	1	78
	12	49	5.0	4	87

Table A1-46: Study 1602, BSID-II Scores

Patient/ Dose Group	Week	Total Raw Score	Chron Age (Mos)	Age Equiv (Mos)	MDI
	26	65	8.3	6	86
	38	79	11.1	10	90
	52	96	14	14	103
	64	102	17.2	16	88
314 20 mg	Baseline	8	1.6	<1	87
	12	42	4.7	4	95
	26	60	8.0	5	85
	38	71	10.7	8	73
	52	78	13.8	10	65
	64	96	16.6	14	76
315 40 mg	Baseline	0	0.4	<1	Not done
	12	43	3.8	4	97
	26	65	7.1	6	96
	38	73	9.8	8	88
	52	93	13	13	105
316 20 mg	Baseline	56	6.7	5	101
	12	71	9.7	8	91
	26	84	13.2	11	102
	38	98	15.9	15	108
	52	109	18.9	17	102
317 40 mg	Baseline	53	6.2	5	80
	12	66	8.9	7	80
	26	68	12.3	7	56
	38	75	15.1	9	52
	52	76	18.7	9	<50
318 40 mg	Baseline	47	5.3	4	83
	12	71	8.4	8	98
	26	77	11.2	9	85
	38	93	14.1	13	97
	52	101	17.3	15	86
319 20 mg	Baseline	9	2.0	<1	62
	12	40	4.3	3	91
	26	66	7.7	7	98
	38	76	10.5	9	94
	52	96	14.4	14	103

10.1.1.17.7 Study 1602: All Adverse Events (incidence table)

Table A1-47: Study 1602 Amendment 002, All AEs

Treated Patients, n =	All 18	20 mg/kg 9	40 mg/kg 9
SOC **AE Preferred Term**	**n (%)**	**n (%)**	**n (%)**
Blood and lymphatic system disorders			
Anemia	10 (56)	5 (56)	5 (56)
Eosinophilia	3 (17)	2 (22)	1 (11)
Lymphadenitis	1 (6)	1 (11)	0
Lymphadenopathy	1 (6)	0	1 (11)
Thrombocythemia	1 (6)	1 (11)	0
Cardiac disorders			
Tachycardia	6 (33)	2 (22)	4 (44)
Bradycardia	3 (17)	2 (22)	1 (11)
Cardiac failure	2 (11)	1 (11)	1 (11)
Cyanosis	2 (11)	0	2 (22)
Arrhythmia	1 (6)	1 (11)	0
Arrhythmia nodal	1 (6)	1 (11)	0
Arrhythmia supraventricular	1 (6)	0	1 (11)
Atrial tachycardia	1 (6)	1 (11)	0
Cardio-respiratory arrest	1 (6)	1 (11)	0
Cardiomegaly	1 (6)	1 (11)	0
Diastolic dysfunction	1 (6)	1 (11)	0
Hypertrophic obstructive cardiomyopathy	1 (6)	0	1 (11)
Myocardial ischemia	1 (6)	0	1 (11)
Tachycardia supraventricular	1 (6)	1 (11)	0
Ventricular extrasystoles	1 (6)	0	1 (11)
Ventricular hypertrophy	1 (6)	0	1 (11)
Congenital, familial and genetic disorders			
Macroglossia	2 (11)	2 (22)	0
Laryngomalacia	1 (6)	1 (11)	0
Leukodystrophy	1 (6)	0	1 (11)
Plagiocephaly	1 (6)	0	1 (11)
Ear and labyrinth disorders			
Hypoacusis	5 (28)	2 (22)	3 (33)
Ear pain	2 (11)	1 (11)	1 (11)
Middle ear effusion	2 (11)	0	2 (22)
Mastoid disorder	1 (6)	0	1 (11)
Endocrine disorders			
Hypoparathyroidism	2 (11)	2 (22)	0
Adrenal insufficiency	1 (6)	0	1 (11)
Eye disorders			
Conjunctivitis	5 (28)	2 (22)	3 (33)
Eye discharge	2 (11)	1 (11)	1 (11)
Blepharitis	1 (6)	0	1 (11)
Eye redness	1 (6)	0	1 (11)
Gastrointestinal disorders			
Diarrhea	10 (56)	6 (67)	4 (44)
Vomiting	10 (56)	4 (44)	6 (67)

Table A1-47: Study 1602 Amendment 002, All AEs

Treated Patients, n =	All 18	20 mg/kg 9	40 mg/kg 9
SOC			
AE Preferred Term	**n (%)**	**n (%)**	**n (%)**
Gastroesophageal reflux disease	5 (28)	2 (22)	3 (33)
Constipation	4 (22)	1 (11)	3 (33)
Dysphagia	4 (22)	3 (33)	1 (11)
Teething	3 (17)	2 (22)	1 (11)
Abdominal distension	2 (11)	2 (22)	0
Retching	2 (11)	1 (11)	1 (11)
Upper gastrointestinal hemorrhage	2 (11)	2 (22)	0
Abdominal pain	1 (6)	1 (11)	0
Abnormal feces	1 (6)	0	1 (11)
Anorectal disorder	1 (6)	0	1 (11)
Esophageal erosion	1 (6)	1 (11)	0
Feces discolored	1 (6)	0	1 (11)
Flatulence	1 (6)	0	1 (11)
Gastric hypomotility	1 (6)	1 (11)	0
Gastritis erosive	1 (6)	1 (11)	0
Gastrointestinal motility disorder	1 (6)	1 (11)	0
Gingivitis	1 (6)	0	1 (11)
Inguinal hernia	1 (6)	1 (11)	0
Intestinal obstruction	1 (6)	1 (11)	0
Mouth ulceration	1 (6)	1 (11)	0
Nausea	1 (6)	0	1 (11)
Pyloric stenosis	1 (6)	1 (11)	0
General disorders and administration site conditions			
Pyrexia	18 (100)	9 (50)	9 (50)
Edema peripheral	3 (17)	1 (11)	2 (22)
Asthenia	2 (11)	0	2 (22)
Catheter related complication	2 (11)	1 (11)	1 (11)
Inflammation localized	2 (11)	1 (11)	1 (11)
Rigors	2 (11)	0	2 (22)
Catheter site rash	1 (6)	0	1 (11)
Catheter site related reaction	1 (6)	0	1 (11)
Developmental delay	1 (6)	0	1 (11)
Edema	1 (6)	0	1 (11)
Fatigue	1 (6)	0	1 (11)
Granuloma	1 (6)	1 (11)	0
Hyperthermia	1 (6)	0	1 (11)
Infusion site reaction	1 (6)	0	1 (11)
Pain	1 (6)	0	1 (11)
Scoliosis	1 (6)	0	1 (11)
Immune system disorders			
Drug hypersensitivity	1 (6)	0	1 (11)
Immunization reaction	1 (6)	1 (11)	0
Seasonal allergy	1 (6)	0	1 (11)
Infections and infestations			
Otitis media	12 (67)	5 (56)	7 (78)
Gastroenteritis	11 (61)	4 (44)	7 (78)

Table A1-47: Study 1602 Amendment 002, All AEs

Treated Patients, n =	All 18	20 mg/kg 9	40 mg/kg 9
SOC			
AE Preferred Term	**n (%)**	**n (%)**	**n (%)**
Pharyngitis	9 (50)	4 (44)	5 (56)
Pneumonia	9 (50)	5 (56)	4 (44)
Upper respiratory tract infection	9 (50)	6 (67)	3 (33)
Catheter related infection	8 (44)	3 (33)	5 (56)
Ear infection	7 (39)	2 (22)	5 (56)
Nasopharyngitis	6 (33)	2 (22)	4 (44)
Viral infection	6 (33)	3 (33)	3 (33)
Bronchiolitis	5 (28)	3 (33)	2 (22)
Oral candidiasis	5 (28)	3 (33)	2 (22)
Respiratory syncytial virus infection	5 (28)	2 (22)	3 (33)
Respiratory tract infection	4 (22)	2 (22)	2 (22)
Tonsillitis	3 (17)	2 (22)	1 (11)
Urinary tract infection	3 (17)	1 (11)	2 (22)
Bacteremia	2 (11)	1 (11)	1 (11)
Dental caries	2 (11)	1 (11)	1 (11)
Eye infection	2 (11)	1 (11)	1 (11)
Influenza	2 (11)	0	2 (22)
Skin infection	2 (11)	1 (11)	1 (11)
Skin infection fungal	2 (11)	0	2 (22)
Tracheitis	2 (11)	1 (11)	1 (11)
Bacteriuria	1 (6)	1 (11)	0
Bronchitis	1 (6)	0	1 (11)
Cellulitis	1 (6)	0	1 (11)
Clostridium colitis	1 (6)	0	1 (11)
Gastritis viral	1 (6)	0	1 (11)
Genital infection fungal	1 (6)	0	1 (11)
Impetigo	1 (6)	0	1 (11)
Localized infection	1 (6)	1 (11)	0
Lower respiratory tract infection	1 (6)	0	1 (11)
Postoperative infection	1 (6)	1 (11)	0
Sepsis	1 (6)	1 (11)	0
Septic shock	1 (6)	0	1 (11)
Sinusitis	1 (6)	0	1 (11)
Urinary tract infection fungal	1 (6)	0	1 (11)
Wound infection	1 (6)	1 (11)	0
Injury, poisoning and procedural complications			
Post procedural pain	4 (22)	1 (11)	3 (33)
Excoriation	3 (17)	2 (22)	1 (11)
Medical device complication	3 (17)	2 (22)	1 (11)
Fracture femur	2 (11)	1 (11)	1 (11)
Arthropod bite	1 (6)	0	1 (11)
Fall	1 (6)	1 (11)	0
Fracture humerus	1 (6)	0	1 (11)
Fracture tibia	1 (6)	0	1 (11)
Hypothermia	1 (6)	0	1 (11)
Iliotibial band syndrome	1 (6)	0	1 (11)

Table A1-47: Study 1602 Amendment 002, All AEs

Treated Patients, n =	All 18	20 mg/kg 9	40 mg/kg 9
SOC			
AE Preferred Term	**n (%)**	**n (%)**	**n (%)**
Injury asphyxiation	1 (6)	1 (11)	0
Postoperative wound complication	1 (6)	0	1 (11)
Thermal burn	1 (6)	0	1 (11)
Investigations			
Oxygen saturation decreased	9 (50)	4 (44)	5 (56)
Acoustic stimulation tests abnormal	2 (11)	1 (11)	1 (11)
Blood potassium decreased	2 (11)	2 (22)	0
Blood pressure decreased	2 (11)	0	2 (22)
Ejection fraction decreased	2 (11)	1 (11)	1 (11)
Heart rate decreased	2 (11)	0	2 (22)
Sputum culture positive	2 (11)	0	2 (22)
Urine output decreased	2 (11)	1 (11)	1 (11)
Alanine aminotransferase increased	1 (6)	0	1 (11)
Aspartate aminotransferase increased	1 (6)	0	1 (11)
Blood bicarbonate decreased	1 (6)	0	1 (11)
Blood calcium increased	1 (6)	1 (11)	0
Blood chloride decreased	1 (6)	1 (11)	0
Blood creatine phosphokinase MB increased	1 (6)	1 (11)	0
Blood creatine phosphokinase increased	1 (6)	0	1 (11)
Blood pressure increased	1 (6)	1 (11)	0
Body temperature increased	1 (6)	0	1 (11)
Fungus urine test positive	1 (6)	0	1 (11)
Hematocrit decreased	1 (6)	0	1 (11)
Hemoglobin decreased	1 (6)	1 (11)	0
PCO2 increased	1 (6)	0	1 (11)
Renal scan abnormal	1 (6)	1 (11)	0
Specific gravity urine increased	1 (6)	0	1 (11)
White blood cell count increased	1 (6)	1 (11)	0
Metabolism and nutrition disorders			
Feeding disorder	4 (22)	3 (33)	1 (11)
Electrolyte imbalance	2 (11)	1 (11)	1 (11)
Hypercalcemia	2 (11)	2 (22)	0
Hyperuricemia	2 (11)	2 (22)	0
Hypochloremia	2 (11)	2 (22)	0
Anorexia	1 (6)	0	1 (11)
Hyperkalemia	1 (6)	0	1 (11)
Hyperphosphatemia	1 (6)	1 (11)	0
Hypocalcemia	1 (6)	1 (11)	0
Hypoglycemia	1 (6)	1 (11)	0
Hypomagnesemia	1 (6)	1 (11)	0
Hyponatremia	1 (6)	1 (11)	0
Metabolic acidosis	1 (6)	1 (11)	0
Musculoskeletal and connective tissue disorders			
Joint contracture	4 (22)	0	4 (44)
Myopathy	2 (11)	0	2 (22)
Osteopenia	2 (11)	1 (11)	1 (11)

Table A1-47: Study 1602 Amendment 002, All AEs

Treated Patients, n =	All 18	20 mg/kg 9	40 mg/kg 9
SOC **AE Preferred Term**	**n (%)**	**n (%)**	**n (%)**
Osteoporosis	2 (11)	1 (11)	1 (11)
Arthralgia	1 (6)	1 (11)	0
Joint swelling	1 (6)	1 (11)	0
Pain in extremity	1 (6)	0	1 (11)
Nervous system disorders			
Hypokinesia	2 (11)	0	2 (22)
Hypotonia	2 (11)	1 (11)	1 (11)
Tremor	1 (6)	0	1 (11)
Vocal cord paresis	1 (6)	1 (11)	0
Psychiatric disorders			
Insomnia	4 (22)	1 (11)	3 (33)
Agitation	3 (17)	0	3 (33)
Irritability	2 (11)	0	2 (22)
Restlessness	2 (11)	1 (11)	1 (11)
Anxiety	1 (6)	0	1 (11)
Renal and urinary disorders			
Hematuria	3 (17)	3 (33)	0
Hypercalciuria	3 (17)	3 (33)	0
Pyuria	3 (17)	2 (22)	1 (11)
Hydronephrosis	1 (6)	1 (11)	0
Kidney enlargement	1 (6)	1 (11)	0
Leukocyturia	1 (6)	1 (11)	0
Nephrolithiasis	1 (6)	1 (11)	0
Oliguria	1 (6)	0	1 (11)
Respiratory, thoracic and mediastinal disorders			
Cough	9 (50)	3 (33)	6 (67)
Respiratory failure	7 (39)	3 (33)	4 (44)
Rhinorrhea	6 (33)	2 (22)	4 (44)
Tachypnea	6 (33)	1 (11)	5 (56)
Respiratory distress	5 (28)	2 (22)	3 (33)
Upper respiratory tract congestion	5 (28)	2 (22)	3 (33)
Increased bronchial secretion	4 (22)	2 (22)	2 (22)
Pneumonia aspiration	4 (22)	3 (33)	1 (11)
Atelectasis	3 (17)	2 (22)	1 (11)
Bronchospasm	3 (17)	1 (11)	2 (22)
Dyspnea	3 (17)	1 (11)	2 (22)
Asthma	2 (11)	1 (11)	1 (11)
Choking	2 (11)	2 (22)	0
Epistaxis	2 (11)	1 (11)	1 (11)
Respiratory tract congestion	2 (11)	0	2 (22)
Rhinitis	2 (11)	0	2 (22)
Rhonchi	2 (11)	2 (22)	0
Aspiration	1 (6)	0	1 (11)
Bradypnea	1 (6)	0	1 (11)
Bronchomalacia	1 (6)	1 (11)	0
Croup	1 (6)	1 (11)	0

Table A1-47: Study 1602 Amendment 002, All AEs

Treated Patients, n =	All 18	20 mg/kg 9	40 mg/kg 9
SOC **AE Preferred Term**	**n (%)**	**n (%)**	**n (%)**
Epiglottic edema	1 (6)	0	1 (11)
Hypercapnia	1 (6)	0	1 (11)
Increased throat secretions	1 (6)	0	1 (11)
Laryngeal stenosis	1 (6)	1 (11)	0
Lung disorder	1 (6)	0	1 (11)
Lung infiltration	1 (6)	1 (11)	0
Nasal congestion	1 (6)	0	1 (11)
Nasal mucosal disorder	1 (6)	0	1 (11)
Pneumothorax	1 (6)	1 (11)	0
Pulmonary edema	1 (6)	0	1 (11)
Rales	1 (6)	0	1 (11)
Respiratory acidosis	1 (6)	1 (11)	0
Respiratory alkalosis	1 (6)	0	1 (11)
Sputum retention	1 (6)	1 (11)	0
Tracheal disorder	1 (6)	0	1 (11)
Skin and subcutaneous tissue disorders			
Rash	13 (72)	6 (67)	7
Dermatitis diaper	6 (33)	3 (33)	3 (33)
Urticaria	6 (33)	4 (44)	2 (22)
Eczema	5 (28)	3 (33)	2 (22)
Blister	3 (17)	0	3 (33)
Hyperhidrosis	3 (17)	1 (11)	2 (22)
Pruritus	3 (17)	1 (11)	2 (22)
Dermatitis contact	2 (11)	1 (11)	1 (11)
Dry skin	2 (11)	2 (22)	0
Skin ulcer	2 (11)	2 (22)	0
Edema facial	1 (6)	1 (11)	0
Erythema	1 (6)	0	1 (11)
Exanthema	1 (6)	0	1 (11)
Livedo reticularis	1 (6)	0	1 (11)
Palmar erythemia	1 (6)	0	1 (11)
Skin irritation	1 (6)	1 (11)	0
Post procedural drainage	1 (6)	1 (11)	0
Vascular disorders			
Flushing	4 (22)	0	4 (44)
Hypertension	3 (17)	0	3 (33)
Hypotension	2 (11)	1 (11)	1 (11)
Pallor	1 (6)	0	1 (11)
Superior vena caval occlusion	1 (6)	0	1 (11)
Syncope	1 (6)	1 (11)	0

10.1.1.17.8 Study 1602: All Serious Adverse Events (incidence and numeric)

Table A1-48: Study 1602 Amendment 002, All SAEs

	SAE Incidence Rates			Numbers of SAEs reported by Term		
	All	20 mg/kg	40 mg/kg	All	20 mg/kg	40 mg/kg
Treated Patients, n =	18	9	9			
SOC						
AE Preferred Term	n (%)	n (%)	n (%)			
Blood and lymphatic system disorders						
Lymphadenopathy	1 (6)	0	1 (11)	1	0	1
Cardiac disorders						
Bradycardia	2 (11)	1 (11)	1 (11)	2	1	1
Arrhythmia	1 (6)	1 (11)	0	1	1	0
Arrhythmia nodal	1 (6)	1 (11)	0	1	1	0
Arrhythmia supraventricular	1 (6)	0	1 (11)	1	0	1
Atrial tachycardia	1 (6)	1 (11)	0	1	1	0
Cardio-respiratory arrest	1 (6)	1 (11)	0	1	1	0
Hypertrophic obstructive cardiomyopathy	1 (6)	0	1 (11)	1	0	1
Tachycardia supraventricular	1 (6)	1 (11)	0	4	4	0
Ventricular extrasystoles	1 (6)	0	1 (11)	1	0	1
Ventricular hypertrophy	1 (6)	0	1 (11)	1	0	1
Congenital, familial and genetic disorders						
Leukodystrophy	1 (6)	0	1 (11)	1	0	1
Ear and labyrinth disorders						
Middle ear effusion	1 (6)	0	1 (11)	1	0	1
Gastrointestinal disorders						
Upper gastrointestinal hemorrhage	2 (11)	2 (22)	0	5	5	0
Diarrhea	1 (6)	0	1 (11)	1	0	1
Dysphagia	1 (6)	1 (11)	0	2	2	0
Esophageal erosion	1 (6)	1 (11)	0	1	1	0
Gastritis erosive	1 (6)	1 (11)	0	1	1	0
Gastroesophageal reflux disease	1 (6)	0	1 (11)	1	0	1
Vomiting	1 (6)	0	1 (11)	1	0	1
General disorders and administration site conditions						
Pyrexia	2 (11)	1 (11)	1 (11)	2	1	1
Catheter related complication	1 (6)	0	1 (11)	2	0	2
Infections and infestations						
Pneumonia	8 (44)	4 (44)	4 (44)	21	16	5
Catheter related infection	5 (28)	1 (11)	4 (44)	7	2	5
Respiratory syncytial virus infection	5 (28)	2 (22)	3 (33)	5	2	3
Bronchiolitis	4 (22)	2 (22)	2 (22)	5	2	3
Gastroenteritis	4 (22)	1 (11)	3 (33)	4	1	3
Viral infection	4 (22)	3 (33)	1 (11)	4	3	1
Nasopharyngitis	2 (11)	0	2 (22)	4	0	4
Otitis	2 (11)	0	2 (22)	2	0	2
Otitis media	2 (11)	1 (11)	1 (11)	3	1	2
Respiratory tract infection	2 (11)	1 (11)	1 (11)	2	1	1
Bacteremia	1 (6)	0	1 (11)	1	0	1
Bronchitis	1 (6)	0	1 (11)	2	0	2

Table A1-48: Study 1602 Amendment 002, All SAEs

	SAE Incidence Rates			Numbers of SAEs reported by Term		
	All	20 mg/kg	40 mg/kg	All	20 mg/kg	40 mg/kg
Treated Patients, n =	**18**	**9**	**9**			
SOC						
AE Preferred Term	**n (%)**	**n (%)**	**n (%)**			
Dental caries	1 (6)	1 (11)	0	1	1	0
Gastritis viral	1 (6)	0	1 (11)	1	0	1
Influenza	1 (6)	0	1 (11)	1	0	1
Localized infection	1 (6)	1 (11)	0	1	1	0
Septic shock	1 (6)	0	1 (11)	1	0	1
Tonsillitis	1 (6)	1 (11)	0	1	1	0
Tracheitis	1 (6)	0	1 (11)	1	0	1
Upper respiratory tract infection	1 (6)	1 (11)	0	1	1	0
Urinary tract infection	1 (6)	0	1 (11)	1	0	1
Injury, poisoning and procedural complications						
Fracture femur	2 (11)	1 (11)	1 (11)	2	1	1
Fracture humerus	1 (6)	0	1 (11)	2	0	2
Fracture tibia	1 (6)	0	1 (11)	1	0	1
Injury asphyxiation	1 (6)	1 (11)	0	1	1	0
Investigations						
Ejection fraction decreased	2 (11)	1 (11)	1 (11)	2	1	1
Oxygen saturation decreased	2 (11)	1 (11)	1 (11)	2	1	1
Heart rate decreased	1 (6)	0	1 (11)	1	0	1
Metabolism and nutrition disorders						
Electrolyte imbalance	1 (6)	1 (11)	0	1	1	0
Musculoskeletal and connective tissue disorders						
Myopathy	1 (6)	0	1 (11)	3	0	3
Nervous system disorders						
Hypokinesia	1 (6)	0	1 (11)	1	0	1
Vocal cord paresis	1 (6)	1 (11)	0	1	1	0
Respiratory, thoracic and mediastinal disorders						
Respiratory failure	7 (39)	3 (33)	4 (44)	15	8	7
Pneumonia aspiration	4 (22)	3 (33)	1 (11)	12	11	1
Respiratory distress	4 (22)	2 (22)	2 (22)	5	2	3
Asthma	2 (11)	1 (11)	1 (11)	2	1	1
Atelectasis	2 (11)	1 (11)	1 (11)	2	1	1
Bronchospasm	1 (6)	0	1 (11)	3	0	3
Cough	1 (6)	0	1 (11)	1	0	1
Dyspnea	1 (6)	1 (11)	0	1	1	0
Pneumothorax	1 (6)	1 (11)	0	1	1	0
Pulmonary edema	1 (6)	0	1 (11)	1	0	1
Rales	1 (6)	0	1 (11)	1	0	1
Respiratory acidosis	1 (6)	1 (11)	0	1	1	0
Sputum retention	1 (6)	1 (11)	0	2	2	0
Skin and subcutaneous tissue disorders						
Rash	1 (6)	0	1 (11)	1	0	1
Urticaria	1 (6)	0	1 (11)	2	0	2
Vascular disorders						
Hypotension	1 (6)	1 (11)	0	1	1	0
Superior vena caval occlusion	1 (6)	0	1 (11)	1	0	1

Table A1-48: Study 1602 Amendment 002, All SAEs

	SAE Incidence Rates			Numbers of SAEs reported by Term		
	All	20 mg/kg	40 mg/kg	All	20 mg/kg	40 mg/kg
Treated Patients, n =	**18**	**9**	**9**			
SOC						
AE Preferred Term	**n (%)**	**n (%)**	**n (%)**			
Syncope	1 (6)	1 (11)	0	1	1	0
Total				**172**	**87**	**85**

10.1.1.17.9 Pooled Results for 1602 and 1702 Studies: All AEs

Table A1-49: Study 1602 and Study 1702, Amendment 002 + Amendment 008 Pooled All AEs

	Patients Reporting
Patients, n =	**39**
SOC	
AE Preferred Term	**n (%)**
Blood and lymphatic system disorders	**17 (44)**
Anemia	12 (31)
Eosinophilia	3 (8)
Lymphadenitis	2 (5)
Lymphadenopathy	2 (5)
Leukocytosis	1 (3)
Neutropenia	1 (3)
Thrombocythemia	1 (3)
Cardiac disorders	**24 (62)**
Tachycardia	9 (23)
Bradycardia	8 (21)
Cardiac failure	4 (10)
Cardio-respiratory arrest	4 (10)
Cyanosis	4 (10)
Arrhythmia	2 (5)
Cardiomyopathy	2 (5)
Arrhythmia nodal	1 (3)
Arrhythmia supraventricular	1 (3)
Atrial tachycardia	1 (3)
Cardiac arrest	1 (3)
Cardiomegaly	1 (3)
Diastolic dysfunction	1 (3)
Extrasystoles	1 (3)
Hypertrophic obstructive cardiomyopathy	1 (3)
Myocardial ischemia	1 (3)
Pericardial effusion	1 (3)
Supraventricular extrasystoles	1 (3)
Tachycardia supraventricular	1 (3)
Ventricular extrasystoles	1 (3)
Ventricular fibrillation	1 (3)
Ventricular hypertrophy	1 (3)
Congenital, familial and genetic disorders	**4 (10)**
Macroglossia	2 (5)
Laryngomalacia	1 (3)
Leukodystrophy	1 (3)

Table A1-49: Study 1602 and Study 1702, Amendment 002 + Amendment 008 Pooled All AEs

Patients, n =	Patients Reporting 39
SOC	
AE Preferred Term	**n (%)**
Plagiocephaly	1 (3)
Ear and labyrinth disorders	**9 (23)**
Hypoacusis	6 (15)
Ear pain	2 (5)
Middle ear effusion	2 (5)
Mastoid disorder	1 (3)
Endocrine disorders	**3 (8)**
Hypoparathyroidism	2 (5)
Adrenal insufficiency	1 (3)
Eye disorders	**11 (28)**
Conjunctivitis	6 (15)
Eye discharge	3 (8)
Blepharitis	1 (3)
Erythema of eyelid	1 (3)
Eye redness	1 (3)
Xerophthalmia	1 (3)
Gastrointestinal disorders	**32 (82)**
Diarrhea	24 (62)
Vomiting	19 (49)
Gastroesophageal reflux disease	10 (26)
Constipation	9 (23)
Dysphagia	6 (15)
Teething	5 (13)
Abdominal distension	4 (10)
Abdominal pain	2 (5)
Mouth ulceration	2 (5)
Retching	2 (5)
Upper gastrointestinal hemorrhage	2 (5)
Abnormal feces	1 (3)
Anorectal disorder	1 (3)
Esophageal erosion	1 (3)
Feces discolored	1 (3)
Flatulence	1 (3)
Gastric hypomotility	1 (3)
Gastritis erosive	1 (3)
Gastrointestinal motility disorder	1 (3)
Gingivitis	1 (3)
Hematemesis	1 (3)
Inguinal hernia	1 (3)
Intestinal obstruction	1 (3)
Nausea	1 (3)
Oral mucosal blistering	1 (3)
Pyloric stenosis	1 (3)
Tongue discoloration	1 (3)
Toothache	1 (3)
General disorders and administration site conditions	**38 (97)**
Pyrexia	36 (92)

Table A1-49: Study 1602 and Study 1702, Amendment 002 + Amendment 008 Pooled All AEs

Patients, n =	Patients Reporting 39
SOC	
AE Preferred Term	**n (%)**
Catheter related complication	7 (18)
Edema peripheral	5 (13)
Pain	4 (10)
Asthenia	3 (8)
Edema	3 (8)
Granuloma	3 (8)
Hyperthermia	3 (8)
Inflammation localized	3 (8)
Edema localized	2 (5)
Fatigue	2 (5)
Lethargy	2 (5)
Rigors	2 (5)
Catheter site ecchymosis	1 (3)
Catheter site erythema	1 (3)
Catheter site phlebitis	1 (3)
Catheter site rash	1 (3)
Catheter site related reaction	1 (3)
Developmental delay	1 (3)
Discomfort	1 (3)
Infusion site reaction	1 (3)
Infusion site swelling	1 (3)
Scoliosis	1 (3)
Hepatobiliary disorders	**1 (3)**
Hepatomegaly	1 (3)
Immune system disorders	**3 (8)**
Drug hypersensitivity	1 (3)
Immunization reaction	1 (3)
Seasonal allergy	1 (3)
Infections and infestations	**37 (95)**
Pneumonia	18 (46)
Otitis media	17 (44)
Upper respiratory tract infection	17 (44)
Gastroenteritis	16 (41)
Pharyngitis	14 (36)
Otitis	13 (33)
Oral candidiasis	12 (31)
Catheter related infection	11 (28)
Bronchiolitis	9 (23)
Nasopharyngitis	9 (23)
Viral infection	7 (18)
Bacteremia	6 (15)
Influenza	6 (15)
Respiratory syncytial virus infection	6 (15)
Respiratory tract infection	5 (13)
Tonsillitis	5 (13)
Tracheitis	5 (13)
Bronchitis	4 (10)

Table A1-49: Study 1602 and Study 1702, Amendment 002 + Amendment 008 Pooled All AEs

Patients, n =	Patients Reporting 39
SOC	
AE Preferred Term	**n (%)**
Urinary tract infection	4 (10)
Skin infection	3 (8)
Skin infection fungal	3 (8)
Cellulitis	2 (5)
Clostridium colitis	2 (5)
Dental caries	2 (5)
Eye infection	2 (5)
Lower respiratory tract infection	2 (5)
Sepsis	2 (5)
Bacteriuria	1 (3)
Gastritis viral	1 (3)
Genital infection fungal	1 (3)
Impetigo	1 (3)
Infection	1 (3)
Localized infection	1 (3)
Pneumonia aspiration	1 (3)
Postoperative infection	1 (3)
Septic shock	1 (3)
Sinusitis	1 (3)
Urinary tract infection fungal	1 (3)
Wound infection	1 (3)
Injury, poisoning and procedural complications	**20 (51)**
Post procedural pain	10 (26)
Medical device complication	6 (15)
Fracture femur	4 (10)
Contusion	3 (8)
Excoriation	3 (8)
Arthropod bite	1 (3)
Arthropod sting	1 (3)
Fall	1 (3)
Fracture humerus	1 (3)
Fracture tibia	1 (3)
Fracture tibia/fibula	1 (3)
Hypothermia	1 (3)
Iliotibial band syndrome	1 (3)
Injury asphyxiation	1 (3)
Joint dislocation	1 (3)
Post procedural hemorrhage	1 (3)
Postoperative wound complication	1 (3)
Thermal burn	1 (3)
Tracheostomy malfunction	1 (3)
Investigations	**28 (72)**
Oxygen saturation decreased	16 (41)
Sputum culture positive	7 (18)
Blood pressure increased	5 (13)
Blood bicarbonate decreased	4 (10)
Blood potassium decreased	4 (10)

Table A1-49: Study 1602 and Study 1702, Amendment 002 + Amendment 008 Pooled All AEs

Patients, n =	Patients Reporting 39
SOC	
AE Preferred Term	**n (%)**
Urine output decreased	4 (10)
Blood chloride decreased	3 (8)
Blood phosphorus increased	3 (8)
Blood pressure decreased	3 (8)
Ejection fraction decreased	3 (8)
Heart rate increased	3 (8)
White blood cell count increased	3 (8)
Acoustic stimulation tests abnormal	2 (5)
Alanine aminotransferase increased	2 (5)
Aspartate aminotransferase increased	2 (5)
Blood creatine phosphokinase increased	2 (5)
Blood urea increased	2 (5)
Culture throat positive	2 (5)
Gallop rhythm present	2 (5)
Heart rate decreased	2 (5)
Hemoglobin decreased	2 (5)
Weight decreased	2 (5)
Blood alkaline phosphatase decreased	1 (3)
Blood calcium increased	1 (3)
Blood creatine phosphokinase MB increased	1 (3)
Blood lactic acid increased	1 (3)
Blood uric acid increased	1 (3)
Body temperature increased	1 (3)
Eosinophil count increased	1 (3)
Fungal test positive	1 (3)
Fungus urine test positive	1 (3)
Hematocrit decreased	1 (3)
Lymph node enlarged	1 (3)
Lymphocyte count decreased	1 (3)
Monocyte count decreased	1 (3)
Neutrophil count increased	1 (3)
PCO2 increased	1 (3)
Platelet count decreased	1 (3)
Renal scan abnormal	1 (3)
Respiratory rate increased	1 (3)
Specific gravity urine increased	1 (3)
Weight increased	1 (3)
White blood cell count decreased	1 (3)
Metabolism and nutrition disorders	**17 (44)**
Feeding disorder	6 (15)
Dehydration	3 (8)
Electrolyte imbalance	2 (5)
Hypercalcemia	2 (5)
Hyperuricemia	2 (5)
Hypocalcemia	2 (5)
Hypochloremia	2 (5)
Hypoglycemia	2 (5)

Table A1-49: Study 1602 and Study 1702, Amendment 002 + Amendment 008 Pooled All AEs

Patients, n =	Patients Reporting 39
SOC **AE Preferred Term**	**n (%)**
Hypokalemia	2 (5)
Anorexia	1 (3)
Fluid imbalance	1 (3)
Fluid retention	1 (3)
Hyperkalemia	1 (3)
Hypernatremia	1 (3)
Hyperphosphatemia	1 (3)
Hypomagnesemia	1 (3)
Hyponatremia	1 (3)
Metabolic acidosis	1 (3)
Weight gain poor	1 (3)
Musculoskeletal and connective tissue disorders	**20 (51)**
Joint contracture	7 (18)
Osteopenia	6 (15)
Myopathy	3 (8)
Arthralgia	2 (5)
Osteoporosis	2 (5)
Joint swelling	1 (3)
Muscle hemorrhage	1 (3)
Pain in extremity	1 (3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (3)**
Fibroma	1 (3)
Nervous system disorders	**6 (15)**
Hypokinesia	2 (5)
Hypotonia	2 (5)
Tremor	2 (5)
Somnolence	1 (3)
Vocal cord paresis	1 (3)
Psychiatric disorders	**10 (26)**
Insomnia	5 (13)
Agitation	4 (10)
Anxiety	2 (5)
Irritability	2 (5)
Restlessness	2 (5)
Renal and urinary disorders	**12 (31)**
Hematuria	4 (10)
Hypercalciuria	4 (10)
Proteinuria	3 (8)
Pyuria	3 (8)
Oliguria	2 (5)
Hydronephrosis	1 (3)
Kidney enlargement	1 (3)
Leukocyturia	1 (3)
Micturition disorder	1 (3)
Nephritis	1 (3)
Nephrolithiasis	1 (3)

Table A1-49: Study 1602 and Study 1702, Amendment 002 + Amendment 008 Pooled All AEs

Patients, n =	Patients Reporting 39
SOC **AE Preferred Term**	**n (%)**
Renal insufficiency	1 (3)
Reproductive system and breast disorders	**2 (5)**
Edema genital	1 (3)
Scrotal swelling	1 (3)
Respiratory, thoracic and mediastinal disorders	**38 (97)**
Cough	18 (46)
Respiratory distress	13 (33)
Respiratory failure	12 (31)
Rhinorrhea	11 (28)
Tachypnea	9 (23)
Bronchospasm	8 (21)
Increased bronchial secretion	7 (18)
Upper respiratory tract congestion	7 (18)
Atelectasis	6 (15)
Nasal congestion	6 (15)
Choking	5 (13)
Dyspnea	5 (13)
Pneumonia aspiration	4 (10)
Asthma	3 (8)
Hypoventilation	3 (8)
Respiratory tract congestion	3 (8)
Aspiration	2 (5)
Epistaxis	2 (5)
Hypoxia	2 (5)
Increased throat secretions	2 (5)
Lung crepitation	2 (5)
Lung disorder	2 (5)
Pulmonary congestion	2 (5)
Pulmonary edema	2 (5)
Respiratory arrest	2 (5)
Rhinitis	2 (5)
Rhonchi	2 (5)
Bradypnea	1 (3)
Bronchomalacia	1 (3)
Croup	1 (3)
Epiglottic edema	1 (3)
Hypercapnia	1 (3)
Increased viscosity of bronchial secretion	1 (3)
Laryngeal stenosis	1 (3)
Lung infiltration	1 (3)
Nasal mucosal disorder	1 (3)
Pain tracheal	1 (3)
Pneumothorax	1 (3)
Rales	1 (3)
Respiratory acidosis	1 (3)
Respiratory alkalosis	1 (3)
Rhinitis allergic	1 (3)

Table A1-49: Study 1602 and Study 1702, Amendment 002 + Amendment 008 Pooled All AEs

Patients, n =	Patients Reporting 39
SOC	
AE Preferred Term	**n (%)**
Sinus congestion	1 (3)
Sputum retention	1 (3)
Tracheal disorder	1 (3)
Skin and subcutaneous tissue disorders	**33 (85)**
Rash	24 (62)
Dermatitis diaper	14 (36)
Urticaria	8 (21)
Eczema	6 (15)
Hyperhidrosis	5 (13)
Pruritus	5 (13)
Dry skin	4 (10)
Blister	3 (8)
Excoriation	3 (8)
Decubitus ulcer	2 (5)
Dermatitis allergic	2 (5)
Dermatitis contact	2 (5)
Edema periorbital	2 (5)
Skin ulcer	2 (5)
Edema facial	1 (3)
Erythema	1 (3)
Exanthema	1 (3)
Livedo reticularis	1 (3)
Palmar erythemia	1 (3)
Skin irritation	1 (3)
Surgical and medical procedures	**1 (3)**
Post procedural drainage	1 (3)
Vascular disorders	**14 (36)**
Flushing	8 (21)
Hypertension	6 (15)
Hypotension	4 (10)
Pallor	2 (5)
Labile blood pressure	1 (3)
Superior vena caval occlusion	1 (3)
Syncope	1 (3)

10.1.2 Study AGLU01702 (Study 1702)

10.1.2.1 Study Design

Study AGLU01702 (Study 1702) is an ongoing, multicenter (n=6), multinational, open-label, historically-controlled, non-randomized, safety, efficacy, pharmacodynamic (PD) and pharmacokinetic (PK) study of alglucosidase (rhGAA) in the treatment of 21 patients with infantile-onset Pompe disease. Eligible patients were to receive IV infusions of rhGAA 20 mg/kg every other week (qow) for 52 weeks followed by a 52-week maintenance phase at the same dose. Patients were eligible for the study if they were more than six months and less than or equal to 36 months of age at the time of first infusion, and had a diagnosis of Pompe disease defined as a deficiency in GAA activity, onset of clinical signs consistent with Pompe disease by 12 months of age, and cardiac hypertrophy. The primary efficacy endpoint of the study was the proportion of patients alive over the course of treatment. Secondary efficacy endpoints included the effect of treatment on respiratory function, cardiac status, motor development, cognitive development, and physical growth. This study had no concurrent control, and no placebo treatment was administered.

Interim efficacy and safety data through Week 52 only were submitted to the BLA. Although the initial 52 weeks of the study have been completed, the 52-week maintenance phase is ongoing as of the time of this review and final results for the entire 104 weeks of the study are not yet available. The last patient received her first dose of rhGAA on 28-May-2004; thus, the study is expected to be completed on or about 28-May-2006.

10.1.2.2 Study Objectives

The overall objectives of the study were to evaluate the safety, efficacy (overall survival), PK and PD of rhGAA 20 mg/kg in patients with infantile-onset Pompe disease ages greater than six months to less than or equal to 36 months at time of first infusion, after 104 weeks of treatment. For the purposes of this interim report, evaluations after 52 weeks of treatment only were assessed.

10.1.2.3 Eligibility Criteria

To be eligible for the study, patients must have been more than six months and less than or equal to 36 months of age at the time of first dose of rhGAA, and have had a diagnosis of infantile-onset Pompe disease defined as onset of clinical symptoms of Pompe disease by 12 months of age, deficient GAA activity ($\leq$2% of normal range by cultured skin fibroblast assay), and cardiac hypertrophy (LVMI $\geq$65 g/m^2 in patients $\leq$12 months of age or >79 g/m^2 in patients >12 months of age). Patients were excluded if they had:

1. Signs and symptoms of cardiac failure AND an ejection fraction (EF) <40%;
2. The presence of a major congenital abnormality;

3. The presence of clinically significant organic disease that, in the opinion of the Investigator, precluded participation in the study or potentially decreased survival; or
4. Had received ERT with GAA from any source.

10.1.2.4 Concomitant Medications and Procedures

No concomitant medications were prohibited from use during the study, other than the exclusion criterion for prior use of ERT with GAA, and the use of all medications was at the discretion of the treating physician. There were no routine prophylactic concomitant medications recommended or prescribed for use during the study or prior to the administration of rhGAA. Placement of an indwelling catheter (central or peripheral) was recommended for delivery of study medication, but catheter placement was at the discretion of the Investigator.

10.1.2.5 Study Visits and Procedures

The study visits and procedures are summarized below in the following tables. All study assessments had a ±14 day window unless otherwise noted.

Table A2-1: Study 1702, Study Visits and Procedures, Screening through Week 26

			Day	Week												
	Screen	Baseline	0	2	4	6	8	10	12	14	16	18	20	22	24	26
Procedure																
Informed consent	X															
Medical history	X															
Head MRI	X															
GAA activity (skin biopsy)	X															
CRIM status		X														
ACE marker allele status			X													
GAA gene mutation analysis			X													
Chest xray	X															
Placement of indwelling catheter		X														
Muscle biopsy for PK & PD		X							X							
Hearing test		X														X
Physical exam	X	X	X		X		X		X							X
Echocardiogram	X	X			X		X		X							X
ECG		X			X		X		X							X
Safety labs (heme & chem)		X			X		X		X							X
Urinalysis		X			X		X		X		X		X		X	
Anti-rhGAA antibody (IgG)			X		X		X		X		X		X		X	
PK			X						X							
AIMS		X			X		X		X							X
PDMS-2		X			X		X		X							X
Motor development milestones assessment		X			X		X		X							X
PEDI and Pompe PEDI		X			X		X		X							X
Modified BSID-II		X							X							X
Modified Leiter-R scale		X							X							X
Weight		X	X		X		X		X		X		X		X	
VS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
RhGAA infusion			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ventilator use	← Continuous monitoring →															
AE assessment	← Continuous monitoring →															
Conmeds/therapy monitoring	← Continuous monitoring →															

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Table A2-2: Study 1702, Study Visits and Procedures, Week 28 through Week 52

	Week												
	28	30	32	34	36	38	40	42	44	46	48	50	52
Procedure													
Muscle biopsy for PK & PD													X
Hearing test													X
Physical exam						X							X
Echocardiogram						X							X
ECG						X							X
Safety labs (heme & chem.)						X							X
Urinalysis	X		X		X		X		X		X		X
Anti-rhGAA antibody (IgG)						X							X
AIMS						X							X
PDMS-2						X							X
Motor development milestones assessment						X							X
PEDI and Pompe PEDI						X							X
Modified BSID-II						X							X
Modified Leiter-R scale						X							X
Weight	X		X		X		X		X		X		X
VS	X	X	X	X	X	X	X	X	X	X	X	X	X
RhGAA infusion	X	X	X	X	X	X	X	X	X	X	X	X	X
Ventilator use	← Continuous monitoring →												
AE assessment	← Continuous monitoring →												
Conmeds/therapy monitoring	← Continuous monitoring →												

10.1.2.6 Randomization and Controls

Study 1702 was an open-label, uncontrolled study. There was no randomization. As infantile-onset Pompe disease is an uniformly fatal disease for which there are no established treatments, and as preliminary information from rhGAA derived from the milk of transgenic animals (Pharming GAA) and CHO cell-derived rhGAA (Synpac) had suggested that ERT with GAA may be beneficial in Pompe disease patients, a placebo control was considered unethical and all patients received active treatment with rhGAA at a starting dose of 20 mg/kg qow. No blinding techniques were used in the context of patient treatment, with the exception of single-blind techniques used for the central cardiologist reading all echocardiograms and ECGs for the first year only (unblinded readings thereafter). A corresponding proportion of patients from an historical control group (Study AGLU-004-00) was presented as a comparator/control (referred to as Historical Reference Subgroup); however, given the highly heterogeneous presentation and progression of Pompe disease in this patient population as demonstrated by the Historical Reference Subgroup, this comparison was of limited utility.

10.1.2.7 Study Medication Dose, Dispensing, and Compliance

RhGAA was supplied to the study sites as a lyophilized product that was reconstituted in sterile water, then further diluted into a fixed total volume of 0.9% NaCl for injection, by the site Pharmacist prior to infusion (volume dependent on patient weight and dose; see study Pharmacy Manual for details). RhGAA infusions were administered in a step-wise manner, beginning with

a slow initial rate (1 mg/kg/hr), with gradual increases every 30 minutes to a maximum rate of infusion of 7 mg/kg/hr (infusion rates could be increased by 2 mg/kg/hr every 30 minutes as tolerated). Typical total infusion time was about four hours.

Dose augmentation or reduction could occur for specific criteria; however, all dosing was to remain within 10 to 40 mg/kg qow. Dose augmentation to 40 mg/kg qow from 20 mg/kg qow could occur following at least 26 weeks of treatment (protocol Amendment 4) for patients meeting specific criteria. Six patients were known to have qualified for dose augmentation (Patients 404, 406, 410, 413, 416, and 421), including three patients (Patients 413, 416, and 421) who received at least one augmented dose during the first 52 weeks of treatment (Patients 404, 406, and 410 received augmented doses during the maintenance phase of the study). Dose reduction could occur at anytime for severe or intolerable reactions defined as 1) liver or other toxicity attributed to rhGAA; 2) symptoms suggestive of immune complex disease attributable to rhGAA; or 3) unmanageable IARs, defined as IARs not responding to pretreatment, rate reduction or treatment during reaction. There were no dose reductions for safety reported during the first 52 weeks of the study.

As all study drug treatments were administered by study personnel, study medication monitoring and recording were under the control of the investigative staff, and all missed or incomplete infusions were documented.

10.1.2.8 Efficacy and Endpoint Measures

All enrolled patients who received at least one dose of rhGAA during the study comprised the population evaluated for safety, efficacy, PK and PD. Data to a cutoff of the Week 52 study visit were analyzed for the study. The study endpoints are:

10.1.2.8.1 Primary Endpoint

The primary efficacy endpoint is the proportion of patients alive over the course of treatment. Exact 95% CIs were constructed around the proportion of patients alive at Weeks 26 and 52, assuming a binomial distribution. For this analysis, non-completers are considered as failures (patients who died or withdrew from the study). Time to death was measured from 1) date of birth, 2) date of first symptoms, 3) date of confirmed diagnosis, and 4) date of treatment initiation. The survival probablities were estimated using Kaplan-Meier methodology. The corresponding proportion of patients alive in an Historical Reference Subgroup of patients was determined and was presented as comparator (from Study AGLU-00-004).

10.1.2.8.2 Secondary Endpoints

Secondary efficacy endpoints were:

- Respiratory function. For patients who were ventilator-free at study onset, the proportion of patients remaining alive and ventilator-free over the course of treatment was measured. Ventilator-free was defined as ventilator-free for a 14-day period bracketing the target time points (Week 26 and 52), or if the patient was ventilator-dependent due to secondary causes (e.g., aspiration) at the target time point, the patient was followed for up to an

additional 30 days. If the patient became ventilator-free for at least 14 consecutive days during that 30-day period, (s)he was considered to be ventilator-free.

- Cardiac status as measured by change from baseline in LVMI and any presence of signs and/or symptoms of cardiac failure.
- Motor development by AIMS scores (for patients ≤18 months of age or >18 months of age for patients who have not met the ceiling of the AIMS [independent ambulation]) and the PDMS-2 scores (for patients >18 months of age), and the achievement and/or maintenance of clinically relevant motor developmental milestones.

10.1.2.8.3 Other Efficacy Variables

- Other indicators of cardiac status (e.g., EF)
- Cognitive function assessed by the MDI of the BSID-II and/or the Brief IQ score of the Leiter-R
- Physical growth by body length, weight and head circumference
- Functional status from baseline to study visits as measured by PEDI scores
- Functional status from baseline to study visits as measured by Pompe PEDI scores

10.1.2.8.4 Safety Endpoints

Safety was assessed by types and incidence of AEs, discontinuations due to AEs, and drug-related, serious and severe AEs, and changes from baseline in physical exams (including vital signs), clinical laboratory assessments including clinical chemistry, hematology and urinalysis, and anti-rhGAA IgG antibody titers, and ECG assessments. Other safety variables included: circulating immune complex detection (as indicated), inhibitory antibody formation in patients testing positive for IgG, anti-rhGAA IgE antibodies, serum tryptase, and complement activation (as indicated).

10.1.2.8.5 PK and PD Measures

PK (plasma rhGAA levels) was assessed at Day 0 and Week 12. PD was assessed by comparing skeletal muscle GAA activity and glycogen content at baseline, and at Week 12 and Week 52 (48 hours after infusion).

10.1.2.9 Other Statistical Considerations

An historical cohort was used as the control population for this study. A corresponding proportion of patients from an historical control group (Study AGLU-004-00, n=168) was determined and presented as a comparator (referred to as Historical Reference Subgroup, n=86) using screening criteria adapted from the Study 1702 eligibility criteria, so that the Subgroup was as comparable as possible to the patients in Study 1702. AGLU-004-00 patients were excluded from Historical Reference Subgroup if they had a GAA activity >2% of mean of the normal range (patients without GAA levels available for assessment were not excluded), died, or were lost to follow-up at less than or equal to six months of age, had an LVMI less than 65 g/m^2 at age less than or equal to 12 months or had an LVMI less than or equal to 79 g/m^2 at age greater than 12 months, had symptoms of congestive heart failure and an EF less than 40%, had a major congenital abnormality, or had clinically significant disease other than Pompe disease. For

additional comparison, an Historical Reference Subset (n =15) was also selected from the Historical Reference Subgroup, whereby patients who died before the median age at which the Study 1702 population received their first infusion (15 months of age) were excluded. These Historical Control Reference Subgroups were of limited utility in evaluating the outcome measures for Study 1702, however, as patients in the control populations were a highly heterogeneous group in terms of presentation and progression of Pompe disease, it was difficult to discern a treatment effect in the treated group vs. the untreated control.

10.1.2.10 Protocol Amendments

There were five protocol amendments to Protocol AGLU01702. The protocol amendments are briefly described as follows:

Amendment 1, dated 05-November-2002: Inclusion criteria changed to allow patients up to 36 months of age to be included in the study, exclusion criterion added to exclude patients who had received ERT with GAA from any source, study size increased to 16 patients (from eight), and other minor changes.

Amendment 2, dated 10-January-2003: Inclusion criteria changed to specify qualifying LVMI by age (for patients ≤12 months or >12 months), biopsy procedure changed so that may be performed under general, regional or local anesthesia, cardiac outcome parameters changed to LVPWT, EF SF, LVMI and others, physical exam to include weight, length and head circumference, and other minor changes.

Amendment 3, 08-August-2003: Study size increased to 20 patients and discontinued patients (who had not received rhGAA) were to be replaced, and other minor changes.

Amendment 4, dated 09-March-2004: Dose augmentation to 40 mg/kg could occur after 26 weeks of treatment for patients meeting specific criteria, definition of ventilator-free changed to 14 consecutive days (from seven) bracketing target time point, ECG assessments added and sent to a central cardiologist for review, interim analysis changed to take place after the fifteenth patient enrolled completed 26 weeks of treatment, and other minor changes.

Amendment 5, dated 07-September-2004: included minor changes to protocol.

10.1.2.11 Study Conduct

The sponsor noted that the study was conducted under ICH/GCP guidelines.

A financial disclosure was included in the submission and notable findings include the following: [redacted] noted payments from the sponsor (honoraria) totaling $5,000, and to [redacted]

A DSMB comprised of three physicians (later added a fourth) knowledgeable about Pompe disease and who had no direct relationship with the study provided medical and ethical guidance related to the conduct of the study. An independent Allergic Reaction Review Board (ARRB) was also established that served in a consultancy role to review reports of moderate or severe IARs and to provide guidance on IAR management. Each member of the ARRB is a physician not directly involved in the study. A central cardiologist read all echocardiograms and ECGs, and the readings were single-blinded in the first year of treatment (no longer blinded thereafter). A central physical therapist scored all motor and cognitive assessments conducted on study patients. Two central laboratories (one each in the US and Europe) were used for standard safety laboratory analyses. All skin fibroblast assays were performed at Duke University Medical Center in Durham, NC, and GAA mutational analyses and ACE marker allele status were performed at the Genzyme specialty laboratory in Framingham, MA.

10.1.2.12 Study Results

Efficacy and safety data for Study 1702 were received in multiple submissions. In the original submission, the sponsor submitted a 52-week interim report with a data cutoff date of 03-September-2004. The original submission included: 1) safety and efficacy (report and datasets) for the first 52 weeks of treatment for the first 15 patients treated; 2) efficacy data on the remaining six patients treated to Week 12; and 3) safety data to a cutoff date of 03-September-2004 for all 21 patients treated. An update to the safety data was submitted in the 4-month safety update on 05-December-2005 (Amendment 005), with data through 31-October-2005. Additional safety and efficacy data were received in Amendments 007 and 008 (on 21-December-2005 and 06-January-2006, respectively) in response to Information Request letters from the Division, which included data through the Week 52 visit for the last six patients enrolled in Study 1702 (previously submitted efficacy data through Week 12 and safety data through 03-September-2004 for these patients). Thus, efficacy and safety data to Week 52 were available for all 21 treated patients for all endpoints in the study and will be included in this review.

10.1.2.12.1 Patient Population

Twenty-two (22) patients were enrolled in Study 1702, and 21 patients received treatment with rhGAA. The first dose of rhGAA was administered to the first patient enrolled on 17-March-2003, and the first dose of rhGAA was administered to the last patient enrolled on 28-May-2004. One patient (Patient 401) died during the baseline period prior to receiving any treatment with rhGAA. This patient died of cardiac arrhythmia and cardiac arrest after receiving anaesthesia for the muscle biopsy procedure (study related procedure). For the remaining 21 patients, 15 patients completed 52 weeks of the study, and six patients were discontinued: five patients died, and one patient discontinued after completing Week 52 (Patient 414). This patient continued to receive rhGAA through participation in an expanded access program. The following table summarizes patient ages at first infusion, and age at the Week 52 visit or discontinuation.

Table A2-3: Study 1702, Summary of Patient Ages at Study Entry, Week 52 Completion and Discontinuation

Patient	Age at First Infusion (mos)	Age at Week 52 Visit (mos)	Age at Discontinuation (mos)
402	17.2	29.3	-
403	37.8	50.0	-
404	8.3	20.2	-
405	13.2	-	17.4
406	16.4	28.5	-
407	8.3	-	11.6
408	43.6	55.7	-
409	6.4	-	7.7
410	37.1	49.4	-
411	10.0	22.1	-
412	8.1	-	14.3
413	7.1	19.3	-
414	24.5	36.4	36.4
415	15.2	27.1	-
416	18.3	30.3	-
417	14.5	26.6	-
418	8.5	20.8	-
419	9.1	-	9.1
420	3.7	15.9	-
421	9.5	21.7	-
422	18.1	30.2	-

There were no screen failures reported.

Five clinical sites in the US and Europe enrolled patients in the study and administered at least the first 26 weeks of treatment. After 26 weeks of treatment, patients could be transferred to regional investigational sites for continuing treatment for the remainder of the study (eight centers: six in the US, one in Germany, and one in the UK). Enrollment by clinical site is summarized in the following table.

Table A2-4: Study 1702, Enrollment by Site

Site ID #	Site (Investigator)	# of Patients Enrolled	Patients Enrolled at Site
01	Durham, NC, USA (Duke Univ. Med. Ctr, PI: P. Kishnani)	6	401*, 403, 407, 411, 416, 420
02	Lyon, France (Pediatrique Hôpital Debrousse, PI : M. Nicolino)	5	405, 415, 419, 421, 422
21	Cincinnati, OH, USA (Cincinnati Children's Hosp. Med. Ctr, PI: N. Leslie)	3	408, 409, 418
81	Gainesville, FL, USA (Shands Hosp. Univ. FL, PI: B. Byrne)	4	402, 404, 406, 412
83	Manchester, UK (Royal Manchester Hosp. PI: JE Wraith)	4	410, 413, 414, 417
Total, n =	5 sites	22	

*Died prior to receiving rhGAA

10.1.2.12.2 Demographics

Baseline demographic data are shown for the 21 treated patients, and for the Historical Reference Subgroup (n=86) and Subset (n=15). Of the 21 patients in Study 1702, 52% were female, and 71% were Caucasian. Fourteen of 21 patients (67%) were free of invasive ventilator support at the time of first infusion, five patients (24%) were on invasive ventilation, and two patients were on noninvasive ventilation. The study population was heterogeneous by age at first symptoms, diagnosis, and first infusion. Mean age at first symptoms was four months (range 0-13 months), mean age at initial diagnosis was nine months (range 0-23 months), and mean age at first infusion was 16 months (range 4-43 months). The Historical Control Subgroup appeared to be reasonably similar by age criteria to the Study 1702 patient population, but the Historical Reference Subset showed some differeneces. The mean and median ages at first symptoms in Study 1702 was less than the Historical Reference Subset, and the range of ages at first symptoms and at initial diagnosis in Study 1702 was broader than for the Reference Subset. As the range of ages at symptom onset and diagnosis may have introduced variability in predicted survival in the study population, this may have weakened the validity of the comparison of survival in the two groups. Demographic data are summarized in the following table. Note: For patients with no age of first symptoms noted, imputed age of first symptoms was date of diagnosis. If date of diagnosis/first symptoms was not known, then the patient was assigned the fifteenth of that month as a date.

Table A2-5: Study 1702 and Historical Reference Subgroup, Demographic Data

	Study 1702 Patients	Historical Reference Subgroup	Historical Reference Subset
Patients, n =	21	86	15
Parameter			
Gender			
Male, n (%)	10 (48)	36 (42)	8 (53)
Female, n (%)	11 (52)	50 (58)	7 (47)
Ethnicity			
Caucasian, n (%)	15 (71)	40 (47)	10 (67)
Black, n (%)	2 (10)	12 (14)	1 (7)
Asian, n (%)	3 (14)	28 (33)	4 (27)
Other/unknown, n (%)	1 (5)	6 (7)	0
Age at First Symptoms (mos)			
Mean	3.9	3.2	5.3
Median	3.1	3.0	4.8
Min, max	0, 12.8	0, 12.2	0.2, 9.4
Age at Initial Diagnosis (mos)			
Mean	8.9	5.9	8.0
Median	6.9	5.8	8.1
Min, max	1.5, 22.9	-5.1, 23.0	1.6, 13.3
Age at First Infusion (mos)			
Mean	15.8	-	-
Median	13		
Min, max	3.7, 43.1		
Ventilator Support at First Infusion			
None, n (%)	14 (67)	-	-
Invasive, n (%)	5 (24)		
Noninvasive, n (%)	2 (5)		

Study 1702 demographic data by individual patient are summarized in the following table:

Table A2-6: Study 1702, Demographic Data by Individual Patient

Patient	Gender	Race	Age at First Symptoms (mos)	Age at Diagnosis (mos)	Age at First Infusion (mos)
402	F	Caucasian	1.5	1.9	17.0
403	M	Caucasian	3.3	13.8	37.3
404	M	Caucasian	3.1	6.7	8.2
405	F	Caucasian	4.9	5.6	13.0
406	M	Caucasian	7.2	10.3	16.2
407	F	Black	1.9	5.5	8.2
408	F	Caucasian	5.1	18.3	43.1
409	M	Caucasian	3.0	4.1	6.3
410	M	Caucasian	0	22.9	36.6
411	M	Black	2.0	6.3	9.8
412	M	Caucasian	6.4	6.9	8.0
413	F	Asian	1.8	4.8	7.0
414	F	Asian	5.7	13.1	24.1
415	M	Caucasian	5.1	11.2	15.0
416	M	Asian	2.6	8.8	18.1
417	F	Caucasian	5.4	11.4	14.3
418	F	Caucasian	2.1	8.2	8.4
419	F	Caucasian	5.0	5.0	9.0
420	F	Other (Lebanese)	1.5	1.5	3.7
421	M	Caucasian	2.5	4.7	9.3
422	F	Caucasian	12.8	15.4	17.8

10.1.2.12.3 Concomitant Medications and Procedures

More than 400 different concomitant medications (conmeds) were reported as having been used during the study, and all 21 treated patients reported using multiple conmeds during the study. The most commonly recorded indications for conmeds use were for conditions associated with underlying disease (e.g., infections, respiratory disorders, cardiac disorders) and for anesthesia or analgesia for study- or disease-related procedures or complications (e.g., biopsies). The most commonly recorded medications by class were antibiotics, anaesthetic and analgesic agents, and cardiovascular system medications. The most commonly reported conmeds by individual medication for the 21 treated patients were: Fentanyl (12 patients), ibuprofen and ketamine (10 each), and Augmentin, lidocaine and vancomycin (9 each).

Pretreatment medications were summarized separately by the sponsor. Five patients were reported to have received any premedication prior to rhGAA administration at anytime during the study. Premedications included antihistamines (4 patients), acetaminophen (3), ibuprofen (1), and glucocorticosteroids (1). Premedication use is summarized by individual patient in the following table:

Table A2-7: Study 1702, Premedication Summary

Patient	Premedication Administrations (at # of Visits)	Comments
407	2 (2)	Weeks 12 and 14, including acetaminophen
408	67 (34)	Day 0 through Week 52 (and in maintenance period), including acetaminophen and diphenhydramine
418	18 (10)	Weeks 34 through 52, including acetaminophen, ibuprofen, diphenhydramine, and promethazine
421	43 (22)	Weeks 2 through 52, including dexchlorpheniramine and methylprednisolone
422	18 (18)	Weeks 18 through 52, including dexchlorpheniramine

Eleven (11) of the 21 treated patients received a central line at baseline and nine patients received a peripheral line (no line placement described for Patient 419). For those patients who received a peripheral line at baseline, seven patients later received a central line at some point during the study (total of 18 of 21 patients known to have received a central line). Thus, it appears likely that the majority of patients in this age group will require central line placement to receive ongoing treatment with rhGAA.

10.1.2.12.4 Compliance with Study Medication

Study medication was administered at the clinical sites; thus, study medication administration and compliance was largely under the control of study personnel. Compliance with study medication was very high. Seventeen (17) of 21 patients received 100% of scheduled study medication, and the remaining four patients received one incomplete or missed one complete infusion during the study either due to illness (3 patients) or staff error (1 patient). Study medication compliance is summarized in the following table:

Table A2-8: Study 1702, Compliance with Study Medication

Patient	Weeks in Study	Complete Doses Received (%)	Comments
402	Through Week 76	39/39 (100%)	
403	Through Week 76	39/39 (100%)	
404	Through Week 76	39/39 (100%)	
405	Through Week 18	10/10 (100%)	Missed Week 4 dose due to dysfunction of catheter (full dose given at Week 5)
406	Through Week 72	37/37 (100%)	
407	Through Week 14	7/8 (88%)	Partial dose at Week 8 due to AE (fever, desaturation due to pneumonia)
408	Through Week 70	36/36 (100%)	Missed Week 26 dose due to port malfunction (full dose given at Week 27)
409	Through Week 6	3/4 (75%)	Partial dose on Day 0 due to staff error
410	Through Week 66	34/34 (100%)	
411	Through Week 64	33/33 (100%)	
412	Through Week 26	14/14 (100%)	
413	Through Week 62	31/32 (97%)	Missed Week 20 infusion due to pyrexia
414	Through Week 52	26/27 (96%)	Missed Week 12 due to pyrexia/illness
415	Through Week 52	27/27 (100%)	
416	Through Week 52	27/27 (100%)	
417	Through Week 52	27/27 (100%)	
418	Through Week 52	27/27 (100%)	
419	Through Day 0	1/1 (100%)	
420	Through Week 52	27/27 (100%)	
421	Through Week 52	27/27 (100%)	Dose escalation to 40 mg/kg Weeks 34 to 52
422	Through Week 52	27/27 (100%)	

10.1.2.12.5 Protocol Deviations and Violations

A protocol deviation log was submitted in the original submission only, with deviations noted through Week 26 only. The majority of protocol deviations were noted (by the sponsor) to be frequent and minor, and were predominantly out of window assessments and infusions, and missed assessments. These deviations were unlikely to have impacted on the interim study results. Protocol violations were notable for violations in entry criteria for 11 of the 21 treated patients, as follows:

- Three patients were granted exceptions to the inclusion criterion for age (requires patients to be greater than six to less than or equal to 36 months of age at first infusion), including Patient 403 who was 37.3 months, Patient 408 who was 43.1 months and Patient 420 who was 3.7 months (not a candidate for Study 1602 as on noninvasive ventilation).
- One additional patient had an age violation at baseline not initially calculated properly by the site: Patient 410 was age 36.6 months at baseline
- Four patients were noted (by this Reviewer) to have been included in the study despite not meeting the inclusion criterion for cardiac hypertrophy at baseline (Patients 402, 414, 415 and 422, all of whom were >12 months of age and had LVMIs <79 g/m^2), and two additional patients (Patients 405 and 418) did not have an LVMI reported at baseline.
- One patient (Patient 413) had a baseline EF of 21%, and signs and symptoms of cardiac failure ("worsening cardiac function") prior to first infusion, in violation of exclusion

criteria (ineligible if EF <40% AND the patient has signs and symptoms of cardiac failure).

The broadening of the study population through violations of the entry criteria allowed for a much more diverse study population (including both more severely-affected patients and patients with more attenuated disease) to be included in the study than originally intended. It is known from the historical control and from the medical literature that even small differences in age at presentation may result in less predictability as to length of survival. That is, small increments in age at diagnosis can result in much longer patient survival (without treatment with ERT), making it more difficult to discern a treatment effect for survival in the older patients. Conversely, the inclusion of a patient younger than six months at first infusion resulted in the inclusion of more severely-affected patient in the study. Similarly, the study population became more heteregeous with the addition of patients at both ends of the spectrum by baseline cardiac findings. The inclusion of patients without the protocol-specified cardiac hypertrophy likely allowed for the inclusion of patients with more attenuated disease, and the inclusion of a patient with poor cardiac function at baseline allowed for the inclusion of a patient with a poor prognosis at baseline. The overall effect of these protocol violations was to allow for a highly hetereogenous study population, thereby making the likelihood of discerning a treatment effect in this study less probable.

10.1.2.12.6 Primary Efficacy Endpoint

The primary efficacy endpoint was the proportion of patients alive at Week 52, with an additional analysis of proportion of patients alive at Week 26. As of the Week 52 milestone, 16 of 21 patients (76%) were alive, and at the Week 26 milestone, 17 of 21 patients were alive (81%). The primary efficacy endpoint results are summarized in the following table.

Table A2-9: Study 1702, Patients Alive at Weeks 26 and 52

Patients, n =	21	**95% CI**
Duration of Treatment		
26 weeks, n (%)	17 (81)	58, 95
52 weeks, n (%)	16 (76)	53, 92

Five patients died during the 52-week treatment period: four patients (405, 407, 409 and 419) during the first 26 weeks of treatment, and one patient (412) between Weeks 26 and 52, at ages 17, 12, 8, 9, and 14 months of age, respectively. Sixteen patients remained alive at the Week 52 milestone, ranging in age from 16 to 56 months.

Survival was additionally analyzed by the sponsor by age at first infusion in the original submission (inclusive of the first 15 patients enrolled only), with patients who were less than or equal to 12 months of age at first infusion (n=6) and patients who were 12 months of age or older at first infusion (n =9) analyzed separately. The Historical Reference Subgroup (n=86) was also divided into three reference subsets comprised of untreated patients known to have survived past the median age at first infusion in Study 1702, including: 1) Subset 1 for patients first infused at age less than or equal to 12 months who had a median age = 8.1 months (n = 60); 2) Subset 2 for

patients first infused at age greater than 12 months who had a median age = 18.1 months (n = 11); and 3) Subset 3 for all patients infused who had a median age = 15.0 months (n = 16).

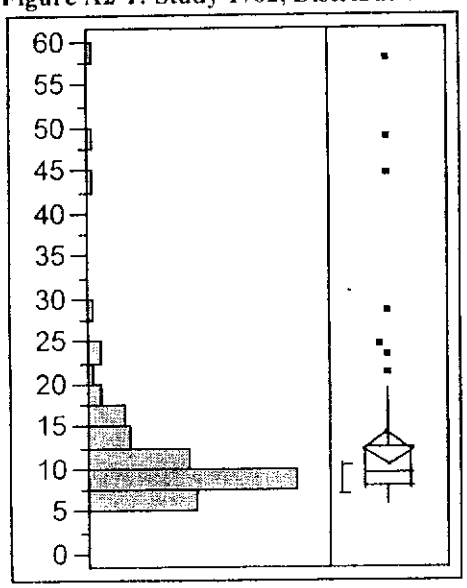
The results for the Study 1702 population show 52-week survival rates of 50% for patients less than or equal to 12 months of age at first infusion, 89% for patients greater than 12 months of age at first infusion, and 73% for the Study 1702 population as a whole. Thus, the survival results are highly variable depending on age at first infusion, with patients surviving to an age greater than 12 months of age prior to first infusion tending to have a longer survival compared to patients diagnosed and treated at less than or equal to 12 months of age. These results are consistent with the known differences in survival by age at diagnosis/presentation seen in the Historical Reference Subgroup and Subsets, and with reports in the medical literature, and the survival rates seen in the Study 1702 populations overlap with the Kaplan-Meier estimates of conditional 52-week survival rates seen in the Historical Reference Subgroup Subsets. Thus, no treatment effect of rhGAA can be discerned from these data. The Kaplan-Meier estimates of conditional 52-week survival rate vs. survival rates seen in the first 15 patients enrolled in Study 1702 separated by age less than or equal to 12 months of age, greater than 12 months of age, and for the population as a whole are summarized from the sponsor's study report in the following table.

Table A2-10: Study 1702, Analysis of Survival by Age at First Infusion as Compared to Historical Reference Subgroup

	Study 1702		Historical Reference Subgroup	
Age Category at 1st Infusion	**Median Age at 1st Infusion (mos)**	**Actual 52-Week Survival Rate, n (%) [95%CI]**	**n =**	**Kaplan-Meier Estimate of Conditional 52-Week Survival Rate % [95% CI]**
≤12 months, n = 6	8.1	3 (50) [12, 88]	60	16% [6%, 26%]
>12 months, n = 9	18.1	8 (89) [52, 100]	11	46% [16%, 75%]
All Patients, n = 15	15.0	11 (73) [45, 92]	16	38% [14%, 61%]

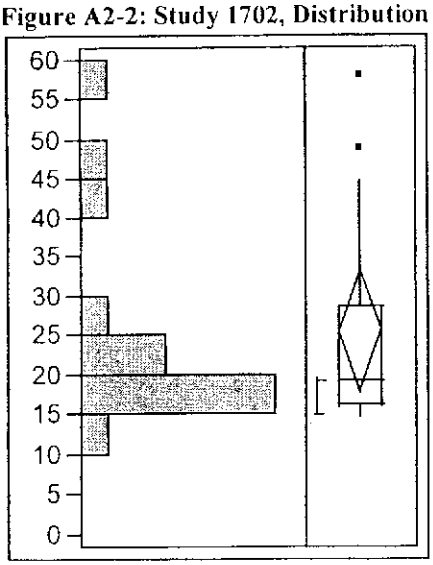
The Historical Reference Subgroup population (n = 86) was further evaluated by this Reviewer. Of the 86 patients, 80 were known to have died, two were known to be alive, and four had unknown status. Of the 78 patients known to have died, mean age at death was 12.2 months (median 9.4, range 6.0 to 57.7 months). These results are consistent with a relatively broad range of length of survival in patients with a heterogeneous age at diagnosis, such as those patients included in Study 1702. Survival to as late as 58 months was seen in this population, making the effect of rhGAA difficult to discern. The distribution of age at death in the Historical Control Subgroup is represented graphically in the following figure.

Figure A2-1: Study 1702, Distribution of Age at Death in the Historical Reference Subgroup (n = 86)



The results for the Historical Reference Subset (n=15), which included only patients who survived to age greater than or equal to 15 months (15 months being the median age at first infusion for the first 15 patients entered in Study 1702), showed a mean survival of 25.3 months (median 19.1, range 15 to 57.7 months). These results are again consistent with a relatively broad range of length of survival in patients with a heterogeneous age at diagnosis, and further underscore the difficulty of discerning a treatment effect in the Study 1702 population with treatment with rhGAA. Distribution of age at death in the Historical Reference Subset is represented graphically in the following figure.

Figure A2-2: Study 1702, Distribution of Age at Death in the Historical Reference Subset (n = 15)



10.1.2.12.7 Secondary Efficacy Endpoints

10.1.2.12.7.1 Respiratory Status

Patients were evaluated by ventilator status at baseline and Week 52. At baseline, 16 of 21 patients were free of invasive ventilator support (Patients 411 and 420 were on noninvasive ventilation). At Week 52, ten of 21 patients remained alive and free of invasive ventilator support (48%). Seven patients had worsening status (e.g., no ventilation → invasive ventilation or the patient died), including five patients who died (Patients 405, 407, 409, 412, and 419) and two patients who became invasive-ventilator dependent (Patients 411 and 413). For the five of 21 treated patients who were receiving invasive ventilation at baseline, one died (Patient 405) and four remained on invasive ventilation (Patients 403, 406, 410 and 416). In no instance did a patient on invasive ventilation discontinue invasive ventilation. One patient (Patient 420) who was on noninvasive ventilation (NIV) at baseline (positive pressure ventilation through a nose piece) was able to discontinue NIV after approximately six months of rhGAA treatment. Patient status at the Week 52 milestone (last updated 18-November-2005, Amendment 008) for the 21 treated patients in Study 1702 is summarized by individual patient in the following table.

Table A2-11: Study 1702, Patient Status at 52-Week Milestone for All Patients (last updated 18-November-2005)

Patient	Ventilator Status at Baseline	Ventilator Status at Week 52	Age at 1st Symptoms (mos)	Age at Diagnosis (mos)	Age at 1st Infusion (mos)	Age at Invasive Ventilator Dependence (mos)	Age at Death (mos)
Worsening status							
405	Invasive	Died	4.9	5.6	13.0	11.7 (prior to study entry)	17.3
407	None	Died	1.9	5.5	8.2	11.6	11.7
409	None	Died	3.0	4.1	6.3	-	7.7
411	Noninvasive	Invasive	2.0	6.3	9.8	16.2	
412	None	Died	6.4	6.9	8.0	-	14.4
413	None	Invasive	1.8	4.8	7.0	18.2	
419	None	Died	5.0	5.0	9.0	9.0	9.0
Mean	-	-	3.6	5.5	8.8		
Median	-	-	3.0	5.5	8.2		
Min, Max	-	-	1.8, 6.4	4.1, 6.9	6.3, 13.0		
No change in status, invasive ventilator dependent at baseline							
403	Invasive	Invasive	3.3	13.8	37.3	32.3 (prior to study entry)	
406	Invasive	Invasive	7.2	10.3	16.2	8.8 (prior to study entry)	
410	Invasive	Invasive	0	22.9	36.6	26.6 (prior to study entry)	
416	Invasive	Invasive	2.6	8.8	18.1	13.0 (prior to study entry)	
Mean	-	-	3.3	14.0	27.1		
Median	-	-	3.0	12.1	27.4		
Min, Max	-	-	0, 7.2	8.8, 22.9	16.2, 37.3		
No change in status or improved, no invasive ventilation at baseline							
402	None	None	1.5	1.9	17.0		
404	None	None	3.1	6.7	8.2		
408	None	None	5.1	18.3	43.1		
414	None	None	5.7	13.1	24.1		
415	None	None	5.1	11.2	15.0		
417	None	None	5.4	11.4	14.3		
418	None	None	2.1	8.2	8.4		
420	Noninvasive	None	1.5	1.5	3.7		
421	None	None	2.5	4.7	9.3		
422	None	None	12.8	15.4	17.8		
Mean	-	-	4.5	9.2	16.1		
Median	-	-	4.1	9.7	14.7		
Min, Max	-	-	1.5, 12.8	1.9, 18.3	3.7, 43.1		
Overall	-	-					
Mean	-	-	3.9	8.9	15.7		
Median	-	-	3.1	6.9	13.0		
Min, Max	-	-	0, 12.8	1.5, 22.9	3.7, 43.1		

When patients were compared by ventilator status at baseline (e.g., invasive ventilation or no ventilation) and by change in status (worsening status or no change/improved), the results showed several trends:

- Patients with worsening status tended to have younger ages at diagnosis and at first infusion than patients who had no change in status. Worsening-status patients had a median age at diagnosis of 5.5 months and a median age at first infusion of 8.2 months,

compared with median ages at diagnosis and first infusion in the no change in status invasive/invasive patients of 12.1 and 27.4 months, respectively, and in the no change no ventilation/no ventilation patients of 9.7 and 14.7, respectively. One exception was Patient 420 who was the youngest patient enrolled in the study (age 3.7 months at first infusion). This patient was on NIV at baseline and discontinued NIV during the study.

- Patients who were maintained on invasive ventilation at baseline and throughout the study were older at diagnosis and first infusion (median ages 12.1 and 27.4 months, respectively) than the other two groups of worsening status (5.5 and 8.2 months, respectively) and no ventilation throughout the study (9.7 and 14.7, respectively)

These findings are consistent with anecdotal and medical literature reports of patients with more severe symptoms (thus, coming to medical attention at younger ages) tending to have a poorer prognosis and more rapidly progressive disease course than patients with slower onset of the disease. As the groupings by age and patient status were very small when the study population was divided into these groupings, no definite conclusions can be drawn from these results. However, these trends seen even in these small patients groupings suggest that patient course over the duration of the study is at least partially dependent on patient age at diagnosis and first infusion, making it extremely difficult to discern or separate treatment effect with rhGAA from the natural progression of the underlying disease.

10.1.2.12.7.2 Cardiac Status

Cardiac parameters were assessed by echocardiography, focusing primarily on LVMI, LMV Z-score and EF, which were assessed at baseline/screening and at Weeks 4, 8, 12, 26, 38 and 52. Irregularities in the data supplied by the sponsor were noted. Some patients were noted to have large differences in cardiac parameters, especially EF values, between assessments that did not appear to be plausible. For example, Patient 420 had an EF of 71% at baseline, 14% at Week 4, and 35% at Week 8 (other examples were noted – please see the subappendix for a listing of cardiac parameters for all patients). In addition, two patients (Patients 405 and 418) did not have LVMIs recorded at baseline, and four patients (Patients 402, 414, 415 and 422) did not have cardiac hypertrophy at baseline (as defined by the inclusion criteria for the study). Despite these limitations in the data, the results for all 21 treated patients are summarized as follows:

Of the 18 of 21 patients with baseline and at least one post-baseline result, 13 patients showed decreases in LVMI from baseline at Week 52 (or last available result), four patients had essentially no change in LVMI, and one patient had an increase in LVMI. For the patient with increased LVMI (Patient 409), this patient had one post-baseline evaluation at Week 4 and the patient died prior to any other assessments having been performed.

For all patients with available results, mean LVMI at baseline was 194 g/m^2, and was 89 g/m^2 at Week 52 (mean change of -100 g/m^2). Decreases in LVMI were notable beginning at approximately Week 8 and there were continued decreases through Week 52. LVM Z-scores at baseline showed that LVM was markedly elevated for most patients compared to normals, with LVM Z-scores ranging from >1.5 to >10 SD above the mean of normal (mean Z-score 6.5). Consistent with the decrease in LVMI, LVM Z-scores showed decreases from baseline at Week 52, and decreases were notable from approximately Week 8. At Week 52 (or last visit), all

patients but one had LVM Z-scores above the mean for normal ranging from approximately 1 to 7 SD above the mean (mean Z-score 2.7). Patient 418 had an LVM Z-score of -1.1 (below the mean of normal) at Week 52; however, this patient did not have any baseline LVM assessment, and the first LVMI recorded for this patient at Week 8 showed an LVMI of 58 g/m^2 (below entry criterion of 65 g/m^2 for patients ≤12 months of age).

Of the 20 of 21 patients with baseline and at least one post-baseline EF result, eleven patients (55%) had an increase in EF from baseline at Week 52 (or last available visit), ranging from +2 to +40%, and nine patients (45%) had a decrease in EF at Week 52 (or last available visit), ranging from -1 to -31%. The cardiac parameters from baseline through Week 52 for the 21 treated patients are summarized in the following table.

Table A2-12: Study 1702 Amendment 008, Cardiac Parameters Baseline through Week 52

	Baseline	Week 4	Week 8	Week 12	Week 26	Week 38	Week 52
Parameter							
LVMI (g/m^2), n =	19	18	17	17	14	11	13
Mean	194	200	156	154	106	96	89
Median	203	191	175	142	90	73	63
Min, max	55, 418	70, 355	58, 312	38, 297	37, 238	45, 195	30, 212
ΔLVMI*(g/m^2), n =	-	17	15	15	13	11	12
Mean	-	-4	-39	-44	-98	-99	-100
Median	-	-3	-15	-28	-86	-55	-89
Min, max	-	-99, +143	-169, +31	-189, +88	-261, -13	-284, -5	-295, -2
LVM Z-Score, n =	19	18	17	17	14	11	13
Mean	6.5	6.8	5.6	5.3	3.7	3.4	2.7
Median	7.6	7.2	6.3	5.9	3.7	2.9	2.0
Min, max	1.7, 10.4	2.8, 9.7	2.1, 9.2	0, 8.5	-0.1, +7.5	+0.7, +6.7	-1.1, +7.2
ΔZ-Score*, n =	-	17	15	15	13	11	12
Mean	-	-0.2	-0.8	-1.4	-3.0	-2.8	-3.4
Median	-	-0.1	-1.0	-1.7	-3.1	-2.1	-2.6
Range	-	-1.6, +1.0	-2.8, +0.9	-3.4, 0.1	-5.9, -1.1	-7.1, -0.4	-8.0, -0.4
EF (%), n =	21	18	18	18	14	13	15
Mean	57	52	52	52	60	61	62
Median	62	54	52	55	63	63	62
Min, max	21, 72	14, 73	21, 81	26, 78	25, 75	43, 81	40, 78
ΔEF* (%), n =	-	18	18	18	14	13	15
Mean	-	-4	-5	-5	+3	+4	+4
Median	-	-1	-6	-6	-1	+7	+4
Min, max	-	-57, +19	-35, +19	-36, +16	-16, +21	-28, +32	-31, +40

*Change from Baseline

Cardiac parameters for the 21 treated patients by individual patient at baseline and Week 52 (or last available visit) are summarized in the following table.

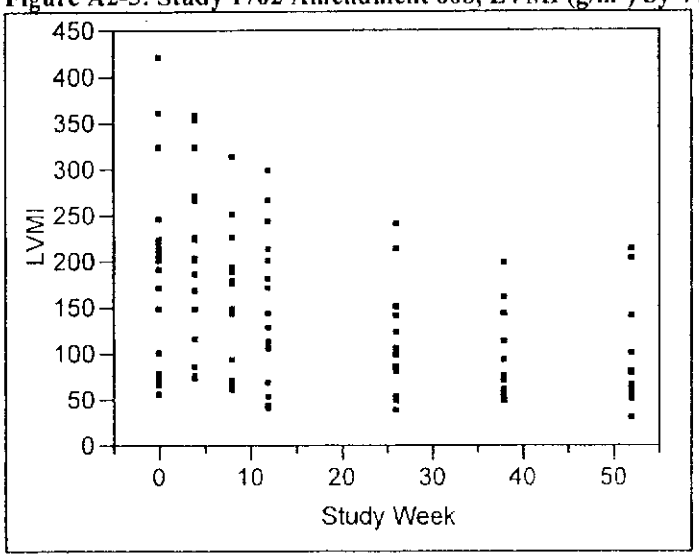
Table A2-13: Study 1702 Amendment 008, Baseline and Last Available Cardiac Parameters and Patient Outcome

Patient	Week	LVMI (g/m^2)	ΔLVMI (g/m^2)	LVM Z-score	EF (%)	ΔEF (%)	Outcome (Start/Stop)
402	0	72	0	2.9	54	0	None
402	52	52	-21	1.1	53	-1	None
403	0	146	0	5.4	67	0	Invasive
403	52	76	-69	2.6	74	+7	Invasive
404	0	358	0	10.0	50	0	None
404	52	63	-295	2.0	78	+28	None
405	0	.	.	.	27	0	Invasive
405	12	241	.	8.0	32	+5	Died
406	0	322	0	8.8	38	0	Invasive
406	52	212	-111	6.9	59	+20	Invasive
407	0	198	0	7.6	67	0	None
407	12	199	+1	7.5	54	-13	Died
408	0	189	0	6.6	62	0	None
408	52	57	-132	1.3	78	+16	None
409	0	243	0	8.5	62	0	None
409	4	265	+22	8.7	42	-20	Died
410	0	209	0	7.3	66	0	Invasive
410	52	100	-109	2.8	68	+2	Invasive
411	0	417	0	10.4	52	0	Noninvasive
411	52	140	-278	5.5	45	-6	Invasive
412	0	212	0	7.7	60	0	None
412	26	103	-108	4.5	74	+15	Died
413	0	207	0	7.7	21	0	None
413	38	112	-95	4.6	60 (Wk 52)	+40 (Wk 52)	Invasive
414	0	63	0	2.2	56	0	None
414	52	54	-9	1.4	62	+6	None
415	0	77	0	3.1	72	0	None
415	52	48	-29	0.8	68	-4	None
416	0	170	0	6.3	63	0	Invasive
416	26	83	-87	3.0	61	-2	Invasive
417	0	221	0	7.8	70	0	None
417	52	79	-142	3.2	55	-15	None
418	0	-	-	-	67	0	None
418	52	29	-	-1.1	60	-6	None
419	0	220	0	7.8	49	0	None
419	NA*	-	-	-	-	-	Died
420	0	203	0	7.6	71	0	Noninvasive
420	52	201	-2	7.2	40	-31	None
421	0	100	0	4.3	59	0	None
421	12/52	104 (Wk12)	+4 (Wk12)	4.4 (Wk12)	64 (Wk 52)	+5 (Wk 52)	None
422	0	55	0	1.7	66	0	None
422	52	49	-6	1.0	70	+4	None

*Patient died prior to any post-baseline results having been obtained

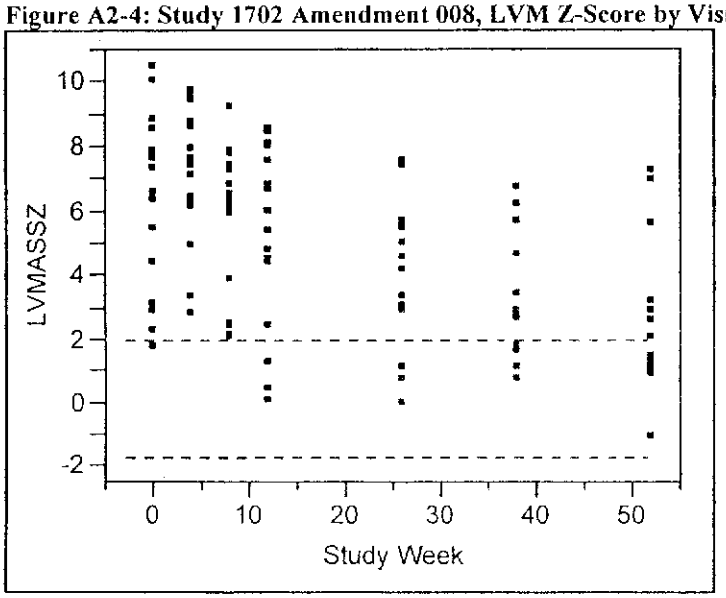
The results for LVMI by study visit from baseline to Week 52 are represented graphically in the following figure.

Figure A2-3: Study 1702 Amendment 008, LVMI (g/m^2) by Visit from Baseline to Week 52



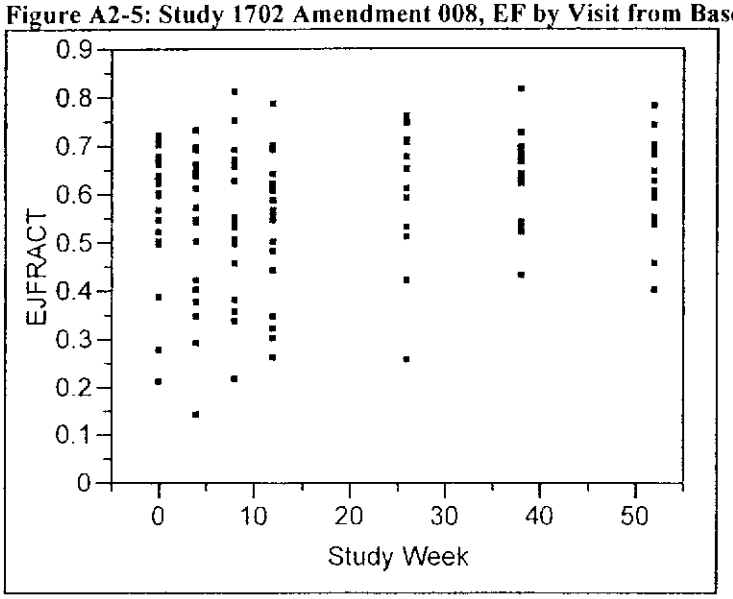
The results for LVM Z-score by study visit from baseline to Week 52 are represented graphically in the following figure.

Figure A2-4: Study 1702 Amendment 008, LVM Z-Score by Visit from Baseline to Week 52



The results for EF by study visit from baseline to Week 52 are represented graphically in the following figure.

Figure A2-5: Study 1702 Amendment 008, EF by Visit from Baseline to Week 52



There did appear to be an association with a baseline EF <40% and outcome. There were three patients with an EF<40% at baseline, two of whom (Patients 405 and 413) had worsening status and one of whom (406) remained ventilator dependent throughout the study, despite increases in EF from baseline in all three patients. The three patients with baseline EF <40% are summarized in the following table.

Table A2-14: Study 1702, Patients with Baseline EF <40% and Outcome

Patient	Week	LVMI (g/m^2)	ΔLVMI (g/m^2)	LVM Z-score	EF (%)	ΔEF (%)	Outcome (Start/Stop)
405	0	.	.	.	27	0	Invasive
405	12	241	.	8.0	32	+5	Died
406	0	322	0	8.8	38	0	Invasive
406	52	212	-111	6.9	59	+20	Invasive
413	0	207	0	7.7	21	0	None
413	38	112	-95	4.6	60 (Wk 52)	+40 (Wk 52)	Invasive

Cardiac status was also assessed by the proportion of patients with signs or symptoms compatible with cardiac failure through Week 52 of the study. Three of 21 patients (Patients 410, 413 and 419) were noted to have findings compatible with cardiac failure during screening/baseline prior to rhGAA administration, and these AEs tended to predict a poor outcome as two of the patients (413 and 419) had worsening status (required invasive ventilation or died, respectively) and one patient (410) remained on invasive ventilation throughout the study. Four patients were noted to have AEs compatible with cardiac failure during the study, one of whom (Patient 410) also had symptoms at baseline. As with cardiac failure AEs at baseline, signs or symptoms of cardiac failure during the study also tended to predict a poor outcome: three patients (405, 407 and 409) died and the fourth patient (410) remained on invasive ventilation throughout the study. It is additionally noted for the seven patients with

cardiac failure AEs at any time during the study, the pharmacodynamic (PD) effects of rhGAA on the cardiac parameters (LVMI, LVM Z-score and EF) were variable and did not appear to be predictive of outcome in these patients. Cardiac AEs compatible with signs or symptoms of cardiac failure are summarized by individual patient in the following table:

Table A2-15: Study 1702, Cardiac AEs Compatible with Signs or Symptoms of Cardiac Failure

Patient	Study Day	AE Verbatim Term	AE Preferred Term	Outcome
Prior to First Infusion				
410	-3	Worsening cardiac failure	Cardiac failure	Invasive/invasive
413	-6	Worsening cardiac function/gallop rhythum (sic) noted	Gallop rhythm present	None/invasive
419	-1	Decreased ejection fraction	Ejection fraction decreased	None/died
Post-first infusion				
405	68	Worsening cardiomyopathy	Cardiomyopathy	Invasive/died
407	28	Decline in cardiac function (decreased EF)	Ejection fraction decreased	None/died
409	44	Acute heart failure	Cardiac failure	None/died
409	44	Acute pulmonary edema	Acute pulmonary edema	None/died
410	20	Worsening heart failure	Cardiac failure	Invasive/invasive
414	62	3rd Heart sound noted on physical exam	Gallop rhythm present	None/none
417	28	S1 S2 S3 Gallop rhythm noted on PE	Gallop rhythm present	None/none
420	266	Worsening cardiomyopathy	Cardiomyopathy	Noninvasive/none

Overall, the cardiac parameter results showed decreases in LVMI and LVM Z-scores that are consistent with the pharmacodynamic effect of ERT, but are not indicative of clinical improvement. Changes in EF also did not appear to predict patient outcome, as there did not appear to be a correlation between worsening patient status and changes in EF (both increases and decreases in EF were seen in these patients). Thus, the relevance of the PD effect of rhGAA treatment on cardiac function is unknown and no clear clinical effect of rhGAA treatment on cardiac function could be definitely determined from the available data. It is additionally noted that cardiac status as assessed by the development of AEs consistent with signs or symptoms compatible with cardiac failure, either prior to receiving treatment rhGAA or during treatment with rhGAA, tended to predict a poor outcome that did not appear to be altered by treatment with rhGAA.

10.1.2.12.8 Other Efficacy Variables

10.1.2.12.8.1 Motor Development

Motor development was assessed by AIMS, Peabody Developmental Motor Scale (PDMS-2) and Pompe PEDI testing. The AIMS and Pompe PEDI tests have been described in the study report for Study 1602. Please refer to the Study 1602 for more details on these tests. An overall assessment of the motor development findings for the AIMS, PDMS-2, and Pompe PEDI tests is provided after the Pompe PEDI summary.

10.1.2.12.8.1.1 AIMS

The AIMS is a widely used observational measure of infant motor performance that assesses motor maturation of the infant from term (40 weeks gestational age) through the age of independent walking (approximately 18 months of age). AIMS describes the motor development

sequence according to the development of postural control relative to the various postural positions: prone, supine, sitting and standing (maximum scores prone 21, supine 9, sit 12 and stand 16). Observations are scored (maximum 58 points for raw score), and the raw score is converted into an age-equivalent score (the age at which 50% of healthy peers achieved such score, indicating the developmental age at which the patient is performing). In Study 1702, the AIMS test was performed in patients who were less than or equal to 18 months of age and had not reached the ceiling (maximum score) for the AIMS (AIMS has a developmental ceiling of 18 months, and is unlikely to be useful for longer term follow-up in this patient population).

The results showed that 14 patients had a baseline and at least one subsequent AIMS evaluation at Week 12 or later, and of these 14 patients, nine had results available to Week 52. The large numbers of patients with missing or incomplete data severely limited the utility of the AIMS testing in this study. For the nine patients with data through Week 52, the results showed that four patients had essentially no gains in motor milestones (Patients 404, 406, 416 and 421), one patient (411) initially gained motor milestones that were subsequently lost by Week 52, and four patients (415, 418, 420 and 422) gained motor milestones through Week 52, although these patients were delayed compared to norms for same-age peers. The results of the AIMS test at baseline and last available result are summarized for the 14 of 21 treated patients with available results at baseline and at least one post-baseline visit at Week 12 or later, in the following table (complete results are listed in the subappendix).

Table A2-16: 1702 Amendment 008, AIMS Results at Baseline and Week 52

Patient	Week	Category Raw Score Prone (21)	Supine (9)	Sit (12)	Stand (16)	Total Raw (58)	Actual Age (mos)	Age Equiv Score (mos)*	Percentile Score
404	0	0	2	1	0	3	7.9		<5%
	64	0	0	7	0	7	22.8	1.3	
405	0	0	0	0	0	0	13.0		<5%
	12	0	0	0	0	0	16.0		<5%
406	0	0	0	0	0	0	16.4		<5%
	64	0	0	0	0	0	31.2	0	<5%
407	0	0	0	0	0	0	8.0		<5%
	12	0	0	1	0	1	11.1		<5%
411	0	0	4	2	0	6	9.3		<5%
	64	0	0	3	0	3	24.9	<0.5	
412	0	0	2	0	0	2	8.0		<5%
	26	0	0	1	0	1	14.3		<5%
413	0	1	6	1	2	10	6.9		<5%
	38	5	9	9	3	26	16.1	6.1	<5%
415	0	1	6	8	1	16	15.0		<5%
	52	15	9	12	3	39	27.1	8.4	
416	0	0	0	0	0	0	18.2		<5%
	52	0	0	0	0	0	30.2	<0.5	
417	0	14	9	11	3	37	14.5		<5%
	12	21	9	12	8	50	17.5		<5%
418	0	4	7	5	1	17	8.4		<5%
	52	21	9	12	8	50	20.6		
420	0	0	0	0	0	0	3.3		<5%
	52	10	9	10	1	30	16.0		<5%
421	0	2	5	7	1	15	9.0		<5%
	52	0	0	0	0	0	22.0		
422	0	14	8	12	3	37	17.6		<5%
	58	21	9	12	16	58	31.5		

*Age equivalent scores not available for patients older than 18 months of age

10.1.2.12.8.1.2 Peabody Developmental Motor Scale (PDMS-2)

The PDMS-2 is a comprehensive measure of motor development that assesses gross and fine motor skills that develop in children from birth through six years of age. It was originally developed to aid in the identification of children with abnormal motor development, and there is considerable experience with the PDMS-2 in the evaluation of high-risk children and children with abnormal motor development due to a variety of conditions. The PDMS-2 provides an assessment of gross and fine motor skills in six subtests. Four of the subtests (Reflexes, Stationary, Locomotion, and Object Manipulation) assess gross motor development, and two subtests (Grasping and Visual-Motor Integration) assess fine motor development. In this study, the PDMS-2 was administered to all patients at baseline. For patients less than or equal to 18 months of age, the AIMS test was administered as the assessment of motor development and the PDMS-2 was not administered again until the closest visit prior to the patient's 12- or 18-month birthday. For patients older than 18 months of age, only the PDMS-2 was administered. The object manipulation subtest of the PDMS-2 test is not intended to be administered until 12

months of age, thus, younger patients did not have baseline data for this subtest. Conversely, the reflexes subtest is administered only during the first year of life and not thereafter. In Pompe disease, proximal muscle weakness is typically more pronounced than distal muscle weakness, and lower limbs more so than upper limbs, and it was anticipated that patients in the study would most likely demonstrate greater impairment in the gross motor subtests, especially involving the lower extremities, than the fine motor subtests. Scores are reported as age-equivalent scores for all subtests.

The results showed that 18 of the 21 treated patients had baseline and at least one subsequent PDMS-2 evaluation at Week 12 or later (not Patients 407, 409, and 419 who died prior to follow-up assessments having been performed). The results for the gross motor subtests were notable for twelve patients showing any increases in age equivalent scores on at least one of the subtests of Stationary, Locomotion and Object Manipulation skills, although in many patients, these gains were minor and all patients showed substantial delays compared to age-matched norms. The remaining six patients showed no progress or regression in these motor subtests. The results for the fine motor subtests were notable for 14 patients showing increases in age equivalent scores in at least one of the subtests of Grasping and Visual-Motor Integration skills. In eight patients, the Grasping or Visual-Motor subtests (or both) results were near or at age-matched norms. Thus, as expected, the fine motor gains were more evident in the study population than gross motor gains. It is not known, however, if the fine motor gains were a result of treatment with rhGAA as these findings are consistent with the natural progression of the underlying disease. The Gross motor subtest age-equivalent scores also tended to be a better predictor of patient outcome than the Fine motor subtest results. That is, patients demonstrating gains in gross motor skills (and who had higher age-equivalent scores) tended to do better (by outcome of death or ventilatory status) than did patients not demonstrating gains. A similar association with gains in fine motor skills was not seen; however, as three of the patients who died did not have follow-up PDMS-2 results, the evaluation of this trend is limited.

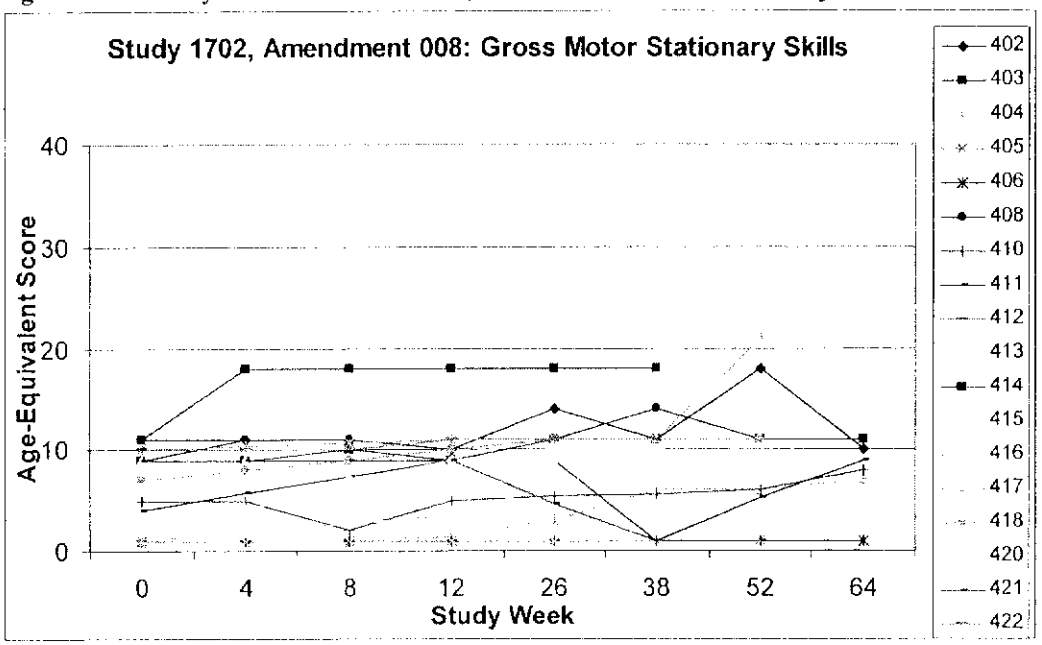
The results of the PDMS-2 test at baseline and last available result are summarized for the 18 of 21 treated patients with available results at baseline and at least one post-baseline result at Week 12 or later, in the following table (complete results are listed in the subappendix). The results are also represented graphically in the following figures.

Table A2-17: Study 1702 Amendment 008, PDMS-2 Results

Patient	Week	Actual Age (mos)	Gross Motor Age Equivalent (mos)			Fine Motor Age Equivalent (mos)		Status (start/end)
			Stationary	Locomotion	Object Manipulation	Grasping	Visual-Motor Integration	
402	0	17.0	9	7	13	14	16	None
	64	32.1	10	10	23	40	28	None
403	0	37.7	9	2	12	12	22	Invasive
	64	52.8	11	8	12	43	>71	Invasive
404	0	7.9	1	1		4	6	None
	64	22.8	7	1	12	10	17	None
405	0	13.0	1	1	12	1	1	Invasive
	12	16.0	1	1	12	1	3	Died
406	0	16.4	1	1	12	1	2	Invasive
	64	31.3	1	1	12	1	3	Invasive
408	0	43.6	11	8	12	28	35	None
	64	58.5	11	8	12	20	52	None
410	0	36.8	5	1	12	1	1	Invasive
	64	52.2	8	2	12	11	35	Invasive
411	0	9.3	4	1		4	7	Noninvasive
	64	24.9	9	2	12	11	19	Invasive
412	0	8.0	1	1		1	3	None
	26	14.3	1	1	12	6	8	Died
413	0	6.9	3	3		5	8	None
	26	13.2	9	5	12	8	10	Invasive
414	0	24.3	11	16	16	20	22	None
	26	30.7	18	18	18	46 (Wk 52)	33 (Wk 52)	None
415	0	15.0	9	7	12	28	14	None
	52	27.1	11	8	12	34	22	None
416	0	18.2	1	1	12	1	4	Invasive
	52	30.2	1	1	12	1	3	Invasive
417	0	14.5	10	7	12	15	17	None
	52	26.6	21	18	16	28	22	None
418	0	8.4	7	7		7	6	None
	52	20.6	11	11	12	15	22	None
420	0	3.3	1	1		1	3	Noninvasive
	52	16.0	9	7	12	14	17	None
421	0	9.0	9	3		8	8	None
	52	22.0	1	1	12	1	3	None
422	0	17.6	10	8	12	34	19	None
	58	31.5	18	18	23	28	34	None

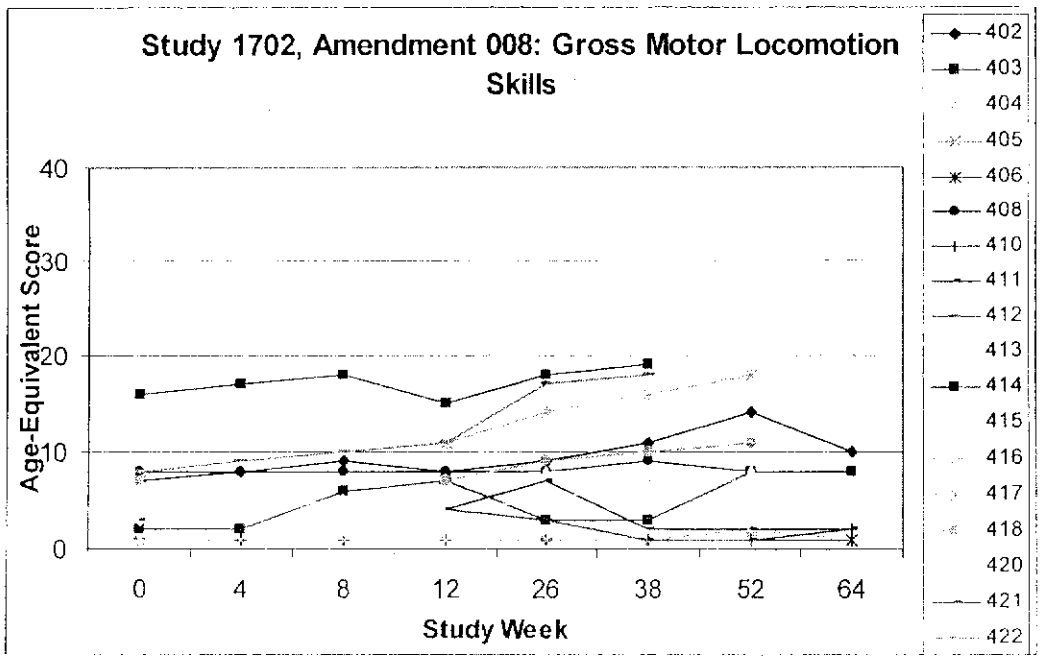
The Gross Motor Stationary skills subtest results in the 18 of 21 treated patients with available results are represented graphically in the following figure.

Figure A2-6: Study 1702 Amendment 008, PDMS Gross Motor Stationary Skills Subtest



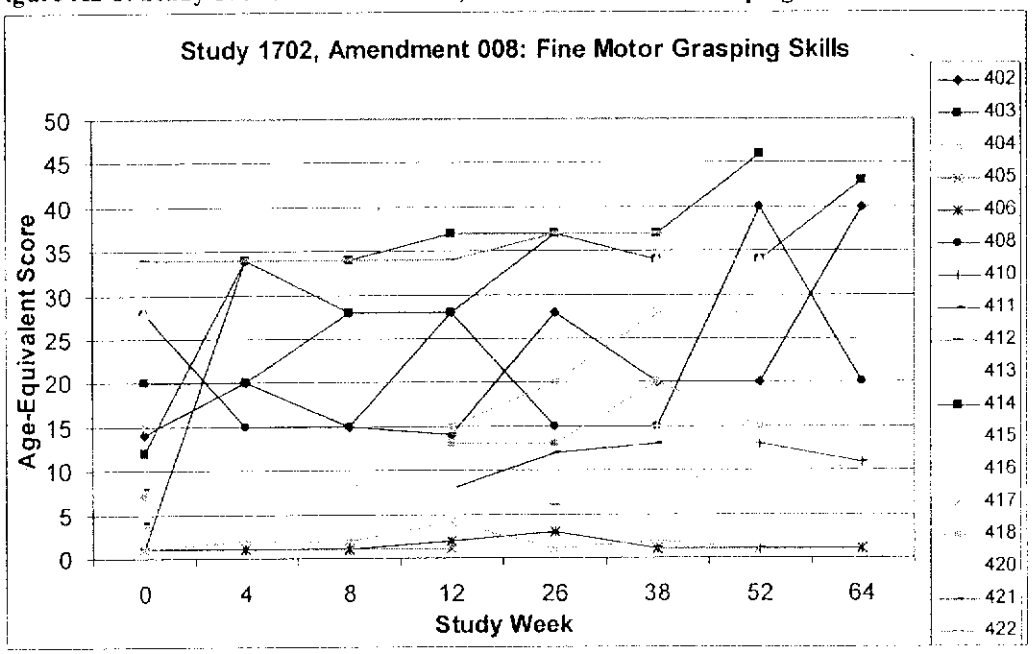
The Gross Motor Locomotion skills subtest results in the 18 of 21 treated patients with available results are represented graphically in the following figure.

Figure A2-7: Study 1702 Amendment 008, PDMS Gross Motor Locomotion Skills Subtest



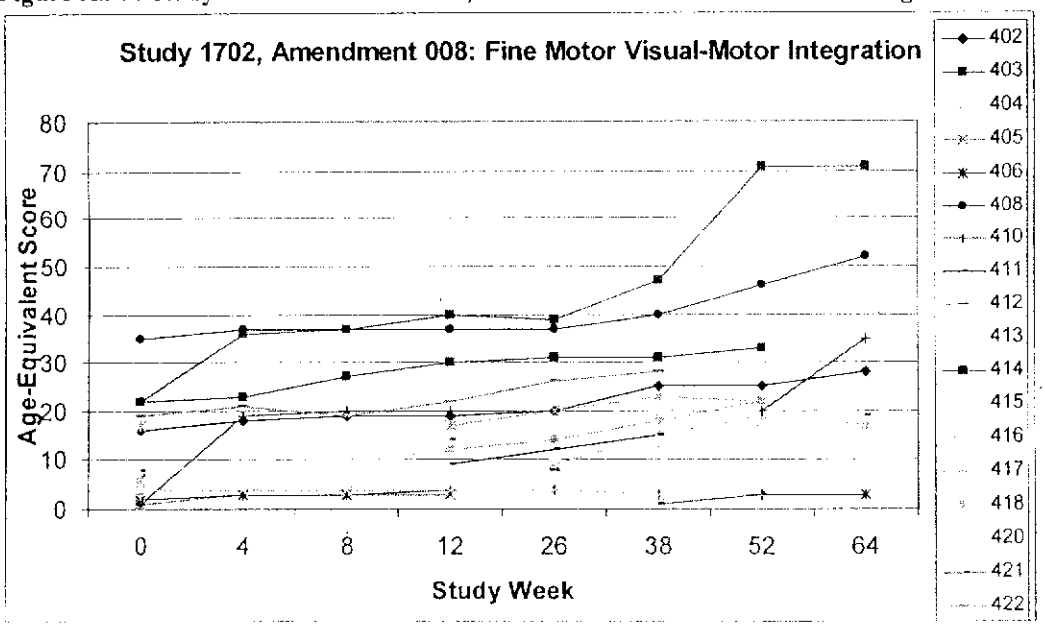
The Fine Motor Grasping stubtest results in the 18 of 21 treated patients with available results are represented graphically in the following figure.

Figure A2-8: Study 1702 Amendment 008, PDMS Fine Motor Grasping Skills Subtest



The Fine Motor Visual-Motor Integration skills subtest results in the 18 of 21 treated patients with available results are represented graphically in the following figure.

Figure A2-9: Study 1702 Amendment 008, PDMS Fine Motor Visual-Motor Integration Skills Subtest



10.1.2.12.8.1.3 Pompe PEDI

The Pompe PEDI is used to assess the functional capabilities of Pompe disease patients, and is intended for children ages six months to seven and a half years of age. The Pompe PEDI is administered as a parental-report questionnaire (scored as "capable" or "unable"), with higher scores indicating better performance. An increase in raw score of one point indicates the acquisition of a new skill. Raw scores are transformed to normative and scaled scores. Normative scores describe how a child is performing compared to same-aged peers without a disability. Scaled scores are reported on a 0-100 continuum and are used to represent function skills achieved (the higher the score, the more skills the child can perform). A clinically meaningful change in functional status has been defined as a gain in the scaled score greater than two times the standard error (SE) of the baseline scaled score. Mobility categories by scaled scores are defined as: limited movement 0-30 for patients, incipient mobility 30-50, basic self mobility 50-70, and advanced skill movement 70-100. Self-care categories by scaled scores are defined as: object use 0-30, incipient self-care 30-50, basic person care 50-70, and advanced self-care 70-100.

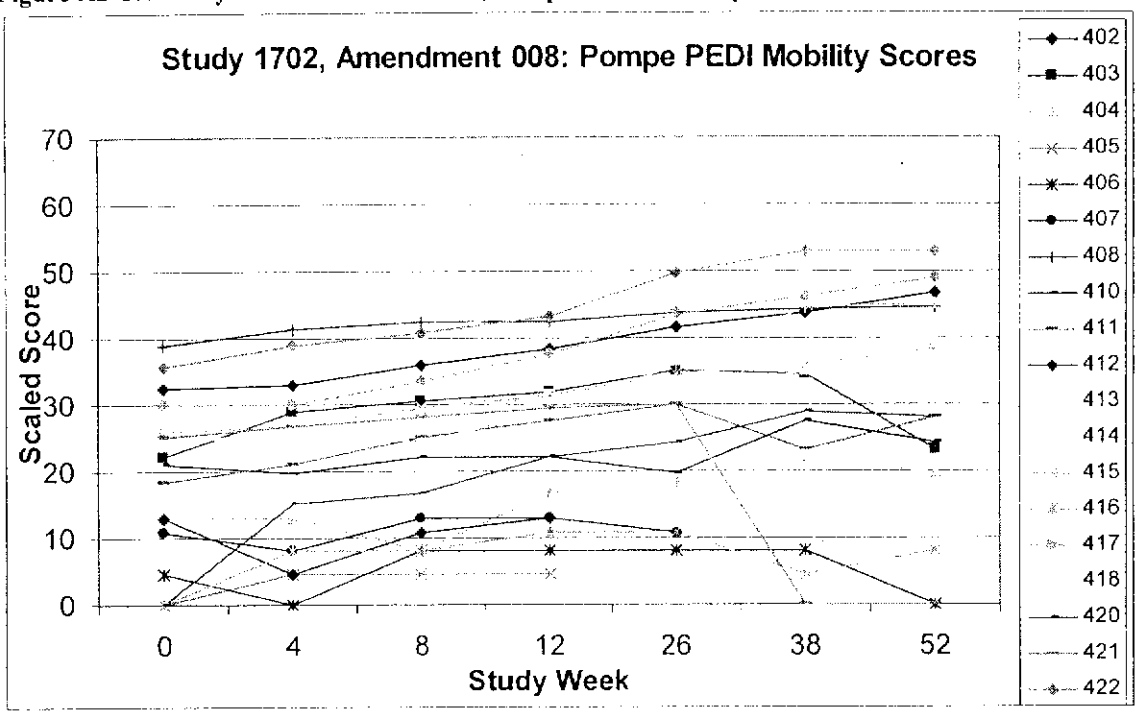
The results showed that 19 of 21 patients had baseline and at least one subsequent Pompe PEDI evaluation at Week 12 or later (not Patients 409 and 419). For the mobility scores, ten of 19 patients with follow-up scores showed clinically relevant increases in scaled scores from baseline, although all patients were delayed compared to same-aged peers. The remaining nine patients showed no improvement or regression in mobility scores. The mobility scores appeared to correlate with patient outcome/respiratory status, with the patients demonstrating gains tending to do well, and the patients not demonstrating gains tending to do poorly. Of the ten patients showing gains in mobility scores, eight did not require ventilatory support and two (who were on invasive ventilation at baseline) remained on invasive ventilation. In the nine patients who did not demonstrate gains in mobility scores, four died, four (who were on invasive ventilation at baseline) remained on invasive ventilation, and one (Patient 421) suffered a cardio-respriatory arrest at Week 32. Patients with higher mobility scores also tended to do better (by outcome of death and ventilation status) than did patients with lower scores. Of the eight patients with a mobility score >30 at the last available visit, seven did not require invasive ventilatory support, whereas of the 13 patients with mobility scores ≤30, five died, five required invasive ventilatory support, and three did not require invasive ventilatory support (however, one of these patients suffered a cardio-respiratory arrest). These results are similar to the results seen for Gross Motor function in the PDMS-2. The Pompe PEDI mobility scores by raw, scaled, and normative scores at baseline and last available result are summarized for the 21 treated patients, in the following table (complete results are listed in the subappendix), and are represented graphically in the following figure.

Table A2-18: Study 1702 Amendment 008, Pompe PEDI Mobility Scores

Patient	Week	Age (mos)	Mobility Scores			Status
			Raw	Scaled (SE)	Normative Std	(Start/End)
402	0	17.0	24	32.42 (1.29)	20.25	None
402	52	29.3	59	46.86	13.77	None
403	0	37.7	10	22.18 (1.83)	<10	Invasive
403	52	50.0	11	23.23	<10	Invasive
404	0	7.9	4	13.08 (2.52)	<10	None
404	52	20.1	8	19.75	<10	None
405	0	13.1	0	0 (5.79)	<10	Invasive
405	12	16.0	1	4.53	<10	Died
406	0	16.4	1	4.53 (3.63)	<10	Invasive
406	52	28.6	0	0	<10	Invasive
407	0	8.0	3	10.8 (2.73)	<10	None
407	12	11.1	4	13.08	<10	Died
408	0	43.6	37	38.81 (1.14)	<10	None
408	52	55.7	52	44.57	<10	None
409	0	6.5	5	15.06 (2.37)	<10	None
409	4	7.2	4	13.08	<10	Died
410	0	36.8	9	21.01 (1.89)	<10	Invasive
410	52	49.4	12	24.22	<10	Invasive
411	0	9.3	7	18.37 (2.1)	10.73	Noninvasive
411	52	22.1	17	28.15	<10	Invasive
412	0	8.0	4	13.08 (2.52)	<10	None
412	26	14.3	3	10.8	<10	Died
413	0	6.9	12	24.22 (1.68)	22.73	None
413	38	16.1	29	35.06	25.45	Invasive
414	0	24.3	65	48.66 (0.93)	36.57	None
414	52	36.6	66	48.96	12.76	None
415	0	15.0	14	25.93 (1.56)	<10	None
415	52	27.1	36	38.39	<10	None
416	0	18.2	0	0 (5.79)	<10	Invasive
416	52	30.2	2	8.07	<10	Invasive
417	0	14.5	20	30.07 (1.35)	15.65	None
417	52	26.6	66	48.96	19.42	None
418	0	8.4	14	25.9 (1.56)	26.24	None
418	52	20.6	54	45.23	28.52	None
419	0	8.9	9	21.01 (1.89)	16.15	None/Died
420	0	3.3	0	0 (5.79)	21.75	Noninvasive
420	52	16.0	17	28.15	11.87	None
421	0	9.0	13	25.12 (1.62)	24.58	None
421	52	22.0	0	0	<10	None
422	0	17.6	30	35.57 (1.23)	26.45	None
422	58	31.5	80	53.01	25.41	None

The Pompe PEDI Mobility scores for the 19 of 21 patients with results available at baseline and at at least one post-baseline visit at Week 12 or later are represented graphically in the following figure.

Figure A2-10: Study 1702 Amendment 008, Pompe PEDI Mobility Scores



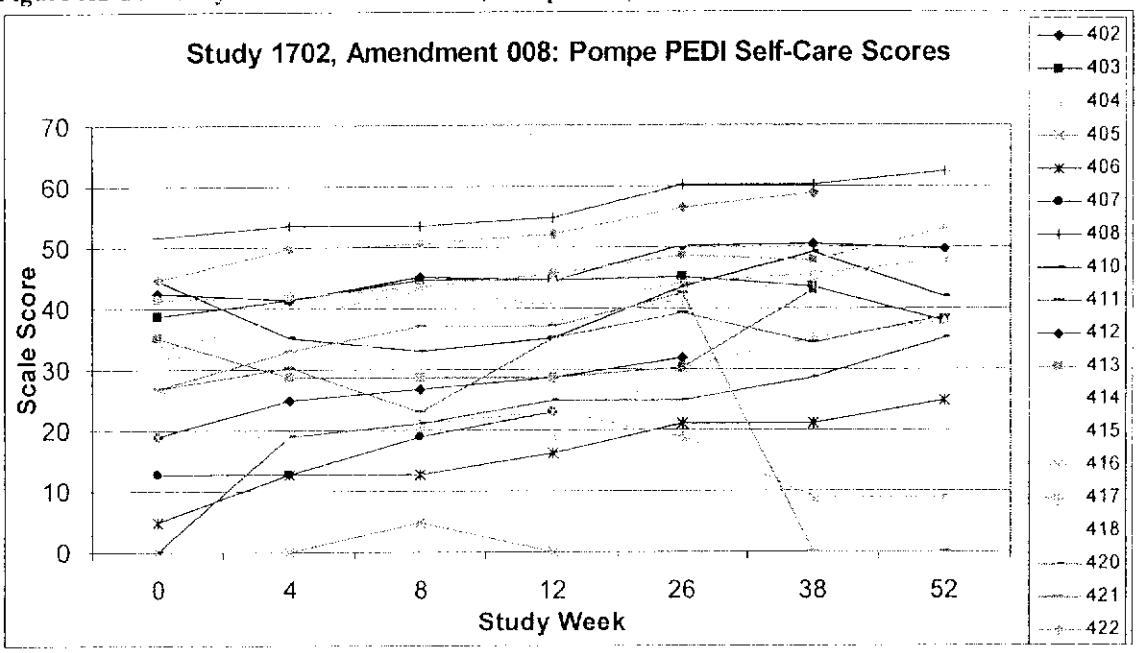
For the self-care scores, 14 of 19 patients with follow-up scores showed clinically relevant increases in scaled scores from baseline, and four patients had self-care scores comparable to normed scores for non-disabled same-aged peers (Patients 413, 417, 418 and 422). This result is not surprising as self-care scores measure levels of function that predominantly involve the use of hands and fingers (fine motor and proximal control), which would be expected to be more preserved in Pompe disease (these results are also consistent with the results seen in the PDMS-2 fine motor subtests). It is not known, however, if the fine motor gains were a result of treatment as these findings are consistent with the natural progression of the underlying disease, and as the patient outcome/respiratory status did not tend to correlate with gains demonstrated in self-care scores (e.g., two of the 14 patients with gains in self-care scores died). The remaining five patients showed no either improvement or regression in self-care scores. The Pompe PEDI self-care scores by raw, scaled, and normative scores at baseline and last available result are summarized for the 21 treated patients in the following table (complete results are listed in the subappendix), and are represented graphically in the following figure.

Table A2-19: Study 1702 Amendment 008, Pompe PEDI Self-Care Scores

Patient	Week	Age (mos)	Self-Care Scores			Status
			Raw	Scaled (SE)	Normative Std	(Start/End)
402	0	17.0	25	42.44 (1.37)	48.02	None
402	52	29.3	39	49.67	35.47	None
403	0	37.7	19	38.57 (1.53)	<10	Invasive
403	52	50.0	18	37.82	<10	Invasive
404	0	7.9	9	26.86 (2.47)	25.82	None
404	52	20.1	18	37.82	19.95	None
405	0	13.1	0	0 (6.28)	<10	Invasive
405	12	16.0	0	0	<10	Died
406	0	16.4	1	4.92 (3.97)	<10	Invasive
406	52	28.6	8	24.97	<10	Invasive
407	0	8.0	3	12.7 (3.45)	<10	None
407	12	11.1	7	23.05	15.15	Died
408	0	43.6	43	51.59 (1.24)	10.81	None
408	52	55.7	69	62.55	21.15	None
409	0	6.7	6	21.03 (2.6)	<10	None
409	4	7.2	3	12.7	<10	Died
410	0	36.8	29	44.66 (1.3)	14.35	Invasive
410	52	49.4	24	41.86	<10	Invasive
411	0	9.3	9	26.86 (2.47)	25.82	Noninvasive
411	52	22.1	19	38.57	21.62	Invasive
412	0	8.0	5	18.79 (2.8)	<10	None
412	26	14.3	12	31.8	27.43	Died
413	0	6.9	15	35.25 (1.79)	49.36	None
413	38	16.1	26	43	49.09	Invasive
414	0	24.3	41	50.64 (1.24)	48.6	None
414	52	36.6	51	55.23	32.55	None
415	0	15.0	13	33.1 (1.98)	29.95	None
415	52	27.1	35	47.71	31.61	None
416	0	18.2	5	18.79 (2.8)	<10	Invasive
416	52	30.2	2	8.99	<10	Invasive
417	0	14.5	23	41.24 (1.4)	45.69	None
417	52	26.6	46	52.99	42.03	None
418	0	8.4	12	31.8 (2.12)	39.69	None
418	52	20.6	36	48.2	43.14	None
419	0	8.9	8	24.97 (2.51)	20.53	None/Died
420	0	3.3	0	0 (6.28)	19.4	Noninvasive
420	52	16.0	15	35.25	34.11	None
421	0	9.0	9	26.86 (2.47)	25.82	None
421	52	22.0	0	0	<10	None
422	0	17.6	29	44.66 (1.3)	52.3	None
422	58	31.5	63	60.18	49.76	None

The Pompe PEDI Self-Care scores for the 19 of 21 patients with results available at baseline and at at least one post-baseline visit at Week 12 or later are represented graphically in the following figure.

Figure A2-11: Study 1702 Amendment 008, Pompe PEDI Self-Care Scores



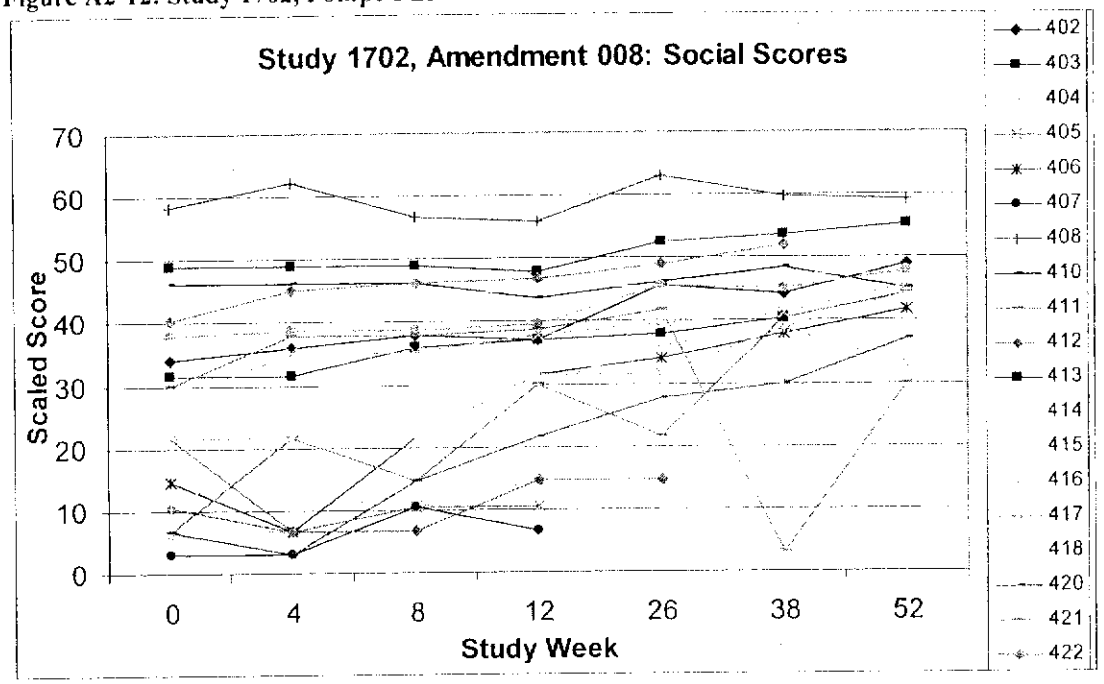
For the Social scores, 13 of 19 patients with follow-up scores showed clinically relevant increases in scaled scores from baseline, and six of these patients had social scores comparable to normed scores for non-disabled same-aged peers (Patients 402, 411, 413, 418, 420, and 422). This result is also not surprising as the social function domain of the Pompe PEDI measured skills such as comprehension, expression, and social interaction, which would be less affected by motor impairment; however, for children who were very ill (e.g., ventilator dependent), the underlying illness likely would have affected the child's abilities in this functional domain. The remaining six patients showed either no improvement or regression in social scores. The Pompe PEDI social scores by raw, scaled, and normative scores at baseline and last available result are summarized for the 21 treated patients in the following table (complete results in the subappendix):

Table A2-20: Study 1702 Amendment 008, Pompe PEDI Social Function Scores

Patient	Week	Age (mos)	Social Function Scores			Status
			Raw	Scaled (SE)	Normative Std	(Start/End)
402	0	17.0	10	34 (1.6)	42.6	None
402	52	29.3	31	49.1	40.1	None
403	0	37.7	31	49.1 (1.2)	36.1	Invasive
403	52	50.0	42	55.4	22.6	Invasive
404	0	7.9	2	6.6 (2.9)	24.2	None
404	52	20.1	6	27.7	<10	None
405	0	13.1	5	21.6 (5.5)	25.2	Invasive
405	12	16.0	3	10.5	<10	Died
406	0	16.4	4	14.7 (3.2)	15.5	Invasive
406	52	28.6	19	41.8	19.3	Invasive
407	0	8.0	1	3.1 (3.1)	20	None
407	12	11.1	2	6.6	24.2	Died
408	0	43.6	47	58.5 (1.3)	40.3	None
408	52	55.7	48	59.2	28.7	None
409	0	6.5	6	27.7 (2.7)	49.9	None
409	4	7.2	6	27.7	49.9	Died
410	0	36.8	26	46.2 (1.2)	32.5	Invasive
410	52	49.4	24	45	<10	Invasive
411	0	9.3	2	6.6 (2.9)	24.2	Noninvasive
411	52	22.1	23	44.4	42.5	Invasive
412	0	8.0	3	10.5 (3.2)	28.9	None
412	26	14.3	4	14.7	15.5	Died
413	0	6.9	8	31.6 (1.8)	54.6	None
413	38	16.1	17	40.4	51.4	Invasive
414	0	24.3	21	43.1 (1.2)	39	None
414	52	36.6	28	47.3	33.9	None
415	0	15.0	6	27.7 (2.7)	33.8	None
415	52	27.1	25	45.6	30.1	None
416	0	18.2	5	21.6 (5.5)	25.2	Invasive
416	52	30.2	9	32.9	<10	Invasive
417	0	14.5	14	37.9 (1.5)	48	None
417	52	26.6	29	47.9	36.8	None
418	0	8.4	3	10.5 (3.2)	28.9	None
418	52	20.6	23	44.4	42.5	None
419	0	8.9	7	30 (2.1)	52.6	None/Died
420	0	3.3	2	6.6 (2.9)		Noninvasive
420	52	16.0	13	37	46.8	None
421	0	9.0	7	30 (2.1)	52.6	None
421	52	22.0	7	30	<10	None
422	0	17.6	17	40.4 (1.3)	51.4	None
422	58	31.5	39	53.7	43.4	None

The Pompe PEDI Social Function scores for the 19 of 21 patients with results available at baseline and at at least one post-baseline visit at Week 12 or later are represented graphically in the following figure:

Figure A2-12: Study 1702, Pompe PEDI Social Function Scores



Thus, overall, the motor development assessments were notable for:

- By the AIMS test, four of 14 patients with available results at baseline and at Week 12 (or later) gained motor milestones from baseline that were maintained through Week 52; however all of these patients were delayed compared to norms for same-age peers.
- By the PDMS-2, 18 patients had results available at baseline and at Week 12 (or later). Results in these patients showed that 12 of 18 patients had modest gains in gross-motor function in one or more category (stationary, locomotion or object manipulation), and all of these patients were substantially delayed compared to age-matched norms. Gains in fine-motor function were more evident, with 14 patients showing increases in scores that approached age-matched norms in eight of these patients. This result is not unexpected, as upper extremity motor function, particularly the distal musculature, is relatively spared compared to lower extremity, proximal motor function in Pompe disease. It is not known, however, if the PDMS-2 results seen in this study were due to treatment with rhGAA, as these findings are consistent with the natural progression of the underlying disease. It is additionally noted that the gross motor function results, and not the fine motor results, tended to be a better predictor of patient outcome (by survival and ventilator status), with patients demonstrating gains in gross motor function tending to have better outcomes.

- The results for the Pompe PEDI scores were similar to the results for the PDMS-2 scores, with ten of 19 patients with available results at baseline and at Week 12 (or later) demonstrating gains in mobility scores; however, all patients had mobility scores that were substantially delayed compared to age-matched norms.

10.1.2.12.8.2 Cognitive Development

Cognitive development was assessed using the BSID-II test, which is used to assess cognitive, language, and personal/social development in children from one through 42 months of age. BSID-II MDI scores within 85-114 are within normal limits relative to age-matched peers, 70-84 show mildly delayed performance, and scores ≤69 show significantly delayed performance. The BSID-II was not intended to be used in children with severe physical impairment and may not accurately reflect cognitive development in the most severely impaired children in this study.

The Leiter-R Brief IQ test was administered to patients ages ≥24 months in combination with the BSID-II until patients reached the ceiling of the BSID-II (age 42 months). The results of the Leiter-R Brief IQ test were submitted to the BLA as raw data in incomplete datasets (with two entries, one each for two patients). The Leiter-R data were unusable and uninterpretable in the format provided by the sponsor and will not be considered further in this review.

The results showed two patients died before follow-up evaluations at or after Week 12 could be obtained (Patients 409 and 419), one patient was beyond the age limits of the test at baseline (Patient 408, age 43 months at baseline), and one patient (Patient 410) did not have a baseline evaluation. Thus, 17 patients had baseline and at least one post-baseline evaluation at Week 12 or later available for review, 12 of whom had results through Week 52. Of these 17 patients, eight patients had MDI scores within the normal range (≥85) at baseline, five had MDI scores in the mildly delayed range, and four patients had an MDI showing significant delay. At the last available visit (at Week 12 or later), seven patients had not changed category by BSID score: four patients had normal scores at baseline and last visit (normal/normal), two were mild/mild, and one was severe/severe. Five patients had a worsening status, including: one patient was normal at baseline and mildly delyed at the last available visit (normal→ mild), three patients were normal → severe, and one patient was mild → severe. Five patients had an improved status, including two patients who were mildly delayed at baseline and normal at the last available visit (mild → normal), and three patients were severe → mild. The changes in BSID-II category results are summarized in the following shift table.

Table A2-21: Study 1702 Amendment 008, BSID-II Shift Table

		Endpoint*		
		Normal	Mild	Severe
Baseline	Normal	4	1	3
	Mild	2	2	1
	Severe	0	3	1

*Last available results at Week 12 or later

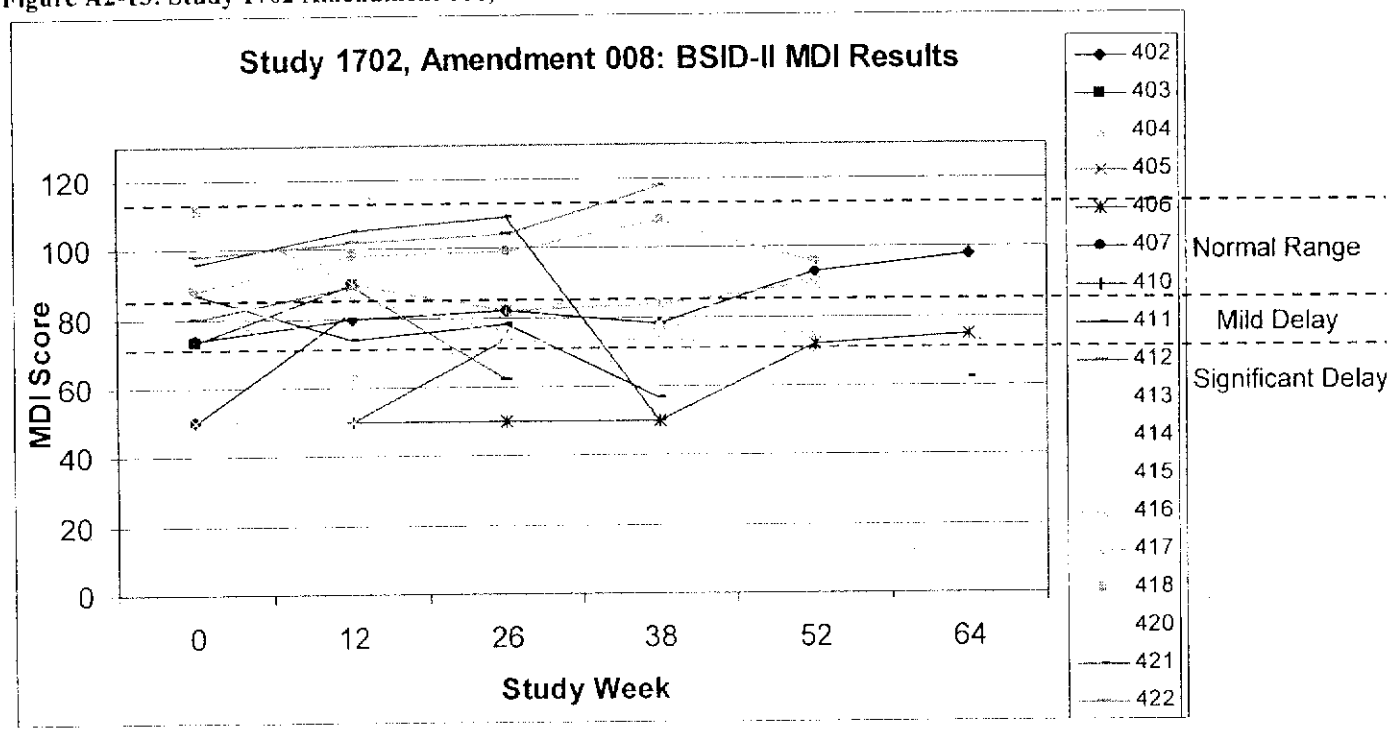
The BSID-II results are also summarized by individual patient for BSID-II scores at baseline and last available result in the following table and are represented graphically in the following figure (a complete listing of results is located in the subappendix).

Table A2-22: Study 1702 Amendment 008, BSID-II Scores

Patient	Week	Raw Score	Age (Mos)	Age Equiv (mos)	MDI	MDI Category
402	0	95	17.0	14	74	Mild
402	64	147	32.1	30	98	Normal
403	0	145	37.7	29	73	Mild
403	38	175	46.7	46	.	Normal*
404	0	64	7.9	6	84	Mild
404	52	102	20.1	16	71	Mild
405	0	10	13.0	0	<50	Severe
405	12	34	16.0	3	<50	Severe
406	0	54	16.4	5	<50	Severe
406	64	135	31.3	25	75	Mild
407	0	28	8.0	2	<50	Severe
407	12	67	11.1	7	82	Mild
408	0	161	43.6	38	.	
408	52	176	55.7	42	.	
409	0	40	6.5	3	54	Severe
410	0	.	36.8	.	.	
410	64	160	52.2	37	-	
411	0	69	9.3	7	87	Normal
411	64	117	24.9	19	62	Severe
412	0	53	8.0	5	80	Mild
412	26	71	14.3	8	62	Severe
413	0	65	6.9	6	96	Normal
413	38	87	16.1	12	77	Mild
414	0	125	24.3	21	84	Mild
414	52	146	36.6	30	82	Mild
415	0	93	15.0	13	89	Normal
415	52	123	27.1	21	62	Severe
416	0	72	18.2	8	<50	Severe
416	52	135	30.2	25	75	Mild
417	0	100	14.5	15	112	Normal
417	52	134	26.6	24	90	Normal
418	0	66	8.4	7	88	Normal
418	52	118	20.6	19	96	Normal
419	0	58	8.9	5	72	Mild
420	0	29	3.3	2	91	Normal
420	52	98	16.0	15	90	Normal
421	0	70	9.0	7	96	Normal
421	38	2	18.6	0	<50	Severe
422	0	107	17.6	17	98	Normal
422	58	146	31.5	30	95	Normal

*Patient's age was >42 months at last evaluation (age 46.7 months), but age equivalent score was 46 months, so will be considered as being within normal limits for age

Figure A2-13: Study 1702 Amendment 008, BSID-II MDI Results



Although these results are, in general, encouraging for the cognitive development of children with Pompe's disease, longer-term follow-up of the cognitive development in these children is needed.

10.1.2.12.8.3 Physical Growth by Body Length, Weight and Head Circumference

Weight, length, and head circumference were measured at regular intervals throughout the study. The dataset for the growth parameters is considered by this Reviewer to be of poor quality, and the results are not felt to be reliable. There were numerous missing datapoints and obvious errors throughout the dataset, which were particularly true for the head circumference and length results where there were numerous instances of implausible results, such as patients appearing to lose length or head circumference from visit to visit.

Despite the limitations in the data, the overall growth parameter results showed that, in general, most patients in the study appeared to gain weight, to increase in length, and to increase their head circumference (up to a point); however, these results are to be interpreted with caution. The overall growth results for the study are summarized in the following table:

Table A2-23: Study 1702 Amendment 008, Growth Parameters for All 21 Patients

	Day 0*	Week 12	Week 26	Week 52
Parameter				
Weight (kg), n =	21	19	17	14
Mean	9.1	10.4	11.5	13.0
Median	8.3	9.6	10.7	12.1
Min, max	5.3, 16	6.1, 14.9	7.8, 16.3	10.3, 19.1
Weight Z-score, n =	21	19	17	14
Mean	-1.3	-0.9	-0.6	-0.3
Median	-1.2	-0.6	-0.5	-0.5
Min, max	-3.9, +3.0	-4.1, +1.7	-3.2, +1.3	-1.7, +1.2
Length (cm), n =	21	19	17	13
Mean	76.7	81.5	85.5	92.2
Median	73.5	79	82	89.5
Min, max	61, 100	68.6, 97.5	74.7, 110	80, 116
Length Z-score, n =	21	19	17	13
Mean	-0.1	0.2	0.3	0.4
Median	0.2	0.1	0.2	0.6
Min, max	-2.7, +3.9	-2.5, 4.1	-2.8, +6.7	-2.5, +3.1
Head Circumference (cm), n =	21	18	15	14
Mean	45.5	46.4	47.6	48.4
Median	45	46	47	48.8
Min, max	39.5, 50.5	40.2, 52.3	44, 52.3	41, 53.5
Head Circumference Z-score, n =	18	15	12	11
Mean	-0.2	-0.6	-0.3	-0.5
Median	-0.5	-0.6	-0.5	-0.1
Min, max	-2.3, +3.8	-3.9, +1.5	-1.6, +1.3	-5.3, +1.6

*Day 0 assessments were used except in a few instances when Baseline assessments were used when no Day 0 assessments were available

Length

Lengths by individual patient are summarized in the following table. Length results are notable for apparent errors in measurements in eight of 19 patients with length measurements available at baseline and follow-up at Week 12 (or later). Patients with length results felt to be unreliable (in the opinion of this Reviewer) are highlighted in the table.

Table A2-24: Study 1702 Amendment 008, Length (cm)

	Patient Number										
Week	**402**	**403**	**404**	**405**	**406**	**407**	**408**	**409**	**410**	**411**	**412**
0	78.5	99	68	71	94	66	100	63.6	89	74.3	71
4	79.8	98	69	72.5	91	65	-	65.2	89	73.5	64
8	79.6	95	68.7	75.2	94	67.5	-	-	84	75.4	74.5
12	82	95.5	71.5	76	97.5	68.6	97	-	93.8	77.8	87
26	84.9	98	74.7	-	110	-	102.5	-	92	82	77
38	86	100.8	78	-	104.5	-	-	-	-	89.1	-
52	87.7	100.9	84	-	101	-	107.2	-	116	89.5	-
64	90.2	100.7	85.5	-	104.3	-	-	-	-	86.5	-
	Patient Number										
Week	**413**	**414**	**415**	**416**	**417**	**418**	**419**	**420**	**421**	**422**	-
0	70	76	81	82.8	73	73.2	70	61	73.5	76.5	-
4	70	79	81	85.2	75	73.4	-	65	75	77	-
8	73	79	82.5	83.5	76	73.7	-	68.9	75.5	78.5	-
12	75	79	82.5	88	74	75.6	-	70.8	76.5	80	-
26	82	80	85	89	79	79	-	75	80.5	83.5	-
38	87	82	87	63	78.7	-	-	77	-	86	-
52	-	84	91	-	82	85.1	-	80	-	90	-
64	-	-	-	-	-	-	-	-	-	-	-

Lengths by individual patients are represented in the following figure using a y-axis scale of 0-140 cm (Figure A3-14), then with the area of interest magnified (Figure A3-15) using a y-axis scale of 60-120 cm.

Figure A2-14: Study 1702, Amendment 008, Length in cm (Scale 0-140 cm)

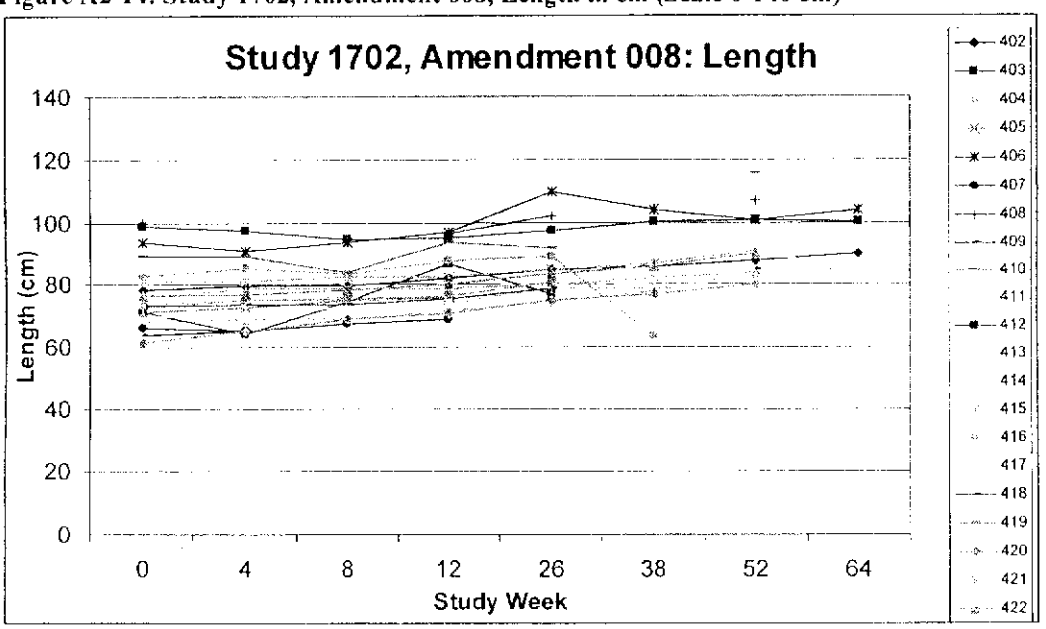
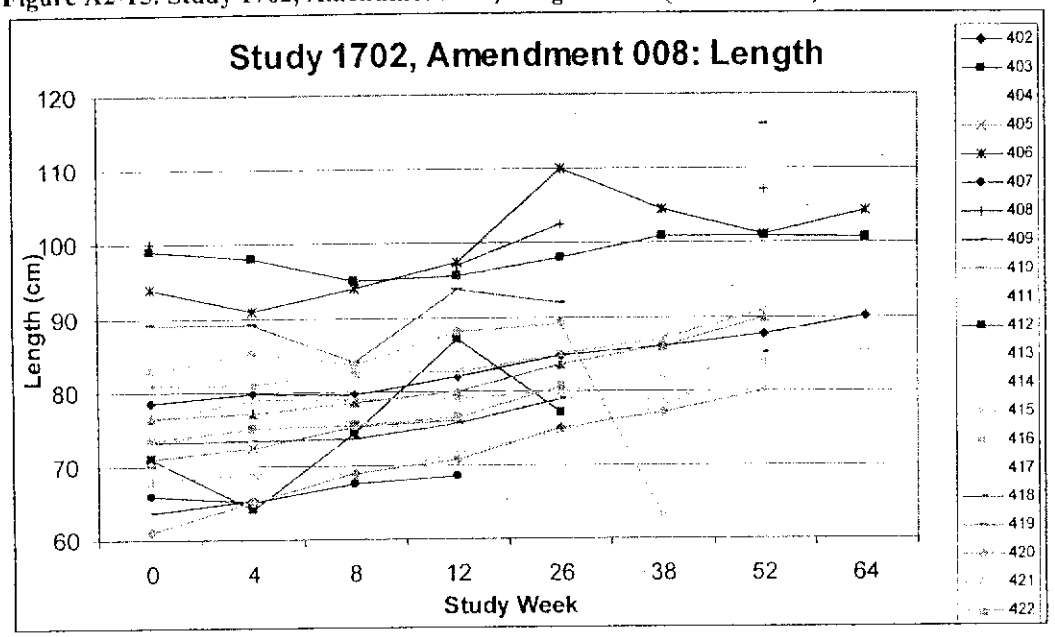
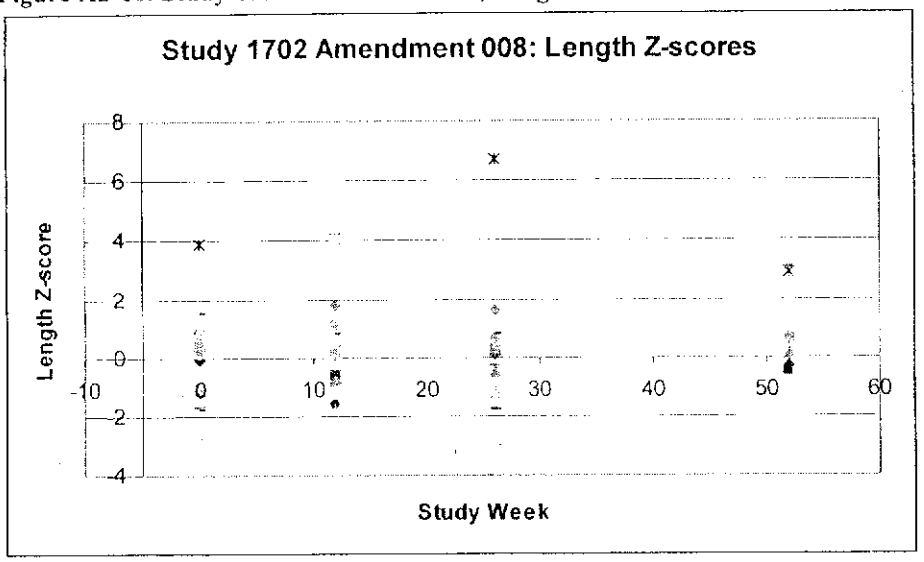


Figure A2-15: Study 1702, Amendment 008, Length in cm (Scale 60-120)



Length z-scores are also represented graphically in the following figure. In general, most length results appeared to fall within 2 SD of the mean for age for the 21 treated patients in the study; however, given the unreliability of the data, these results should be interpreted with caution.

Figure A2-16: Study 1702 Amendment 008, Length Z-Scores for All 21 Patients



Head Circumference

Head circumferences by individual patient are summarized in the following table. These results are notable for apparent errors in measurements in six of 19 patients with head circumference measurements available at baseline and follow-up at Week 12 (or later). Patients with head circumference results felt to be unreliable (in the opinion of this Reviewer) are highlighted in the table.

Table A2-25: Study 1702 Amendment 008, Head Circumference (cm)

	Patient Number										
Week	**402**	**403**	**404**	**405**	**406**	**407**	**408**	**409**	**410**	**411**	**412**
0	47	50.5	43.5	45	49.5	49	49	41.5	47.7	44.6	44.5
4	47.5	52.5	43	45	50	40.1	-	42.5	48	44.3	44.5
8	47.5	52.5	39	45.1	50	40.3	-	-	48	44.1	44.5
12	48	52.3	-	46	50	40.2	51.6	-	49	45.7	44
26	49	52.3	46.5	-	-	-	51.7	-	50	46.1	45
38	49.5	53.5	47	-	49.5	-	-	-	-	46.5	-
52	49	53.5	48	-	51.5	-	50.8	-	51	41	-
64	48.8	53.5	49	-	50.3	-	-	-	-	46.9	-

	Patient Number										
Week	**413**	**414**	**415**	**416**	**417**	**418**	**419**	**420**	**421**	**422**	-
0	41.5	47.5	46	49.1	44	41	43.5	39.5	46.5	45	-
4	41.5	48	46.5	48.5	44	42.2	-	41	45	-	-
8	43	48	45.8	48.3	44	42.5	-	42.4	45	45.5	-
12	43	48	45.6	49	45	42.5	-	43.1	46.5	46	-
26	44	48.5	47	49	46	-	-	44.5	46.5	48.5	-
38	45.3	48.5	47.5	48.5	46	-	-	45	-	48	-
52	-	49	48	49	47	45.2	-	45.5	-	48.5	-

Head circumferences by individual patients are represented in the following figure using a y-axis scale of 0-60 cm (Figure A3-17), then with the area of interest magnified (Figure A3-18) using a y-axis scale of 40-56 cm.

Figure A2-17: Study 1702, Amendment 008, Head Circumference in cm (Scale 0-60 cm)

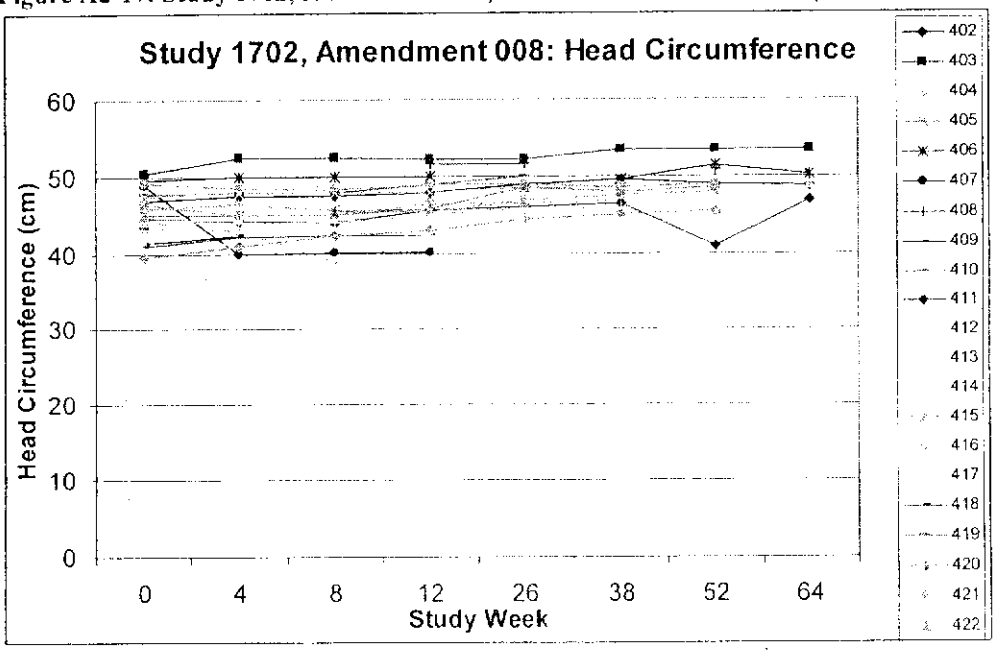
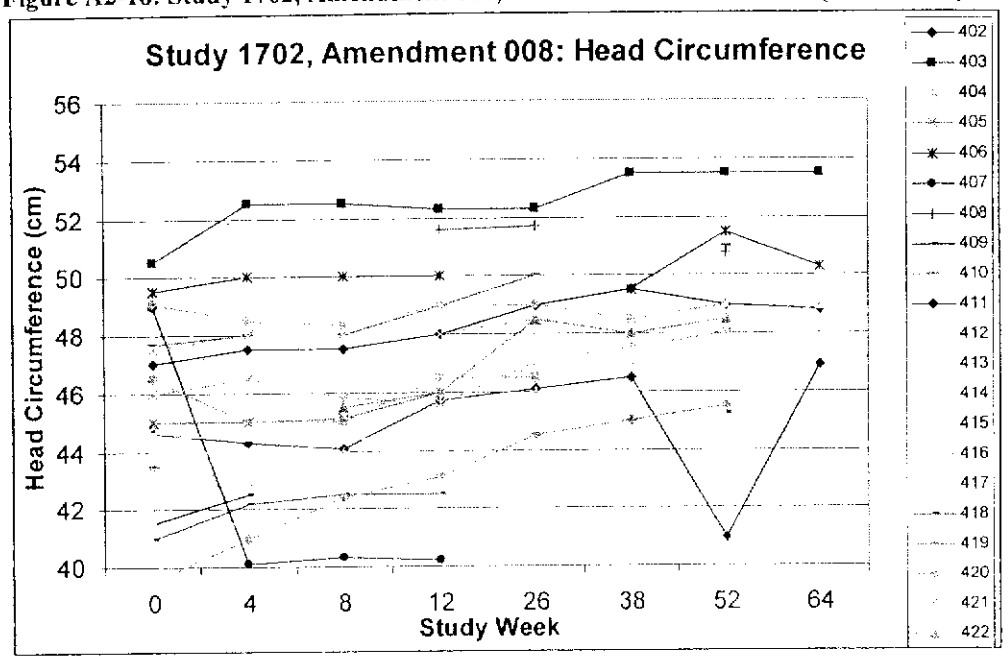
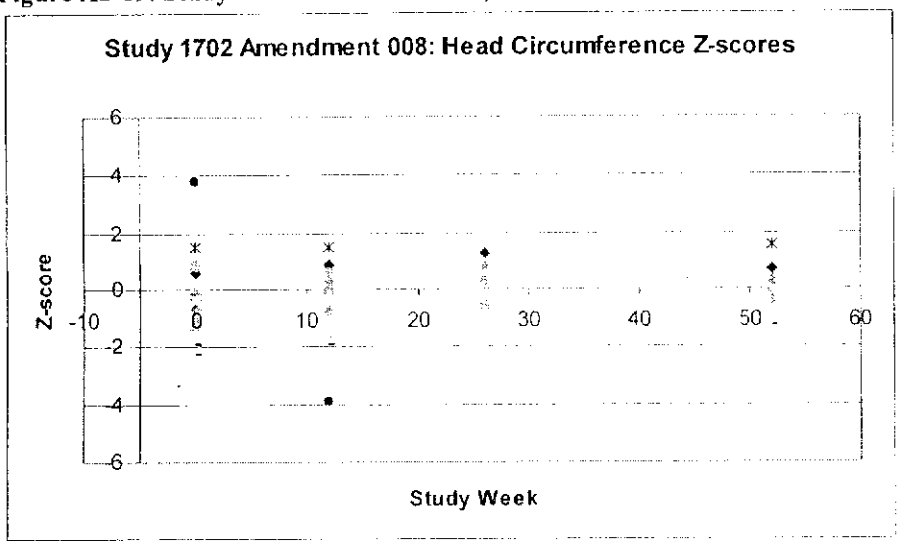


Figure A2-18: Study 1702, Amendment 008, Head Circumference in cm (Scale 40-56)



Head circumference z-scores are also represented graphically in the following figure. In general, most head circumference z-score results appeared to fall within 2 SD of the mean for age for the 21 treated patients in the study; however, given the unreliability of the data, these results should be interpreted with caution

Figure A2-19: Study 1702 Amendment 008, Head Circumference Z-Scores for All 21 Patients



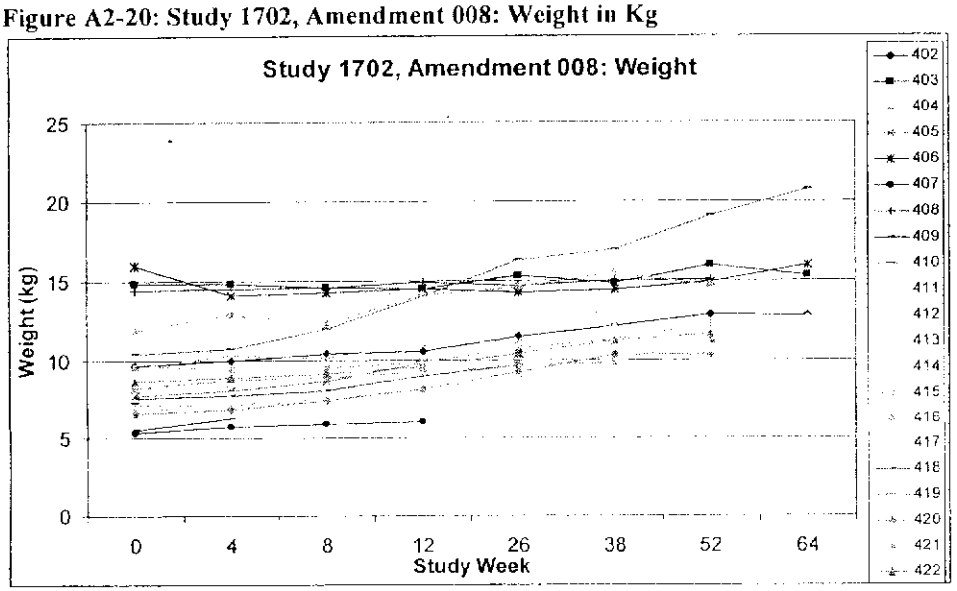
Weight

Weight results over time by individual patient are summarized in the following table and are represented graphically in the following figure. No obvious errors in the weight parameters were noted.

Table A2-26: Study 1702 Amendment 008, Weight (kg)

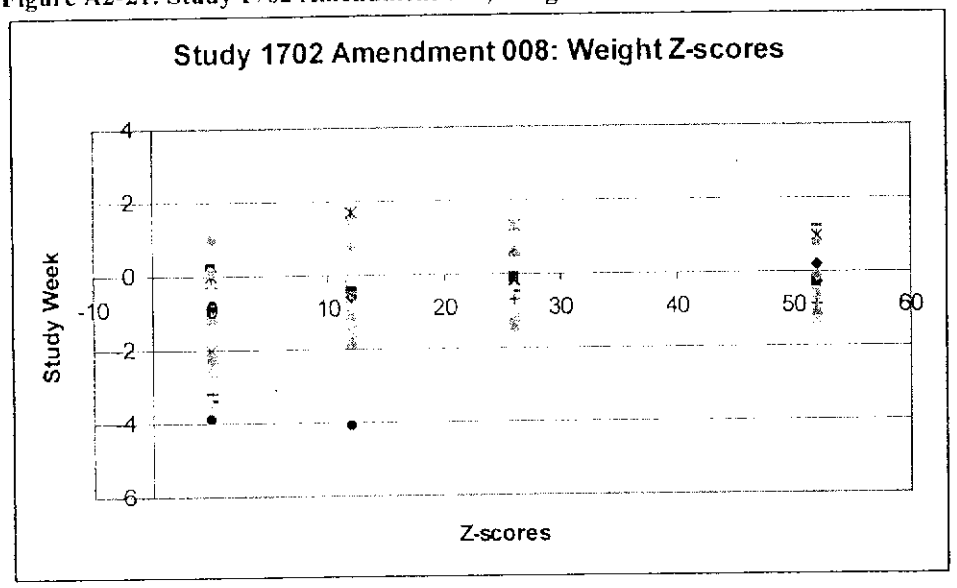
	Patient Number										
Week	**402**	**403**	**404**	**405**	**406**	**407**	**408**	**409**	**410**	**411**	**412**
0	9.7	14.8	6.8	7.8	16	5.3	14.4	5.5	10.4	9.1	7.3
4	10	14.8	7.2	8.1	14.1	5.7	14.5	6.3	10.7	8.7	7.8
8	10.4	14.6	7.6	8.7	14.3	5.9	14.6	-	12	9	7.9
12	10.6	14.5	8.2	9.8	14.5	6.1	14.9	-	14	9.3	7.5
26	11.5	15.3	9	-	14.3	-	14.7	-	16.3	10.7	7.8
38	12.1	14.8	9.9	-	14.4	-	15	-	17	9.9	-
52	12.9	16	11.2	-	14.9	-	15.1	-	19.1	11	-
64	12.8	15.3	11.6	-	16	-		-	20.7	12.6	-
	Patient Number										
Week	**413**	**414**	**415**	**416**	**417**	**418**	**419**	**420**	**421**	**422**	-
0	6.6	9.6	9.7	11.9	7.2	7.6	7.3	6.6	8.3	8.7	-
4	6.6	10.3	9.4	12.9	7.1	7.8	-	6.9	8.8	8.9	-
8	8.1	10.2	9.5	12.3	7.5	8.1	-	7.5	8.9	9.2	-
12	8.6	11	9.9	14.1	7.9	9	-	8.2	9.3	9.6	-
26	10.8	11.2	10.7	14.6	8.9	9.7	-	9.3	9.7	10.4	-
38	12.1	11.5	11.3	15.5	9.4		-	10.3	9.8	11.2	-
52	-	11.9	12.2	14.7	10.5	11.1	-	10.3	-	11.6	-
64	-	-	-	-	-	-	-	-	-	-	-

Figure A2-20: Study 1702, Amendment 008: Weight in Kg



Weight Z-scores over time by individual patient are also represented graphically in the following figure.

Figure A2-21: Study 1702 Amendment 008, Weight Z-Scores for All 21 Patients



Thus, the results for growth overall show that most patients appeared to gain weight, to increase in length, and to increase their head circumference during the study. However, due to the poor quality of the data, these data are unlikely to represent the true results of the study, and no conclusions will be drawn from the growth results.

10.1.2.12.9 Exploratory Analysis

10.1.2.12.9.1 CRIM Status and ACE Marker Allele Status

Circulating Reactive Immune Material (CRIM) status was determined from skin fibroblast assay in all patients. A patient was considered to be CRIM positive if the presence of any bands corresponding to the apparent molecular weight of major protein forms of GAA were detected in samples on Western blot assay (including 110, 95, 76 or 70 kDa forms). Angiotensin-converting enzyme (ACE) marker allele status was determined by polymerase chain reaction (PCR) amplification of genomic DNA. ACE is encoded in the DCP-1 gene, and polymorphisms consist of the absence (deletion, D allele) or presence (insertion, I allele) of a 287-base pair DNA Alu fragment located within intron 16 of the DCP-1 gene. The D allele may encourage the growth of type II muscle fibers (anaerobic metabolism) while the I allele may encourage the growth of type I muscle fibers (oxidative metabolism). This was evaluated for exploratory purposes only.

Fifteen (15) of 18 patients were CRIM positive, and three patients (407, 418, and 420) were CRIM negative at baseline. There was no obvious correlation between CRIM status and patient outcome over the course of this study. The ACE marker results showed that three of 18 patients had no results available, four patients were I/I, three patients were D/D and eight patients were

I/D. There was no obvious correlation between ACE marker allele status and outcome. The results are summarized in the following table.

Table A2-27: Study 1702, CRIM and ACE Marker Allele Status

Patient	CRIM Status	ACE Marker Allele Status	Baseline Status	Outcome
402	Positive	I/D	None	None
403	Positive	I/D	Invasive	Invasive
404	Positive	I/I	None	None
405	Positive	D/D	Invasive	Died
406	Positive	I/I	Invasive	Invasive
407	Negative	I/D	None	Died
408	Positive	D/D	None	None
409	Positive	Unknown	None	Died
410	Positive	Unknown	Invasive	Invasive
411	Positive	I/D	Noninvasive	Invasive
412	Positive	D/D	None	Died
413	Positive	D/D	None	Invasive
414	Positive	I/I	None	None
415	Positive	I/I	None	None
416	Positive	I/I	Invasive	Invasive
417	Positive	D/D	None	None
418	Negative	NA	None	None
419	Positive	Unknown	None	Died
420	Negative	D/D	Noninvasive	None
421	Positive	I/D	None	None
422	Positive	D/D	None	None

10.1.2.12.9.2 GAA mutations and GAA Activity

GAA mutational analysis results were available in 18 of 21 treated patients. The results showed that almost all patients had different mutations and most were compound heterozygotes. An analysis by GAA mutation was, therefore, not possible. GAA activity on muscle biopsy results were available in 19 of 21 treated patients at baseline, and of these patients, 14 had detectable GAA activity and five patients had GAA activity below the level of quantification at (lower limit of quantification of assay 3.0 nmol/hr/g wet tissue). No normal values for GAA activity in muscle biopsy specimens were provided, and according to the sponsor (personal communication) no normal ranges for GAA activity in muscle biopsy specimens are currently known. The results are summarized in the following table:

Table A2-28: Study 1702, GAA Mutations and Baseline GAA Activity

Patient	Maternal Allele	Maternal Allele: Class of Mutation	Paternal Allele	Paternal Allele: Class of Mutation	Baseline GAA Activity
402	670C>T	Missense (amino acid substitution)	925G>A	Missense	12.1
403	1556T>C	Missense	1441T>C	Missense	NA
404	1735G>A	Missense	655G>A	Missense	8.9
405	N/A	N/A	N/A	N/A	BQL
406	525delT	Frameshift leading to protein truncation	1448G>T	Missense	9.3
407	766_785delinsC	Frameshift leading to protein truncation	2432delT	Frameshift leading to protein truncation	BQL
408	3G>A	Loss of initiator Met; No protein produced?	923A>C	Missense	23.2
409	Unknown	Unknown	Unknown	Unknown	BQL
410	Unknown	Unknown	Unknown	Unknown	19.8
411	2560C>T	Nonsense	1933G>A	Missense	4.8
412	1561G>A	Missense	1827delC	Nonsense	BQL
413	2804T>C	Missense	2804T>C	Missense	BQL
414	796T>C	Missense	1316T>A	Missense	28
415	1655T>C	Missense	2560C>T	Nonsense	16.8
416	1978C>T	Missense	784G>A	Missense	7.2
417	1040C>G	Missense	1003G>A	Missense	31.5
418	N/A	N/A	N/A	N/A	9.3
419	Unknown	Unknown	Unknown	Unknown	NA
420	1209delC	Frameshift leading to protein truncation	1209delC	Frameshift leading to protein truncation	33.5
421	1655T>C	Missense	2237G>A	Nonsense	18.7
422	670C>T	Missense	670C>T	Missense	14.4

10.1.2.12.10 Immunogenicity

The immunogenicity results for all 21 patients show that 19 of 21 patients developed anti-rhGAA antibodies at anytime during the study. For the two patients who did not develop anti-rhGAA antibody, one patient (Patient 419) had no post-baseline antibody results, and the other patient (Patient 409) had antibody results available at baseline and Week 4 only. For the 19 of 21 patients with positive anti-rhGAA antibodies, one patient (Patient 407) had anti-rhGAA antibodies at baseline, and this patient's antibody titers increased markedly through Week 12 (last available antibody titer). Ten patients developed antibodies at Week 4, five patients at Week 8, and two patients at Week 12, and one patient at Week 38. One patient (411) with a positive antibody titer during the study had an antibody titer of zero at the end of the study. Most of the remaining patients had antibody titers that either continued to increase or remained elevated during the study and at the last available visit. Antibody titers by individual patient are summarized in the following table and in the following figure:

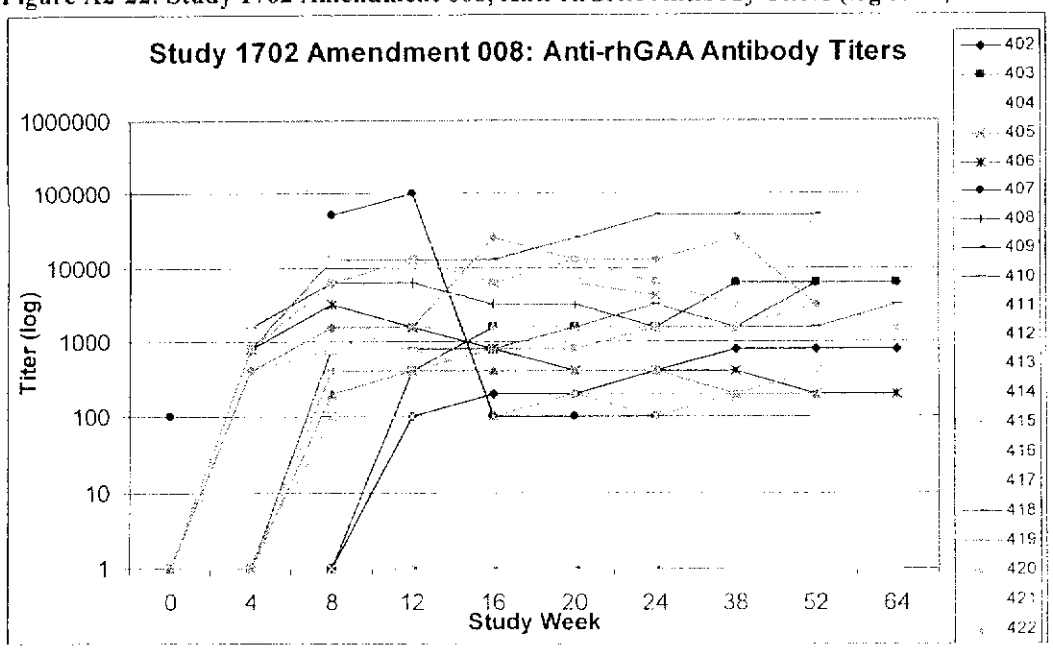
Table A2-29: Study 1702 Amendment 008, Anti-rhGAA Antibody Titers

	Patient Number										
Week	**402**	**403**	**404**	**405**	**406**	**407**	**408**	**409**	**410**	**411**	**412**
0	0	0	0	0	0	100	0	0	0	0	0
4	0	0	400	800	800	-	1600	0	0	0	100
8	0	0	800	12800	3200	51200	6400	-	800	400	800
12	100	400	1600	12800	1600	102400	6400	-	800	400	3200
16	200	1600	1600	6400	800	-	3200	-	800	400	6400
20	200	1600	1600	-	400	-	3200	-	1600	400	6400
24	400	1600	1600	-	400	-	1600	-	3200	400	6400
38	800	6400	1600	-	400	-	1600	-	1600	0*	-
52	800	6400	3200	-	200	-	6400	-	1600	0*	-
64	800	6400	1600	-	200	-	6400	-	3200	0*	-
	Patient Number										
Week	**413**	**414**	**415**	**416**	**417**	**418**	**419**	**420**	**421**	**422**	-
0	0	0	0	0	0	0	0	0	0	0	-
4	1600	0	0	0	200	800	-	400	800	0	-
8	12800	0	100	400	800	6400	-	1600	6400	200	-
12	-	-	100	400	800	12800	-	1600	12800	400	-
16	25600	-	100	800	400	12800	-	25600	6400	400	-
20	25600	0	200	800	200	25600	-	12800	12800	400	-
24	6400	0	100	1600	-	51200	-	12800	6400	400	-
38	12800	200	200	1600	200	51200	-	25600	3200	200	-
52	12800	400	200	3200	200	51200	-	3200	-	200	-
64	-	-	-	-	-	-	-	-	-	-	-

*Results listed as "pending" in the submission. Per personal communication with the sponsor, these results are negative.

Antibody titers by individual patient are represented graphically in the following figure (log scale).

Figure A2-22: Study 1702 Amendment 008, Anti-rhGAA Antibody Titers (log scale, zero values entered as 1)



Immunogenicity was further explored by comparing classes of GAA gene mutations (e.g., missense, nonsense), CRIM status, and peak titers with patient outcome (ventilator status or death); however, missing data limited the utility of this exploration. For the seven patients with a poor outcome (worsening status or death), two patients had no post-baseline antibody titers beyond Week 4 and three patients had no GAA mutational analyses. The available data in the worsening-status patients tended to show higher risk gene mutations (nonsense or frameshift/protein truncation) mutations in at least one allele (in three of four patients with available data), one patient was CRIM negative (Patient 407 who was homozygous for a frameshift mutation), and four of the five patients with available antibody titer results had peak titers >6400. In the 14 patients with no change (or improved) status during the study, seven of 12 patients with available GAA mutation analyses had lower risk (missense) mutations in both alleles, and two patients were CRIM negative (one patient was homozygous for a frameshift mutation, the other patient had no mutation analysis available). Five of 14 patients had peak antibody titers >6400 at any time during the study. In general, it appears that patients with higher risk mutations tended to have higher peak antibody titers, and the patients with higher antibody titers tended to have a poorer outcome, although this was not a consistent finding throughout the study. The results for the exploratory immunogenicity analysis by individual patient are summarized in the following table.

Table A2-30: Study 1702, Antibody Analysis/Exploration

Patient	Maternal/Paternal Alleles: Mutation Class	CRIM Status	Peak Titers	Start/Outcome
405	NA/NA	Positive	12800	Invasive/died
407	Frameshift (protein truncation)/ Frameshift (protein truncation)	Negative	102400	None/died
409	Unknown/unknown	Positive	0 (Week 4 only)	None/died
411	Nonsense/Missense	Positive	400	Noninvasive/invasive
412	Missense/Nonsense	Positive	6400	None/died
413	Missense/Missense	Positive	25600	None/invasive
419	Unknown/unknown	Positive	0 (Baseline only)	None/died
402	Missense/Missense	Positive	800	None/none
403	Missense/Missense	Positive	6400	Invasive/invasive
404	Missense/Missense	Positive	3200	None/none
406	Frameshift (protein truncation)/ missense	Positive	3200	Invasive/invasive
408	Loss of initiator Met (no protein?)/ Missense	Positive	6400	None/none
410	Unknown/unknown	Positive	3200	Invasive/invasive
414	Missense/Missense	Positive	400	None/none
415	Missense/Nonsense	Positive	200	None/none
416	Missense/Missense	Positive	3200	Invasive/invasive
417	Missense/Missense	Positive	800	None/None
418	NA/NA	Negative	51200	None/None
420	Frameshift (protein truncation)/ Frameshift (protein truncation)	Negative	25600	Noninvasive/None
421	Missense/Nonsense	Positive	12800	None/None
422	Missense/Missense	Positive	400	None/None

10.1.2.12.11 Pharmacokinetic (PK) and Pharmacodynamic (PD) Measures

The PK and PD results have been reviewed separately by the Clinical Pharmacology Reviewer (see review by Rajpal, Anil M.D.), and will be treated only briefly here. Plasma rhGAA PK parameters were available for 20 patients at baseline and for 16 patients at Week 12. The results showed that the single-dose and multiple-dose PK parameters were similar to results seen for Study 1602 (please see Study 1602 study report for PK results), and that the PK data were unchanged at Week 12, suggesting that the PK profile of rhGAA does not change after repeated exposure.

For the measure of muscle GAA activity by muscle biopsy at baseline and Week 52, GAA activity was noted to increase from baseline levels in eight of eight patients with results available at baseline and at Week 52 (median values 8.1 nmol/hr/g at baseline to 86.5 nmol/hr/g at Week 52), consistent with rhGAA uptake into skeletal muscle. However, for the PD measure of skeletal muscle glycogen content at baseline and at Weeks 12 and 52, the sponsor noted inconsistencies in the results by the two different assays used. That is, glycogen content was scored as stable, increased, or decreased from baseline in the assays, and different results were obtained in the two assays for many of the patients with available results (n=9 with available results at baseline and Week 12 and 52). The results for skeletal muscle glycogen content will be considered as exploratory only and no conclusions will be drawn from the results. The Clinical Pharmacology Reviewer additionally noted that there was no clear trend of skeletal muscle glycogen content with dose (20 mg/kg or 40 mg/kg qow) or with time since starting treatment (results from Studies 1602 and 1702 combined).

10.1.2.13 Efficacy Summary

The efficacy results from Study 1702 show the following:

1. Problems with the conduct and reporting of this study were noted.
    a. Eleven of the 21 treated patients were noted to be protocol violators by the study entry criteria, including four patients who were younger or older than the inclusion criteria allowed, two patients without baseline LVMI measures at baseline, four patients with LVMI results below the required lower limits for study entry, and one patient with an EF <40% AND signs and symptoms of cardiac failure at study entry. These protocol violations resulted in a much broader, more heterogeneous study population than originally planned. Although it would have been difficult to discern a treatment effect of rhGAA in the protocol-defined study population due to the unpredictable nature of the disease progression in this Pompe disease patient population and the lack of a concurrent control group, the broadening of the study population through protocol violations only contributed to this difficulty, making it almost impossible to discern a treatment effect of rhGAA in the treated study population.
    b. Numerous irregularities in the data were noted. This was especially true for the growth parameters (especially length and head circumference) where there were numerous missing datapoints and obvious errors throughout the dataset. Of the 20 of 21 patients with baseline and at least one post-baseline result for length,

eight patients had one (or more) clearly erroneous measurement(s). For head circumference, six patients had at least one clearly erroneous measurement. Due to the large number of errors, it was felt that the growth measurements data were unreliable and no conclusions will be drawn or inferred from the growth results. Obvious errors were also noted in the cardiac parameter results, although to a lesser degree, and the cardiac results are to be interpreted with caution.

2. For the primary endpoint of proportion of patients alive at Week 52, 16 of the 21 treated patients (76%) were alive at the Week 52 milestone. Analyses were performed by the sponsor to try to discern an rhGAA treatment effect, including comparison of age at death in an Historical Control Subgroup (n=86) and Subset (n=15) comprised of patients who were similar to the treated population in age at symptom onset and diagnosis. The results of these analyses showed that the age range at death in the Historical Control groups was broad, and overlapped with the findings (to date) in this study. Due to the highly heterogeneous rate of progression to death in this Pompe disease patient population, and as there was no concurrent control group for the study, it is not possible to state whether survival was prolonged in these patients with rhGAA treatment.

3. Evaluation of respiratory status at baseline and Week 52 showed that at baseline, 16 of 21 patients were free of invasive ventilator support, including two patients on noninvasive ventilation, and five patients were on invasive ventilator support. For the five patients who were receiving invasive ventilator support at baseline, one died and four remained on invasive ventilation throughout the study. For the 16 patients not on invasive ventilatory support at baseline, ten remained free of ventilatory support, four died, and two required invasive ventilation. Thus, at Week 52, seven patients had a worsening status, including five patients who died, and two patients not on invasive ventilatory support at baseline who became invasive-ventilator dependent. A trend was noted in that patients with worsening status tended to have younger ages at diagnosis and at first infusion than patients who had no change in status. This result is consistent with anecdotal and medical literature reports (including the Historical Control Group findings) that show that patients with more severe symptoms (who come to medical attention at younger ages) tend to have a poorer prognosis and more rapidly progressive disease course than patients with older ages at symptom onset and diagnosis. Thus, the findings for the respiratory status endpoint appear to be at least partially dependent on the patients' ages at diagnosis and first infusion, and make it extremely difficult to determine whether there was a treatment effect with rhGAA in this population, or if the findings were consistent with the natural progression of the underlying disease.

4. The cardiac parameters of LVMI, LVM Z-score, and EF were evaluated from baseline through Week 52. The results for LVMI showed that, overall, there was a mean decrease in LVMI from baseline to Week 52 of 100 g/m^2 (mean LVMI at baseline was 194 g/m^2 and at Week 52 was 89 g/m^2). In the 18 patients with LVMI results at baseline and at least one post-baseline visit, 13 patients had decreases in LVMI, four had no change in LVMI and one patient had an increase in LVMI at Week 52 (or last available visit). The results for the LVM Z-scores were similar to the results for LVMI. The EF results

showed highly variable results, with changes in EF ranging from -31% to +40%, with eleven patients having an increase in EF and ten patients having a decrease in EF at the last available study visit. There did not appear to be an association between change from baseline in EF and patient outcome. However, an EF of <40% at baseline, or the development of signs and symptoms of cardiac failure at anytime during the study (from screening through last available visit) tended to be associated with a poor outcome (e.g., ventilator dependence or death). Thus, although a pharmacodynamic effect of rhGAA treatment was seen in this study by decreasing LVMI and LVM- Z-score, there was no clear benefit on cardiac or clinical outcome seen with rhGAA treatment.

5. Motor development was assessed using the AIMS, Pompe PEDI and PDMS-2 tests (these testing instruments were assessed as appropriate and complimentary by the Pediatric Consultant to the Division). The results were consistent across the three tests evaluated, although interpretation of these test results was limited somewhat by missing data, especially in the sicker patients. Overall, the results appear to show that about half of the patients had modest gains in gross motor function (i.e., predominantly proximal, lower extremity muscle strength and function), but these patients were delayed compared to non-disabled, same-age peers. The other half of patients had little to no meaningful gains (or regression) in gross motor function. Fine motor function (i.e. predominantly distal, upper extremity muscle function) was much more preserved, however, with most patients demonstrating gains in fine motor function. These motor development results are not surprising as in Pompe disease, proximal muscle weakness typically presents first and is more pronounced than distal muscle weakness, and lower limbs (and truncal musculature) are more affected than upper limbs. It is not known, however, if the fine motor gains (or preservation) in these patients was the results of treatment with rhGAA as these findings are consistent with the natural progression of the underlying disease. It was additionally noted that patient outcome tended to be associated with gross motor gains and function, but not with fine motor gains and function. That is, patients with higher gross motor scores tended to do better (by the outcome of death or ventilatory-support) than did patients with little or no gains and lower gross motor scores.

6. Cognitive development was assessed by the BSID-II test. Overall, the results were encouraging as most patients scored within a normal to mildly delayed range; however longer-term follow-up is needed.

7. Immunogenicity data showed that 19 of 21 patients developed anti-rhGAA antibodies at anytime during the study. Antibody titers were high (>6400) at anytime during the study in nine of 19 patients with positive antibody, and tended to remain elevated in most patients throughout the study. High antibody titers also tended to be associated with high-risk mutations (e.g., frameshift or nonsense mutations in at least one allele), and patients with the highest titers tended to have poorer outcomes.

In summary, no definite effect of rhGAA treatment on patient outcome (death or ventilatory dependence), respiratory status, cardiac function, growth, or gross or fine motor development could be determined in this study. Although discerning anything less than a dramatic

treatment effect in this Pompe disease population would have been difficult due to the highly heterogeneous presentation and progression of the disease in this Pompe disease age group and as there was no concurrent control group, the numerous violations of the study entry criteria and the overall poor quality of the data in this study further undermined the ability of this Reviewer to interpret the study results. Therefore, no substantial efficacy can be determined from the results of Study 1702, and it is recommended that inclusion of any information from this study into the product labeling be limited to overall patient status until such time as a treatment benefit with rhGAA in this patient age group can be established.

10.1.2.14 Review of Safety

Safety was assessed by types and incidence of Adverse Events (AEs), discontinuations due to AEs, and drug-related, serious and severe AEs, and changes from baseline in physical exams (including vital signs), clinical laboratory assessments including clinical chemistry, hematology, urinalysis, and anti-GAA antibody IgG titers, and ECG assessments. Other safety variables included: circulating immune complex detection (as indicated), inhibitory antibody formation in patients testing positive for IgG, anti-rhGAA IgE antibodies, serum tryptase, and complement activation (as indicated). Safety data are available up until the cutoff date of 03-September-2004 for the first 15 patients entered into the study, and to the Week 52 milestone in the last six patients entered in the study (that is, through at least the Week 52 milestone in all 21 treated patients).

10.1.2.14.1 Exposure

Myozyme exposure for the 21 treated patients as of Amendment 008 ranged from 1 to 76 weeks of qow infusions (1 to 39 infusions). Exposure by individual patient is summarized in the following table:

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Table A2-31: Study 1702, Amendment 008, Exposure to Myozyme

Patient	Weeks in Study	# of Infusions
402	76	39
403	76	39
404	76	39
405	18	10
406	72	37
407	14	8
408	70	36
409	6	4
410	66	34
411	64	33
412	26	14
413	62	31
414	52	26
415	52	27
416	52	27
417	52	27
418	52	27
419	1	1
420	52	27
421	52	27
422	52	27
Mean	50	26
Median	52	27
Min, max	1, 76	1, 39

10.1.2.14.2 Adverse Events

Adverse Events (AEs) were collected from the signing of Informed Consent through study completion; however, unless otherwise noted, only treatment emergent AEs, defined as those that started following initiation of study medication (Day 0, day of first infusion) through study completion are included here. Recurrent or continuing AEs were counted only once (unless otherwise specified). AE incidence rates were calculated using all patients who received at least one dose of study medication as the denominator (n=21). All AEs were coded by the sponsor using the Medical Dictionary for Regulatory Activities (MedDRA), and are presented by AE Preferred Term; however, inconsistencies in coding were noted by this Reviewer, and in some instances, re-coding occurred (so differences in numbers and frequencies for some AEs between this Reviewer's results and the sponsors results are noted). AEs were tabulated and analyzed using the aex_1.xpt datset in Amendment 008 of the submission, which (per personal communication with the sponsor) represents the complete AE datset for Study 1702 through the Week 52 visit for the last patient enrolled, with the exeption of updated AEs for some patients (as of the 4-month safety update) in Amendment 005, which were reviewed separately and are not summarized here.

There were 105 AEs captured in the database that had their onset prior to the date of first infusion (Screening/Baseline period), or for which no AE start date was noted. These Screening/Baseline AEs were notable for one patient (401) experiencing ventricular fibrillation

resulting in cardiac arrest and death during general anaesthesia for the baseline muscle biopsy procedure, but prior to rhGAA exposure (cardiac arrhythmia AEs are discussed in greater detail in the Other Adverse Events section below). The Screening/Baseline AEs were otherwise noted to be consistent with underlying disease and will not be further disucussed.

There were >700 AEs reported during the study (approximately 200 AE preferred terms) and all 21 patients reported multiple AEs. Individual patients reported from 6 to 100 AEs (from 6 to 50 different AE terms) per patient. AEs were reported most commonly in the infections and infestations, and Respiratory, thoracic and mediastinal disorders System Organ Classes (SOCs). In general, reported AEs tended to reflect the underlying disease (e.g., respiratory and infectious AEs), or were AEs commonly seen with enzyme/protein infusions (e.g., rash, fever/pyrexia). By AE Preferred Term, the rates of AEs reported were highest for pyrexia (17 of 21 patients reporting, 80%), diarrhea (14, 67%), rash (11, 52%), and vomiting, pneumonia, and cough (9 each, 43%). The most commonly reported AEs (by incidence rates) are summarized in the following table (cutoff arbitrarily selected as ≥4 or >20% of patients reporting, for a complete list of the incidence of all AEs reported during the study, please refer to the subappendix).

Table A2-32: Study 1702, Amendment 008, Most Common (≥4 Patients) AEs by SOC and AE Preferred Term

SOC AE Preferred Term (recode)	Patients Reporting (%)	#s of AEs Reported by Term
Cardiac disorders	**12 (57)**	
Bradycardia	5 (24)	14
Gastrointestinal disorders	**17 (81)**	
Diarrhea	14 (67)	38
Vomiting	9 (43)	29
Constipation	5 (24)	9
Gastroesophageal reflux disease	5 (24)	7
General disorders and administration site conditions	**20 (95)**	
Pyrexia	18 (86)	68
Catheter related complication	5 (24)	9
Infections and infestations	**19 (90)**	
Pneumonia	9 (43)	19
Upper respiratory tract infection	8 (38)	19
Oral candidiasis	7 (33)	12
Ear infection	6 (29)	8
Gastroenteritis	5 (24)	5
Otitis media	5 (24)	6
Pharyngitis	5 (24)	11
Bacteremia	4 (19)	5
Bronchiolitis	4 (19)	4
Influenza	4 (19)	5
Injury, poisoning and procedural complications	**12 (57)**	
Post procedural pain	6 (29)	12
Investigations	**15 (71)**	
Oxygen saturation decreased	7 (33)	12
Sputum culture positive	5 (24)	9
Blood pressure increased	4 (19)	4
Musculoskeletal and connective tissue disorders	**10 (48)**	
Osteopenia	4 (19)	4
Respiratory, thoracic and mediastinal disorders	**20 (95)**	
Cough	9 (43)	28
Respiratory distress	8 (38)	11
Bronchospasm	5 (24)	9
Nasal congestion	5 (24)	5
Respiratory failure	5 (24)	7
Rhinorrhea	5 (24)	8
Skin and subcutaneous tissue disorders	**18 (86)**	
Rash	11 (52)	24
Dermatitis diaper	8 (38)	14
Vascular disorders	**7 (33)**	
Flushing	4 (19)	8

10.1.2.14.3 Deaths

Six patients died during the study. One patient (401) died of cardiac arrest (ventricular fibrillation) prior to receiving any study medication. Cause of death in five patients who died during the 52-week treatment period included cardiorespiratory arrest/cardiac arrhythmia in four

patients, and was unknown in one patient (412). The deaths in these six patients are summarized in the following table.

Table A2-33: Study 1702, Deaths During 52-Week Treatment Period

Patient	Age at Death (mos)	Study Month	Cause (verbatim)
401	8.6	Never treated	V fib Cardiac arrest
405	17.3	18.6	Cardiac and respiratory stop
407	11.7	15.3	Cardiorespiratory arrest
409	7.7	6.3	Arrythmia due to hypertrophic cardiomyopathy
412	14.4	28.0	Cause of Death is unknown. Source Data indicates (patient) had taken a deep breath, exhaled and expired.
419	9.2	0.1 (Day 4)	Cardiac arrest

10.1.2.14.4 Infusion Associated Reactions (IARs)

Infusion Associated Reactions (IARs) were defined by the sponsor as those AEs occurring on the day of infusion from the onset of the infusion up to and including the 2-hour observation period AND were assessed by the Investigator as at least possibly related to rhGAA. By this definition, a total of 39 IARs (19 different AE terms) were reported in nine patients. Flushing was the most commonly reported IAR, reported by four patients (19%). All reported IARs by incidence and by numbers of IARs reported are summarized in the following table:

Table A2-34: Study 1702, Amendment 008, IARs All

	IAR Incidence Rates	Numbers IARs by Term
Treated Patients, n =	21	
Patients Reporting any IAR, n (%)	7 (33)	
AE Preferred Term	**n (%)**	
Flushing	4 (19)	8
Rash	2 (10)	8
Cough	2 (10)	3
Blood pressure increased	2 (10)	2
Oxygen saturation decreased	2 (10)	2
Pyrexia	2 (10)	2
Tachypnea	1 (5)	2
Agitation	1 (5)	1
Bronchospasm	1 (5)	1
Edema periorbital	1 (5)	1
Heart rate increased	1 (5)	1
Hyperhidrosis	1 (5)	1
Lethargy	1 (5)	1
Pallor	1 (5)	1
Pruritus	1 (5)	1
Respiratory rate increased	1 (5)	1
Tachycardia	1 (5)	1
Tremor	1 (5)	1
Urticaria	1 (5)	1
Total		**39**

IARs were also evaluated by individual patient. Thirty-three (33) of the 39 IARs were reported by 5 patients. IARs by individual patient are summarized in the following table.

Table A2-35: Study 1702, Amendment 008, Number of IARs Reported by Patient

Patient	# of IARs	IAR Terms	Peak Ab Titers	Start/Outcome
402	0	-	800	None/none
403	0	-	6400	Invasive/invasive
404	0	-	3200	None/none
405	2	Pallor (1), tremor (1)	12800	Invasive/died
406	2	Flushing (2)	3200	Invasive/invasive
407	4	Pyrexia (1), blood pressure increased (1), heart rate increased (1), respiratory rate increased (1)	102400	None/died
408	8	Flushing (2), cough (1), oxygen saturation decreased (1), blood pressure increased (1), pruritus (1), lethargy (1), rash (1)	6400	None/none
409	0	-	0	None/died
410	0	-	3200	Invasive/invasive
411	0	-	400	Noninvasive/invasive
412	0	-	6400	None/died
413	0	-	25600	None/invasive
414	6	Bronchospasm (1), oxygen saturation decreased (1), edema periorbital (1), tachycardia (1), tachypnea (1), urticaria (1)	400	None/none
415	0	-	200	None/none
416	0	-	3200	Invasive/invasive
417	0	-	800	None/none
418	8	Rash (7), pyrexia (1)	25600	None/none
419	1	Tachypnea (1)	0	None/died
420	0	-	25600	Noninvasive/none
421	7	Flushing (3), cough (2), agitation (1), hyperhidrosis (1)	12800	None/none
422	1	Flushing (1)	400	None/none

10.1.2.14.5 Serious Adverse Events (SAEs)

A total of 89 SAEs, including 50 different AE terms, were reported by 18 of 21 patients. Six patients died. SAEs tended to reflect the underlying disease (e.g., respiratory and infectious terms) or treatment intervention complications (e.g., catheter related infection). The most commonly reported SAEs were pneumonia (8 patients, 38%), respiratory distress (6, 29%), and respiratory failure (5, 24%). The most commonly reported SAEs (reported by ≥2 patients) by incidence and by numbers of reported SAEs are summarized in the following table (for a complete listing of all SAEs reported, please refer to the subappendix).

Table A2-36: Study 1702, Amendment 008, Most Commonly Reported SAEs (by ≥2 Patients)

	SAE Incidence Rates	Numbers of SAEs by Term
Treated Patients, n =	**21**	
Patients Reporting any SAE, n (%)	**18 (86)**	
AE Preferred Term		
Pneumonia	8 (38)	10
Respiratory distress	6 (29)	7
Respiratory failure	5 (24)	7
Cardio-respiratory arrest	3 (14)	4
Catheter related infection	3 (14)	4
Pyrexia	3 (14)	4
Cardiomyopathy	2 (10)	2
Hypoxia	2 (10)	2
Respiratory arrest	2 (10)	2
Vomiting	2 (10)	2
Total		**89**

The number of SAEs reported by indidivual patient ranged from zero to 11, and as expected, patients with the poorest outcomes (e.g., death or requiring ventilatory support) tended to experience the most SAEs. SAEs by individual patient are summarized in the following table:

Table A2-37: Study 1702, Amendment 008, Number of SAEs Reported by Patient

Patient	# of SAEs	SAE Terms	Start/ Outcome
402	0		None/none
403	3	Pyrexia (2), catheter site erythema (1)	Invasive/invasive
404	6	Upper respiratory tract infection (3), catheter related infection (2), gastroenteritis (1)	None/none
405	9	Bradycardia (1), cardiomyopathy (1), cardiorespiratory arrest (1), dehydration (1), hyperthermia (1), renal insufficiency (1), sepsis (1), somnolence (1), ventricular fibrillation (1)	Invasive/died
406	5	Bacteremia (1), catheter related infection (1), clostridium colitis (1), pneumonia (1), respiratory distress (1)	Invasive/invasive
407	4	Cardiorespiratory arrest (1), ejection fraction decreased (1), hypoxia (1), pneumonia (1)	None/died
408	2	Dyspnea (1), vomiting (1)	None/none
409	3	Arrhythmia (1), cardiac failure (1), pulmonary edema (1)	None/died
410	7	Respiratory distress (2), fracture (1), leukocytosis (1), pneumonia (1), pyrexia (1), respiratory arrest (1)	Invasive/invasive
411	5	Respiratory distress (2), tracheitis (2), respiratory failure (1)	Noninvasive/invasive
412	3	Respiratory arrest (1), respiratory distress (1), respiratory failure (1)	None/died
413	11	Respiratory failure (3), pneumonia (2), respiratory syncytial virus infection (2), cough (1), hypoxia (1), influenza (1), vomiting (1)	None/invasive
414	9	Bronchospasm (1), edema periorbital (1), oxygen saturation decreased (1), pneumonia (1), respiratory distress (1), respiratory failure (1), tachycardia (1), tachypnea (1), urticaria (1)	None/none
415	3	Bronchitis (2), diarrhea (1)	None/none
416	3	Hypoventilation (1), post procedural hemorrhage (1), pyrexia (1)	Invasive/invasive
417	0		None/none
418	0		None/none
419	1	Cardiac arrest (1)	None/died
420	4	Cardiomyopathy (1), catheter related infection (1), pneumonia (1), respiratory distress (1)	Noninvasive/none
421	9	Cardio-respiratory arrest (2), pneumonia (2), asthenia (1), gastroesophageal reflux disease (1), hypertension (1), lung disorder (1), pulmonary congestion (1)	None/none
422	2	Asthma (1), pneumonia (1)	None/none

10.1.2.14.6 Other Adverse Events: Cardiac Arrhythmias

Cardiac arrhythmia AEs were noted to have occurred in two patients during the Screening/Baseline period and at Day 1 during the study. In both patients, the AEs occurred after administration of general anaesthesia for study-related procedures. One patient (401) experiencing ventricular fibrillation resulted in cardiac arrest and death during induction of anaesthesia for the baseline muscle biopsy procedure. This patient died prior to receiving any treatment with rhGAA. An additional patient (413) was noted to experience bradycardia and hypotension during anaesthesia for surgical procedures during the study. The cardiac arrhythmia events associated with anaesthesia use during Study 1702 are summarized in the following table.

Table A2-38: Study 1702, Cardiac Arrhythmias Associated with Anaesthesia

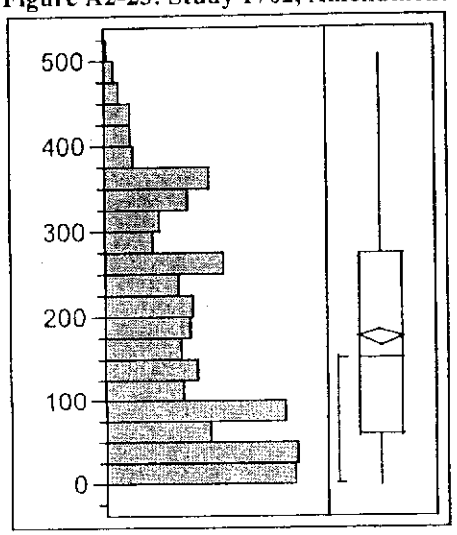
Patient	Study Day	AE Preferred Term
401	6 days post-signing ICF	Cardiac arrest
401	6 days post-signing ICF	Ventricular fibrillation
413	1	Bradycardia during anaesthesia for surgical procedures
413	1	Hypotension during anaesthesia for surgical procedures

At least four patients in Study 1602 also experienced cardiac arrhythmias during anaesthesia for procedures, and similar events have been noted to occur in infantile-onset Pompe disease patients in other Genzyme-sponsored rhGAA studies, presumably due to underlying cardiac hypertrophy. These findings lead to a revision of the Investigator's Brochure and heightened aswareness and training for the Investigators regarding the use of anaesthetic agents in the infantile-onset Pompe disease population.

10.1.2.14.7 Adverse Events Over Time

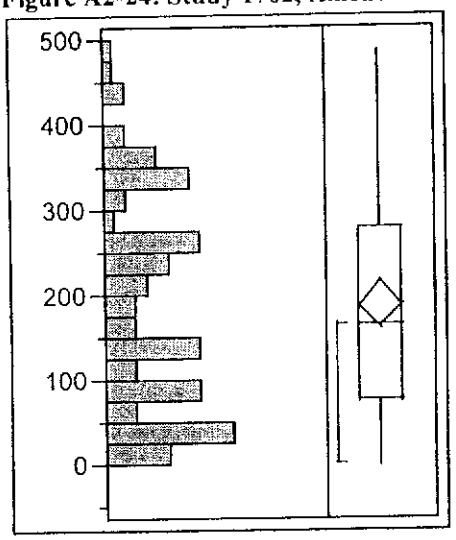
AEs were assessed over the duration of the study, and in general, the occurrence of AEs tended to be fairly evenly distrubted over time. The numbers of AEs reported by study day are represented graphically in the following figure (fewer AEs reported after approximately Day 375 is consistent with fewer patients with exposure to study treatment after Day 375).

Figure A2-23: Study 1702, Amendment 008, AEs Reported Over Time (Study Days)



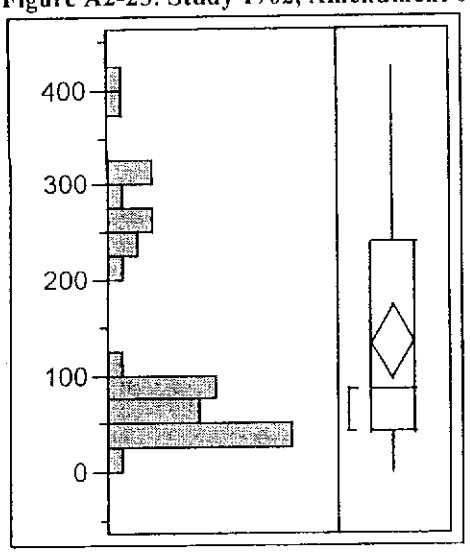
The SAEs reported over time showed similar results to AEs over time, with the occurrence of SAEs appearing to be fairly evenly distributed over time. The numbers of SAEs reported by study day are represented graphically in the following figure:

Figure A2-24: Study 1702, Amendment 008, SAEs Reported Over Time (Study Days)



IARs over time appeared to show IARs occurring more commonly in the first 100 days of the study. One possible explanation for this is that most of the patients who experienced the many of the IARs (Patients 407, 408, 418, 421 and 422) were pretreated with medications (such as acetaminophen, antihistamines, and steroids) as the study went on, presumably to prevent IARs from occurring. The numbers of IARs reported by study day are represented graphically in the following figure.

Figure A2-25: Study 1702, Amendment 008, IARs Reported Over Time (Study Days)



10.1.2.14.8 Laboratory Results

In general, there were no notable patterns of clinical laboratory abnormalities seen in the study.

10.1.2.15 Safety Summary

The safety results from Study 1702 show the following:

1. AEs were frequently reported in this study, and all 21 patients reported multiple AEs. This is not unexpected due to the severity of the underlying disease and the medically fragile conditions of the study patients. In general, AEs tended to reflect underlying disease (e.g., respiratory and infectious AEs), or were AEs commonly seen with enzyme/protein infusions (e.g., rash, fever/pyrexia). By AE preferred term, the most commonly reported AEs (by incidence rates) were pyrexia (80% of patients), diarrhea (67%), rash (52%), and vomting, pneumonia and cough (43% each).

2. There were six deaths in the study. One patient (401) died in the screening/baseline period of cardiac arrhythmia and cardiac arrest during general anaesthesia administration for the baseline muscle biopsy (study-related procedure), but never received treatment with rhGAA. Five patients died of cardiorespiratory arrest/cardiac arrhythmia (four patients), and the cause of death in one patient was unknown (verbatim "stopped breathing"). No other patient discontinued study participation during the first 52 weeks of the study, and the remaining 16 patients completed the first 52 weeks of the study.

3. IARs were reported in nine patients. The IARs reported by more than one patient were flushing (four patients), and rash, cough, increased blood pressure, decreased oxygen saturation, and pyrexia (two patients each). In general, IARs tended to be reported more commonly in patients with higher anti-rhGAA antibody titers, but this was not consistently true for all patients with high (>6400) titers of antibody. Five patients were pretreated with medications (antipyretics, antihistamines, and/or steroids) during the study, and all patients but two were able to receive >90% of scheduled rhGAA doses (Patients 407 and 409 missed one partial dose of study medication each due to illness and staff error, respectively).

4. SAEs were reported in 18 of 21 treated patients, and tended to reflect underlying disease (e.g., respiratory and infectious SAEs) or treatment intervention complications (catheter-related infection). The most commonly reported SAEs were pneumonia (8 patients, 38%), respiratory distress (6, 29%) and respiratory failure (5, 24%). Serious cardiac arrhythmia AEs were also noted in two patients at any time during the study, and were associated with anaesthesia use for procedures. One patient died in the baseline period prior to receiving rhGAA (Patient 401 – see deaths #2 above), and one patient experienced bradycardia and hypotension. The risk of cardiac complications during anaesthesia is felt to be due to the underlying cardiac hypertophy seen in infantile-onset Pompe disease patients.

In summary, the safety experience seen with rhGAA treatment in this study tends to reflect the underlying medical condition of the patients, and is consistent with the administration of enzyme/protein infusions seen with other ERTs. Pompe disease is a fatal condition with progressive to death, usually due to respiratory failure, in months to years in patients in the age group represented in this study. Although efficacy has not been established in this population, given the poor prognosis of the patients without treatment, the safety profile of rhGAA in this patient population appears to acceptable for continued study; however, further evaluation over a longer time period under study-monitoring conditions is warranted.

10.1.2.16 Conclusions and Recommendations

The results of the 52-week interim analysis for Study 1702 failed to definitely establish the efficacy of rhGAA in this patient population. Interpretation of this study was complicated by the lack of a concurrent control group, a large number of protocol violators by study entry criteria, and the overall poor quality of the data for several of the endpoints. For the primary endpoint of proportion of patients alive at Week 52, the proportion of survivors and age-at-death appeared to overlap with an historical control population of similar age and severity who were selected from a retrospective review of medical records. Secondary endpoints of respiratory and motor function also were consistent with anecdotal and medical literature reports of the expected progression of the disease in this patient population. That is, patients with worsening status (e.g., death or ventilator dependence) tended to be younger than patients with stable status during the study, consistent with a more rapidly progressive disease course in patients with first symptoms and diagnosis at younger ages. Motor development showed modest gains in gross motor function in approximately half of the patients in the study, but most patients showed gains in fine motor function. This result is consistent with the earlier presentation and progression of proximal, lower extremity (and truncal) motor involvement and the relative sparing of distal motor function earlier in the course of the disease. These findings make it extremely difficult to determine whether there was a treatment effect with rhGAA in this population, or if the findings were due to the natural progression of the underlying disease.

Longer-term treatment with rhGAA in this population is needed, as are continued assessments of growth, development (motor and cognitive) and safety. This study was designed as an 104-week study, and the remaining approximately one year of efficacy and safety data is to be submitted to the BLA by the sponsor at the earliest possible time.

10.1.2.17 Subappendix: Study 1702

10.1.2.17.1 All AEs

Table A2-39: Study 1702 Amendment 008, All AEs by SOC and AE Preferred Term

SOC AE Preferred Term (recode)	Patients Reporting (%)
Blood and lymphatic system disorders	**6 (29)**
Anemia	2 (10)
Leukocytosis	1 (5)
Lymphadenitis	1 (5)
Lymphadenopathy	1 (5)
Neutropenia	1 (5)
Cardiac disorders	**12 (57)**
Bradycardia	5 (24)
Cardio-respiratory arrest	3 (14)
Tachycardia	3 (14)
Cardiac failure	2 (10)
Cardiomyopathy	2 (10)
Cyanosis	2 (10)
Arrhythmia	1 (5)
Cardiac arrest	1 (5)
Extrasystoles	1 (5)
Pericardial effusion	1 (5)
Supraventricular extrasystoles	1 (5)
Ventricular fibrillation	1 (5)
Ear and labyrinth disorders	**1 (5)**
Hypoacusis	1 (5)
Eye disorders	**4 (19)**
Conjunctivitis	1 (5)
Erythema of eyelid	1 (5)
Eye discharge	1 (5)
Xerophthalmia	1 (5)
Gastrointestinal disorders	**17 (81)**
Diarrhea	14 (67)
Vomiting	9 (43)
Constipation	5 (24)
Gastroesophageal reflux disease	5 (24)
Abdominal distension	2 (10)
Dysphagia	2 (10)
Teething	2 (10)
Abdominal pain	1 (5)
Hematemesis	1 (5)
Mouth ulceration	1 (5)
Oral mucosal blistering	1 (5)
Tongue discoloration	1 (5)
Toothache	1 (5)
General disorders and administration site conditions	**20 (95)**
Pyrexia	18 (86)

Table A2-39: Study 1702 Amendment 008, All AEs by SOC and AE Preferred Term

SOC AE Preferred Term (recode)	Patients Reporting (%)
Catheter related complication	5 (24)
Pain	3 (14)
Edema	2 (10)
Edema localized	2 (10)
Edema peripheral	2 (10)
Granuloma	2 (10)
Hyperthermia	2 (10)
Lethargy	2 (10)
Asthenia	1 (5)
Catheter site ecchymosis	1 (5)
Catheter site erythema	1 (5)
Catheter site phlebitis	1 (5)
Discomfort	1 (5)
Fatigue	1 (5)
Inflammation localized	1 (5)
Infusion site swelling	1 (5)
Hepatobiliary disorders	**1 (5)**
Hepatomegaly	1 (5)
Infections and infestations	**19 (90)**
Pneumonia	9 (43)
Upper respiratory tract infection	8 (38)
Oral candidiasis	7 (33)
Ear infection	6 (29)
Gastroenteritis	5 (24)
Otitis media	5 (24)
Pharyngitis	5 (24)
Bacteremia	4 (19)
Bronchiolitis	4 (19)
Influenza	4 (19)
Bronchitis	3 (14)
Catheter related infection	3 (14)
Nasopharyngitis	3 (14)
Tracheitis	3 (14)
Tonsillitis	2 (10)
Cellulitis	1 (5)
Clostridium colitis	1 (5)
Infection	1 (5)
Lower respiratory tract infection	1 (5)
Respiratory syncytial virus infection	1 (5)
Respiratory tract infection	1 (5)
Sepsis	1 (5)
Skin infection	1 (5)
Skin infection fungal	1 (5)
Urinary tract infection	1 (5)
Viral infection	1 (5)
Injury, poisoning and procedural complications	**12 (57)**
Post procedural pain	6 (29)
Contusion	3 (14)
Medical device complication	3 (14)

Table A2-39: Study 1702 Amendment 008, All AEs by SOC and AE Preferred Term

SOC AE Preferred Term (recode)	Patients Reporting (%)
Fracture femur	2 (10)
Arthropod sting	1 (5)
Fracture tibia/fibula	1 (5)
Joint dislocation	1 (5)
Post procedural hemorrhage	1 (5)
Tracheostomy malfunction	1 (5)
Investigations	**15 (71)**
Oxygen saturation decreased	7 (33)
Sputum culture positive	5 (24)
Blood pressure increased	4 (19)
Blood bicarbonate decreased	3 (14)
Blood phosphorus increased	3 (14)
Heart rate increased	3 (14)
White blood cell count increased	3 (14)
Blood chloride decreased	2 (10)
Blood potassium decreased	2 (10)
Blood urea increased	2 (10)
Culture throat positive	2 (10)
Gallop rhythm present	2 (10)
Urine output decreased	2 (10)
Weight decreased	2 (10)
Alanine aminotransferase increased	1 (5)
Aspartate aminotransferase increased	1 (5)
Blood alkaline phosphatase decreased	1 (5)
Blood creatine phosphokinase increased	1 (5)
Blood lactic acid increased	1 (5)
Blood pressure decreased	1 (5)
Blood uric acid increased	1 (5)
Ejection fraction decreased	1 (5)
Eosinophil count increased	1 (5)
Fungal test positive	1 (5)
Hemoglobin decreased	1 (5)
Lymph node enlarged	1 (5)
Lymphocyte count decreased	1 (5)
Monocyte count decreased	1 (5)
Neutrophil count increased	1 (5)
Platelet count decreased	1 (5)
Respiratory rate increased	1 (5)
Weight increased	1 (5)
White blood cell count decreased	1 (5)
Metabolism and nutrition disorders	**9 (43)**
Dehydration	3 (14)
Feeding disorder	2 (10)
Hypokalemia	2 (10)
Fluid imbalance	1 (5)
Fluid retention	1 (5)
Hypernatremia	1 (5)
Hypocalcemia	1 (5)
Hypoglycemia	1 (5)

Table A2-39: Study 1702 Amendment 008, All AEs by SOC and AE Preferred Term

SOC AE Preferred Term (recode)	Patients Reporting (%)
Weight gain poor	1 (5)
Musculoskeletal and connective tissue disorders	**10 (48)**
Osteopenia	4 (19)
Joint contracture	3 (14)
Arthralgia	1 (5)
Muscle hemorrhage	1 (5)
Myopathy	1 (5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (5)**
Fibroma	1 (5)
Nervous system disorders	**1 (5)**
Somnolence	1 (5)
Tremor	1 (5)
Psychiatric disorders	**3 (14)**
Agitation	1 (5)
Anxiety	1 (5)
Insomnia	1 (5)
Renal and urinary disorders	**7 (33)**
Proteinuria	3 (14)
Hematuria	1 (5)
Hypercalciuria	1 (5)
Micturition disorder	1 (5)
Nephritis	1 (5)
Oliguria	1 (5)
Renal insufficiency	1 (5)
Reproductive system and breast disorders	**2 (10)**
Edema genital	1 (5)
Scrotal swelling	1 (5)
Respiratory, thoracic and mediastinal disorders	**20 (95)**
Cough	9 (43)
Respiratory distress	8 (38)
Bronchospasm	5 (24)
Nasal congestion	5 (24)
Respiratory failure	5 (24)
Rhinorrhea	5 (24)
Atelectasis	3 (14)
Choking	3 (14)
Hypoventilation	3 (14)
Increased bronchial secretion	3 (14)
Tachypnea	3 (14)
Dyspnea	2 (10)
Hypoxia	2 (10)
Lung crepitation	2 (10)
Pulmonary congestion	2 (10)
Respiratory arrest	2 (10)
Upper respiratory tract congestion	2 (10)
Aspiration	1 (5)
Asthma	1 (5)
Increased throat secretions	1 (5)

Table A2-39: Study 1702 Amendment 008, All AEs by SOC and AE Preferred Term

SOC AE Preferred Term (recode)	Patients Reporting (%)
Increased viscosity of bronchial secretion	1 (5)
Lung disorder	1 (5)
Pain tracheal	1 (5)
Pulmonary edema	1 (5)
Respiratory tract congestion	1 (5)
Rhinitis allergic	1 (5)
Sinus congestion	1 (5)
Skin and subcutaneous tissue disorders	**18 (86)**
Rash	11 (52)
Dermatitis diaper	8 (38)
Excoriation	3 (14)
Decubitus ulcer	2 (10)
Dermatitis allergic	2 (10)
Dry skin	2 (10)
Edema periorbital	2 (10)
Hyperhidrosis	2 (10)
Pruritus	2 (10)
Urticaria	2 (10)
Eczema	1 (5)
Vascular disorders	**7 (33)**
Flushing	4 (19)
Hypertension	3 (14)
Hypotension	2 (10)
Labile blood pressure	1 (5)
Pallor	1 (5)

10.1.2.17.2 All SAEs

Table A2-40: Study 1702 Amendment 008, All SAEs

Treated Patients, n = Patients Reporting any SAE, n (%)	SAE Incidence Rates 21 18 (86)	Numbers of SAEs by Term
AE Preferred Term		
Pneumonia	8 (38)	10
Respiratory distress	6 (29)	7
Respiratory failure	5 (24)	7
Cardio-respiratory arrest	3 (14)	4
Catheter related infection	3 (14)	4
Pyrexia	3 (14)	4
Cardiomyopathy	2 (10)	2
Hypoxia	2 (10)	2
Respiratory arrest	2 (10)	2
Vomiting	2 (10)	2
Upper respiratory tract infection	1 (5)	3
Bronchitis	1 (5)	2
Respiratory syncytial virus infection	1 (5)	2
Tracheitis	1 (5)	2
Arrhythmia	1 (5)	1

Table A2-40: Study 1702 Amendment 008, All SAEs

	SAE Incidence Rates	Numbers of SAEs by Term
Asthenia	1 (5)	1
Asthma	1 (5)	1
Bacteremia	1 (5)	1
Bradycardia	1 (5)	1
Bronchospasm	1 (5)	1
Cardiac arrest	1 (5)	1
Cardiac failure	1 (5)	1
Catheter site erythema	1 (5)	1
Clostridium colitis	1 (5)	1
Cough	1 (5)	1
Dehydration	1 (5)	1
Diarrhea	1 (5)	1
Dyspnea	1 (5)	1
Edema periorbital	1 (5)	1
Ejection fraction decreased	1 (5)	1
Fracture femur	1 (5)	1
Gastroenteritis	1 (5)	1
Gastroesophageal reflux disease	1 (5)	1
Hypertension	1 (5)	1
Hyperthermia	1 (5)	1
Hypoventilation	1 (5)	1
Influenza	1 (5)	1
Leukocytosis	1 (5)	1
Lung disorder	1 (5)	1
Oxygen saturation decreased	1 (5)	1
Post procedural hemorrhage	1 (5)	1
Pulmonary congestion	1 (5)	1
Pulmonary edema	1 (5)	1
Renal insufficiency	1 (5)	1
Sepsis	1 (5)	1
Somnolence	1 (5)	1
Tachycardia	1 (5)	1
Tachypnea	1 (5)	1
Urticaria	1 (5)	1
Ventricular fibrillation	1 (5)	1
Total		89

10.1.2.17.3 Cardiac Parameters

Table A2-41: Study 1702 Amendment 008, Cardiac Parameters by Individual Patient, All 21 Patients to Week 52

Patient	Week	EF (%)	ΔEF (%)	LVM Z-Score	ΔLVM Z-Score	LVMI	ΔLVMI
402	0	54	0	2.9	0	72	0
402	4	61	6	3.3	0.4	83	10
402	8	62	8	2.4	-0.5	65	-7
402	12	62	7	1.2	-1.7	51	-22
402	26	53	-2	0.7	-2.2	45	-27
402	38	63	9	1.6	-1.3	57	-16
402	52	53	-1	1.1	-1.8	52	-21
403	0	67	0	5.4	0	146	0
403	4	66	-1	6.4	1.0	184	38
403	8	75	8	6.3	0.9	177	31
403	12	70	3	.	.	.	.
403	26	.	.	.	.	.	.
403	38	54	-13	3.4	-2.0	91	-55
403	52	74	7	2.6	-2.8	76	-69
404	0	50	0	10.0	0	358	0
404	4	69	19	9.4	-0.6	321	-37
404	8	38	-12	7.2	-2.8	188	-169
404	12	56	6	6.6	-3.4	169	-189
404	26	61	11	4.1	-5.9	97	-261
404	38	68	18	2.9	-7.1	73	-284
404	52	78	28	2.0	-8.0	63	-295
405	0	27	0	.	.	.	.
405	4	34	7	8.6	.	269	.
405	8	21	-6	7.8	.	225	.
405	12	32	5	8.0	.	241	.
406	0	38	0	8.8	0	322	0
406	4	37	-1	7.3	-1.5	223	-99
406	8	35	-3	7.8	-1.0	248	-74
406	12	30	-8	8.0	-0.8	264	-58
406	26	25	-13	7.5	-1.3	238	-84
406	38	52	14	6.7	-2.1	195	-127
406	52	59	20	6.9	-1.9	212	-111
407	0	67	0	7.6	0	198	0
407	4	40	-27	7.6	0	198	0
407	8	49	-18	7.4	-0.2	191	-7
407	12	54	-13	7.5	-0.1	199	1
408	0	62	0	6.6	-0.0	189	0
408	4	73	10	6.4	-0.2	183	-7
408	8	81	19	6.5	-0.1	186	-3
408	12	78	16	4.7	-1.9	125	-64
408	26	76	14	2.8	-3.8	82	-108
408	38	69	7	.	.	.	.
408	52	78	16	1.3	-5.3	57	-132
409	0	62	0	8.5	0	243	0
409	4	42	-20	8.7	0.2	265	22
410	0	66	0	7.3	0	209	0

Table A2-41: Study 1702 Amendment 008, Cardiac Parameters by Individual Patient, All 21 Patients to Week 52

Patient	Week	EF (%)	ΔEF (%)	LVM Z-Score	ΔLVM Z-Score	LVMI	ΔLVMI
410	4	54	-12	9.6	0	352	143
410	8	54	-12	.	.	.	.
410	12	58	-8	8.5	-1.1	297	88
410	26	65	-1	5.4	-4.2	148	-61
410	38	66	0	.	.	.	.
410	52	68	2	2.8	-6.8	100	-109
411	0	52	0	10.4	0	418	0
411	4	50	-2	9.7	-0.7	355	-62
411	8	45	-6	9.2	-1.2	312	-106
411	12	48	-4	8.4	-2.0	263	-155
411	26	70	19	7.3	-3.1	212	-206
411	38	52	1	5.6	-4.8	140	-277
411	52	45	-6	5.5	-4.9	140	-278
412	0	60	0	7.7	0	212	0
412	4	57	-3	6.1	-1.6	145	-66
412	8	55	-5	5.9	-1.8	143	-69
412	12	69	9	5.4	-2.3	126	-85
412	26	74	15	4.5	-3.2	103	-108
413	0	21	0	7.7	0	207	0
413	4	29	8	7.9	0.2	221	13
413	8	33	12	6.7	-1.0	175	-33
413	12	26	5	6.8	-0.9	179	-28
413	26	42	21	5.0	-2.7	122	-86
413	38	53	32	4.6	-3.1	112	-95
413	52	60	40	.	.	.	.
414	0	56	0	2.2	0	63	0
414	4	69	13	2.8	0.6	73	9
414	8	67	10	2.5	0.3	68	5
414	12	.	.	.	.	.	.
414	26	71	15	1.1	-1.1	50	-13
414	38	62	6	1.8	-0.4	59	-5
414	52	62	6	1.4	-0.8	54	-9
415	0	72	0	3.1	0	77	0
415	4	54	-18	2.8	-0.3	70	-6
415	8	65	-6	2.1	-1.0	62	-15
415	12	64	-8	2.4	-0.7	65	-12
415	26	70	-2	1.0	-2.1	49	-28
415	38	64	-8	0.7	-2.4	45	-32
415	52	68	-4	0.8	-2.3	48	-29
416	0	63	0	6.3	0	170	0
416	4	63	0	6.2	-0.1	167	-3
416	8	50	-13	6.5	0.2	176	7
416	12	44	-19	4.4	-1.9	111	-59
416	26	61	-23	3.0	-3.3	83	-87
416	38	.	.	.	.	.	.
416	52	.	.	.	.	.	.
417	0	70	0	7.8	0	221	0
417	4	54	-16	7.4	-0.4	202	-19
417	8	69	-1	5.8	-2.0	140	-81
417	12	48	-22	5.9	-1.9	142	-80

Table A2-41: Study 1702 Amendment 008, Cardiac Parameters by Individual Patient, All 21 Patients to Week 52

Patient	Week	EF (%)	ΔEF (%)	LVM Z-Score	ΔLVM Z-Score	LVMI	ΔLVMI
417	26	67	-2	3.3	-4.5	79	-142
417	38	81	12	2.6	-5.2	69	-152
417	52	55	-15	3.2	-4.6	79	-142
418	0	67	0	.	.	.	.
418	4	.	.	.	.	.	.
418	8	49	-17	2.1	.	58	.
418	12	55	-12	0.4	.	41	.
418	26	51	-16	-0.1	.	37	.
418	52	60	-6	-1.1	.	30	.
419	0	49	0	7.8	0	220	0
420	0	71	0	7.6	0	203	0
420	4	14	-57	7.1	-0.5	183	-20
420	8	35	-35	6.1	-1.5	146	-57
420	12	34	-36	7.5	-0.1	210	7
420	26	59	-12	5.6	-2.0	138	-65
420	38	43	-28	6.2	-1.4	160	-43
420	52	40	-31	7.2	-0.4	201	-2
421	0	59	0	4.3	0	100	0
421	4	64	5	4.9	0.6	113	14
421	8	53	-6	3.8	-0.5	90	-9
421	12	60	1	4.4	0.1	104	4
421	52	64	5	.	.	.	.
422	0	66	0	1.7	0	55	0
422	4	.	.	.	.	.	.
422	12	50	-16	0	-1.7	38	-17
422	26	.	.	.	.	.	.
422	38	72	7	1.1	-0.6	50	-5
422	52	70	4	1.0	-0.7	49	-6

10.1.2.17.4 AIMS Test

Table A2-42: 1702 Amendment 008, AIMS Results at Baseline and Week 52

Patient	Week	Category Raw Score				Total Raw (58)	Actual Age (mos)	Age Equiv Score (mos)	Percentile Score
		Prone (21)	Supine (9)	Sit (12)	Stand (16)				
404	0	0	2	1	0	3	7.9		<5%
	4	0	0	1	0	1	9.1		<5%
	8	0	0	1	0	1	10.0		<5%
	12	0	2	1	0	3	11.0		<5%
	26	0	0	2	0	2	14.2		<5%
	38	0	0	2	0	2	17.0		<5%
	52	0	0	2	0	2	20.1		
	64	0	0	7	0	7	22.8	1.3	
405	0	0	0	0	0	0	13.0		<5%
	4	0	1	0	0	1	14.0		<5%
	8	0	0	0	0	0	14.9		<5%
	12	0	0	0	0	0	16.0		<5%
406	0	0	0	0	0	0	16.4		<5%
	4	0	0	0	0	0	17.4		<5%

Table A2-42: 1702 Amendment 008, AIMS Results at Baseline and Week 52

Patient	Week	Category Raw Score Prone (21)	Supine (9)	Sit (12)	Stand (16)	Total Raw (58)	Actual Age (mos)	Age Equiv Score (mos)	Percentile Score
	8	0	0	0	0	0	18.3		<5%
	12	0	0	0	0	0	19.2		<5%
	26	.	.	.	.	.	-		
	38	.	.	.	.	.	-		
	52	0	0	0	0	0	28.6	0	<5%
	64	0	0	0	0	0	31.2	0	<5%
407	0	0	0	0	0	0	8.0		<5%
	4	0	0	1	0	1	9.2		<5%
	8	0	0	1	0	1	10.1		<5%
	12	0	0	1	0	1	11.1		<5%
411	0	0	4	2	0	6	9.3		<5%
	4	3	4	3	0	10	10.8		<5%
	8	3	4	5	0	12	11.6		<5%
	12	5	5	7	1	18	12.4		<5%
	26	10	9	11	2	32	15.8		<5%
	38	0	4	2	0	6	18.8	1.1	<5%
	52	0	0	5	0	5	22.1	0.8	<5%
	64	0	0	3	0	3	24.9	<.5	
412	0	0	2	0	0	2	8.0		<5%
	4	0	0	0	0	0	9.1		<5%
	8	0	0	0	0	0	10.3		<5%
	12	0	0	1	0	1	11.1		<5%
	26	0	0	1	0	1	14.3		<5%
413	0	1	6	1	2	10	6.9		<5%
	4	2	6	3	2	13	8.1		<5%
	8	5	7	8	2	22	9.0		<5%
	12	2	7	9	2	20	10.0		<5%
	26	7	6	9	3	25	13.2		<5%
	38	5	9	9	3	26	16.1	6.1	<5%
415	0	1	6	8	1	16	15.0		<5%
	4	1	7	9	1	18	16.0		<5%
	8	2	7	9	1	19	17.0		<5%
	12	2	8	9	1	20	18.1		<5%
	26	.	.	.		.	-		
	38	14	9	12	3	38	24.0	8.3	
	52	15	9	12	3	39	27.1	8.4	
416	0	0	0	0	0	0	18.2		<5%
	4	0	0	0	0	0	19.2		<5%
	8	0	0	0	0	0	20.2		<5%
	12	.	.	.	.	.	-		
	26	.	.	.	.	.	-		
	38	0	0	0	0	0	27.0	0	<5%
	52	0	0	0	0	0	30.2	<.5	
417	0	14	9	11	3	37	14.5		<5%
	4	15	8	11	3	37	15.5		<5%
	8	13	9	11	3	36	16.4		<5%
	12	21	9	12	8	50	17.5		<5%
418	0	4	7	5	1	17	8.4		<5%

Table A2-42: 1702 Amendment 008, AIMS Results at Baseline and Week 52

Patient	Week	Category Raw Score Prone (21)	Supine (9)	Sit (12)	Stand (16)	Total Raw (58)	Actual Age (mos)	Age Equiv Score (mos)	Percentile Score
	4	7	9	8	1	25	9.6		<5%
	8	8	9	7	0	24	10.3		<5%
	12	11	9	10	1	31	11.2		<5%
	26	19	9	12	8	48	14.6		<5%
	38	21	9	12	10	52	17.3		<5%
	52	21	9	12	8	50	20.6		
420	0	0	0	0	0	0	3.3		<5%
	4	2	3	1	0	6	4.7		<5%
	8	3	5	1	0	9	5.6		<5%
	12	4	6	1	1	12	6.4		<5%
	26	8	9	6	0	23	9.7		<5%
	38	4	9	9	3	25	12.7		<5%
	52	10	9	10	1	30	16.0		<5%
421	0	2	5	7	1	15	9.0		<5%
	4	1	6	8	1	16	10.5		<5%
	8	2	7	9	1	19	11.3		<5%
	12	2	7	10	1	20	12.2		<5%
	26	2	6	9	1	18	15.6		<5%
	38	0	0	0	0	0	18.6		
	52	0	0	0	0	0	22.0		
422	0	14	8	12	3	37	17.6		<5%
	4	15	8	12	4	39	18.9		<5%
	8	17	9	12	6	44	19.9		
	12	18	9	12	8	47	21.1		
	26	21	9	12	13	55	24.0		
	38	21	9	12	14	56	26.7		
	52	.	.	.	.	.	-		
	58	21	9	12	16	58	31.5		

10.1.2.17.5 PDMS-2

Table A2-43: Study 1702 Amendment 008, PDMS-2 Results

Patient	Week	Actual Age (mos)	Gross Motor Age Equivalent (mos) Stationary	Locomotion	Object Manipulation	Fine Motor Age Equivalent (mos) Grasping	Visual-Motor Integration
402	0	17.0	9	7	13	14	16
	4	18.1	11	8	12	20	18
	8	19.1	11	9	12	15	19
	12	20.1	10	8	13	14	19
	26	23.3	14	9	12	28	20
	38	26.0	11	11	12	20	25
	52	29.3	18	14	15	20	25
	64	32.1	10	10	23	40	28
403	0	37.7	9	2	12	12	22
	4	38.7	9	2	12	34	36

Table A2-43: Study 1702 Amendment 008, PDMS-2 Results

Patient	Week	Actual Age (mos)	Gross Motor Age Equivalent (mos)			Fine Motor Age Equivalent (mos)	
			Stationary	Locomotion	Object Manipulation	Grasping	Visual-Motor Integration
	8	39.7	10	6	12	34	37
	12	40.6	9	7	12	37	40
	26	43.8	11	3	12	37	39
	38	46.7	11	3	12	34	47
	52	50.0	11	8	12	34	>71
	64	52.8	11	8	12	43	>71
404	0	7.9	1	1		4	6
	4	9.1					
	8	10.0	1	1		1	3
	12	11.0					
	26	14.2	3	1	12	8	9
	38	17.0	6	1	12	14	15
	52	20.1	6	2	12	12	19
	64	22.8	7	1	12	10	17
405	0	13.0	1	1	12	1	1
	4	14.0	1	1	12	1	3
	8	14.9	1	1	12	1	3
	12	16.0	1	1	12	1	3
406	0	16.4	1	1	12	1	2
	4	17.4	1	1	12	1	3
	8	18.3	1	1	12	1	3
	12	19.2	1	1	12	2	4
	26	22.4	1	1	12	3	4
	38	25.2	1	1	12	1	3
	52	28.6	1	1	12	1	3
	64	31.3	1	1	12	1	3
408	0	43.6	11	8	12	28	35
	4	44.6	11	8	12	15	37
	8	45.3	11	8	12	15	37
	12	46.4	10	8	12	28	37
	26	49.6	11	8	12	15	37
	38	52.5	14	9	12	15	40
	52	55.7	11	8	12	40	46
	64	58.5	11	8	12	20	52
410	0	36.8	5	1	12	1	1
	4	38.1	5	1	12	34	19
	8	39.1	2	1	12	28	20
	12	40.0	5	1	12	28	20
	26	.					
	38	.					
	52	49.4	6	1	12	13	20
	64	52.2	8	2	12	11	35
411	0	9.3	4	1		4	7
	4	.					
	8	.					
	12	12.4	9	4	12	8	9
	26	15.8	9	7	12	12	12

Table A2-43: Study 1702 Amendment 008, PDMS-2 Results

Patient	Week	Actual Age (mos)	Gross Motor Age Equivalent (mos)			Fine Motor Age Equivalent (mos)	
			Stationary	Locomotion	Object Manipulation	Grasping	Visual-Motor Integration
	38	18.8	1	2	12	13	15
	52	22.1					
	64	24.9	9	2	12	11	19
412	0	8.0	1	1		1	3
	4	.					
	8	.					
	12	.					
	26	14.3	1	1	12	6	8
413	0	6.9	3	3		5	8
	4	8.1	4	4		7	9
	8	9.0	7	5		7	7
	12	10.0	9	4		8	7
	26	13.2	9	5	12	8	10
	38	16.1	9	7	12	14	13
	52	.					
414	0	24.3	11	16	16	20	22
	4	25.4	18	17	16	20	23
	8	26.6	18	18	16	28	27
	12	28.1	18	15	13	28	30
	26	30.7	18	18	18	37	31
	38	33.4	18	19	19	37	31
	52	36.6				46	33
415	0	15.0	9	7	12	28	14
	4	.					
	8	.					
	12	18.1	9	7	12	15	17
	26	21.2	10	8	12	34	18
	38	24.0	10	8	12	34	20
	52	27.1	11	8	12	34	22
416	0	18.2	1	1	12	1	4
	4	19.2	1	1	12	2	4
	8	20.2	1	1	12	2	4
	12	21.0	1	1	12	4	4
	26	24.2	1	1	12	1	4
	38	27.0	1	1	12	2	3
	52	30.2	1	1	12	1	3
417	0	14.5	10	7	12	15	17
	4	.					
	8	.					
	12	17.5	11	11	12	15	17
	26	20.6	11	14	13	20	20
	38	23.4	11	16	15	28	23
	52	26.6	21	18	16	28	22
418	0	8.4	7	7		7	6
	4	.					
	8	.					
	12	11.2	10	7		13	12

Table A2-43: Study 1702 Amendment 008, PDMS-2 Results

Patient	Week	Actual Age (mos)	Gross Motor Age Equivalent (mos)			Fine Motor Age Equivalent (mos)	
			Stationary	Locomotion	Object Manipulation	Grasping	Visual-Motor Integration
	26	14.6	11	9	12	13	14
	38	17.3	11	10	12	20	18
	52	20.6	11	11	12	15	22
420	0	3.3	1	1		1	3
	4	.					
	8	.					
	12	.					
	26	.					
	38	12.7	9	7	12	15	12
	52	16.0	9	7	12	14	17
421	0	9.0	9	3		8	8
	4	.					
	8	.					
	12	12.2	9	4		14	14
	26	.					
	38	18.6	1	1	12	1	1
	52	22.0	1	1	12	1	3
422	0	17.6	10	8	12	34	19
	4	18.9	10	9	12	34	21
	8	19.9	10	10	12	34	19
	12	21.1	11	11	12	34	22
	26	24.0	11	17	20	37	26
	38	26.7	11	18	24	37	28
	52	.					
	58	31.5	18	18	23	28	34

10.1.2.17.6 Study Pompe PEDI Datasets

10.1.2.17.6.1 Mobility

Table A2-44: Study 1702 Amendment 008, Pompe PEDI Mobility Scores

Patient	Week	Age (mos)	Mobility Scores		
			Raw	Scaled	Normative Std
402	0	17.0	24	32.42	20.25
402	4	18.1	25	32.96	21.32
402	8	19.1	31	36.08	<10
402	12	20.1	36	38.39	12.42
402	26	23.3	44	41.69	20.19
402	38	26.0	50	43.88	<10
402	52	29.3	59	46.86	13.77
403	0	37.7	10	22.18	<10
403	4	38.7	18	28.81	<10
403	8	39.7	21	30.67	<10
403	12	40.6	23	31.85	<10
403	26	43.8	29	35.06	<10
403	38	46.7	28	34.55	<10

Table A2-44: Study 1702 Amendment 008, Pompe PEDI Mobility Scores

Patient	Week	Age (mos)	Mobility Scores		
			Raw	Scaled	Normative Std
403	52	50.0	11	23.23	<10
404	0	7.9	4	13.08	<10
404	4	9.1	4	13.08	<10
404	8	10.0	2	8.07	<10
404	12	11.0	6	16.81	<10
404	26	14.2	7	18.37	<10
404	38	17.0	10	22.18	<10
404	52	20.1	8	19.75	<10
405	0	13.1	0	0	<10
405	4	14.0	1	4.53	<10
405	8	14.9	1	4.53	<10
405	12	16.0	1	4.53	<10
406	0	16.4	1	4.53	<10
406	4	17.4	0	0	<10
406	8	18.3	2	8.07	<10
406	12	19.2	2	8.07	<10
406	26	22.4	2	8.07	<10
406	38	25.2	2	8.07	<10
406	52	28.6	0	0	<10
407	0	8.0	3	10.8	<10
407	4	9.2	2	8.07	<10
407	8	10.1	4	13.08	<10
407	12	11.1	4	13.08	<10
408	0	43.6	37	38.81	<10
408	4	44.6	43	41.3	<10
408	8	45.3	46	42.44	<10
408	12	46.4	46	42.44	<10
408	26	49.6	50	43.88	<10
408	38	52.5	51	44.24	<10
408	52	55.7	52	44.57	<10
410	0	36.8	9	21.01	<10
410	4	38.1	8	19.75	<10
410	8	39.1	10	22.18	<10
410	12	40.0	10	22.18	<10
410	26	43.2	8	19.75	<10
410	38	46.3	16	27.46	<10
410	52	49.4	12	24.22	<10
411	0	9.3	7	18.37	10.73
411	4	10.8	9	21.01	16.15
411	8	11.6	13	25.12	24.58
411	12	12.4	16	27.46	10.51
411	26	15.8	20	30.07	15.65
411	38	18.8	11	23.23	<10
411	52	22.1	17	28.15	<10
412	0	8.0	4	13.08	<10
412	4	9.1	1	4.53	<10
412	8	10.3	3	10.8	<10
412	12	11.1	4	13.08	<10
412	26	14.3	3	10.8	<10

Table A2-44: Study 1702 Amendment 008, Pompe PED1 Mobility Scores

Patient	Week	Age (mos)	Mobility Scores		
			Raw	Scaled	Normative Std
413	0	6.9	12	24.22	22.73
413	4	8.1	14	25.93	26.24
413	8	9.0	17	28.15	30.8
413	12	10.0	22	31.28	37.2
413	26	13.2	21	30.67	16.83
413	38	16.1	29	35.06	25.45
414	0	24.3	65	48.66	36.57
414	4	25.4	68	49.53	20.95
414	8	26.6	62	40.91	16.19
414	12	28.1	52	44.57	<10
414	26	30.7	63	48.06	10.87
414	38	33.4	71	50.7	17.74
414	52	36.6	66	48.96	12.76
415	0	15.0	14	25.93	<10
415	4	16.0	15	26.71	<10
415	8	17.0	19	29.47	14.47
415	12	18.1	22	31.28	18.01
415	26	21.2	28	34.55	<10
415	38	24.0	31	36.08	<10
415	52	27.1	36	38.39	<10
416	0	18.2	0	0	<10
416	4	19.2	2	8.07	<10
416	8	20.2	2	8.07	<10
416	12	21.0	3	10.8	<10
416	26	24.2	3	10.8	<10
416	38	27.0	1	4.53	<10
416	52	30.2	2	8.07	<10
417	0	14.5	20	30.07	15.65
417	4	15.5	20	30.07	15.65
417	8	16.4	26	33.5	22.38
417	12	17.5	34	37.49	30.23
417	26	20.6	49	43.52	24.49
417	38	23.4	57	46.23	30.85
417	52	26.6	66	48.96	19.42
418	0	8.4	14	25.9	26.24
418	4	9.6	15	26.71	27.84
418	8	10.3	12	24.22	22.73
418	12	11.2	18	28.81	32.15
418	26	14.6	31	36.08	27.46
418	38	17.3	52	44.57	44.16
418	52	20.6	54	45.23	28.52
420	0	3.3	0	0	21.75
420	4	4.7	5	15.06	44.68
420	8	5.6	6	16.81	47.33
420	12	6.4	10	22.18	18.55
420	26	9.7	12	24.22	22.73
420	38	12.7	18	28.81	13.17
420	52	16.0	17	28.15	11.87
421	0	9.0	13	25.12	24.58

Table A2-44: Study 1702 Amendment 008, Pompe PEDI Mobility Scores

Patient	Week	Age (mos)	Mobility Scores		
			Raw	Scaled	Normative Std
421	4	10.5	15	26.71	27.84
421	8	11.3	17	28.15	30.8
421	12	12.2	19	29.47	14.47
421	26	15.6	20	30.07	15.65
421	38	18.6	0	0	<10
421	52	22.0	0	0	<10
422	0	17.6	30	35.57	26.45
422	4	18.9	37	38.81	13.41
422	8	19.9	42	40.91	18.35
422	12	21.1	48	43.16	23.65
422	26	24.0	69	49.83	39.32
422	38	26.7	80	53.01	30.32
422	58	31.5	80	53.01	25.41

10.1.2.17.6.2 Self-Care

Table A2-45: Study 1702 Amendment 008, Pompe PEDI Self-Care Scores

Patient	Week	Age (mos)	Self-Care Scores		
			Raw	Scaled	Normative Std
402	0	17.0	25	42.44	48.02
402	4	18.1	23	41.24	45.69
402	8	19.1	30	45.18	36.38
402	12	20.1	29	44.66	35.22
402	26	23.3	40	50.15	47.51
402	38	26.0	41	50.64	37.4
402	52	29.3	39	49.67	35.47
403	0	37.7	19	38.57	<10
403	4	38.7	23	41.24	<10
403	8	39.7	29	44.66	14.35
403	12	40.6	29	44.66	14.35
403	26	43.8	30	45.18	<10
403	38	46.7	27	43.58	<10
403	52	50.0	18	37.82	<10
404	0	7.9	9	26.86	25.82
404	4	9.1	4	16.09	<10
404	8	10.0	3	12.7	<10
404	12	11.0	5	18.79	<10
404	26	14.2	11	30.34	24.6
404	38	17.0	15	35.25	34.11
404	52	20.1	18	37.82	19.95
405	0	13.1	0	0	<10
405	4	14.0	0	0	<10
405	8	14.9	1	4.92	<10
405	12	16.0	0	0	<10
406	0	16.4	1	4.92	<10
406	4	17.4	3	12.7	<10
406	8	18.3	3	12.7	<10
406	12	19.2	4	16.09	<10

Table A2-45: Study 1702 Amendment 008, Pompe PEDI Self-Care Scores

Patient	Week	Age (mos)	Self-Care Scores		
			Raw	Scaled	Normative Std
406	26	22.4	6	21.03	<10
406	38	25.2	6	21.03	<10
406	52	28.6	8	24.97	<10
407	0	8.0	3	12.7	<10
407	4	9.2	3	12.7	<10
407	8	10.1	5	18.79	<10
407	12	11.1	7	23.05	15.15
408	0	43.6	43	51.59	10.81
408	4	44.6	47	53.44	15.38
408	8	45.3	47	53.44	15.38
408	12	46.4	50	54.78	18.67
408	26	49.6	63	60.18	22.45
408	38	52.5	63	60.18	22.45
408	52	55.7	69	62.55	21.15
410	0	36.8	29	44.66	14.35
410	4	38.1	15	35.25	<10
410	8	39.1	13	33.1	<10
410	12	40.0	15	35.25	<10
410	26	43.2	27	43.58	<10
410	38	46.3	38	49.18	<10
410	52	49.4	24	41.86	<10
411	0	9.3	9	26.86	25.82
411	4	10.8	11	30.34	35.59
411	8	11.6	7	23.05	15.15
411	12	12.4	15	35.25	34.11
411	26	15.8	20	39.29	41.91
411	38	18.8	14	34.24	11.95
411	52	22.1	19	38.57	21.62
412	0	8.0	5	18.79	<10
412	4	9.1	8	24.97	20.53
412	8	10.3	9	26.86	25.82
412	12	11.1	10	28.68	30.93
412	26	14.3	12	31.8	27.43
413	0	6.9	15	35.25	49.36
413	4	8.1	10	28.68	30.93
413	8	9.0	10	28.68	30.93
413	12	10.0	10	28.68	30.93
413	26	13.2	11	30.34	24.6
413	38	16.1	26	43	49.09
414	0	24.3	41	50.64	48.6
414	4	25.4	42	51.1	38.3
414	8	26.6	42	51.1	38.3
414	12	28.1	29	44.66	25.57
414	26	30.7	42	51.1	29.96
414	38	33.4	49	54.32	36.98
414	52	36.6	51	55.23	32.55
415	0	15.0	13	33.1	29.95
415	4	16.0	19	38.57	40.53
415	8	17.0	26	43	49.09

Table A2-45: Study 1702 Amendment 008, Pompe PEDI Self-Care Scores

Patient	Week	Age (mos)	Self-Care Scores		
			Raw	Scaled	Normative Std
415	12	18.1	22	40.62	44.49
415	26	21.2	28	44.1	33.98
415	38	24.0	31	45.7	37.54
415	52	27.1	35	47.71	31.61
416	0	18.2	5	18.79	<10
416	4	19.2	5	18.79	<10
416	8	20.2	6	21.03	<10
416	12	21.0	7	23.05	<10
416	26	24.2	5	18.79	<10
416	38	27.0	2	8.99	<10
416	52	30.2	2	8.99	<10
417	0	14.5	23	41.24	45.69
417	4	15.5	24	41.86	46.88
417	8	16.4	27	43.58	50.22
417	12	17.5	31	45.7	54.31
417	26	20.6	37	48.69	44.24
417	38	23.4	35	47.71	42.05
417	52	26.6	46	52.99	42.03
418	0	8.4	12	31.8	39.69
418	4	9.6	13	33.1	43.34
418	8	10.3	14	34.24	46.54
418	12	11.2	18	37.82	56.57
418	26	14.6	23	41.24	45.69
418	38	17.3	29	44.66	52.3
418	52	20.6	36	48.2	43.14
420	0	3.3	0	0	19.4
420	4	4.7	5	18.79	58.32
420	8	5.6	6	21.03	62.97
420	12	6.4	8	24.97	20.53
420	26	9.7	8	24.97	20.53
420	38	12.7	10	28.68	21.39
420	52	16.0	15	35.25	34.11
421	0	9.0	9	26.86	25.82
421	4	10.5	13	33.1	43.34
421	8	11.3	17	37.04	54.38
421	12	12.2	17	37.04	37.57
421	26	15.6	25	42.44	48.02
421	38	18.6	0	0	<10
421	52	22.0	0	0	<10
422	0	17.6	29	44.66	52.3
422	4	18.9	39	49.67	46.42
422	8	19.9	41	50.64	48.6
422	12	21.1	44	52.04	51.73
422	26	24.0	54	56.5	61.69
422	38	26.7	60	58.97	53.85
422	58	31.5	63	60.18	49.76

10.1.2.17.6.3 Social Function

Table A2-46: Study 1702 Amendment 008, Pompe PEDI Social Function Scores

Patient	Week	Age (mos)	Social Function Scores		
			Raw	Scaled	Normative Std
402	0	17.0	10	34	42.6
402	4	18.1	12	36.1	45.4
402	8	19.1	14	37.9	24.3
402	12	20.1	13	37	21.7
402	26	23.3	25	45.6	45.9
402	38	26.0	23	44.4	26.7
402	52	29.3	31	49.1	40.1
403	0	37.7	31	49.1	36.1
403	4	38.7	31	49.1	36.1
403	8	39.7	31	49.1	36.1
403	12	40.6	29	47.9	34.6
403	26	43.8	37	52.6	30.8
403	38	46.7	39	53.7	32.7
403	52	50.0	42	55.4	22.6
404	0	7.9	2	6.6	24.2
404	4	9.1	2	6.6	24.2
404	8	10.0	3	10.5	28.9
404	12	11.0	4	14.7	34.1
404	26	14.2	4	14.7	15.5
404	38	17.0	7	30	36.9
404	52	20.1	6	27.7	<10
405	0	13.1	5	21.6	25.2
405	4	14.0	2	6.6	<10
405	8	14.9	3	10.5	<10
405	12	16.0	3	10.5	<10
406	0	16.4	4	14.7	15.5
406	4	17.4	2	6.6	<10
406	8	18.3	5	21.6	<10
406	12	19.2	8	31.6	6.4
406	26	22.4	10	34	13.3
406	38	25.2	14	37.9	<10
406	52	28.6	19	41.8	19.3
407	0	8.0	1	3.1	20
407	4	9.2	1	3.1	20
407	8	10.1	3	10.5	28.9
407	12	11.1	2	6.6	24.2
408	0	43.6	47	58.5	40.3
408	4	44.6	52	62.3	46.3
408	8	45.3	44	56.6	37.3
408	12	46.4	43	56	36.3
408	26	49.6	53	63.2	39.9
408	38	52.5	49	59.9	32.6
408	52	55.7	48	59.2	28.7
410	0	36.8	26	46.2	32.5
410	4	38.1	26	46.2	32.5

Table A2-46: Study 1702 Amendment 008, Pompe PEDI Social Function Scores

Patient	Week	Age (mos)	Social Function Scores		
			Raw	Scaled	Normative Std
410	8	39.1	26	46.2	32.5
410	12	40.0	22	43.8	29.5
410	26	43.2	26	46.2	20.6
410	38	46.3	30	48.5	24.3
410	52	49.4	24	45	<10
411	0	9.3	2	6.6	24.2
411	4	10.8	5	21.6	42.5
411	8	11.6	4	14.7	34.1
411	12	12.4	7	30	36.9
411	26	15.8	5	21.6	25.2
411	38	18.8	17	40.4	31.2
411	52	22.1	23	44.4	42.5
412	0	8.0	3	10.5	28.9
412	4	9.1	2	6.6	24.2
412	8	10.3	2	6.6	24.2
412	12	11.1	4	14.7	34.1
412	26	14.3	4	14.7	15.5
413	0	6.9	8	31.6	54.6
413	4	8.1	8	31.6	54.6
413	8	9.0	12	36.1	60
413	12	10.0	13	37	61.2
413	26	13.2	14	37.9	48
413	38	16.1	17	40.4	51.4
414	0	24.3	21	43.1	39
414	4	25.4	22	43.8	24.9
414	8	26.6	23	44.4	26.7
414	12	28.1	24	45	28.4
414	26	30.7	25	45.6	27.2
414	38	33.4	28	47.3	30.7
414	52	36.6	28	47.3	33.9
415	0	15.0	6	27.7	33.8
415	4	16.0	11	35.1	44
415	8	17.0	11	35.1	44
415	12	18.1	14	37.9	48
415	26	21.2	16	39.6	29
415	38	24.0	18	41.1	33.2
415	52	27.1	25	45.6	30.1
416	0	18.2	5	21.6	25.2
416	4	19.2	5	21.6	<10
416	8	20.2	5	21.6	<10
416	12	21.0	8	31.6	6.4
416	26	24.2	8	31.6	6.4
416	38	27.0	15	38.8	10.6
416	52	30.2	9	32.9	<10
417	0	14.5	14	37.9	48
417	4	15.5	15	38.8	49.2
417	8	16.4	15	38.8	49.2
417	12	17.5	16	39.6	50.3
417	26	20.6	25	45.6	45.9

Table A2-46: Study 1702 Amendment 008, Pompe PEDI Social Function Scores

Patient	Week	Age (mos)	Social Function Scores		
			Raw	Scaled	Normative Std
417	38	23.4	24	45	44.2
417	52	26.6	29	47.9	36.8
418	0	8.4	3	10.5	28.9
418	4	9.6	5	21.6	42.5
418	8	10.3	7	30	52.6
418	12	11.2	7	30	52.6
418	26	14.6	12	36.1	45.4
418	38	17.3	15	38.8	49.2
418	52	20.6	23	44.4	42.5
420	0	3.3	2	6.6	
420	4	4.7	1	3.1	
420	8	5.6	4	14.7	
420	12	6.4	5	21.6	42.5
420	26	9.7	6	27.7	49.9
420	38	12.7	7	30	36.9
420	52	16.0	13	37	46.8
421	0	9.0	7	30	52.6
421	4	10.5	14	37.9	62.3
421	8	11.3	14	37.9	62.3
421	12	12.2	15	38.8	49.2
421	26	15.6	19	41.8	53.4
421	38	18.6	1	3.1	<10
421	52	22.0	7	30	<10
422	0	17.6	17	40.4	51.4
422	4	18.9	24	45	44.2
422	8	19.9	26	46.2	47.5
422	12	21.1	27	46.8	49.2
422	26	24.0	31	49.1	55.7
422	38	26.7	36	52	48.4
422	58	31.5	39	53.7	43.4

10.1.2.17.7 BSID-II

Table A2-47: Study 1702 Amendment 008, BSID-II Scores

Patient	Week	Raw Score	Age (Mos)	Age Equiv (mos)	MDI
402	0	95	17.0	14	74
402	12	110	20.1	17	80
402	26	121	23.3	20	82
402	38	128	26.0	22	78
402	52	140	29.3	26	93
402	64	147	32.1	30	98
403	0	145	37.7	29	73
403	12	160	40.6	38	90
403	26	.	.	.	.
403	38	175	46.7	46	.
404	0	64	7.9	6	84
404	12	67	11.0	7	64
404	26	82	14.2	11	73

Table A2-47: Study 1702 Amendment 008, BSID-II Scores

Patient	Week	Raw Score	Age (Mos)	Age Equiv (mos)	MDI
404	38	95	17.0	14	74
404	52	102	20.1	16	71
405	0	10	13.0	0	<50
405	12	34	16.0	3	<50
406	0	54	16.4	5	<50
406	12	71	19.2	8	<50
406	26	82	22.4	11	<50
406	38	75	25.2	9	<50
406	52	130	28.6	23	72
406	64	135	31.3	25	75
407	0	28	8.0	2	<50
407	12	67	11.1	7	82
408	0	161	43.6	38	.
408	12	.	.	.	.
408	26	.	.	.	.
408	38	168	52.5	.	.
408	52	176	55.7	42	.
410	0	.	36.8	.	.
410	12	118	40.0	19	<50
410	26	152	43.2	34	74
410	38	157	46.3	36	.
410	52	.	.	.	.
410	64	160	52.2	37	.
411	0	69	9.3	7	87
411	12	77	12.4	9	74
411	26	92	15.8	13	78
411	38	93	18.8	13	57
411	52	.	22.1	.	.
411	64	117	24.9	19	62
412	0	53	8.0	5	80
412	12	70	11.1	7	89
412	26	71	14.3	8	62
413	0	65	6.9	6	96
413	12	78	10.0	10	98
413	26	78	13.2	10	71
413	38	87	16.1	12	77
414	0	125	24.3	21	84
414	12	135	28.1	25	82
414	26	146	30.7	30	98
414	38	142	33.4	27	84
414	52	146	36.6	30	82
415	0	93	15.0	13	89
415	12	98	18.1	15	71
415	26	111	21.2	17	74
415	38	119	24.0	19	72
415	52	123	27.1	21	62
416	0	72	18.2	8	<50
416	12	76	21.0	9	<50
416	26	.	24.2	.	.
416	38	127	27.0	22	78

Table A2-47: Study 1702 Amendment 008, BSID-II Scores

Patient	Week	Raw Score	Age (Mos)	Age Equiv (mos)	MDI
416	52	135	30.2	25	75
417	0	100	14.5	15	112
417	12	103	17.5	16	90
417	26	111	20.6	17	82
417	38	122	23.4	20	84
417	52	134	26.6	24	90
418	0	66	8.4	7	88
418	12	82	11.2	11	98
418	26	94	14.6	14	99
418	38	112	17.3	18	108
418	52	118	20.6	19	96
420	0	29	3.3	2	91
420	12	56	6.4	5	86
420	26	68	9.7	7	76
420	38	87	12.7	12	99
420	52	98	16.0	15	90
421	0	70	9.0	7	96
421	12	89	12.2	12	105
421	26	103	15.6	16	109
421	38	2	18.6	0	<50
422	0	107	17.6	17	98
422	12	125	21.1	21	102
422	26	135	24.0	25	104
422	38	147	26.7	30	118
422	52	.	.	.	.
422	58	146	31.5	30	95

10.1.2.17.8 Growth Parameters

10.1.2.17.8.1 Weight and Length

Table A2-47: Study 1702, Weight and Length

			Weight			Length		
Patient	Week	Age (mos)	kg	Z-score	%ile	cm	Z-score	%ile
402	0	17.2	9.7	-0.9	18	78.5	-0.1	46
402	4	18.1	10	-0.8	21	79.8	0	50
402	8	19.1	10.4	-0.6	27	79.6	-0.4	36
402	12	20.2	10.6	-0.6	27	82	0.1	53
402	26	23.3	11.5	-0.3	40	84.9	0.1	55
402	38	26.1	12.1	-0.1	44	86	-0.1	47
402	52	29.3	12.9	+0.2	54	87.7	-0.3	38
402	64	32.2	12.8	-0.3	39	90.2	-0.2	41

Table A2-47: Study 1702, Weight and Length

			Weight			Length		
Patient	Week	Age (mos)	kg	Z-score	%ile	cm	Z-score	%ile
403	0	37.8	14.8	0.2	56	99	0.8	78
403	4	38.8	14.8	0.1	52	98	0.4	64
403	8	39.6	14.6	-0.2	44	95	-0.6	29
403	12	40.6	14.5	-0.3	38	95.5	-0.6	28
403	26	43.9	15.3	-0.1	46	98	-0.4	35
403	38	46.8	14.8	-0.7	25	100.8	-0.1	45
403	52	50.0	16	-0.3	40	100.9	-0.5	31
403	64	52.9	15.3	-0.9	18	100.7	-0.9	18
404	0	8.3	6.8	-2.6	1	68	-1.1	13
404	4	9.0	7.2	-2.1	2	69	-0.7	23
404	8	10.0	7.6	-2.0	2	68.7	-1.4	8
404	12	11.0	8.2	-1.7	5	71.5	-0.8	22
404	26	14.2	9	-1.9	3	74.7	-1.2	11
404	38	17.0	9.9	-1.3	9	78	-0.8	21
404	52	20.2	11.2	-0.6	27	84	0.2	58
404	64	23.0	11.6	-0.7	25	85.5	-0.1	44
405	0	13.2	7.8	-2.0	2	71	-1.1	13
405	4	14.1	8.1	-2.0	2	72.5	-1.0	16
405	8	15.1	8.7	-1.5	6	75.2	-0.5	31
405	12	16.0	9.8	-0.6	27	76	-0.6	29
406	0	16.3	16	3.0	100	94	3.9	100
406	4	17.4	14.1	1.8	96	91	2.8	100
406	8	18.3	14.3	1.7	96	94	3.4	100
406	12	19.3	14.5	1.7	96	97.5	4.1	100
406	26	22.5	14.3	1.3	90	110	6.7	100
406	38	25.2	14.4	1.1	87	104.5	5.0	100
406	52	28.5	14.9	1.0	85	101	2.9	100
406	64	31.3	16	1.5	93	104.3	3.3	100
407	0	8.2	5.3	-3.9	0	66	-1.2	12
407	4	9.2	5.7	-3.8	0	65	-2.0	2
407	8	10.2	5.9	-3.9	0	67.5	-1.5	6
407	12	11.2	6.1	-4.1	0	68.6	-1.6	6
408	0	43.6	14.4	-0.3	40	100	0.6	71
408	4	44.6	14.5	-0.3	38	.	-	-
408	8	45.5	14.6	-0.3	37	.	-	-
408	12	46.4	14.9	-0.2	40	97	-0.6	29
408	26	49.7	14.7	-0.7	24	102.5	0.2	58
408	38	52.6	15	-0.7	24	.	-	-
408	52	55.7	15.1	-0.9	19	107.2	0.6	72
408	64	.	.	-	-	.	-	-
409	0	6.2	5.5	-3.4	0	63.6	-1.8	4
409	4	7.2	6.3	-2.8	0	65.2	-1.7	4
410	0	37.1	10.4	-3.2	0	89	-1.7	4
410	4	38.0	10.7	-3.0	0	89	-1.9	3
410	8	39.0	12	-1.9	3	84	-3.5	0
410	12	39.9	14	-0.5	30	93.8	-0.9	19
410	26	43.3	16.3	0.5	70	92	-1.8	4
410	38	46.1	17	0.6	73	.	-	-
410	52	49.4	19.1	1.2	89	116	3.1	100

Table A2-47: Study 1702, Weight and Length

Patient	Week	Age (mos)	Weight kg	Weight Z-score	Weight %ile	Length cm	Length Z-score	Length %ile
410	64	52.2	20.7	1.5	94	.	-	-
411	0	10.0	9.1	-0.4	36	74.3	0.7	75
411	4	10.7	8.7	-1.1	13	73.5	-0.1	48
411	8	11.7	9	-1.1	13	75.4	0.2	57
411	12	12.5	9.3	-1.1	14	77.8	0.6	71
411	26	15.9	10.7	-0.4	33	82	0.8	79
411	38	18.8	9.9	-1.6	5	89.1	2.0	98
411	52	22.1	11	-1.0	15	89.5	1.3	90
411	64	24.9	12.6	-0.1	46	86.5	-0.1	46
412	0	8.1	7.3	-1.5	7	71	0.6	71
412	4	9.1	7.8	-1.8	4	64	-3.4	0
412	8	10.2	7.9	-2.0	2	74.5	0.3	61
412	12	11.1	7.5	-2.5	1	87	4.0	100
412	26	14.3	7.8	-3.2	0	77	-0.5	33
413	0	7.1	6.6	-1.6	6	70	0.9	81
413	4	8.1	6.6	-1.6	6	70	0.9	81
413	8	9.0	8.1	-0.2	41	73	1.4	92
413	12	9.9	8.6	-0.1	46	75	1.6	95
413	26	13.2	10.8	1.0	85	82	2.7	100
413	38	16.0	12.1	1.4	91	87	3.1	100
413	52	.	.	-	-	.	-	-
414	0	24.5	9.6	-2.4	1	76	-2.7	0
414	4	25.4	10.3	-1.7	4	79	-2.1	2
414	8	26.5	10.2	-2.0	2	79	-2.3	1
414	12	27.5	11	-1.3	10	79	-2.5	1
414	26	30.5	11.2	-1.4	7	80	-2.8	0
414	38	33.3	11.5	-1.4	8	82	-2.6	1
414	52	36.4	11.9	-1.3	9	84	-2.5	1
415	0	15.2	9.7	-1.1	13	81	0.8	80
415	4	16.2	9.4	-1.6	5	81	0.5	69
415	8	17.1	9.5	-1.7	4	82.5	0.6	74
415	12	18.2	9.9	-1.5	7	82.5	0.3	63
415	26	21.2	10.7	-1.2	12	85	0.2	59
415	38	24.0	11.3	-1.0	15	87	0.0	52
415	52	27.1	12.2	-0.6	27	91	0.7	76
416	0	18.3	11.9	0.1	53	82.8	0.1	55
416	4	19.3	12.9	0.9	75	85.2	0.6	71
416	8	20.2	12.3	0.2	60	83.5	0	52
416	12	21.0	14.1	1.4	91	88	1.1	87
416	26	24.3	14.6	1.3	91	89	0.6	73
416	38	27.2	15.5	1.6	94	63	-7.4	0
416	52	30.3	14.7	0.8	79	.	-	-
417	0	14.5	7.2	-3.5	0	73	-1.2	12
417	4	15.4	7.1	-3.9	0	75	-0.9	19
417	8	16.4	7.5	-3.6	0	76	-0.9	18
417	12	17.3	7.9	-3.3	0	74	-0.9	19
417	26	20.6	8.9	-2.6	1	79	-1.8	4
418	0	8.5	7.6	-0.8	21	73.2	1.5	93
418	4	9.5	7.8	-1.0	16	73.4	1.0	85

Table A2-47: Study 1702, Weight and Length

Patient	Week	Age (mos)	Weight kg	Weight Z-score	Weight %ile	Length cm	Length Z-score	Length %ile
418	8	10.3	8.1	-1.0	16	73.7	0.6	74
418	12	11.2	9	-0.4	36	75.6	0.8	80
419	0	8.8	7.3	-1.2	12	70	0.3	62
420	0	3.7	6.2	1.0	84	61	0.2	59
420	4	4.6	6.9	0.6	72	65	1.0	84
420	8	5.5	7.5	0.6	74	68.9	1.8	96
420	12	6.5	8.2	0.8	80	70.8	1.8	97
421	0	9.5	8.3	-1.2	12	73.5	0.4	66
421	4	10.5	8.8	-1.0	16	75	0.5	68
421	8	11.4	8.9	-1.2	11	75.5	0.2	58
421	12	12.3	9.3	-1.1	14	76.5	0.1	55
422	0	18.1	8.7	-2.2	1	76.5	-1.0	15
422	4	19.0	8.9	-2.2	1	77	-1.2	12
422	8	19.4	9.2	-2.1	2	78.5	-1.0	16
422	12	20.8	9.6	-1.8	4	80	-0.8	21

10.1.2.17.8.2 Head Circumference

Table A2-48: Study 1702, Head Circumference

Patient	Week	Age	Head Circumference Cm	Head Circumference Z-score	Head Circumference %ile
402	0	17.2	47	0.6	73
402	4	18.1	47.5	0.8	79
402	8	19.1	47.5	0.7	75
402	12	20.2	48	0.9	82
402	26	23.3	49	1.3	90
402	38	26.1	49.5	1.3	91
402	52	29.3	49	0.7	76
402	64	32.2	48.8	0.4	64
403	0	37.8	50.5	-	-
403	4	38.8	52.5	-	-
403	8	39.6	52.5	-	-
403	12	40.6	52.3	-	-
403	26	43.9	52.3	-	-
403	38	46.8	53.5	-	-
403	52	50.0	53.5	-	-
403	64	52.9	53.5	-	-
404	0	8.3	43.5	-1.2	11
404	4	9.0	43	-1.6	5
404	8	10.0	39	-5.3	0
404	12	11.0		-	-
404	26	14.2	46.5	-0.4	34
404	38	17.0	47	-0.4	36
404	52	20.2	48	0	49
404	64	23.0	49	0.4	65

Table A2-48: Study 1702, Head Circumference

Patient	Week	Age	Head Circumference Cm	Z-score	%ile
405	0	13.2	45	-0.2	44
405	4	14.1	45	-0.4	35
405	8	15.1	45.1	-0.5	31
405	12	16.0	46	0	51
406	0	16.3	49.5	1.5	94
406	4	17.4	50	1.7	96
406	8	18.3	50	1.6	94
406	12	19.3	50	1.5	93
406	26	22.5	.	-	-
406	38	25.2	49.5	0.5	71
406	52	28.5	51.5	1.6	95
406	64	31.3	50.3	0.7	75
407	0	8.2	39	3.8	100
407	4	9.2	40.1	-3.4	0
407	8	10.2	40.3	-3.5	0
407	12	11.2	40.2	-3.9	0
408	0	43.6	49	-	-
408	4	44.6	.	-	-
408	8	45.5	.	-	-
408	12	46.4	51.6	-	-
408	26	49.7	51.7	-	-
408	38	52.6	.	-	-
408	52	55.7	50.8	-	-
408	64	.	.	-	-
409	0	.	41.5	-1.9	2.8
409	4	7.2	42.5	-1.6	6
410	0	37.1	47.7	-	-
410	4	38.0	48	-	-
410	8	39.0	48	-	-
410	12	39.9	49	-	-
410	26	43.3	50	-	-
410	38	46.1	.	-	-
410	52	49.4	51	-	-
410	64	52.2	.	-	-
411	0	10.0	44.6	-0.7	25
411	4	10.7	44.3	-1.2	11
411	8	11.7	44.1	-1.7	5
411	12	12.5	45.7	-0.6	27
411	26	15.9	46.1	-0.9	18
411	38	18.8	46.5	-1.0	15
411	52	22.1	41	-5.3	0
411	64	24.9	46.9	-1.3	10
412	0	8.1	44.5	-0.1	48
412	4	9.1	44.5	-0.8	22
412	8	10.2	44.5	-1.1	14
412	12	11.1	44	-1.5	7
412	26	14.3	45	-1.6	6
413	0	7.1	41.5	-1.4	8
413	4	8.1	41.5	-1.4	8

Table A2-48: Study 1702, Head Circumference

Patient	Week	Age	Head Circumference Cm	Z-score	%ile
413	8	9.0	43	-0.6	28
413	12	9.9	43	-0.9	18
413	26	13.2	44	-0.9	17
413	38	16.0	45.3	-0.5	30
413	52	.	.	-	-
414	0	24.5	47.5	0	49
414	4	25.4	48	0.2	60
414	8	26.5	48	0.2	56
414	12	27.5	48	0.1	53
414	26	30.5	48.5	0.2	58
414	38	33.3	48.5	0.1	54
414	52	36.4	49	0.3	60
415	0	15.2	46	-0.8	21
415	4	16.2	46.5	-0.6	28
415	8	17.1	45.8	-1.3	10
415	12	18.2	45.6	-1.6	6
415	26	21.2	47	-0.9	19
415	38	24.0	47.5	-0.8	22
415	52	27.1	48	-0.6	26
416	0	18.3	49.1	0.9	82
416	4	19.3	48.5	0.3	64
416	8	20.2	48.3	0.2	58
416	12	21.0	49	0.6	72
416	26	24.3	49	0.3	61
416	38	27.2	48.5	-0.3	38
416	52	30.3	49	-0.1	44
417	0	14.5	44	-1.4	9
417	4	15.4	44	-1.5	6
417	8	16.4	44	-1.7	5
417	12	17.3	45	-1.1	14
417	26	20.6	46	-0.7	24
418	0	8.5	41	-2.3	1
418	4	9.5	42.2	-1.6	6
418	8	10.3	42.5	-1.7	5
418	12	11.2	42.5	-1.9	3
419	0	8.8	43.5	-0.2	43
420	0	3.7	39.5	-0.7	23
420	4	4.6	41	-0.3	39
420	8	5.5	42.4	0.2	60
420	12	6.5	43.1	0.3	62
421	0	9.5	46.5	0.8	79
421	4	10.5	45	-0.7	25
421	8	11.4	45	-0.9	17
421	12	12.3	46.5	0	50
422	0	18.1	45	-1.1	14
422	4	19.0	.	-	-
422	8	19.4	45.5	-1.0	17
422	12	20.8	46	-0.7	24

10.1.3 Juvenile- and Adult-Onset Pompe Disease Summary

All of the information on juvenile/childhood- and adult-onset ("late-onset") patients that was submitted to the application was submitted for 24 patients, who were treated in five separate studies and expanded access programs. Five patients were treated in Study AGLU02804 (a GCP-compliant study), and the remaining 19 patients were treated in expanded access programs and non-GCP trials. All of the information was open-label and uncontrolled. These 24 patients do not constitute the entire number of "late-onset" patients exposed to Myozyme in expanded access programs (EAPs) and clinical trials (excluding patients participating in the ongoing, double-blind, placebo-controlled Study AGLU02704), and the true "late-onset" patient exposure is not known.

10.1.3.1 Overview

The 24 patients included in this summary participated in the following studies and EAPs:

- Study AGLU02804 was an open-label, nonrandomized, uncontrolled, single-center, 26-week, safety and efficacy study of five juvenile-onset Pompe disease patients ages 6 to 15 years at study entry (median age 12.7 years), with onset of first symptoms at ages 1 to 12 years. All patients were able to ambulate at least 10 meters (m) at baseline, and patients on invasive ventilation at baseline were excluded. All patients received Myozyme 20 mg/kg qow for 26 weeks. The main efficacy measures were changes from baseline at Week 26 in distance walked in six minutes (six-minute walk test, 6MWT), and pulmonary function test (PFT) parameters.

- The remaining 19 patients were treated in four different studies and expanded access programs, and the information was submitted predominantly as narratives. The study designs for these studies and programs are described as follows:

    - Study AGLU02503 is an ongoing, open-label, European expanded access program of Myozyme 20 mg/kg qow in the treatment of severely affected juvenile-onset Pompe disease patients. Four patients were enrolled in the EAP, but only three patients received treatment with rhGAA (one patient died prior to receiving any treatment). All patients enrolled in the EAP had documented signs or symptoms of Pompe disease at age greater than 12 months, were 21 years of age or younger at study entry, had documented GAA deficiency, and were severely affected (non-ambulatory and needing assisted ventilation). The initial report submitted in the original submission to the application contained information on the first 26 weeks of treatment in these patients. A 52-week update was received in Amendment 002 for two of the patients (one patient died at Week 20).
    - Study AGLU02103 is an ongoing, open-label, extension, safety and efficacy study of Myozyme 30 mg/kg qow in a single juvenile-onset patient, who had

previously received 3.7 years of rhGAA treatment (Pharming and Synpac formulations) under INDs —

- International EAP is an ongoing EAP conducted outside the US, which provides Myozyme to patients with infantile-, juvenile- and adult-onset Pompe disease. Fifty-four patients have been enrolled in this EAP as of 08-March-2005, and narratives for 14 of these patients were submitted to the application from this EAP, including 13 juvenile-onset patients and one muscular-variant infantile-onset patient (IW).
- AGLU02603 (US EAP) is an ongoing, open-label, expanded access program conducted in the US for severely affected patients with juvenile- and adult-onset Pompe disease, who did not meet the clinical eligibility criteria for enrollment in an ongoing study of Myozyme. The first patient was enrolled December 2004. Narratives on two patients were submitted to the application from this EAP.

These studies are summarized in the following table:

Table A3-1: Myozyme Clinical Development Program, Juvenile/Childhood- and Adult-Onset Studies

Study	Population	Description
AGLU02804	Juvenile-onset (age range 1-6 yrs), n=5	OL, uncontrolled, non-randomized, single-center, 26-week, PK, safety, and efficacy study of Myozyme 20 mg/kg qow to 5 patients with juvenile-onset Pompe disease. Patients were ages 6 to 15 years (median 12.7 years) at baseline, with symptom onset at ages 1 to 12 years. All patients could ambulate 10 m at baseline, and patients on invasive ventilation at baseline were excluded.
AGLU02503	Juvenile-onset (age range at symptom onset 1-3 yrs), n=3	OL, European, expanded access, safety and efficacy program of Myozyme 20 mg/kg qow in 3 patients with clinically advance juvenile-onset Pompe disease (04-November-2003 to ongoing). Four patients were enrolled, and 3 received treatment. Patients were ages 9, 17 and 19 years at study entry, and had onset of signs and symptoms of Pompe disease at >12 months to ≤21 years. The objective of the study was to provide acces to treatment with Myozyme to these patients.
AGLU02103	Juvenile-onset (age 11 yrs), n=1	OL, extension, safety and efficacy study of Myozyme 30 mg/kg qow in 1 juvenile-onset Pompe disease patient who had previously received 3.7 years of Pharming and Synpac rhGAA formulations under INDs — (AGLU02103 conducted from 11-Apr-2003 to ongoing). The patient was age 16 years at first rhGAA treatment, and age 20 years at first Myozyme treatment.
International EAP	Infantile-, juvenile- and adult-onset (1 patient age at symptom onset 6 months c/w infantile-onset muscular variant, remaining 13 patients, juvenile-onset, age range 2-35 yrs), n=13	An expanded access program conducted outside the US providing Myozyme to patients of any age (infantile-, juvenile- and adult-onset) with Pompe disease. 54 patients have been enrolled as of 08-March-2005.
AGLU02603 (US EAP)	Juvenile- and adult-onset (ages 2 and 21 yrs), n=2	Ongoing, OL, expanded access study in the US for severely affected patients with Pompe disease who do not meet the clinical eligibility criteria for enrollment in an ongoing study of Myozyme.
AGLU02704 (LOTS)	Limited safety data available only	Multicenter, international, randomized, double-blind, placebo-controlled, 52-week, PK, safety, and efficacy study of Myozyme in about 80 juvenile- and adult-onset Pompe disease patients. First patient was enrolled August 2005, enrollment was completed March 2006, and study completion is anticipated in March 2007.
Total	**n=24**	

10.1.3.2 Study AGLU02804

Study AGLU02804 (Study 2804) is a single-center, open-label, 26-week (14-infusion), efficacy, safety, and PK study of Myozyme 20 mg/kg qow in five subjects (3M, 2F) with juvenile-onset Pompe disease. Eligible patients must have been ≥5 and <18 years of age, had a confirmed diagnosis of Pompe disease by either a GAA gene mutation or deficient GAA activity, and had clinical signs and symptoms of Pompe disease as demonstrated by muscle weakness in the lower extremities (by manual muscle testing, MMT). Patients must have been able to perform pulmonary and muscle testing, and have been able to ambulate ten meters (using assistive devices if necessary) at baseline. Patients were excluded if they required the use of invasive ventilatory support or noninvasive ventilatory support while awake and in an upright position. Outcomes assessments, including respiratory function by PFTs, muscle strength by MMT and hand-held dynamometry (HHD), and functional status as assessed by the 6MWT were performed at scheduled visits. PK testing was assessed at baseline and at Weeks 12 and 26. Safety was assessed by the occurrence of AEs throughout the study.

Preliminary review of the data showed that all patients had a confirmed diagnosis of Pompe disease by GAA deficiency or genotyping, were between the ages of 13 months to 11.6 years, and had onset of first symptoms at age one year or older (range 1 to 6.5 years). At baseline, all patients exhibited clinical features consistent with juvenile-onset Pompe disease, including scoliosis, lordosis, joint contractures, abnormal gait, and difficulties in mobility (climbing, running). No patient had cardiac hypertrophy at baseline. The median age at first Myozyme infusion in the study was 12.7 years (range 5.9 to 15.2 years).

The efficacy results

PK (activity of rhGAA in plasma) was characterized on Day 0, at Week 12 (7th infusion) and at Week 26 (14th infusion). There were no appreciable differences in any parameter between the Day 0, Week 12 and Week 24 results. The results are summarized in the following table.

Table A3-5: Study 2804, PK Parameters

Parameter*	Day 0	Week 12	Week 24
Cmax (ng/mL)	306,921 ±104,801	368,904 ±63,629	310,883 ±65,866
Tmax (H)	3.37	3.42	3.43
AUC_{∞} (h.ng/mL)	1,435,034 ± 182,724	1,689,479 ± 252,296	1,471,771 ± 230,970
$T_{1/2}$ (h)	2.71 ± 0.36	2.88 ± 0.61	2.59 ± 0.23
CL (mL/h/kg)	14.1 ±1.66	12.1 ±1.89	13.9 ±2.30
V_{ss}** (mL/kg)	56.0 ±12.2	47.2 ±9.66	53.8 ± 10.7

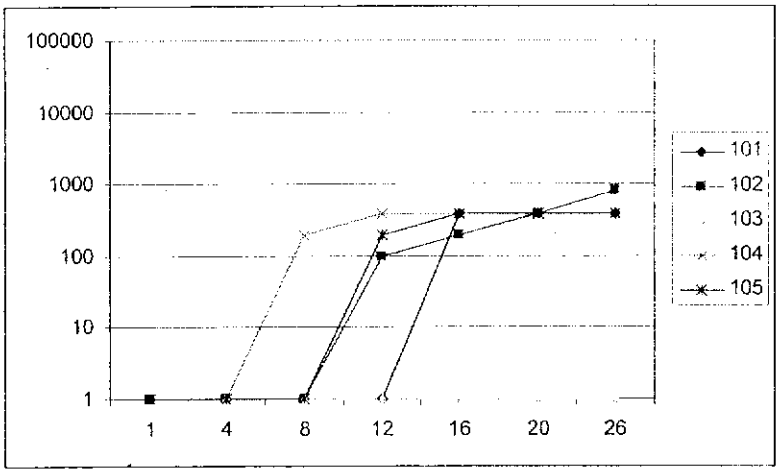
*mean ±SD except for Tmax
**Volume of distribution at steady state

Immunogenicity testing showed that four of five patients developed anti-rhGAA IgG antibodies, with titers ranging from 100 to 800, and seroconversion occurred at Weeks 8 or 16 in these four patients. There were no reports of concomitant medications used specifically for allergic prophylaxis prior to Myozyme use and there were no IARs reported. The results are summarized in the following table and in the following figure (logarithmic scale).

Table A3-6: Study 2804, Anti-rhGAA Antibody (IgG) Titers

	Subject Number				
Week	**101**	**102**	**103**	**104**	**105**
0	0	0	-	0	0
4	0	0	0	0	0
8	0	0	0	200	0
12	0	100	0	400	200
16	400	200	0	400	400
20	400	400	0	400	400
26	400	800	0	400	400

Figure A3-1: Study 2804 Anti-rhGAA Antibody (IgG) Titers (log scale)



Safety results showed that there were a total of 34 reported AEs, one of which occurred prior to study drug administration (nausea one day prior to first infusion). For the 33 remaining treatment-emergent AEs (reported during or after first infusion), all patients experienced more than one AE (range 3-12 AEs reported per patient), there were no deaths, no patient discontinued treatment for any reason, and there were no IARs reported. The most frequently reported AEs were headache and pharyngitis (reported by 3 patients each). The most commonly reported (by ≥2 patients) AEs (incidence rates and numbers of AEs by preferred term) are summarized in the following table.

Table A3-7: Study 2804, Most Commonly (by ≥2 Patients) Reported AEs

	AE Incidence Rates	Numbers of AEs Reported
Treated Patients, n =	**5**	
Patients Reported any AE, n (%)	**5 (100)**	
AE Preferred Term	n (%)	
Headache	3 (60)	4
Pharyngitis	3 (60)	3
Abdominal pain upper	2 (40)	5
Malaise	2 (40)	2
Rhinitis	2 (40)	2

One SAE was reported: a traffic accident reported by Patient 103 after 166 days (at approximately Week 23) after the first infusion. The event was assessed by the Investigator as unrelated. No other notable AEs were reported.

In summary, the efficacy results for Study AGLU02804 were highly subjective, highly dependent on patient effort, and are uninterpretable in an open-label, uncontrolled study. The safety data were relatively unremarkable. This study is not adequate to describe the risk/benefit profile of Myozyme in juvenile-onset Pompe disease patients, and is not adequate to support an indication for the use of Myozyme in this population. Further study in the juvenile- (and adult-) onset Pompe disease population in blinded, controlled trials is needed.

10.1.3.3 Non-GCP Studies and Expanded Access Programs: Summary of Patient Narratives

The information from the narratives in the 19 remaining juvenile- and adult-onset patients (those patients not enrolled in Study AGLU02804), for whom information was submitted to the application are briefly summarized as follows:

- 18/19 patients were ventilator-dependent at baseline, and 18/19 were wheelchair dependent at baseline, consistent with advanced stage of disease.
- All information for these patients was submitted as narratives.
- Wide range of treatment lengths was reported (20 weeks to 8 years).
- Quality of the information was, for the most part, exceedingly poor. Details were few, at times contradictory, and in at least one case, the narrative was illegible.
- One patient had a definite response to treatment (Patient — - see below), and this patient's clinical history was most consistent with the muscular-variant infantile-onset form of Pompe disease.
- No ventilator dependent patient was shown to have been able to discontinue ventilatory support. However, five patients were reported to have decreased the numbers of hours per day on ventilator support (ranging from a decreased requirement of 3 to 10 hours per day). No objective data were submitted to support this, and in some cases, narratives had conflicting information.
- Remaining patients had few objective signs of change.

The information on these patients is summarized in more detail by individual patient, by study, as follows:

15 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

Overall, the information on the 19 juvenile- and adult-onset patients from EAPs, submitted to the application in the form of narratives, was extremely diverse, and the length of treatment, doses of Myozyme administered, safety and outcomes assessments measured, and the scope of information provided in the narratives were highly variable, and highly subjective. Thus, these data were of limited utility in defining either a treatment effect or a safety profile of Myozyme administration in the juvenile- and adult-onset population.

10.1.3.4 Additional Clinical Programs

Additional clinical programs being conducted for Myozyme in the juvenile- and adult-onset population include:

- AGLU02704: Ongoing randomized (Myozyme vs. placebo), double-blind, placebo-controlled, 52-week, safety, efficacy and PK study in approximately 80 juvenile- and adult-onset Pompe disease patients. Enrollment began August, 2005, and was completed March, 2006 (expected completion approximately March, 2007).
- AGLU02303: Completed 12-month, prospective, observational study in late-onset Pompe disease patients intended to characterize the clinical presentation of late-onset Pompe disease and to assist in the design and planning of Study AGLU02704. Preliminary 3-month data were submitted, but had limited useful information.
- Pompe Registry

Essentially no information has been received regarding any of these programs. These programs are summarized in the following table:

Table A3-18: Additional Myozyme Clinical Development Programs

Program	Description
AGLU02704	Randomized, DB, multi-center, multi-national, safety, efficacy and PK study of 52-weeks of Myozyme treatment in late-onset Pompe disease patients. Enrolled is planned to start in mid-2005.
AGLU02303	12-month, prospective, multi-center, multi-national, observational study initiated Mar-2004, which intends to better characterize the clinical presentation of late-onset Pompe disease and assist in determining clinical efficacy endpoints for the planned placebo-controlled study AGLU02704.
Pompe Disease Registry	An established database that will be used to follow and collect long-term observational data on patients with Pompe disease.

10.1.3.5 Conclusion

The safety and efficacy information submitted for juvenile- and adult-onset Pompe disease patients submitted in these five clinical studies and expanded access was of limited utility in determining the risk/benefit profile of Myozyme in this Pompe disease population. These results tended to be highly subjective with few objectively or consistently collected outcomes measures available for review, and there have been no adequate and well-controlled studies completed to date in the juvenile- and adult-onset population. Thus, no assessment of the effect of Myozyme treatment on juvenile- and adult-onset Pompe disease patients is possible from the available data, and results from blinded, controlled studies in this population are needed.

10.1.3.6 Appendix: Late-Onset Studies

10.1.3.6.1 Walton & Gardner-Medwin Scores

Table A3-19: Walton & Gardner-Medwin Scores

Grade	Description
0	Preclinical. All activities normal
1	Walks normally. Unable to run freely.
2	Detectable defect in posture or gait. Climbs stairs without using the banister.
3	Climbs stairs only with the banister.
4	Walks without assistance. Unable to climb stairs.
5	Walks without assistance. Unable to rise from a chair.
6	Walks only with calipers or other aids.
7	Unable to walk. Sits erect in a chair. Able to roll a wheel chair and eat and drink normally.
8	Sits unsupported in chair. Unable to roll wheel chair or unable to drink from a glass unassisted.
9	Unable to sit erect without support or unable to eat or drink without assistance.
10	Confined to bed. Required help for all activities

10.1.3.6.2 All AEs

Table A3-20: Study 2804, All AEs

	AE Incidence Rates	Numbers of AEs Reported
Treated Patients, n =	5	
Patients Reported any AE, n (%)	**5 (100)**	
AE Preferred Term	n (%)	
Headache	3 (60)	4
Pharyngitis	3 (60)	3
Abdominal pain upper	2 (40)	5
Malaise	2 (40)	2
Rhinitis	2 (40)	2
Allergic rhinitis	1 (20)	1
Diarrhea	1 (20)	1
Excoriation	1 (20)	1
Gastroenteritis	1 (20)	1
Keloid scar	1 (20)	1
Molluscum contagiosum	1 (20)	1
Otalgia	1 (20)	1
Pediculus capitus	1 (20)	1
Pyrexia	1 (20)	1
Respiratory tract infection	1 (20)	1
Sinusitis	1 (20)	3
Traffic accident	1 (20)	1
Upper respiratory tract infection	1 (20)	1
Visual acuity decreased	1 (20)	1
Wheezing	1 (20)	1

10.1.3.6.3 All Conmeds

Table A3-21: Study 2804, All Reported Conmeds

Treated Patients, n =	**5**
Conmeds	**n (%)**
Paracetamol	5 (100)
L-alanine	3 (60)
Cefuroxime	3 (60)
Emla	3 (60)
Fentanyl	3 (60)
Heparin	3 (60)
Lidocaine	3 (60)
Propofol	3 (60)
Bupivacaine	2 (40)
Ibuprofen	2 (40)
Acetaminophen + codeine	1 (20)
Acetylcysteine	1 (20)
Amoxicillin + clavulanate	1 (20)
Amoxicillin	1 (20)
Atropine	1 (20)
Cefaclor	1 (20)
Centella Asiatic extract (cream)	1 (20)
Cromoglicate	1 (20)
Fluticasone	1 (20)
Glucose + electrolytes	1 (20)
Granisetron	1 (20)
Homeopathic preparation	1 (20)
Hydrocortisone (cream)	1 (20)
Hyoscine	1 (20)
Isoflurane	1 (20)
Loperamide	1 (20)
Malathion	1 (20)
Mivacurium	1 (20)
Paraffin	1 (20)
Povidine-Iodine	1 (20)
Silicone products (gel)	1 (20)
Tocopherol	1 (20)

10.2 Line-by-Line Labeling Review

Recommend approval pending labeling negotiations with the sponsor.

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3) Haley SM, Fragala MA, Aseltine R, Ni P, Skrinar AM. Development of a disease-specific disability instrument for Pompe disease. Pediatr Rehabil 2003;6(2):77-84.

4) Winkel LPF, Van den Hout JMP, Kamphoven JHJ, Disseldorp JAM, Remmerswaal M, Arts WFM, Loonen MCB, Vulto AG, Van Doorn PA, De Jong G, Hop W, Smit GPA, Shapira SK, Boer MA, van Diggelen OP, Reuser AJJ, Van der Ploeg AT. Enzyme replacement therapy in late-onset Pompe's disease: A three-year follow-up. Ann Neurol 2004;55:495-502.

April 27, 2006
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4-27-06

To: File
Through: Amy Rosenberg, M.D., Director, DTP, HFD-122

Amy Rosenberg 4-27-06

Re: Immunogenicity Review of BLA 125141/0, Myozyme

Sponsor: Genzyme 617-768-6358
Date received: July 29, 2005
The first action due date: **January 27, 2006**.
Major Amendment with new action due date: **April 27, 2006**

Summary
Recombinant human GAA (rhGAA) was shown in clinical trials to exert a significant survival benefit for patients with infantile onset Pompe's Disease. However, not all patients experienced such benefit, and, for some the quality of life was poor. Immune responses to the product are important modifiers of both the safety and efficacy of the product. A validated human GAA specific IgG assay revealed IgG binding antibody in more than 89% of patients in both 1602 (16/18) and 1702 (14/15) clinical trials. As to safety, antibody responses are a risk factor for infusion reactions, which were observed in 43% of the patients, and are highly correlated with treatment failure. Moreover, three patients experienced anaphylactic or severe anaphylactoid reactions, necessitating interruption of the infusion and administration of antihistamines, hydrocortisone, inhalational albuterol and epinephrine or oxygen treatment. Treatment had to be terminated in one patient. As to effects on efficacy, a significant correlation was revealed between antibody titer and invasive ventilation by reviewing clinical data of trial 1602 ($p<0.05$). The current neutralization assay, which measures inhibition of enzymatic activity, should be validated. Moreover, it is important that the company determine whether human GAA antibody inhibits the binding and entry of GAA into muscle cells. The validation of these assays, and subsequent testing of positive patient sera are PMCs. Another key issue, given the devastating consequences of antibody formation in some patients, is whether neutralizing antibody responses can be anticipated in some patients, given the nature of their genetic mutations and the level of GAA protein expressed. In order to determine whether there is strong correlation between the type of genetic mutation and antibody titer within trial 1602, it is critical to examine the genetic mutations of patients, the level of GAA protein in a non-enzymatic assay (immune

assay), and whether such patients develop antibody responses that lead to a poor outcome. Such a study has been requested as a PMC for development of a tolerance inducing protocol. . Three IgE positive cases were reported along with other 38 patients with allergy-like responses after infusion.

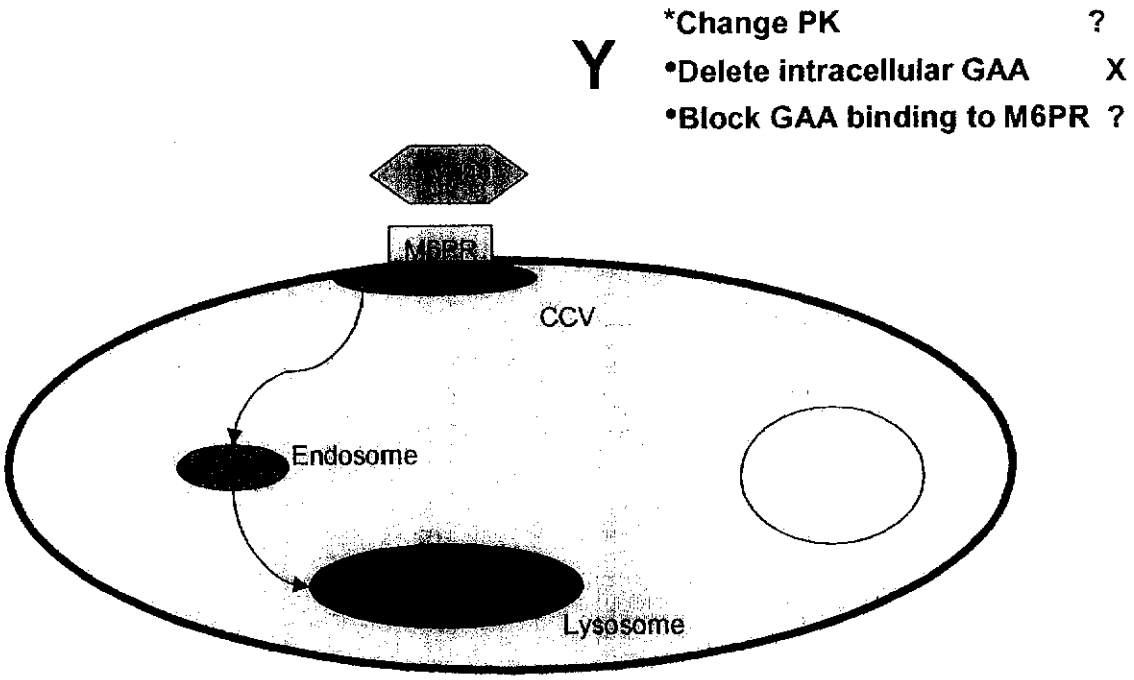
Review

Pompe disease (glycogen storage disease type II/ acid maltase deficiency) is an autosomal recessive genetic disorder caused by a deficiency of acid α-glucosidase (GAA, acid maltase) in muscle. The GAA defect results in lysosomal glycogen accumulation and eventually rupture of the lysosome, resulting in cellular dysfunction, particularly in cardiac, respiratory, and skeletal muscle tissue. Infantile-onset Pompe disease is uniformly lethal, usually by 1 year of age, resulting from cardiorespiratory failure. Replacement therapy with enzyme GAA, though experimental, is the only therapy that addresses the genetic defect. All other therapies, such as invasive ventilation etc, are supportive

There are several critical steps for GAA treatment. First GAA is taken up by target cells in a Mannose-6-Phosphate receptor dependent fashion, endocytosed via clathrin coated vesicles (CCV), fused with endosomes, then with lysosomes where they exert their activity. During this migration, the full length 110 kDa GAA is processed into a 95kDa intermediate in the late endosomes/lysosomes (No responsible specific proteinase has been identified), and then into the fully activated 76 and 70 kDa species in a proteinase dependent manner (Wisselaar et al. 1993. Structural and Functional Changes of Lysosomal Acid a-Glucosidase during Intracellular Transport and Maturation. The Journal Of Biological Chemistry 268: 2223-2231. Raben N 2002)

There are several possible functional effects of anti-GAA antibody: 1) binds to rhGAA and changes its PK 2) blocks the uptake of rhGAA via M-6-PR; 3) neutralizes processed GAA in lysosome.

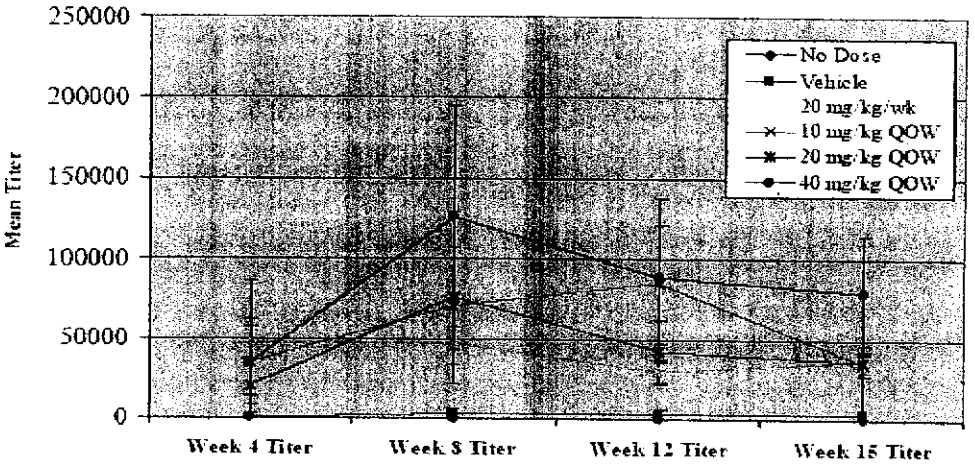
Possible Targets of GAA Antibody



Effects of GAA antibody in animal models

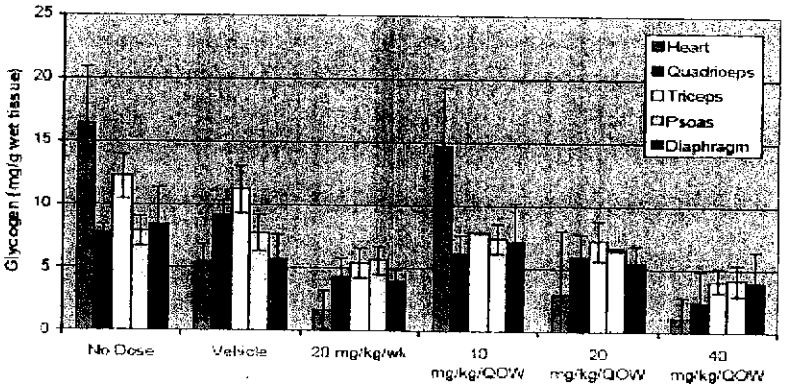
An exon 6 double knockout mouse was cloned by Dr. Raben, and as reported, no GAA transcription and translation was detected in this clone (Raben et al. 1998). These mice can live up to nine months without developing overt clinical symptoms, for a mouse, but the heart is typically enlarged and the electrocardiogram is abnormal. In GAA knockout mice (3-4 month old) high titer antibody was induced in all dosage groups (20 mg/kg/wk, 10,20,40 mg/kg/every other week). The highest antibody titer was induced by 40 mg/kg/QOW. t½ was reduced from 144 minutes in naïve mice to 85 minutes in the immunized mice.

Figure 2.6.2.2-13:
IgG Antibody Titers in GAA Knockout Mice Following Weekly and Every Other Week Dosing With Myozyme (Genzyme 02-1165Pga)



QOW = Every other week

Figure 2.6.2.2-12:
Glycogen Depletion in Selected Tissues Following Weekly and Every Other Week Dosing With Myozyme to GAA Knockout Mice (Genzyme 02-1165Pga)



QOW = Every other week

Mice treated with 40 mg/kg/QOW (iv injection) had the lowest glycogen content in all five tissues, indicating that the induced GAA antibody did not block the entry of GAA into muscles or neutralizing GAA activity inside or outside of cells. Glycogen in cardiac muscle was very sensitive to GAA treatment and almost completely disappeared after 21 weekly treatment and no comments on the heart enlargement/EKG abrnormalities were reported(Rabin 04).

Monkeys injected with 4, 20, 100 mg/kg of human GAA all mounted high titer anti-GAA antibody responses from day29 up to day 169. t½ was increased in both male and female immunized monkeys (study 6354-152). All monkeys survived in apparent good health (with normal heart rate and respiration rate) until scheduled for sacrifice. No tissue GAA or glycogen content was reported for monkeys in this study although liver and heart GAA were increased (more than 30 fold increase in liver) in study 6354-157. Therefore it is unclear whether antibodies could enter the cell and cross inhibit monkey enzyme. To do so would require that antibody cross the cell membrane, which is theoretically possible via interactions with the FcR. However, entrance into acidic lysosomal compartments would be expected to degrade the antibody molecules and the FcR (Mellman et al 1984). This issue is most relevant for trials of late-onset disease where there is a fear that antibody may neutralize endogenous enzyme. The protein sequence identity between human GAA and monkey GAA is not known as the monkey GAA protein sequence was not found in the Swiss Prot database. Mouse data revealed only an 80% identity with human GAA. The reason for antibody mediated enhancement of GAA in the monkey likely pertains to previous findings in which the presence of neutralizing antibody to cytokines prolonged cytokine PK due to prevention of binding of cytokine to cellular cytokine receptor, and to diminished renal excretion and catabolism (Finkelman et al 1999).

Human Clinical Trials with Myozyme (GAA)

I. Assay Validation

Testing of patient sera with three validated assays is generally required for a full immunogenicity assessment before approval. These assays are the IgG binding assay, neutralization assay, and IgE assay.

	Assay	Validation report	Validated	Data
Human	**IgG**	**Yes**	**Yes**	**Yes**
	Neutralizing assay	**Yes**	Yes	Yes (1/39)
	IgE	Yes	Yes	3/38

Validation of human IgG assay

Assay procedure

Serum samples are diluted and incubated in microtiter plates previously coated with CHO-derived rhGAA produced at Genzyme and blocked with HSA. Following incubation, the wells are washed and HRP-conjugated mouse anti-human IgG Fc-specific

antibody is added. The presence of IgG antibody bound to rhGAA is detected by adding TMB substrate and measuring absorbance at 450nm.

Assay validation

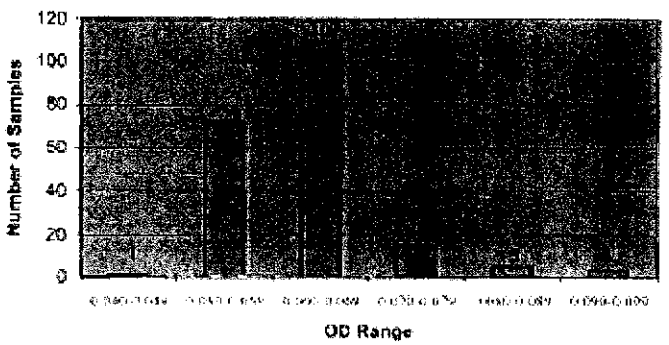
Specificity

Four human positive sera only reacted with rhGAA, but not rhb-glucocerebrosidase, rhα-galactosidae, and rhL-iduronidase, indicating the assay is specific for GAA.

	α-glu	IDU	β-glu	α-gal
Positive Control (Mean OD)	0.731	0.327	4.000	4.000
Sample 1				
Sample 2				
Sample 3				
Sample 4				
Sample Mean	-	0.057	0.050	0.053

Cut off value

The cut off value is 0.077, determined by calculating the 95th percentile of values from 205 normal volunteers.



OD Value	n
0.040-0.049	1
0.050-0.059	72
0.060-0.069	109
0.070-0.079	15
0.080-0.089	5
0.090-0.099	3
Total	205

n	205
mean	0.062
SD	0.007
min	[illegible]
max	[illegible]
mean + 4SD	0.092 (0.09)
95th Percentile	0.077 (0.08)

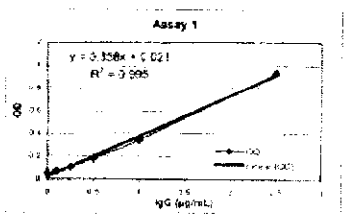
Limit of detection

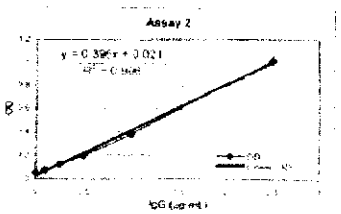
The LOD was determined with affinity purified GAA-specific IgG and calculated by adding 3SD to the mean OD of the 20 replicates of the zero standard and interpolating the resulting OD value from the linear portion of the standard curve. The LOD was established as the mean interpolated concentrations of GAA-specific IgG from the three patients assayed. The limit of detection is 91 ng/ml, (No dilution factor was calculated.)

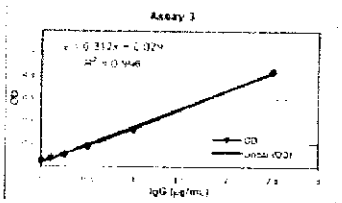
Assay 1	
Mean	0.050
SD	0.001
%CV	2.4
3SD	0.004
Mean + 3SD	0.054
Interpolated (ug/mL)	0.093

Assay 2	
Mean	0.049
SD	0.002
%CV	4.8
3SD	0.007
Mean + 3SD	0.056
interpolated (ug/mL)	0.089

Assay 3	
Mean	0.051
SD	0.003
%CV	5.38
3SD	0.008
Mean + 3SD	0.059
interpolated (ug/mL)	0.093







Precision

Three operators each completed four assays with four serum samples with CV less than 17%.

Repeatability of titer determination

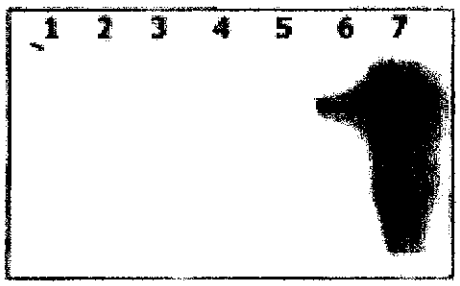
Three operators repeated the titer determination of four serum samples three or four times and the difference between operators was found to be less than or equal to one dilution.

Limit of quantitation
The levels of IgG present at 0.08 OD were 0.025 and 0.050 ug/ml of 1:100 serum. The mean value times the dilution factor 100 is the LOQ, 3.75ug/ml of serum.

Others
Samples are stable at <-15C up to 9 months and are stable through 3 freeze-thaw cycles.
Samples can be stored at 2-8C for up to 24 hours.
Plate coating stability: Plates may be coated up to four days when stored at 2-8C.
Plate homogeneity: No trends were apparent throughout the plate.

Confirmation assay

To confirm the antigen specificity of the antibody response, the sponsor employed a radioimmunoprecipitation (RIP) assay, based on the immunoprecipitation of ^{125}I labeled rhGAA with either rabbit anti-GAA serum or GAA affinity purified human anti-GAA IgG. Anti-GAA IgG only immunoprecipitated GAA, but not the other three proteins tested. The LOD of the RIP assay is 0.1 ug/ml.



Lane	
1	rhIDU
2	rhα-GAL
3	rhGCR
4	Empty
5	Negative Control
6	Positive Control
7	Label

IgE ELISA assay
Intra- and Inter-assay precission were determined with a hybrid positive control (a rabbit anti-rhGAA polyclonal antibody covalently conjugated to a purified non-specific human IgE molecule) and mouse anti-human IgE-HRP conjugate and the %CV values were less than 5.3 and 16, respectively. The normal range cutoff OD value for 1:2, 1:4, and 1:8 dilutions is ≤0.09, ≤0.08, and ≤0.08, respectively. Plates coating is stable up to 4 days at 4 ^{0}C and no trends were apparent. Samples are stable through 3 freeze-thaw cycles and up to 24 hours at 4 ^{0}C. The mouse anti-human IgE-HRP did not cross-react with human IgG and IgM. However, the sensitivity of the assay has not determined in terms of human anti-GAA IgE although the LOD for the hybrid positive control is 2.6ng/ml. Serum from the newly reported three IgE positive cases will provide the positive control and can be used for the determination of the assay sensitivity.

II. Immune response after GAA treatment

Hypersensitivity Responses

There are two types of hypersensitivity responses: anaphylactic (IgE) or anaphylactoid (IgG or non immune mediated)

- Two serum IgE positive cases (136-740 and 813-565 — with anaphylactic responses were reported this month in expanded study AGLU02203. 813-565 (date of birth — , first infusion — at a dose of 20 mg/kg, had rash after the 3ml of infusion on , — . Anti-histamine was given and infusion was completed at a lower rate (50%). The following 4 infusions were all associated with rash, twice with vomiting, no report of blood pressure abnormality and last two reported infusions were not completed . Brick test was negative. No data were provided regarding complement and tryptase. Patient 813-565- — was positive for IgE, negative for complement and tryptase. No information is available for the third IgE positive patient at this time.

- Also reported were other 35 IgE negative cases with hypersensitivity responses out of 280 cases total.

- Complement activation in 4/7, tryptase was increased in 1/7. A new case (16709 — , date of birth —) of complement activation and increase serum tryptase (23.7 ug/L, normal <14.7 ug/L) with chest and throat tightness 12 days after first infusion (20 mg/kg) in a late onset female patient was reported April 7, 06. This patient was enrolled in AGLU02704. IgG antibody status is unclear. This patient is IgE negative.

IARs (infusion-associated reactions)

- IARs (infusion-associated reactions) were reported in 24 (43%) of 56 patients.
- 20mg/kg: urticaria, rash, vomiting, fever, retching
- 40mg/kg: urticaria, rash, vomiting, tachycardia, cyanosis, hypertension, hypotension, cough and rale, flushing
- Higher antibody titer is likely to be associated with a higher incidence of IARs. There were no IARs in three seronegative patients. Thus, given the high prevalence of antibody responses and the lack of IARs in seronegative patients, IARs are likely immunologically mediated, ie, anaphylactoid responses
- Treated by reduced infusion rate, interruption of infusion, anti-histamines.

IgG mediated immunoresponses

There are many licensed and experimental enzyme therapies for enzyme deficiency disorders . The immunoconversion rate differs among diseases. For example, in Gaucher's disease 13% of patients became seroconversion and 90% of them tolerized

after 30 months of alglucerase (glucocerebrosidase) therapy (Rosenberg M. 1999). This low rate pertains to the presence of enzyme protein, although mutated and inactive, at significant enough levels to induce immune tolerance in the vast majority of patients. In contrast, in Fabry's disease, the seroconversion rate is as high as 88%, reflecting the null or minimal levels of enzyme encoded on a gene located on the X chromosome (Wilcox et al 2004). Interestingly, female patients did not make antibody responses although they presented with disease, affirming that the presence of residual enzyme protein confers tolerance.

Binding Antibody via ELISA

Treatment with GAA induced a high rate (91%) of seroconversion in infantile-onset Pompe patients. Most seroconversion was observed during the first 4-8 weeks of treatment. Patients in the 40 mg/kg appear to have higher titers over time than patients in the 20 mg/kg group.

Trial	1602 (<6 months)		1702 (6-36 months)
mg/kg	20	40	20
Total patients	9	9	15
Seroconverted	8	8	14
% seroconverted	88.9	88.9	93

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FIGURE 7.1

ANTIBODY TITER OVER TIME - AGLU01602

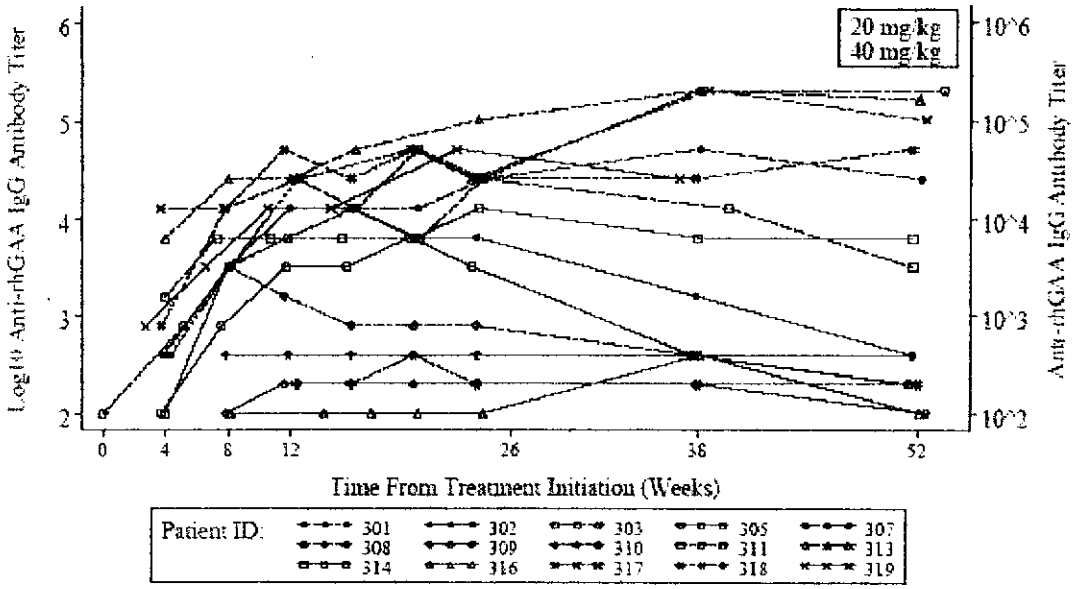
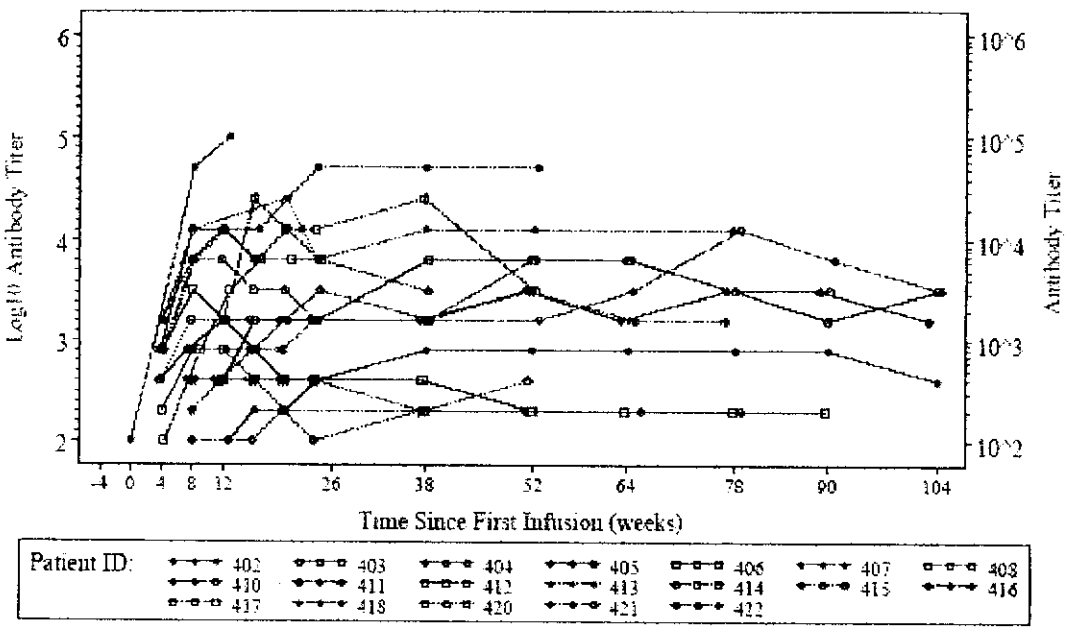


FIGURE 7.2

ANTIBODY TITER OVER TIME
AGLU01702



GAA Antibody In Human

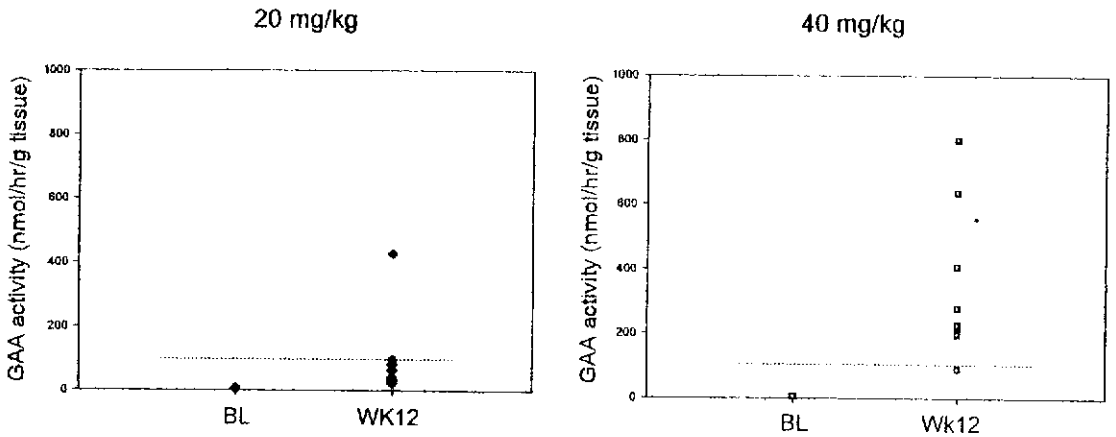
- On day 0 (all patients were GAA antibody negative) and after 12 wks of treatment (most patients were GAA antibody positive) CL, Vss, and t½ were not significantly different and the values were 22ml/hr/kg, 67ml/kg, and 2.8 hr, respectively.

- All patients exhibited an increase in muscle GAA activity from baseline to 26 WK (0.0 to 146 nmol/hr/g) (see below figure for 12 week data)

- 15/18 patients had stable or decreased muscle glycogen content in 1602 trial.

- The reduction of muscle glycogen content is limited in patients of 1702 trial.

Skeletal muscle GAA activity-1602 trial



There is no relationship between GAA activity and antibody titer *at week 12*. Also, the 40mg/kg dose delivers enough enzyme to mimic the normal level (shown by the dashed lines in the figures above). Muscle GAA activity was examined at 52 weeks in only four patients: 12wk/52wk values are 22/69 (patient 305), 33/139 (306), 53/49 (310), and 279/141 (301), respectively. Did patients 301 and 310, where the activity went down over time have high titers of antibody? You should comment. Muscle GAA activity should be examined for all patients at week 52 or later time points.

NEUTRALIZING ANTIBODY

A research assay was used to test for the presence of inhibitory antibodies to rhGAA in the serum samples of IgG seropositive patients.

* Serial dilutions of patient serum were incubated with a fixed amount of rhGAA (2000 nmol/hr/mL) for 1 hour at 37°C. The samples were then diluted and analyzed for rhGAA enzyme activity.

* The activity in each sample and the percent inhibition were calculated relative to a control sample containing 2000 nmol/hr/mL of rhGAA incubated under the same conditions

* Neutralizing antibody was assessed in all patients with current assay (based on enzyme activity) and more than 10% inhibitory activity was only found in one patient (1/39).

Intra-assay precision

%CV is less than 19% for two operators each with 4 replicates with dilutions up to 1:128 of positive inhibition control sera.

Inter-assay precision

Figure 9. Overall Inter-Assay Precision Sample #1: Between Analysts

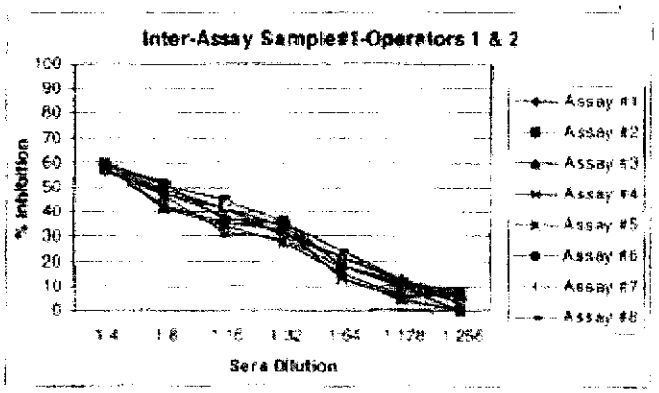
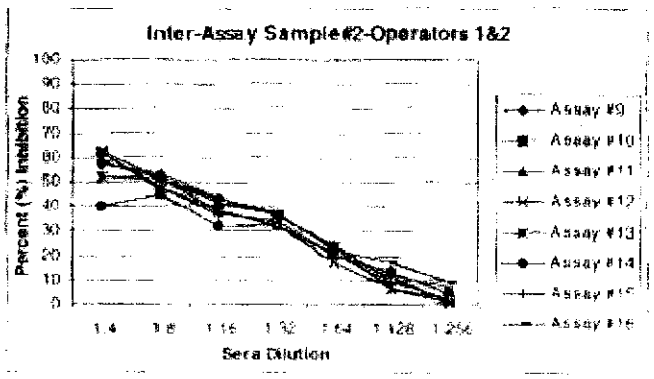


Figure 10. Overall Inter-Assay Precision Sample #2: Between Analysts



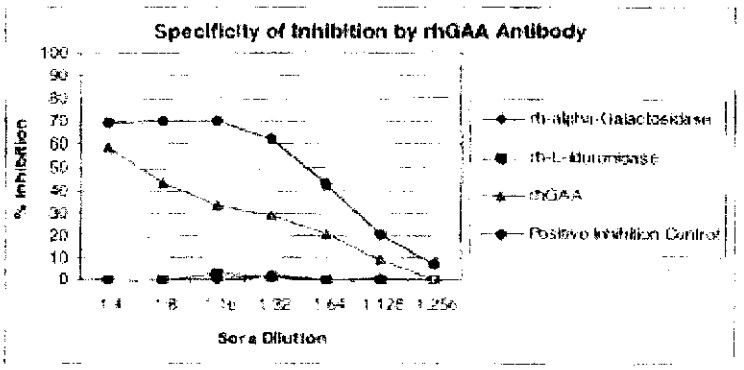
%CV is less than 20% for two samples with dilution up to 1:64 by two operators with multiple assays.

Specificity

Table 18. Specificity of Percent (%) Inhibition of rhGAA by Antibody
Mean values of Percent (%) Inhibition of Duplicate Wells

Antibody Specificity	SAMPLE DILUTION						
	1:4	1:8	1:16	1:32	1:64	1:128	1:256
rh-L-Iduronidase	0.0	0.0	0.0	2.2	0.0	0.4	0.0
rh-α-Galactosidase	0.0	0.0	2.8	1.1	0.0	0.0	0.0
rhGAA	**59.0**	**43.3**	**33.1**	**28.8**	**20.3**	**9.0**	**0.0**
Positive Inhibition Control	69.2	70.0	70.4	62.2	42.7	20.9	7.0

Figure 16. Specificity of Percent (%) Inhibition of rhGAA by Antibody



The assay is only inhibited by positive anti-GAA antibody, not antibodies to other proteins.

LOD

Based on maximum percent inhibition value of 8.6% of 32 normal human sera and the failing precision (%CV) of samples exhibiting <20% inhibition seen both the intra- and inter-assay precision studies, an LOD of 20% was established.

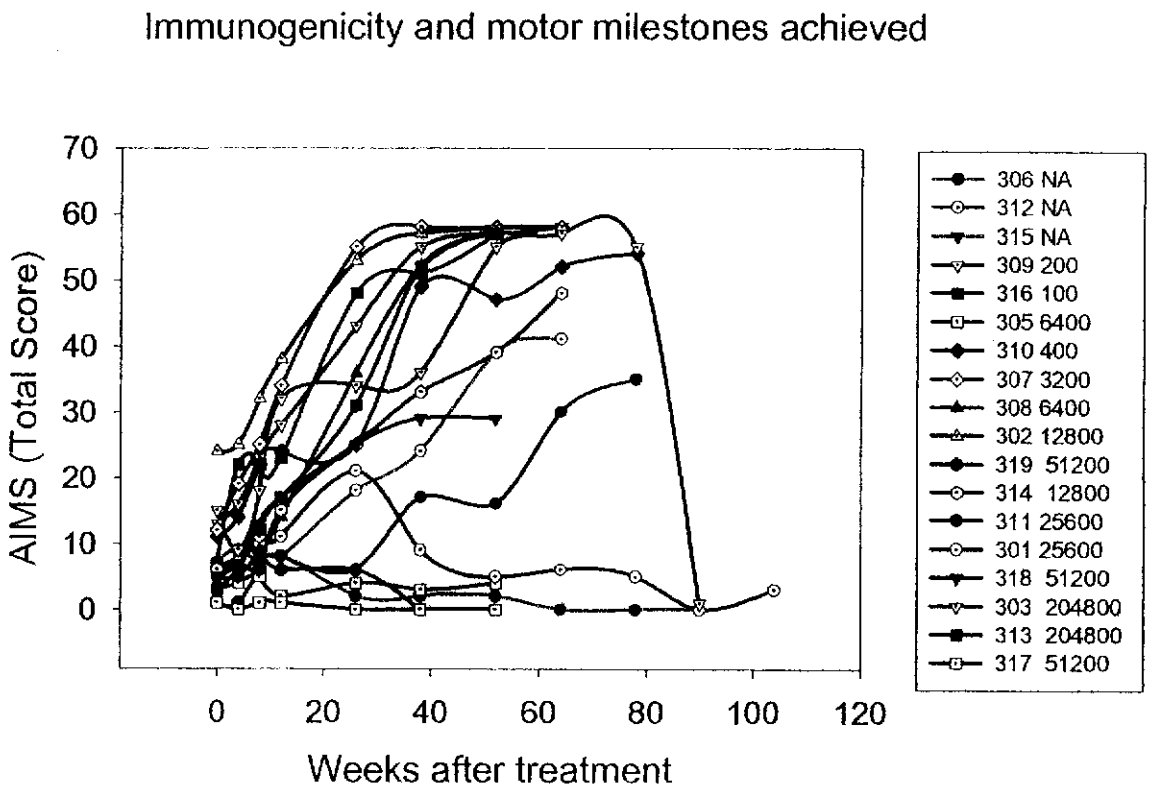
Sample stability

Samples are stable (1) at 2-8 ^{0}C for 24 hours with inhibitory activity ranged 85.1-109.4%, and (2) up to 3 freeze/thaw cycles with inhibitory activity ranged 78 to 118%.

IMMUNOGENICITY: CLINICAL SIGNIFICANCE

Motor Milestones

Most patients in 1602 trial achieved more motor milestones during myozyme treatment. Four patients 317, 306, 319 and 305 did not achieve more milestones during treatment and all become antibody positive. Patient 306 become antibody positive (1:200) as reported on Sep-26-05. Two patients (301 and 303) with high titer antibody achieved more milestones initially, then lost almost all milestones achieved.



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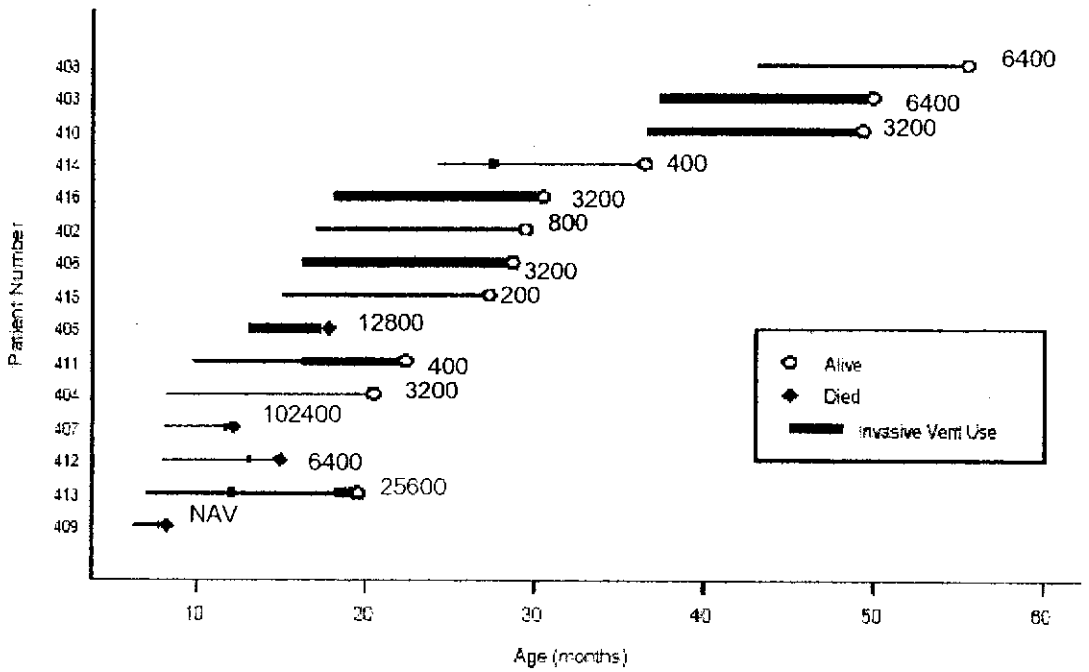
Invasive ventilation/death

In the 1702 trial, five patients were on invasive ventilation at the beginning of treatment. Patient 309 died before seroconversion. Three other patients (405, 407, 412) died and all had high titer peak value of antibody. Patient 405 was invasively ventilated prior to beginning treatment.No invasive vent use was indicated for patient 407 and 412.. It is likely that the high titer of antibody might contribute partly to the death of the three patients. Two patients went on invasive ventilation during treatment, one (patient 413) had a peak titer of 1:25600, the other (411) 1:400.

Figure 11-2 Individual Survival Profiles for the First 15 Treated Patients



In trial 1602, seven patients went on invasive ventilation and two of them died (305, 303). Six of the seven patients had high peak titer of antibody and among them five patients that are alive (on invasive ventilation) have persistent high titer antibody up to September 26, 2005, indicating a correlation between antibody titer and duration and invasive ventilation ($p<0.05$). In most ventilation-free patients that had higher peak antibody titer serum IgG titer decreased dramatically overtime.

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High titer antibody and invasive ventilation

Patient Number	Treatment Group (mg/kg)	Highest Ab Titer	Latest Ab Titer Sep-26-05	Status as of 15-Sep-05
301	40	25600	51200	Invasive
303	40	204800	409600	Invasive*
305	20	6400	200	Invasive/died
306	20	NA	200	Invasive
313	40	204800	1638400	Invasive
317	40	51200	102400	Invasive
319	20	51200	25600	Invasive
308	40	6400	100	None
309	20	200	400	None
310	20	400	400	None
311	40	25600	1600	None
312	20	NA	NA	None
302	20	12800	200	None
314	20	12800	3200	None
315	40	NA	NA-	None
316	20	100	100	None
307	40	3200	400	None
318	40	51200	51200	None

Immune response and GAA genetic mutations and protein levels of Pompe patients

Although there is likely a trend that patients with nonsense and frameshift mutations had higher antibody titer, the number of patients who underwent a mutational analysis is limited.

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ON ORIGINAL

Patient Number	Treatment Group (mg/kg)	Highest Ab Titer	Latest Ab Titer Sep-26-05	Class of Mutation	
				Maternal	Paternal
301	40	25600	51200	Inframe deletion	frameshift
313	40	204800	1638400	Nonsense	Nonsense
314	20	12800	3200	Frameshift	Frameshift
319	20	51200	25600	Splicesite mutation	Frameshift
318	40	51200	51200	Inframe deletion	Inframedeletion
310	20	400	400	Inframe deletion	Inframe deletion
317	40	51200	102400	N/A	N/A
303	40	204800	409600	N/A	N/A
305	20	6400	200	N/A	N/A
306	20	NA	200	Missense	Missense
311	40	25600	1600	Msisense	Missense
312	20	NA	NA	N/A	N/A
309	20	200	400	Missense	Missense
302	20	12800	200	Missense	Missense
315	40	NA	NA	Missense	Missense
316	20	100	100	Nonsense	Missense
308	40	6400	100	Missense	Frameshift
307	40	3200	400	Missense	Nonsense

It appears that there is a relationship between high titer antibody and nonsense/frameshift mutations. It is critical to determine the genetic mutations of patients corresponding to numbers 303, 305, 312, and 317 for a full assessment of whether there is a significant correlation between antibody titer and genetic mutations (double nonsense/frameshift vs at least one missense) within trial 1602.

Comment: The genetic mutations of patients numbered 303, 305, 312, and 317 should be determined to assess the relationship between antibody titer and genetic mutations.

When an analysis was performed with combined data from trials 1602 and 1702 (all patients without genetic information were excluded), it was found that there is a

significant correlation between antibody titer and genetic mutations (double nonsense/frameshift vs at least one missense) ($p<0.01$).

Trial 1702. Antibody titer and genetic mutations

Patient Number	Treatment Group (mg/kg)	Highest Ab Titer	Class of Mutation	
			Maternal	Paternal
407	20	102400	Frameshift	Frameshift
405	20	12800	NA	NA
410	20	3200	NA	NA
409	20	NA	NA	NA
412	20	6400	Missense	Missense
413	20	25600	Missense	Missense
415	20	3200	Missense	Nonsense
402	20	800	Missense	Missense
406	20	3200	Frameshift	Missense
415	20	200	Missense	Missense
414	20	400	Missense	Missense
411	20	400	Missense	Missense
404	20	3200	Missense	Missense
408	20	6400	Missense	Missense
403	20	6400	Missense	Missense

Patient 407, 405, 409, and 412 died.

The inclusion criterion included enzyme *activity* less than 1%. However, enzyme activity is a less critical parameter than protein level (including active and inactive enzyme). In respect of this, endogenous GAA protein levels in these patients were not assessed before treatment and were not correlated to antibody status.

It is critically important to understand the relationships among genetic mutation, protein levels, and immune response. Published data (Amalfitano et al 2001) showed that patients without endogenous GAA protein produced high titer of antibody, and that AIMS score (a developmental score) dropped when antibody titer went up. Whereas in the patient with GAA protein but no activity, no antibody was induced and AIMS score went up, indicating that the absence of GAA protein may prone to high titer of antibody after GAA treatment (see figure below)

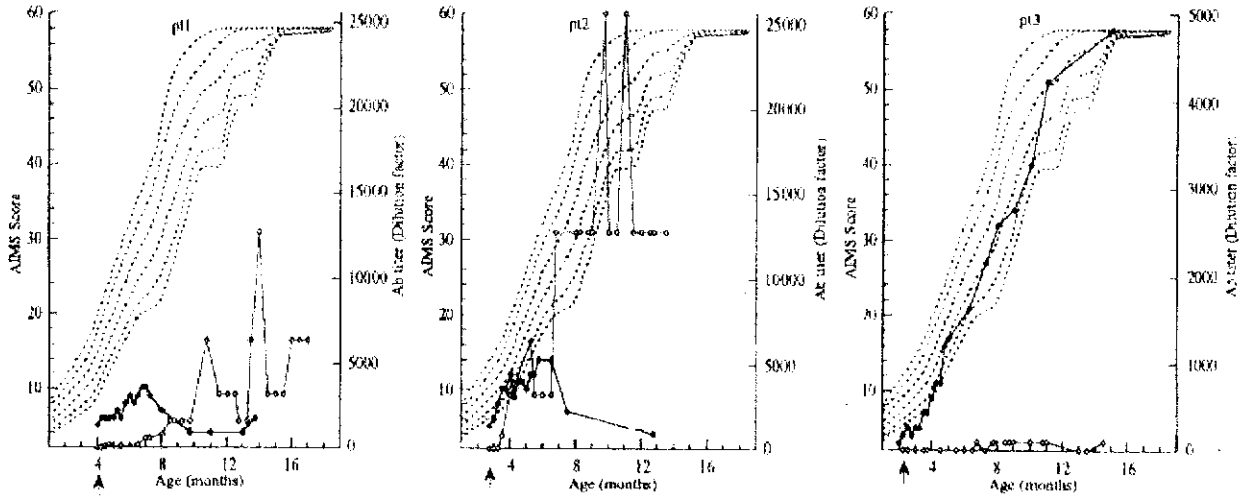
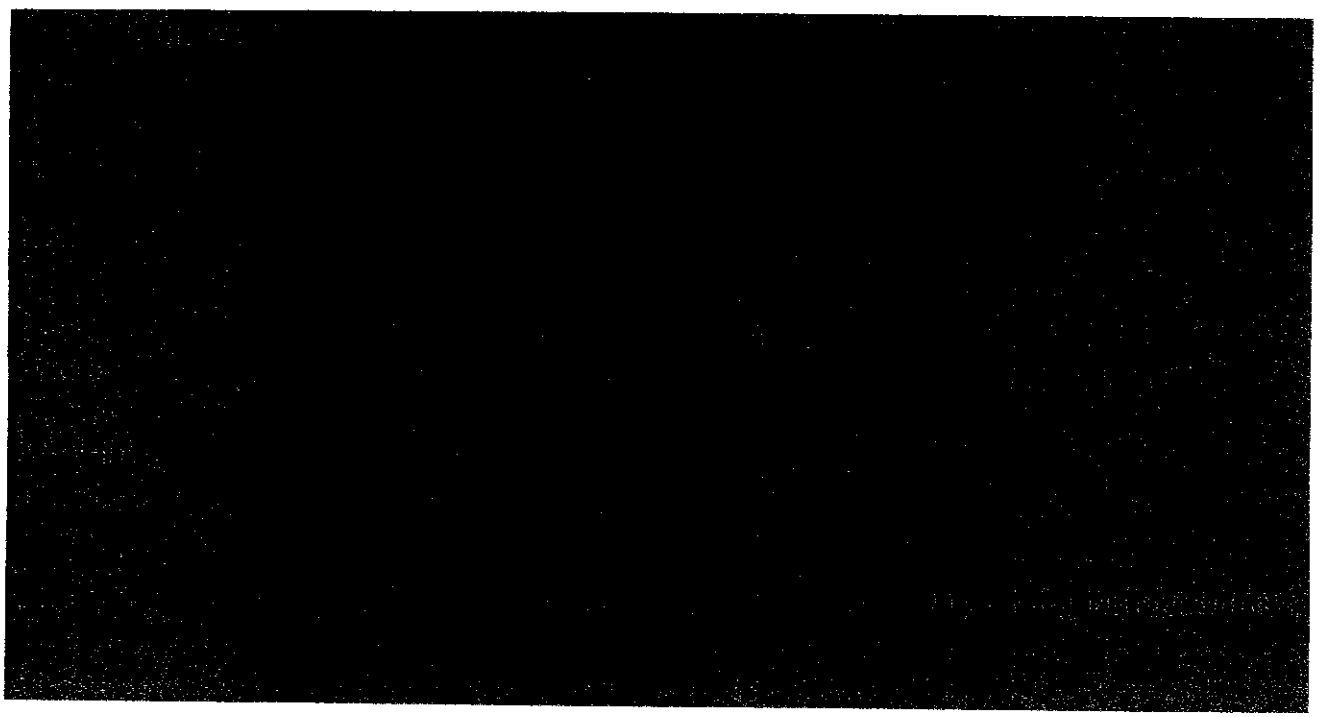


Fig. 3 Longitudinal data on motor development as assessed by AIMS (closed diamonds) and titer of anti-rhGAA antibody (open diamonds) in three patients with infantile Pompe disease receiving enzyme replacement therapy. The arrow indicates when the enzyme therapy was initiated. AIMS scores in normal subjects are plotted as dotted curves against age (5th, 10th, 25th, 50th, 75th, and 90th percentile, from bottom to top).

Since there is significant correlation between high titer antibody and onset of invasive ventilation/death and there is a significant correlation between high titer antibody and genetic mutations (double nonsense/frameshift vs at least one missense), a consideration of Pompe treatment is proposed as following:



* More data are needed for the inclusion of GAA protein levels in the final consideration. One concern with protein is the molecular weight of mutated GAA protein.

Comments: In the case of enzyme replacement therapy for diseases such as Pompe disease, genetic mutations may cause no protein to be produced, or may produce proteins which are devoid of or defective in enzymatic activity. When there is no protein translated in cells, a "protein knockout" status, the protein is not presented to the immune system and thus, native protein used as enzyme replacement is viewed as "foreign" and an immune response is mounted (Amalfitano et al 2001). In the case of activity defective enzymes, although these proteins have lost their enzymatic activity, they nonetheless have exposed the host's immune system to the protein and induced some level of immune tolerance. Thus, when native enzymes are used for therapy, they are not viewed as completely "foreign", and the immune response is weak or abrogated. Another important consideration regarding antibodies, as was mentioned earlier is the possibility that antibody to enzyme can get into cells and neutralize endogenous (or exogenous) enzyme within the cell. When binding or neutralizing antibodies are generated against these therapeutic enzymes, it is unlikely that these antibodies are capable of crossing living cell membranes and targeting these intracellular proteins in FcR negative cells, such as skeletal or cardiac muscle. Even in FcR positive cells, such as macrophages, the internalized IgG and FcR will be degraded (Mellman et al. 1984). Thus, residual enzyme present in cells may not be subject to effects of antibody, only exogenously administered product. Whether the generated antibody inhibits the entry of the replacement enzymes or not, therefore their therapeutic effects of the replacement enzymes, warrants further case by case investigation.

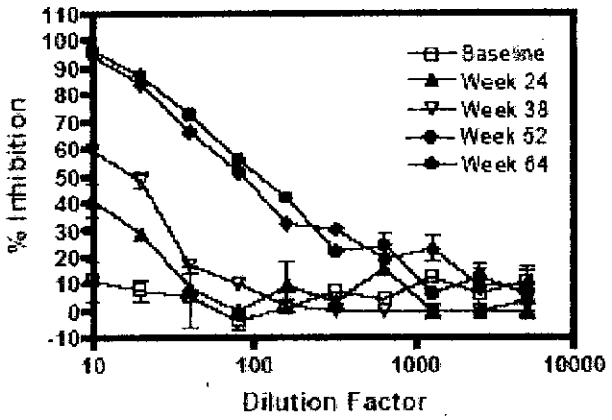
Status Of Uptake Inhibition Assay

In trial 1602, a significant survival benefit was seen in treated patients at age 12 and 18 month. A validated human GAA specific IgG assay revealed IgG binding antibody in more than 89% of patients in both 1602 (16/18) and 1702 (14/15) clinical trials. A significant correlation was revealed between antibody titer and invasive ventilation in trial 1602 ($p<0.05$). The presence of neutralizing antibody was assessed by measurement of inhibition of enzymatic activity and the results revealed that only one out of 39 patients generated antibody which inhibited enzymatic activity. However, it is possible that this assay is not sufficiently sensitive to reveal neutralizing activity as the assay has not been validated. Moreover, it is important that the company determine whether such patients possess antibody that inhibits the binding and entry of GAA into muscle cells in addition to inhibition of enzymatic activity.

An assay to assess inhibition of binding and entry of enzyme into cells was recently developed by Genzyme. It is a flow cytometry-based assay using fluorescently-labeled enzyme to assess antibody interference on cellular GAA uptake. This assay reflects GAA uptake through the cation independent mannose-6-phosphate receptor (CI M6PR) on cells. Briefly, rhGAA is conjugated to the fluorescent dye Oregon Green succinimidyl ester via lysine residues. The conjugated enzyme (GAA-OG) was shown to be internalized into human fibroblasts and could be specifically and competitively inhibited by exogenous mannose-6-phosphate. An affinity purified rabbit anti-GAA is used as a positive control. The utility of this approach was shown by the positive findings in this

assay from the patient that developed inhibitory antibody (enzyme activity). The attached graph shows data from the only patient (8101313) with inhibitory antibody activity in the enzyme based assay. Pre- and post treatment sera from Patient 8101313 were analyzed in this enzyme uptake assay. Serum obtained prior to treatment showed low background levels of uptake inhibition, whereas serum obtained post treatment demonstrated inhibition of uptake which increased over time with more than 95% inhibition at later times. This patient was on invasive ventilation at the time of last report. No data from other patients have been reported yet.

Figure 10:
Patient 8101313 - Inhibition of Uptake of rhGAA in the Presence of Patient Serum



The question here is whether antibodies that inhibit enzyme uptake are more prevalent in sera from patients on invasive ventilation versus patients not requiring ventilation. The sponsor should report further results of assay qualification and test sera from all antibody positive patients in the clinical trials. Preferably we would like to see a considerable analysis to assess whether development of such antibodies predicts a negative outcome and whether development of neutralizing antibodies correlates with genetic mutation. Muscle GAA activity should be re-examined in patients who developed entry inhibitory antibody or under invasive ventilation,

Should neutralizing antibodies correlate strongly with genetic mutation and with poor outcome, consideration should then be given to 1) prophylactic treatment of high risk patients with immunomodulators simultaneous to onset of enzymatic treatment, or 2) treatment post-antibody development with immune suppressors/immunomodulators to reverse antibody production. Although this approach was indeed successfully applied by Brady et al to a Gaucher's patients who developed resistance to glucocerebrosidase, a Pompe's patient who underwent similar therapy developed immune complex disease and nephritic syndrome (Hunley et al. 2004). This was also the case of a Factor IX deficient patient undergoing a similar protocol (Dharniharka et al. 1998). Thus for severe genetic mutations leading to a CRIM negative state, alternative tolerance inducing protocols should be developed, both for naïve patients as well as for patients with ongoing antibody responses.

In order to determine whether there is strong correlation between the type of genetic mutation and antibody titer within trial 1602, it is critical to examine the genetic mutations of patient number 303, 305, 312, and 317, because it appears that patients with the most severe mutations (double nonsense, deletion, or frameshift) who lack or have very low levels of endogenous GAA protein are at the highest risk for development of antibodies that affect clinical efficacy. Unfortunately, of the four patients only one patient's data may be available. Nevertheless, when an analysis was performed with combined data from trials 1602 and 1702 (all patients without genetic information were excluded), it revealed a significant correlation between antibody titer and genetic mutations (double nonsense/frameshift vs at least one missense) ($p<0.01$). It should be further evaluated whether genetic mutations (double nonsense, deletion, or frameshift), which can be determined before treatment, could be used as an indicator for prophylaxis against antibody production.

Tolerance Induction

There are several potential candidates useful for tolerance induction, although only one has been tested in human for the indication of tolerance induction. Thus, Brady et al treated a Gaucher's patient that developed Nab with cytoxan, plasma exchange, IVIG and continued Ceredase and reversed the antibody response. As mentioned above, this protocol did not succeed with a Pompe's and Factor IX patient, but rather induced immune complex disease and nephrotic syndrome. Other promising therapies include CTLA4-Ig alone or together with a modified regimen of anti-CD40L mAb, and non-depleting anti-CD4mAb. These treatments are aimed at prevention or reversal of the immune state.

Regarding approaches to preventing development of antibody, treatment with CsA and Aza plus antigen for 60 days induced tolerance in a canine model of enzyme replacement therapy (Kakkis et al. PNAS 2004). Of note, successful tolerance was induced by CsA and Aza for α-L-indronidase and α-glucosidase, which similarly depend on mannose-6-phosphate receptor mediated uptake. The protocol and the data from Kakkis' paper are shown below.

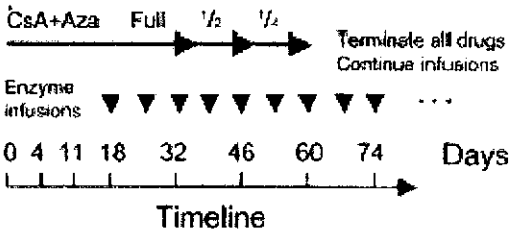


Fig. 1. Immune tolerance induction regimen. The tolerance regimen is diagrammed including CsA plus Aza dosing and rhIDU infusions. On day 0, full-dose CsA plus Aza are initiated (CsA, 25 mg/kg per day divided two times per day; Aza, 5 mg/kg every other day) and are later tapered to one-half the initial dose on day 32 and one-fourth the initial dose on day 46 and terminated on day 60. Low-dose rhIDU (0.056 mg/kg) infusions begin as indicated on day 18 and continue weekly thereafter.

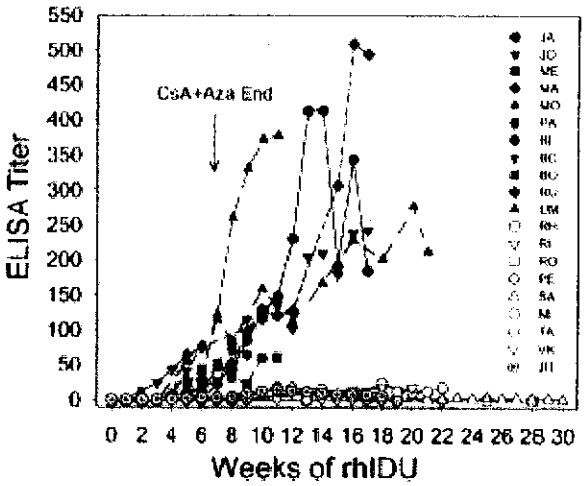


Fig. 2. Immune response to rhIDU in canines. The ELISA titer (OD units/µl of serum) of anti-rhIDU antibodies are plotted vs. weeks of rhIDU infusions for canines treated with the tolerance regimen (open symbols) and for those treated without the tolerance regimen (filled symbols) as indicated in Table 1. The data show that 8 canines treated with the optimum regimen have low anti-rhIDU titers for up to 6 months whereas 11 canines infused with rhIDU, with inadequate or no tolerance regimen, mounted substantial immune responses. Preimmune serum was drawn at week 0, 18 days after starting the CsA plus Aza drug regimen and before the first infusion was administered. Canine JH was treated with the every-other-day CsA regimen and has gray symbols to distinguish it from the other tolerant canines. The nontolerant canines BI, BC, and BO are included for completeness although they received 5 weeks or less of rhIDU and are not included in Table 1 for this reason.

This protocol is also effective in preventing IgE response although the number of canines is limited.

CTLA-4Ig (Abatacept) is approved recently and may be a good candidate, although in the regimen given, it was immunosuppressive rather than tolerance inducing. With recurrent infusions of enzyme in the presence of CTLA4-Ig, it is possible that tolerance may be achievable. Moreover, both CTLA4-Ig and a modified regimen of anti-CD40L antibody may prove to be most effective. An alternative approach could be treatment with a non-depleting CD4 mAb which induces tolerance to soluble proteins in baboons (Winsor-Hines 2004). Theoretically treatments that inhibit antigen presentation, may therefore reduce or block the development of T helper for B cells, and the production of long

lasting T dependent antibody production. However, tolerance induction would be an exploratory indication for Abatacept. Finally, a non depleting anti-CD4 (Ponath et al 2004) mAb successfully tolerized non-human primates to aggregated horse Ig. This antibody is in clinical trials for tolerance induction in the setting of Factor VIII deficiency and SLE.

In summary, it should be determined first whether Nab that inhibits cellular uptake and trafficking, or inhibits enzymatic activity is the cause of therapy failure (on invasive ventilation or death) and how strongly this adverse outcome correlates with specific gene mutations. If there is a strong correlation, effective tolerance induction should be considered in those at very high risk.

Drug product used in 1602 and 1702 trials

Four 160L scale lots were used in the 1602 trials. In the 1702 trial 13 patients were first treated by 30L/60L scale lots GA062, GA063 or GA079 for up to 26 weeks, then treatment was continued with 160L scale product lots 608345, 608341, 930018, or 751295. Treatment with 30L/60L scale lots is not necessarily associated with high titer antibody responses (7/13 patients with titer 1:3200 or less)

Table 3
Muscle acid α-glucosidase activity and glycogen content in infantile Pompe disease patients treated with rhGAA

	GAA activity (nmol/hr/mg protein)	Glycogen content (% wet weight)
Patient 1		
Pretherapy	0.41	5.90
Posttherapy	0.95	7.50
Patient 2		
Pretherapy	0.67	5.68
Posttherapy	1.97	4.42
Patient 3		
Pretherapy	0.1	5.13
Posttherapy	1.84	1.43
Control	23.92 ± 8.63	0.94 ± 0.55[a]

[a]Upper normal limit; 1.5%.

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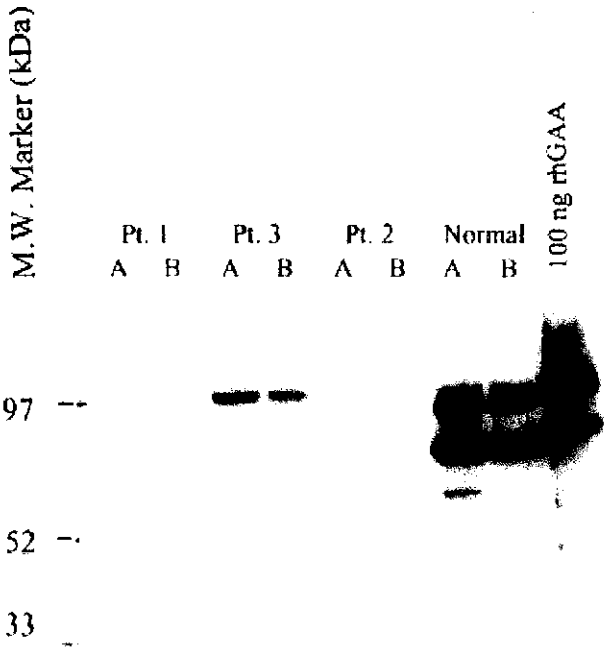

Fig. 5 Western blot analysis of acid α-glucosidase in fibroblasts. A and B represent results from two separate flasks of fibroblasts. Normal fibroblasts contain predominantly 95 and 76 kD GAA, while patient 3 has only 110 kD precursor form of GAA.

Post-marketing commitments in negotiating with sponsor

1. To provide information from a validated cell-based neutralizing antibody assay to evaluate the potential effect of GAA antibody on mannose-6-phosphate receptor dependent enzyme uptake using human fibroblast cells. Results will be submitted by June 30, 2006.

2. To provide results using the validated inhibition of enzyme uptake into human fibroblast assay from all patients in Studies AGLU01602 and AGLU01702, as well as all patients in clinical studies or the expanded access program for Myozyme who have become invasively ventilated since February 2, 2006. Results will be submitted by October 31, 2006.

3. As clinic PMC # 6
   Genzyme commits to designing and implementing an immune tolerance protocol in Pompe disease patients who have significant antibody titers, or the presence of neutralizing antibody, and are failing treatment. Genzyme commits to designing and implementing a preventive immune tolerance protocol in Pompe's patients at high risk of the development of significant immune responses to product. This would involve 1) establishing the correlation among genotype, the level of α-glucosidase protein (non-enzymatic assay), and the presence and levels of binding, IgE, and neutralizing antibodies over time, using validated assays; and 2) developing an immune tolerance regimen that would be implemented before or concomitant with onset of therapy for those at high risk. Additionally, Genzyme

commits to monitoring antibody positive patients, whose immune responses are not associated with loss of efficacy or severe hypersensitivity responses, at regular intervals over an extended period of time (ie, 18-24 months) to specifically assess if a sub-population of patients become tolerant with routine treatment. Reports from preclinical studies to assess potential tolerance regimens and a commitment for timelines for a subsequent clinical study will be submitted to CDER by December 29, 2006.

Genzyme commits to developing a protocol which will be used to provide guidance to physicians for the use of tolerance inducing regimens for patients who are currently failing treatment because of a robust antibody response and to submit this protocol by October 31, 2006.

MEDICAL OFFICER CONSULT

Division Of Pediatric Drug Development HFD 960

SPONSORS: Genzyme

NAME: Myozyme

NUMBER: STN BLA 125141/0

CLASS: Enzyme Replacement Therapy

MEDICAL OFFICER: Hari Cheryl Sachs, MD, FAAP **REVIEW DATE:** March 20, 2006

REVIEW SUMMARY:

The Division of Pediatric Drug Development was asked to comment on the: 1) ability to extrapolate efficacy and safety from the infantile Pompe patients to the other Pompe disease variants 2) recommendations on the measures used to assess motor and cognitive development in the patients with other variants of Pompe disease and for long-term follow-up of the infantile Pompe patients 3) postmarketing commitments.

In general efficacy can be extrapolated between two populations when the course of disease and the effect of the drug, both beneficial and adverse, are sufficiently similar (see 21 CFR 201.57(f)9(iv) and 21 CFR Subpart B 314.55.) In this case, the course of disease in the infantile form of Pompe's differs significantly from other Pompe variants in that the disease in the infantile form is rapidly progressive and that cardiac symptomatology is evident. Therefore, the data obtained in Study AGLU 2704 will be essential to establishing efficacy and safety in the older Pompe patients.

The motor and cognitive developmental scales, namely the PEDI/Pompe PEDI, GMFM, WPPSI and WISC-III utilized to assess secondary outcomes in the older pediatric population are appropriate and compliment each other. Additional measures suggested by the sponsor (particularly Handheld dynamometry, six minute walk test, PPVT, and Leiter–R) will be useful to augment these assessments.

In addition, follow-up information should include standardized measurements of growth (e.g., height and weight, HC for children <3 years), hearing and vision evaluations, and serial MRI's.

Preliminary data suggest a correlation between high levels of neutralizing antibodies to Myozyme therapy and clinical deterioration/ventilator dependence. Assessing long-term follow-up of these patients, particularly those with high titers of neutralizing antibodies is warranted.

OUTSTANDING ISSUES:

Genzyme has been asked to submit additional information on manufacturing, chemistry and reproductive toxicity. A phase IV protocol has not been submitted. The proposed trade name of Myozyme will also be changed.

SIGNATURES

Reviewer:	*Hari Cheryl Sachs, MD, FAAP*	**Date:**	*3/20/2006* 3/20/06
Acting Team Leader:	*Jean Temeck, MD*	**Date:**	*3/20/2006* 3/20/06
Acting Division Director:	*Lisa Mathis, M.D.*	**Date:**	*3/20/2006* 3/20/06

M E M O R A N D U M

Date received: January 18, 2006
Date assigned: January 18, 2006
Date review completed: Mar 8, 2006
Due Date requested: Mar 16, 2006

From: Hari Cheryl Sachs, M.D., Medical Officer
Division of Pediatric Drug Development
Office of Counter Terrorism and Pediatric Drug Development

Through: Jean Temeck, M.D., Acting Team Leader
Lisa Mathis, M.D. Acting Division Director
Division of Pediatric Drug Development
Office of Counter Terrorism and Pediatric Drug Development

To: Brian Harvey, MD
Division Director
Division of Gastroenterology Drug Products

Subject: BLA 125141

Name of Drug: Myozyme (alglucosidase alfa)

Sponsor: Genzyme

NDA Number: STN 125141/0

Formulation: Intravenous

Approved Indications: none

Consult question: The Division of Pediatric Drug Development was asked to comment on the:
1) ability to extrapolate efficacy and safety from the infantile form of Pompe's disease to other Pompe variants
2) measures used to assess motor and cognitive development in the late-onset patients and for long-term follow-up of the infantile Pompe patients
3) post marketing commitments.

Material Reviewed

Sponsor's submission- Amendment 008-10, Clinical study reports AGLU01602, Clinical study report AGLU01704
Medical officer Review (Myozyme)
Memo Oct 6, 2004: Division of Neuropharm: Acceptable Measures of Cognition, Learning and Memory.

Brief literature review (motor and cognitive assessment scales in pediatric patients, hearing and vision loss in storage diseases)

Background Information:

Myozyme, which is a form of recombinant human acid α-glucosidase (rhGAA) is a novel enzyme replacement therapy (ERT) for an orphan disease (Pompe's disease). Pompe's disease is characterized by progressive muscle weakness due to deficiency of acid α -glucosidase (GAA). Deficiency of GAA results in accumulation of glycogen in the lysozymes of multiple cells, predominately in muscle cells. (Kishnani 2004) Depending on the specific mutation and level of GAA, the clinical spectrum varies (Kroos 2004, Raben 2002). In general, the lower the enzyme activity, the earlier symptoms occur and the greater the severity of disease. The infantile form, with absent or minimal GAA activity, is the most severe, with progressive cardiorespiratory failure. Affected infants usually present with hypotonia and cardiomegaly within the first 4 months of life and do not survive past 2 years of age (Hesselink 2003, Kishnani 2004). Typically, patients with the juvenile and adult forms have residual GAA activity and present later, without cardiac involvement. Nonetheless, in all patients, skeletal muscle function declines resulting in progressive difficulties in ambulation and wheelchair dependence along with respiratory insufficiency and ultimately cardiorespiratory failure. The CNS and spinal column is thought to be spared in all forms. Unlike other glycogen storage diseases, since glycogen accumulates in the lysosomes and not outside the lysosomes, hypoglycemia and other abnormalities of glucose metabolism do not occur (Kishnani 2004).

Currently, there are no approved pharmaceutical therapies for Pompe's disease; only supportive and palliative therapies are available. Specific enzyme replacement has been successful in other storage diseases and has been approved for Gaucher's disease, Mucopolysaccharidosis Type I and Fabry's disease.

Summary of submission under evaluation:

Genzyme submitted a pivotal clinical study (AGLU1602) of 18 infantile patients, comparing survival without invasive ventilation after one year (52 weeks) of therapy to 61 historical controls. This randomized dose-ranging study enrolled 18 enzyme-naive patients with infantile-onset Pompe's disease, diagnosed by clinical symptoms and deficient endogenous GAA activity in mononuclear cells or skin fibroblasts by an accredited laboratory. The median age of diagnosis was 4.3 months, although one patient was diagnosed prenatally. Patients were excluded if older than 26 weeks, had preexisting respiratory symptoms (low pulse oximetry or hypercarbia), other congenital anomaly, and prior investigational drug treatment.

Treatment was initiated between 1.2 and 6.1 months (corrected for gestational age, median age 5.3 months). Patients received 20 to 40 mg/kg of Myozyme IV (160 L lot preparation) every other week. Ventilator-free survival at 18 months of age was significantly improved compared with historical controls: 13/18 (72 %) vs. 1/61 (< 2%). In addition, many patients experienced gains in motor development on the initial assessments. Since the infantile form of Pompe's disease is uniformly fatal and therapies currently nonexistent, the ventilator-free survival benefit for Myozyme intervention is significant. Unfortunately, analysis of neutralizing antibody levels suggests a correlation between the need for invasive ventilation (and clinical deterioration) and high levels of neutralizing antibodies. Moreover, although the motor gains

were significant, the majority of patients remained significantly delayed compared to normal-aged peers. Regression of developmental milestones was also observed for 2/18 patients after the end of the trial.

In addition to the pivotal study in infantile patients, the sponsor has submitted data derived from open label trials in other Pompe patients (see Appendix I). The largest trial thus far, Study AGLU01702, is an ongoing, multicenter (n=6), multinational, open-label, non-randomized, safety, efficacy, pharmacokinetic and pharmacodynamic study of 21 patients with infantile-onset Pompe disease. Preliminary analysis of the data for the first 15 patients (ages >6 months to 43 months of age) did not demonstrate a treatment effect with respect to improved survival, respiratory status or motor development that could be differentiated from the natural progression of the disease.

The definitive efficacy trial in the older Pompe patients, Study AGLU 2704, will be a 1 year, multicenter, randomized, placebo-controlled study of Myozyme therapy in late-onset Pompe patients utilizing the 6 mile walk test as the primary efficacy outcome. Patients in these trials come from many countries and ethnic backgrounds, with a large proportion from Taiwan and Israel.

I. Extrapolation

In general efficacy can be extrapolated between two populations when the course of disease and the effect of the drug, both beneficial and adverse, are sufficiently similar. Additional supporting data such as bridging pharmacokinetic/pharmacodynamic data and safety assessments are usually required (see Appendix II- 21 CFR 201.57(f)9(iv) and 21 CFR Subpart B 314.55.)

According to Dr. Pariser and the review division, "Pompe disease encompasses a wide range of phenotypes, all of which include varying degrees of myopathy, but differ in the age of onset, extent of organ involvement and rate of progression to death. The classic infantile-onset disease is the most severe, with clinical findings of cardiomegaly, hypotonia, hepatomegaly and death due to cardiorespiratory failure usually before the age of 2 years. The adult-onset (late-onset) disease is at the other extreme and is typically a slowly progressive proximal myopathy with onset as late as the second to sixth decade of life and involves only skeletal muscle. Between the two extremes is a heterogeneous group of presentations, usually without cardiac involvement and with a progressive course of myopathy including major impairment of respiratory function. Death in all forms of the disease usually results from respiratory failure."

The literature also supports the concept that the course of the disease is not the same in the infantile patients and in the older-onset patients; namely the lack of cardiac pathology in the older patients and slower rate of progression (Kroos 2004, Raben 2002, Hesselink 2003, Kishnani 2004).

To demonstrate efficacy in the late-onset patients, the 6 minute walk test has been chosen as a measure of clinical benefit. In addition to proving this modest clinical benefit, the sponsor must demonstrate that the drug is safe in the late-onset patients. Unlike the infantile Pompe patients who have no measurable GAA activity, patients with other variants of Pompe's disease do have residual GAA activity. One major safety concern is that if neutralizing antibody to synthetic GAA develops, cross reactivity to endogenous GAA may occur. The effect of this specific antibody on endogenous GAA, which may be protected in the lysosomes, is unknown.

Conclusion Extrapolation:

In general, efficacy can be extrapolated between two populations when the course of disease and the effect of the drug, both beneficial and adverse, are sufficiently similar. Additional supporting data such as bridging pharmacokinetic/pharmacodynamic data and safety assessments are usually required (see Appendix I: 21 CFR 201.57(f)9(iv) and 21 CFR Subpart B 314.55.) In this case, the course of disease in the infantile patient differs significantly from the other Pompe variants in that the disease is rapidly progressive and that cardiac symptomatology is evident in the infantile form. Moreover, the effect on efficacy and safety of neutralizing antibody to Myozyme in patients dependent on endogenous GAA production is unknown. The data obtained in the late-onset study is needed to establish efficacy and safety in this patient population.

II. Motor and Neuropsychiatric Assessments

For long-term follow-up of the infantile patients and for children with the other Pompe variants, the sponsor has utilized several motor and cognitive assessments. These scales are described below with a brief review of the literature supporting their use in children.

A. Motor Assessments

To assess motor outcomes, the scales used in the infantile Pompe patients included the Alberta Infant Motor Scale (AIMS), Pediatric Disability Index (PEDI) and the POMPE Pediatric Disability Index (POMPE PEDI). In the other Pompe variants, the scales used include the Pompe PEDI, Gross Motor Function Measure (GMFM), Peabody (PDMS-2) and six-minute walking test. In addition, muscle strength was assessed by handheld dynamometry, the Wagner Gardner-Medwin scale, and the Medical Research Council (MRC) scale. The Hammersmith Functional Motor Scale and the six minute walk were described for several patients.

The table below is a summary of the motor scales used to evaluate Pompe patients in the studies performed or proposed by Genzyme. The AIMS, PEDI and POMPE PEDI were reviewed in our previous consult regarding infantile Pompe patients. These motor assessments are included in the table below for completeness.

MOTOR ASSESSMENTS USED TO EVALUATE POMPE PATIENTS
(Adapted from Handbook of Physical Therapy, Long and Toscano)
list of abbreviations at end of table

Scale	Age Limits	Population Used to Validate	Assesses	Reliability and Validity	Applications	Comments/Limitations
AIMS (Piper and Darrah, 2002)	Birth to 18 months	2,202 healthy children	Spontaneous movement repertoire: • Prone • Supine • Sitting • Standing • Motor Performance • Weight-bearing • Posture • Anti-gravity movements	Inter-rater reliability (r=0.96-0.99); Test- Retest 0.86-0.99; Concurrent validity with PDMS (r=0.90-0.99) and the motor scale of the BSID II (r=0.94-0.97)	Term, preterm infants, cerebral palsy (CP)	Limits- Developmental ceiling of 18 months Normative sample stratified by sex and age but not by race or ethnicity Validated in Taiwan- inter-rater and intra-rater ICC-0.97-0.99

Scale	Age Limits	Population Used to Validate	Assesses	Reliability and Validity	Applications	Comments/Limitations
			To identify delay			
DDST-2 (Frankenburg 1992)	Birth to 6 years	2,096 healthy children	• Fine motor/adaptive • Gross motor, • Language • Personal/social	Inter-rater- 0.99; Test-retest- 0.90	Multiple- healthy children, development and social status, risk factor for delay, school readiness, maternal exposures, environmental exposure, chronic illness, hearing and vision impairments,	Low specificity (0.43) International (standardized on > 1000 children in Canada, China, Finland, Israel, Japan, Singapore, Philippines, United Arab Emirates Widely used
GMFM (Russell, et al)	5 mo- 16 years	Cerebral palsy (no normative group)	Changes in Gross Motor Function Five dimensions: • Lying/rolling • Sitting • Crawling/kneeling • Standing • Walking/running/jumping • Gross motor ability in standard environment	Inter-rater ICC 0.75-0.99, Test-retest 0.99	Cerebral palsy (CP) and interventions in CP, Down syndrome, malaria	Responsive to change over time in CP patients Used on large number of children International, Chinese ICC > 0.9
HHD	3 years-adult	1,417healthy 5-18 year olds	Strength of isometric muscle contraction	For ages 2-13 years; ICC >0.7 Test-retest >0.90	Multiple: CP, Duchenne muscular dystrophy (DMD), myelomengocele, spinal muscular atrophy (SMA), juvenile rheumatoid arthritis, kidney transplant, cystic fibrosis, epilepsy, depression, hearing impaired, Mucopolysaccharidosis (MPS) I and VI, Glycogen storage disease Type 1	Technique important, fatigue occurs with repetition Normal values vary with gender, age, and height International Not widely used
HFMS (Main 2003)	3 mo- 19 years	35 healthy children < 2 years; 58 patients with SMA	20 Motor tasks, each scored on 3 points • 2- unaided • assisted • unable	Inter-rater > 99 %; Test-retest >0.90	SMA, DMD, and other congenital myopathies	Developmental ceiling 2 years Validated on SMA patients Not widely used
Medwin-Gardner Wagner (Walton 1974)	N/A	N/A	Functional achievement Descriptive Scale Grade 0-10 0- All activities normal 1- Walks normally. Unable to run freely 2- Detectable defect in posture or gait. Climbs stairs without using the banister 3- Climbs stairs only with banister 4- Walks without assistance. Unable to climb stairs. 5- Walks without assistance. Unable to rise from a chair 6- Walks only with calipers or other aids 7-Unable to walk. Sits erect in chair. Able to roll a	N/A	N/A	N/A

Scale	Age Limits	Population Used to Validate	Assesses	Reliability and Validity	Applications	Comments/Limitations
			wheelchair and eat and rink normally 8- Sits unsupported in chair. Unable to roll wheelchair or unable to drink from glass unassisted 9- Unable to sit erect without support or unable to eat or drink without assistance 10- Confined to bed. Requires help for all activities			
MRC	5 years-adult	N/A	Clinical scale of muscle strength 0=No contraction 1=Flicker or trace of contraction 2=Active movement, with gravity eliminated 3=Active movement against gravity 4=Active movement against gravity and resistance 5=Normal power (NOTE: Grades 4-, 4 and 4+ may be used to indicate movement against slight, moderate and strong resistance respectively)	ICC > 0.65 individual muscles; ICC > 0.80 muscle groups	DMD, ALS, congenital myopathy, polyneuropathy, nerve injury, repair of nerve injury, dorsal rhizotomy	Most studies small Does not measure fine motor International
PDMS-2 (Folio 1983)	Birth- 83 months	2,003 healthy children	Fine and Gross Motor Abilities • Reflexes • Stationary • Locomotion • Object manipulation • Grasping • Visual-motor integration Obtain DMQ (mean 100, SD 15)	Test-retest- 2-11 mo (0.89), 12-17 mo (0.96); Reliability and validity as discriminative measure r =0.96	Preterm , high risk infants, small for gestational age infants, osteogenesis imperfecta, congenital heart disease, maternal exposures, children conceived via *in vitro* fertilization	Separate scores for gross and fine motor International Normed and standardized; discriminative, documents delay Developmental ceiling 7 years
PEDI (Haley et al., 1992)	6 mo- 7.5 years	412 healthy children; 102 children with motor delays (CP, spina bifida, arthritis)	Gross motor abilities in daily environment • Mobility • Function • Self Care Designed to assess continuum of disability in wide clinical range	Inter-rater for mobility scale: normative sample ICC is 0.96-1.0 and for disabled ICC is 0.84-1.0; Test-retest 0.76-1 ICC; Concurrent validity with Batelle Developmental Inventory (r = 0.7-0.8)	Pompe, CP, surgery (Selective dorsal rhizotomy, epilepsy) orthopedic conditions (Osteogenesis imperfecta)	Limits: Developmental floor 6 mo and ceiling 7.5 years. International: Translated into European languages Normative sample limited Asian (3/412)
POMPE PEDI (Haley 2003)	6 mo-14 years	790 healthy children	Gross motor abilities in daily environment • Mobility • Function • Self Care Designed to assess continuum	Chi squares all < 11.5 (usually < 5)	Pompe disease	Normative sample limited for Asian, n =11 (1 %) Specific for Pompe patients Developmental ceiling 14

Scale	Age Limits	Population Used to Validate	Assesses	Reliability and Validity	Applications	Comments/Limitations
			of disability in wide clinical range			years
6MWT	5 years to adult	N/A	Exercise tolerance	ICC > 0.94 Healthy and obese children	Congenital heart disease, pulmonary hypertension, heart/lung transplantation, cerebral palsy, cystic fibrosis, juvenile rheumatoid arthritis Mucopolysaccharidosis (MPS I and VI)	International Limitations: subjective, depends on cooperation and motivation Normal values vary with age, gender

Abbreviations used in the table above:

AIMS- Alberta Infant Motor Scale
DDST- Denver Development Screening Test
GMFM Gross Motor Function Measure
HFMS Hammersmith Functional Motor Scale
HHD- Hand-held Dynamometry
MRC- Medical Research Council scale
PDMS-2: Peabody Developmental Motor Scales, 2nd edition
PEDI: Pediatric Disability Inventory
6MWT- Six Minute Walk Test
ICC= Intra-class correlation coefficients
DMQ- Developmental Motor Quotient
N/A- Not available

Denver Development (see cognitive measures)

Gross Motor Function Measure (GMFM)

The Gross Motor Function Measure (GMFM) is a performance based measure designed for children with cerebral palsy to evaluate change in gross motor function. The GMFM score is based on 88 items progressing through five developmental stages: 1) lying and rolling, 2) sitting, 3) crawling and kneeling, 4) standing and 5) walking/running/jumping. Each task is scored from 1 (severely abnormal) to five (consistently normal). The scores are expressed as a percentage of the maximum possible score relative to the number of tests performed (Boyce 1995). A score of 100 % is granted for maximum performance while a change in score of 6 % is considered clinically significant (Ubhi 2000).

The GMFM is standardized in children with CP, with reliability, validity and responsiveness to change over time (Russell 1998, 2000, McCarthy 2002, Vos-Vromans 2005). The original GMFM-88 has been adapted to a difficulty continuum via the Rasch analysis. The resulting GMFM-66 yields an interval score; representing overall gross motor ability and can detect change over time (Wang 2005, Tieman 2004, Avery 2003). The GMFM is considered to have discriminative validity and is capable of differentiating between children with and without learning disabilities and between children with low- and appropriate- birth weight (Russell 1998).

The GMFM is widely used for examining children with cerebral palsy (Harries 2004, Fazzi 2005, Russell 2005) and interventions in CP such as dorsal rhizotomy and botulinum toxin (Ubhi 2000, Boyd 2001, Ketelaar 2001, Linder 2001, McLaughlin 2002, Reddihough 2002, Steinbok 2002, Kondo 2004,and Ostensjo 2004). Other applications include patients with spinal muscular atrophy (Iannacone 2003),

Down syndrome (Russell 1998, 2000, Gemus 2001), malaria (Carter 2006) and acupuncture therapy (Sun 2004).

This scale has also been used to validate other measures such as the Gross Motor Functional Classification System (Russell 2000, Oeffinger 2004), Pediatric Outcomes Data Collection Instrument or PODCI (McCarthy 2002, Abel 2003, Damiano 2005), PEDI (McCarthy 2002, Haley 2003), Child Health Questionnaire (McCarthy 2002), and the 1 minute walk test for CP (McDowell 2005). The GMFM is recognized internationally with use in Australia (Boyd 2001, Reddihough 2002, Saigal 2005), Canada (Gowland 1995, Steinbock 2002, Avery 2003), China (Sun 2004, Wong 2005, Wei 2006), Germany (Linder 2001), Italy (Fazzi 2005), Japan (Kondo 2004), the Netherlands (Ketelaar 2001, Ostensjo 2004)

Reviewer comment: The GMFM has been studied in large numbers of children, in numbers comparable to the AIMS and PEDI. In addition, reliability has been evaluated in Chinese children (Shi 2006). The GMFM has also been used in Israel (Harries 2004) and Taiwan (Yang 1999, Wang 2006). The GMFM is recommended by the NIH Muscular Dystrophy Research Task Force (2003) and used in the Cochrane review of baclofen. One weakness of the GMFM is the lack of normative data (Long 2002). This measure also has a developmental ceiling of 48 months (Vos-Vromans 2005). [Note: A developmental ceiling of 48 months means that the scale will not be discriminative for assessment of gross motor function in children who have gross motor skills that exceed the developmental ceiling.] Genzyme did not state which version of the GMFM is being used. Although both scales are considered to be useful, the GMFM-66 is considered to be more responsive to change (Wang 2006, Wei 2006).

Handheld Dynamometry

Handheld dynamometry (HHD) provides an objective measure of the strength of isometric muscle contraction in both upper and lower extremities (Wiley 1998). HHD was normed on > 1400 healthy children (Newman 1984) and may be done reliably even in young children, including preschoolers (Gajdosik 2005, Lehman 2002, Lee 2003, Taylor 2004), school age (Ager 1984, Bowman 1984) and adolescents (Mathiowetz 1986). Normative values vary with age, height and gender (Newman 1984, Rauch 2002). The technique for obtaining HHD is important as fatigue occurs quickly (Rauch 2002, Newman 1984). Typically, 3-4 measurements are obtained. The dynamometer must be sized and set appropriately (Merkies , Firrell 1996). HHD is reliable in children with muscular disorders including Duchenne muscular dystrophy (Stuberg 1988), cerebral palsy (Wessel 1999) and myelomengocele (Effgen 1992).

Dynamometry has also been used to assess children's strength in a wide range of other conditions. Neuromuscular disorders include myelomeningocele (Effgen 1992, Aronin 1995), Duchenne Muscular Dystrophy (Araujo 1995), polyneuropathy (Merkies 2000).
SMA (Merlini 2004), cerebral palsy (Wiley 1998, Dodd 2003, Taylor 2004), Mucopolysaccharidosis type VI (Swiedler 2005) and Glycogen storage disease type I (Schwahn 2002). Muscle strength in children with JRA (Lindehammar 1998, Wessel 1999), kidney transplants, cystic fibrosis, epilepsy (Rauchy 2002), depression (Emerson 2001) and hearing loss (Ellis 2000) has also been studied with hand-held dynamometry. In addition, the effects of anticonvulsant treatment (Wettengl 2000) and wrestling (Roemmich 1996) have also been studied with this technique.

Hand-held dynamometry has been used world-wide as part of a multinational trial in Australia, Brazil, England, France, Germany and Portugal (Swiedler 2005). In addition, studies in Canada (Wessel 1999), Italy (Merlini 2004), India (Bhave 1985), Japan (Fukunaga 1992) and the Netherlands (Lindchammar 1998, Merkies 2000) have used this measure.

Reviewer comment: *The number of trials utilizing hand-held dynamometry for patients with storage diseases similar to Pompe is small, as well as the number of patients in each trial who have been evaluated using this technique (typically < 40 patients) Hand held dynamometry reflects one aspect of muscle function at a specific muscle site (Rauch 2002) and HHD is volitional (Newman 1984). Although HHD can measure change in a group of patients, it does not measure change in an individual over time (Taylor 2004). Muscle force correlates with timed tests of walking, climbing, and rising out of a chair (Merlini 2004) and related to functional capabilities such as ability to walk, climb stairs and perform self-care (Gajdosik 2005). This measure of strength does not necessarily permit judgment of coordination, flexibility or fluidity of movement (Rauch 2002). For example, hand strength does not necessarily correlate with dexterity (Lee 2003).*

Hammersmith Functional Motor Scale (HFMS)

Hammersmith Functional Motor Scale is a rating scale developed for children with spinal muscular atrophy (Kroksmark 2000, Messina 2004). Intended to detect changes in significantly delayed patients, the HFMS is based on 20 items that normal children typically achieve by age 2 years. Tasks begin with head lifting and progress to ascending/ descending stairs. Each task is scored on 3 points (2- unaided, 1- assisted and 0- unable) with the maximum score of 40 (Main 2003, Mercuri 2006). The HFMS has been used in patients with Duchenne muscular dystrophy and other congenital myopathies. A small number of trials in children have used the HFMS in London (Messina 2004) and Italy (Mercuri 2006).

Reviewer comment: One weakness of the HFMS is its developmental ceiling of 2 years. The number of trials using this score, the patient populations and the number of patients in these trials is relatively small compared to the AIMS, GMFM and PEDI.

Medical Research Council Scale (MRC scale)

The MRC is a clinical scale developed by the Medical Research Council of the United Kingdom to assess muscle strength in patients with neuromuscular disease. Muscle activity is graded on a scale of 0 to 5 where 0 is no contraction and 5 is normal power. Reliability is fair for individual muscle groups (ICC >0.65 to 0.93) and individual muscles (>0.80- 0.99). Proximal muscles tend to have higher reliability values, while gravity-dependent muscles the lowest (Florence 1992).

The MRC scale has been used to classify a broad range of neuromuscular diseases in children and adolescents, including Duchene (DMD) Muscular Dystrophy (Heckmatt 1988, Scott 1982, Florence 1992, Angelini 1994, Sewry 1996, and Hyde 2001), polyneuropathy (Merkies 2000) and Guillian Barre (Kalita 2001). In addition, the MRC has been used to examine children with epilepsy (van Empelen 2004) and brachial plexus injury (Songcharoen 1996, Puri 2004). The MRC has been used to assess repair of nerve injury (Vastamaki 1993, Daoutis 1994, Hudson 1997, Ozdemir 2004)) and dorsal rhizotomy in children with cerebral palsy (Gul 1999).

In addition to Great Britain, the MRC scale has been used all over the world including Canada (Gul 1999), France (Sewry 1996), Greece (Daoutis), India (Puri 2004), Italy (Angelini 1994), Portugal (de Carvalho 2003), the Netherlands (Vastamaki 1993, Merkies 2000, Hyde 2001, van Empelen 2004), S. Africa (Hudson 1997), Thailand (Songcharoen 1996) and Turkey (Ozdemir 2004).

Reviewer comment: The MRC scale is complex and does not measure fine motor control (Merkies 2000). The MRC appears to be a clinical measure for classification purposes. The MRC does appear to correlate with muscle strength and ability. In 61 patients with DMD, a numeric calculation of total muscle strength (% MRC = sum of grade scores x 100/number of muscles tested x 5) correlated with walking times and detected declines in physical performance over 3 years (Scott 1982). Most studies involving children that used the MRC scale involved small numbers of patients.

Medwin-Gardner Wagner Scale

The Medwin-Gardner Wagner scale is a descriptive scale of functional achievement, classifying patient's activities as grade 0 (normal) to grade 10 (confined to bed and requiring help for all activities).

Reviewer comment: Genzyme provided one reference for this scale. A literature search for this scale did not produce additional references in children.

Peabody (PDMS-2)

Normed and standardized on 617 children from birth to 83 months of age, the Peabody Developmental Motor Scale (PDMS-2) assesses fine and gross motor skills. The normative sample includes almost 100 two-year olds. The PDMS-2 consists of 6 subtests: reflexes, stationary, locomotion, object manipulation, grasping and visual-motor integration. Raw scores can be converted into age equivalent and standard scores yielding a Developmental Motor Quotient (DMQ). The mean DMQ is 100, with a standard deviation of 15 (Provost 2000). Children with scores < 80 are classified to be at risk (Arendt 1999). The PDMS is considered to have excellent test-retest and inter-rater reliability with ICC 0.84 to 0.99 (van Hartingsveldt 2005).

The Peabody has been used to evaluate high risk infants (Goyen 2002, Miller-Loncar 2005), small for gestational infants (Sommerfelt 1996, 2002) and children with osteogenesis imperfecta (Cintas 2003) and congenital heart disease (Swillen 2005). The effects of breast feeding (Angelsen 2001), maternal substance abuse [i.e., cocaine (Arendt 1999, Nelson 2004, Miller 2005) or tobacco exposure (Trasti 1999)] and mode of delivery (Bartlett 2000) have been evaluated with the PDMS 2. The PDMS-2 was also used to evaluate children conceived via *in vitro* fertilization techniques (Ponjaert 2004). In pilot studies, the Peabody has been used to evaluate treatment of childhood hemiparesis (Willis 2002).

The PDMS-2 has been used in a multicenter trial in Belgium Denmark, England, and Sweden (Ponjaert-Kristoffersen 2005). In addition, the Peabody has been used in trials located in Australia (Goyen 2002), Canada (Majdener 2005, Cintas 2003, and Bartlett 2000), the Netherlands (Trasti 1999, Sommerfelt 1996, 2002, van Hartingsveldt 2005) and Taiwan (Chen 2002).

Other measures have been validated with the PDMS-2, including the Brief Assessment of Motor Function (Cintas 2003), Test of Infant Motor Performance (Kolobe 2004) and the Posture and Fine Motor Assessment (Case-Smith 1992).

Reviewer comment: The PDMS-2 is a normed referenced measure which permits measuring progress in children with known disabilities or delays and it differentiates between fine and gross motor skills (Long 2002). However, age equivalent scores [scores corresponding to a typical developmental age] for the PDMS-2 and BSID-II agree but not the standard scores [scores relative to the mean of the test]. Compared with BSID-II, the PDMS-2 tends to classify more children as delayed. (Provost 2002) The PDMS-2 may not be sensitive for fine motor delay compared with the Movement Assessment Battery for Children. [The MABC is an American motor scale which rates manual dexterity, ball skills and balance in children ages 4-12 years (van Hartingsveldt 2005)]. In typically developing infants, there is a large variability between scores (Damiano 2003). The Peabody also has a developmental ceiling of 7 years.

Six Minute Walking Test

The six-minute walking test (6MWT) is a self-paced measure used to evaluate exercise tolerance (Garofano 1999) under submaximal conditions. Norms vary with height, gender and weight, where males generally out-perform females and overweight children perform less well (Norman 2005). Although the 6MWT is somewhat subjective in that
cooperation and motivation may affect results (Garofano 1999), the test is reproducible with ICC's > 0.94 in healthy children.

In pilot studies, the distance achieved during the 6MWT for healthy and obese children correlates with oxygen consumption, measures of lung capacity, peak power and anaerobic thresholds (Drinkard 2001,Li 2005). The 6MWT has been used to evaluate children with congenital heart disease (Moalla 2005), pulmonary hypertension (Nakayama 2001, Barst 2002, Kothari 2002, Maiya 2005) and heart/lung transplantation (Nixon 1996, Venuta 2000). In addition, the 6MWT has been used to assess the exercise tolerance of children with cerebral palsy (Maltais 2004), cystic fibrosis (Upton 1988), juvenile rheumatoid arthritis (Klepper 1999, Paap 2005) and other connective tissue disorders (Oudiz 2004). Moreover, this test has been used to evaluate enzyme replacement therapies in other Mucopolysaccharidosis such as MPS I (Wraith 2004) and MPS VI (Harmatz 2005, Swiedler 2005).

The 6MWT has been used in a multi-international trial including countries such as: Australia, Brazil, England, France, Germany, and Portugal (Swiedler 2005). In addition,
this test has been used in other studies in Australia (Harmatz 2004), Canada (Maltais 2004), China (Li 2005), England (Maiya 2005), France (Moalla 2005), Italy (Venuta 2000), Japan (Nakayama 2001) and the Netherlands (Paap 2005).

Variants of the 6MWT include the 12 minute walk test utilized in overweight adolescents (Drinkard 2001, Norman 2005) and the 2 minute walk test used in patients with cystic fibrosis (Upton 1988).

Reviewer comment: This timed test, although yielding some measure of function, is subjective, depending on effort and motivation (Garofano 1999). Nonetheless, a variant of the 6 minute walk test (the 12 minute walk test) was used in the approval of Naglazyme for the treatment of MPS I. The reliability in patients

with decreased muscle function is less clear than the reliability in healthy children and patients with congenital heart disease.

General Conclusion: Validity of Motor Scales Utilized:

The PEDI/Pompe PEDI, AIMS, and BSID-II, utilized to assess secondary outcomes in the infantile Pompe population are appropriate and compliment each other. The PEDI/Pompe PEDI evaluates gross motor activities, mobility and self-care tasks while the AIMS assesses spontaneous movements and the BSID examines fine and gross motor skills.

The AIMS and BSID II scales are unlikely to be useful for patients with the other Pompe variants, as these scales have a developmental ceiling of 18 months and 3.5 years respectively. The GMFM (gross motor function), PDMS-2 (fine and gross motor) and PEDI/Pompe PEDI will be more useful in older or more able patients, although the PDMS-2 has a developmental ceiling of 7 and the Pompe PEDI has only been validated in a relatively small number of patients.

The AIMS, BSID-II, PEDI, GMFM, and PDMS-2 have been normed and standardized in a large number of children. They are widely used in many different countries and are considered to be reliable. The other measures used by the sponsor (hand-held dynamometer and six-minute walk test) may augment these assessments.

B. Cognitive measures

The Bayley Scale of Infant Development (BSID-II), Denver Developmental Screening Test (DDST-II), Wechsler Preschool and Primary Scale of Intelligence – Revised (WPPSI-R), Wechsler Intelligence Scale for Children – III (WISC-III), Peabody Picture Vocabulary Test, Modified Leiter International Performance Scale Revised (Leiter-R) are the cognitive and language outcome measures used thus far by Genzyme in the Myozyme Trials. The BSID-II was administered for patients < 42 months, the WPPSI-R to ages 42 months to 7¼ years and the WISC-III to patients > 7 years, 3 months of age. The Leiter-R was administered concomitantly with the BSID-II in patients starting at age 24 months, until the developmental ceiling of the BSID-II was reached (age 3). The DDST-II and PPVT were described in several groups of patients.

In June 2004, the Division of Neurology Drug Products (DNP) commented on the appropriateness of cognitive scales proposed to evaluate "cognition, memory and psychometric testing" in [redacted] Written Request. The WISC-III and WPPSI-R were among the tests endorsed by DNP due to "use in research studies and evaluation of children with suspected learning disabilities in the public school system."

The table below is a summary of the cognitive scales used to evaluate Pompe patients in the studies performed or proposed by Genzyme. The modified BSID-II, used in the assessment of the infantile population, is included in the table below for completeness.

COGNITIVE MEASURES USED TO EVALUATE POMPE PATIENTS

Scale	Age Limits	Population Used to Validate	Assesses	Goodness of Fit	Applications	Comments/Limitations
BSID-II (Bayley 1993)	1-42 months	1,700 normal Children	• Cognitive • Fine and Gross Motor • Behavioral Mean of 100 and SD 16	Inter-rater: motor- r = 0.75. Mental- r= 0.96; Test-retest: motor- 0.78, mental- 0.87; Concurrent validity: PDMS-2 age equivalent; Reliability > 0.75; WPPSI-R- 0.73;McCarthy- 0.79	Multiple: preterm and term infants, prenatal exposures, toxins, trauma, abuse, congenital defects, surgery	Includes 100 patients in each 2 mo subset Limit: developmental age of 3.5 years Poor predictor of cognitive function at school age Inability to distinguish between gross and fine motor International
DDST-II (Frankenburg 1992)	Birth to 6 years	2,096 normal Colorado children	• Fine motor/adaptive • Gross motor, • Language • Personal/social	Inter-rater- 0.99; Test-retest- 0.90	Multiple- healthy children, development and social status, risk factor for delay, school readiness, maternal exposures, environmental exposure, chronic illness, hearing and vision impairments,	Low specificity (0.43) International (standardized on > 1,000 children in Canada, China, Finland, Israel, Japan, Singapore, Philippines, United Arab Emirates) Widely used
Leiter-R (Roid 1997)	2-20 11/12 years	1,719 normal children and adolescents; and 692 "atypical" children	Intelligence in nonverbal • Visualization and reasoning • Attention and memory	Reliability (>0.88); Correlation (0.86) with WISC	Multiple- healthy children, learning disabled and gifted, genetic syndromes, autism, hearing impairment, metabolic disorders, maternal exposures	International, including Taiwan Greater variability than WISC-III
PPVT (Dunn 1997)	2-90 years	2,725 normal adults and children that included 2,000 children and adolescents	Receptive vocabulary via picture scale	Reliability >0.82; Test-retest >0.90	Multiple: anemia, autism, hearing impairment, cochlear implants, genetic syndrome, toxins, neonatal interventions, maternal exposures	International, including Taiwan Smaller number of trials and patients compared with WISC-III
WPPPSI-R	2½ - 7¼ years	1,700 Normal children	Cognitive functioning (Full scale IQ) Acquired knowledge, verbal reasoning and comprehension (Verbal IQ) Fluid reasoning, spatial processing, attentiveness, visual-motor (Performance IQ)	Reliability > 0.89; Test-retest >0.86; Correlates with BSID-II, WISC- III (>0.80)	Multiple: genetic, chronic diseases, metabolic diseases, maternal exposure, toxins, trauma, environmental effects, interventions	International Gold standard Age-standardized
WISC-III	6-16 years	1,100 Normal children	• Verbal IQ • Performance IQ • Full scale IQ	Gold Standard	Multiple: healthy children, learning disabilities, genetic disorders, prematurity, toxic exposure, maternal exposures, *in vitro* fertilization	Recently updated to WISC-IV International Gold Standard Age-standardized

Abbreviations used in the table above:

BSID-II- Bayley Scales of Infant Development
DDST-II- Denver Development Screening Test II
Leiter-R- Leiter- Revised
PPVT- Peabody Picture Vocabulary Test
WPPSI-R - Wechsler Preschool and Primary Scale of Intelligence-Revised
WISC-III- Wechsler Intelligence Scale for Children

Denver Development

The Denver Development Screening Test II (DDST II) is a widely used screening test developed to identify children who may be at risk for developmental delays (Frankenberg 1992). The timing of developmental milestones achieved by over 2,000 children with ages from birth to 6 years was used to standardize the Denver. The DDST II examines four domains of development: fine motor/adaptive, gross motor, language and personal/social via 225 items. Each item is rated as pass, fail, refusal or no opportunity. The developmental age for each task ('a pass") is equivalent to the age 90 % of the normative group achieved the skill.

A literature search for the DDST-II revealed over 100 citations. In the past few years alone, the Denver has been used to examine development and social status (de Lourdes 2005, Isranurug 2005) as well as to identify risk factors for delay in school performance (Halpern 2000) or language delay (Eapen 2004). The DDST-II has been used to assess school readiness (Perera 2005) and to correlate skills necessary to climb in tub with the likelihood of accidental burns (Asalio 2005). The DDST has been used to investigate the effects of maternal diabetes (Plagemann 2005) and maternal diet (Daniels 2004) on cognitive outcomes. Development for children with a history of hypoglycemia (Brand 2005), iron deficiency (Akman 2004), congenital heart disease (Chen 2004), choroid plexus cysts (Hung 2002) and blindness (Levtzion-Korach 2000) have been assessed with the DDST-II.

The Denver is one of the most widely used screening measures and is accepted world-wide (Rydz 2005). The DDST has been translated into multiple languages including Chinese and Japanese (Chen 2003). It has been normed and standardized for over 1,000 children in Bangkok (Sriyaporn 1994), Canada (Cadman 1987), Finland (Tenovuo 1988), Israel (Shapira 1983), Philippines (Williams 1986), Singapore (Lim 1996), Taiwan (Chen 2003), and the United Arab Emirates (Eapen 2004). In addition, the Denver has been used in trials in Argentina (Lejarraga 2002), Australia (Rossiter 1993), Brazil (de Lourdes 2005), England (Daniels 2004), Germany (Plagemann 2005), Israel (Levtzion-Korach 2000), Middle East (al Naquib 1999), Sri Lanka (Perera 2005), Netherlands (Brand 2005), Thailand (Isaranurug 2005), Turkey (Akman 2004), United Arab Emirates (Eapen 2004), and Taiwan (Chen 2004, 2003, Hung 2002).

Reviewer comment: The DDST has been standardized in thousands of children in many different countries. Valid outcomes are dependent on proper administration and scoring (Frankenburg 1988). However, the DDST is not considered to be a particularly sensitive or specific measure (Borowitz 1986, Greer 1989, Glascoe 1992). The Denver is less sensitive and comprehensive than the BSID-2 (Brand 2005). For preterm infants, the DDST incorrectly identified up to 42 % of delayed preterm infants as normal (Elliman 1985). Although several studies suggest abnormal results with the Denver can predict delays at school age (Greer 1989, Struner 1985), the developers of the DDST-II do not recommend predicting later developmental status from an earlier screening test (Frankenburg 1988). Motor impairment may also impair ability to perform cognitive tasks on the Denver (Perera 2005). In addition, the findings on the Denver may vary with the population (Brachlow 2001). For instance, local norms are needed in Taiwan (Huang 2002), which may necessitate additional validation in Taiwanese children (Chen 2003).

Leiter-R

The Leiter- Revised is a nonverbal scale to measure intelligence, based on abstract concepts. This battery consists of 20 subtests assessing visualization and reasoning; attention and memory. In addition to a standard score, a growth score provided for each.
Mean IQ is 100 +/- 10 for children aged 2- 20 years (Ratcliffe 1979). The Leiter has been validated in kindergarten children (Reeve 1983).

The Leiter has been used to assess intelligence in a wide variety of disorders including genetic syndromes including Down syndrome (Pastore 2000), autism (Tsatsanis 2003, Mangeot 2001), Fragile X (Skinner 2005) and Costello syndrome (Axelrad 2004). In addition, studies have also been performed in deaf children with (Kutz 2003, Khan 2005) and without cochlear implants (Eastbrook 2001), children with cerebral palsy, and language disorders (Ratcliffe 1979). The Leiter has been used in children with metabolic diseases such as aspartylglucosaminuria (Arvio 1992), children treated with thioridazine (Breuning 1983) and infants of mothers with seizure disorders (Gaily 1988). Not only has the Leiter been used to monitor intelligence in patients with disabilities (speech impairment, cognitive delay, attention disorders, and learning disabilities) but also it has been used to examine intelligence in gifted children (Arvio 1993).

The Leiter has been used in Hispanic and European children (Flemmer 1997) in countries such as England (Khan 2005), Finland (Gally 1988, Arvio 1992), and Italy (Pastore 2000). In addition, the Leiter has been used in a large number of Taiwanese children (Tsai 2005: n= 1,192). This instrument correlates with the WISC (Alper 1958, Ratcliffe 1979,Tsatsanis 2003), Vineland (Tsatsanis 2003), Standford Binet (Alper 1958, Ratcliffe 1979,) and Woodcock-Johnson (Roid 2000). The Leiter has been used to validate other scales (Arvio 1992).

Reviewer comment: Although the Leiter correlates with the WISC, the Leiter has greater variability. Also, since partial credit cannot be given, the Leiter may penalize careless mistakes in children with average or above intelligence (Ratcliffe 1979).

Wechsler Preschool and Primary Scale of Intelligence-Revised WPPSI-R

The Wechsler Preschool and Primary Scale of Intelligence-Revised is a measure of intelligence typically used in children ages 3-7 years. Genzyme has chosen to administer the WPPSI-R in patients aged 42 months to 7¼ years. The WPPSI-R includes verbal and performance subscales. The verbal scale is divided into information, comprehension, arithmetic, vocabulary, plus a similarity subscale designed to measure problem-solving ability. The performance scales include object assembly, geometric design, block design, mazes, and visual-detail subscales designed to assess nonverbal problem solving, perceptual organization and speed and visual-motor proficiency.

The WPPSI-R has been used to assess a wide range of children and exposures. A literature search for the WPPSI-R yielded hundreds of citations. In the past few years, the WPPSI-R has been used to examine the effects of television (Li 2004, Zimmerman 2005) and solvents (Laslo-Baker 2004) on development as well as multiple maternal exposures such as cocaine (Frank 2005, Singer 2004, Morrow 2004, Nelson 2004), seizures (Gally 1988(and tobacco (Trasti 1999). In addition, the effects of birth weight (Sommerfelt 2002), hypothermia (Adelson 2005), hydrocephalus (Lindquist 2005), morphine sulfate (MacGregor 1998) and mode of conception (Ponjaert-Kristoffersen 2005) on cognitive outcomes have

been monitored via the WPPSI-R. The cognitive outcomes for children with diseases such as hypothyroidism (Selva 2005), leukemia (Duffner 2004, Jansen 2005) and disorders of metabolism (Arvio 1992) have been also determined with the WPPSI-R.

The WPPSI-R is internationally accepted in countries including Canada (Laslo-Baker 2004), Greece, England, the Netherlands (Ponjaert-Kristoffersen 2005), Japan (Oki 1992) and Taiwan (Tsai 2005). Moreover the WPPSI-R has been used to validate other measures including the Ages and Stages Questionnaire (Klamer 2005, Portage (Arvio 1993) and Clinical Evaluation of Language- Preschool (Morrow 2005)/

Reviewer comment: The Wechsler family of tests is considered to be the gold standard. The WPPSI-R is endorsed by the AAP as well as DNP. The age range for the WPPSI-R overlaps slightly with the WISC-III. The WPPSI-III- heavily weighted for word knowledge and does not assess memory (Lichtenberger 2005).

Wechsler Intelligence Scale for Children (WISC-III)

The Wechsler Intelligence Scale for Children- III in an age-standardized measure of verbal, performance and full scale IQ in children aged 6-16 years. The WISC-III was administered to Pompe patients > 7¼ years. The WISC-III yields an average ± SD IQ score of 100 ±15. IQ scores above 130 are very superior, 120-129 superior, and 110-119 high average. Average scores are 90-109 and 80-89 is low average. Scores 70-79 are considered to be borderline, while scores < 69 are deficient.

A literature search for trials utilizing this measure yielded hundreds of citations in a wide variety of conditions. In the past few years alone, the WISC-III has been used to assess development in children with a history of prematurity (Cooke 2005, Lefebvre 2005) or bronchopulmonary dysplasia (Doyle 2005). Effects on cognition of prenatal exposures such as cocaine (Frank 2005) or treatments in the neonatal period such as breastfeeding (Jain 2002) salt supplementation (Dahhan 2002) and hypothermia (Adelson 2005) have also been examined with the WISC-III. Cognitive development in children conceived via intracytoplasmic sperm injection (Ponjaert-Kristoffersen 2005) and children born to mothers with mental retardation (Chen 2006) have also been monitored by the WISC-III. In addition, learning needs in school age children (Strand 2004) and for patients with disabilities (speech impairment, cognitive delay, attention deficits, learning disabilities) and gifted children have been determined with the WISC-III (Roid 2000). The effect of disease states such as anemia (Kordas 2004), leukemia (Jansen 2005), hypothyroidism (Selva 2005), hydrocephalus (Lindquist 2005), genetic disorders such as autism, 18 q deletion (Semrud-Clikeman 2005), neurofibromatosis (Hyman 2005) and Asperger syndrome (Mottron 2004) or toxins including solvents (Laslo-Baker 2004) and lead (Koller 2004) have been followed with the WISC-III. Finally, the WISC has been used to follow the development of children with neurologic disorders such as seizures (Northcott 2005) and cerebral palsy (Fazzi 2005), as well as treatment of patients with these diseases (Korkman 2005).

The WISC-III is internationally accepted and has been used in multicenter trials in Belgium, England, Greece and the Netherlands (Ponjaert-Kristoffersen 2005). In addition, it has been used in Brazil (Braga 2005), Canada (Laslo-Baker 2004, Mottron 2004), Italy (Fazzi 2005), Germany (Feldmann 2003) and Mexico (Kordas 2004). Moreover, the WISC has been used in several trials in Taiwan (Chu Chen 2002, Yang 2004, Tsai 2005).

Several other measures of intelligence have been validated with the WISC, including the California Verbal Learning Test (Donders 2003, O'Jile 2005), Leiter (Alper 1958, Roid 2000), British Picture Vocabulary Scale and Raven Progressive Matrices (Mottron 2004). The WISC has been used to examine the relevance of College Board tests (Baade 2004) and Quantitative EEG (Thatcher 2005).

Reviewer comment: The WISC-III is considered to be one of the top five neuropsychiatric assessments by clinical neuropsychologists in the US and Canada (Rabin 2005). It is considered to be the gold standard (Mottron 2004) and is endorsed by the AAP as well as DNP. The WISC-III has been used in greater than 10,000 children, demonstrating a high consistency in IQ over time, particularly for children ages 10-13 years (Strand 2004). Unfortunately, the long term stability of subsets in children with disabilities is poor (Watkins 2004) and the WISC-III is relatively insensitive to changes in executive function and frontal defects in brain-injured children (Braga 2005). Since the instructions are spoken, scores may be less reliable since they must be adjusted for hearing-impairment (Khan 2005). There is now a new version that is available, the WISC-IV.

Peabody Picture Vocabulary Test-Revised (PPVT-R)

The Peabody Picture Vocabulary Test- Revised is an un-timed test of receptive vocabulary in children and adults ages 2-90 years. The normative sample of 2,725 normal included 2,000 children and adolescents. During the PPVT-R, 204 groups of 4 pictures are shown to the child, who must identify the one that matches the target word. The Peabody does not require a motor response. The test is scored by subtracting errors from the ceiling and converted to standard score for age (Rydz 2005). The mean $\pm$ SD of the PPVT-R is 100 $\pm$10 and raw scores can be converted to age-adjusted scores.

The PPVT-R is considered to be reliable as it correlates with the WISC in emotionally disturbed children (Ollendick 1974), as well as normal children (Rydz 2005). It also correlates with the Kaufman Assessment Battery for Children (Rydz 2005) and the Vineland Adaptive Scale of Behavior (Msall 2005).

The PPVT-R has been used in large trials of preschool children (> 1,000) to assess school readiness (Rock 2005). The Peabody has been used to evaluate language in a wide variety of conditions including anemia (Kordas 2004), autism (Aman 2004, Coudoris 2003, Dawson 1987), hearing impairment (Wake 2005, Eisenberg 2004, Moeller 2000), epilepsy (Northcott 2005), obesity (O'Callaghan 1997), short stature (Stathis 1999), sleep apnea (Emancipator 2006) and genetic syndromes (Miolo 2005, Axelrad 2004, Ross 2000). The PPVT-R has also been used to examine exposure to substances such as cocaine (Manrique 2004) and lead (Mendelsohn 1998, Kordas 2004). Moreover the effects of interventions such as estrogen therapy (Ross 2000), ECMO (Nield 2000), indomethacin (Ment 2000), tympanostomy tubes (Paradise 2003) and breast or formula feeding (Jacobson 1999, Auestad 2003, Oddy 2003) on speech have been observed with the PPVT-R. Language development in children with a history of forceps delivery (Wesley 1993), neonatal intensive care (Jennische 2003), traumatic brain injury (Levin 2001), intraventricular hemorrhage (Ment 2000), and low- or very low-birth weight (Ment 2003, McCarton 1997) have been assessed by the PPVT-R. The Peabody has also been used with other measures to monitor cognitive outcomes longitudinally (Ment 2003, To 2004, Pittman 2005, Webster 2005, McCormick 2006) and to identify risk factors for developmental delays (Yokinawa 1999, Pan 2004, To 2004, Basilio 2005).

While the Peabody was originally developed in England, it has been used in Africa (Carter 2006), Australia (Northcott 2005, Wake 2005), Brazil (Basilio 2005), Canada (Webster 2005), France (Webster 2004), Mexico (Kordas 2004), Spain (Manrique 2004), Sweden (Jennische 2003) and Taiwan (Chen 2002). It has been translated into several languages (Webster 2004).

The PPVD was used to validate the California Developmental Inventory (Pan 2004), the Miller Assessment for Preschoolers (Fulks 2005) and SCAN- A screening test for auditory processing disorders (Keith 1989).

Reviewer comment: As a nonverbal measure, the Peabody supplements information regarding language development derived from measures such as the WPPSI-R (Ment 2000). In addition, the PPVT-R does not require a motor response; thus, it may be useful for patients with motor disabilities (Ment 2003). The PPVT-R measures receptive speech only; other measures are required to assess expressive language (Webster 2004). The PPVT-R may underestimate intelligence compared to WISC in autism and mental retardation, and overestimate intelligence in average to high- achieving children (Mottron 2004). Some investigators believe picture vocabulary testing is not an adequate measure of intelligence (Jain 2002).

General Conclusion: Validity of Cognitive Scales Utilized:

The Wechsler tests, the WISC-III and WPPSI-R, which are age-standardized and have been internationally validated and are considered to be the "gold standard," are certainly the most appropriate measures to assess cognitive function. The Leiter-R, PPVT and the DDST-II will complement these measures. The DDST-II is the least sensitive of the measures with respect to identifying children with delays. Note that most of these assessments may be adversely impacted by hearing, vision or motor impairments (Levtzion-Korach 2000, Losch 2004, Ozmert 2005, Rando 2005).

III. Recommendations: Post marketing commitments:

Preliminary data suggests that in infantile-onset patients, Myozyme significantly improves ventilator-free survival and is associated with gains in motor skills. However, these infants are still significantly delayed compared to their normal peers. Regression in motor skills was noted in 2/8 infantle-onset patients who who had demonstrated gains in motor function at week 52 and who continued to be followed after study completion. Preliminary data also suggests that the development of high titers to Myozyme is associated with clinical deterioration, including the need for invasive ventilation.

All Pompe patients should be followed to determine the long-term effects of Myozyme therapy on ventilator-free survival, motor function and cognitive development. Persistence of gains in motor function should be determined. All patients should be followed for long-term safety, including the development of antibodies to Myozyme.

The following parameters should be monitored:

Fine and Gross Motor Function:

Developmental follow-up should include age-appropriate motor scales described above, particularly the AIMS, GMFM and PEDI/Pompe PEDI. The other measures (HHD, 6MWT, MRC, HMFS) that the sponsor proposes to use are reasonable supportive measures.

Cognition

Since most untreated patients with the infantile form of Pompe disease do not survive past 18 months, cognitive development with prolonged survival is unknown. Cognitive development should be monitored periodically by age appropriate standard measures such as the BSID-II, WPPPSI-R and WISC III. The other scales (Leiter-R) proposed by the sponsor are reasonable supportive measures

Language

In addition to the PPVT-2, which measure receptive speech, the sponsor may wish to use other well-known language inventories which measure expressive speech such as the Early Language Milestone-2, Preschool Language Scale III or Clinical Evaluation of Language.

Growth

Growth parameters need to be standardized with repeated (at least 3) measurements at each time point. In younger patients, recumbent length should be measured in a standard manner on an appropriate measuring board. Height must be measured via stadiometry for older children. (see "Evaluation of the Effects of Orally Inhaled and Intranasal Corticosteroids on Growth in Children."). Height and weight should also be correlated with nutritional and feeding status. For younger children, recumbent length and weight should be correlated with gestational age as well. In addition, head size should be monitored in a standardized manner. Accurate head circumference measurements may be particularly useful because both microcephaly and macrocephaly are associated with developmental delays

Neuro-imaging

Central nervous system glycogen deposition has been observed rarely in Pompe patients (Martini 2001). The effects or amount of CNS glycogen with prolonged survival is unknown. As proposed by the sponsor, neuroimaging should include MRI with clinical deterioration or at periodic intervals. Other measures such as event related potentials (ERP), functional MRI, diffusion tensor imaging (DTI) and magnetic resonance spectroscopy (MRS) are still considered to be research tools and are not well-validated (Thomas 2003). ERP may reflect EEG activity during specific sensory or cognitive stimuli and may be useful to assess covert attention, recognition memory, and long term recall. Functional MRI and MRS have been used to examine the relationship between the brain and behavior. DTI is thought to provide a measurement of myelination (Thomas 2003).

Hearing Screening

Hearing loss was observed in several patients during enzyme therapy. Although hearing loss may be related to progression of disease with deposition of glycogen in the cochlea (Kamphoven 2004), the effect of therapy on hearing deficits are unknown. Similar hearing deficits are noted in other lysosomal diseases such as alpha and beta mannsidosis (Springer 2005, Bedilu 2002), Kanazki disease (Umehara 2004), Fabry disease (Hajioff 2003) and Mucopolysaccharidosis II (Peck 1984). Auditory function has improved gradually with enzyme replacement in Fabry disease (Hajioff 2003) and in animal models of other

Mucopolysaccharidosis (type VII- O'Connor 1998) disease. Moreover, hearing should be monitored since deficits will impact standard neurocognitive testing.

Vision screening

Vision should be monitored routinely by an ophthalmologist for general and slit lamp exam. Visual deficits may influence motor and cognitive achievements and assessments (Levtzion-Korach 2000, Ozmert 2005, Rando 2005). Although not typical, ocular glycogen deposits (Pokorney 1982, Goebel 1978, Libert 1977) and vision loss (Kroos 1997) have been reported for patients with Pompe disease. Corneal clouding or blindness is related to glycogen deposition in other lysosomal storage diseases, such as Mucopolysaccharidosis type VI (Harmatz 2004), alpha-mannisidosis (Springer 2005).

Antibody status

Antibody status should be monitored in all patients. The effects of antibody development on the efficacy and safety of this form of enzyme replacement must be examined. Included in this assessment should be the relationship of antibody development to deteriorations in motor and respiratory function and, hence, survival.

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Appendix I- Myozyme Clinical Development Program

Table 1: RhGAA (Genzyme) Clinical Development Program, Infantile-Onset Studies		
Study	**Population**	**Description**
AGLU-004-00	Infantile-onset All patients, n=168 Historical control subgroup, n=62	Observational, natural history study of 168 infantile-onset Pompe disease patients conducted between Feb-2002 and Nov-2002. This study included data obtained using a retrospective chart review of 168 untreated patients diagnosed with infantile-onset Pompe disease with the purpose of better characterizing the natural course of the disease. No investigational treatment was administered. A subgroup of patients selected for similar age and severity (historical control subgroup) was used as the comparator/control for Study 1602.
AGLU01602 (Study 1602) (Pivotal)	classic infantile-onset, n=18	Randomized (to dose), open-label (OL), multi-center, multi-national, safety, efficacy, PK, PD, and dose-ranging study of rhGAA (Genzyme) 20 mg/kg or 40 mg/kg qow in 18 infantile-onset Pompe disease patients ages ≤6 months at the time of first infusion. Study 1602 was conducted from 26-May-2003.
AGLU01702 (Study 1702)	classic infantile- and childhood/juvenile-onset, n=21	OL, uncontrolled, multi-center, multi-national, safety, efficacy, PK and PD study of rhGAA (Genzyme) 20 mg/kg qow in 21 infantile-onset Pompe disease patients ages >6 to ≤36 months at time of first infusion. Study 1702 was conducted from 17-Mar-2003 to ongoing. All 21 have completed at least 52 weeks of the study.
AGLU02203	Age at onset ≤6 months in all 5 patients (4 probable muscular variant and 1 probable classic infantile-onset), n=5	OL, uncontrolled, US expanded-access, safety and efficacy study of rhGAA (Genzyme) 20 mg/kg qow in 5 Pompe disease patients at an advanced stage of disease progression (29-Dec-2003 to ongoing). Patients had a mean age of 10.3 years at study entry.
AGLU02003	5 classic infantile-onset who began ERT at age range of 2.4 to 8 months, and 2 patients who began ERT at ages 5 and 6 years). n=7	OL, extension, safety and efficacy study of rhGAA (Genzyme) 10, 20 or 40 mg/kg qow in 7 infantile-onset patients who had previously received treatment with a prior formulation of rhGAA (Synpac) (10-Apr-2003 to ongoing). Patients were a mean age of 22 months at Synpac rhGAA treatment entry (median 5 months), and 41 months at rhGAA (Genzyme) treatment entry (median 30 mos). Three patients were on ventilation (invasive and non-invasive) at baseline. Two patients died during the study at ages 32 and 33 months.
AGLU1205-02	Classic infantile-onset, n=1	OL, extension study of rhGAA (Genzyme) 20-40 mg/kg qweek in a single (1) infantile-onset Pompe disease patient who had previously received rhGAA (Synpac and Pharming) for 3 years under INDs [redacted] Study AGLU1205-02 conducted from 12-June-2003 to ongoing). First infusion at 3 months (Pharming rh-GAA), and rhGAA (Genzyme) at age 41 months. Few follow-up outcomes measures were performed (e.g., motor data), noted as being in noncompliance with the protocol, but noted to be ventilator-dependent since age 40 months. Currently receiving rhGAA (Genzyme) 40 mg/week
Total	**n=52**	

Table 2: RhGAA (Genzyme) Clinical Development Program, Juvenile/Childhood- and Adult-Onset Studies		
Study	**Population**	**Description**
AGLU02804	Juvenile-onset (age range 1-6 yrs), n=5	OL, single-center, 26-week, safety, efficacy and PK study of rhGAA (Genzyme) 20 mg/kg qow in 5 patients with juvenile-onset Pompe disease. Patients ages 6 to 15 years (median 12.7 years) at baseline, with symptom onset at ages 1 to 12 years. All patients could ambulate 10 m at baseline for 6MWT. Patients on invasive ventilation were excluded.
AGLU02503	Juvenile-onset (age range at symptom onset 1-3 yrs), n=3	OL, European EAP for the treatment of severely affected late-onset Pompe disease patients with rhGAA (Genzyme) 20 mg/kg qow (04-Nov-2003 to ongoing). 4 patients enrolled, and 3 received treatment (1 patient died prior to receiving any treatment). Eligibility: documented signs or symptoms of Pompe disease at age >12 mos, age ≤21 years at time of study entry, documented GAA deficiency and were severely affected (non-ambulatory and needing assisted ventilation).
AGLU02103	Juvenile-onset (age 11 yrs), n=1	OL, extension, safety and efficacy study of rhGAA (Genzyme) 30 mg/kg qow in 1 late-onset Pompe disease patient who had previously received 3.7 years of Pharming and Synpac rhGAA under INDs (AGLU02103 conducted from 11-Apr-2003 to ongoing).
International EAP	Infantile-, juvenile- and adult-onset (1 subject age at symptom onset 6 months c/w infantile-onset muscular variant, remaining 13 patients age range 2-35 yrs); n=14	An expanded access program conducted outside the US providing rhGAA (Genzyme) to patients with infantile- and late-onset Pompe disease. 54 patients have been enrolled as of 08-Mar-2005.
AGLU02603 (US EAP)	Juvenile- and adult-onset (ages 2 and 21 yrs), n=2	Ongoing, OL, expanded access study in the US for severely affected patients with late-onset Pompe disease who do not meet the clinical eligibility criteria for enrollment in an ongoing study of rhGAA (Genzyme). The first patient was enrolled Dec-2004.
Total	**n=25**	

APPEARS THIS WAY
ON ORIGINAL

Appendix II- Regulations for Extrapolation

21 CFR 201.57
(iv) FDA may approve a drug for pediatric use based on adequate and well-controlled studies in adults, with other information supporting pediatric use. In such cases, the agency will have concluded that the course of the disease and the effects of the drug, both beneficial and adverse, are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. The additional information supporting pediatric use must ordinarily include data on the pharmacokinetics of the drug in the pediatric population for determination of appropriate dosage. Other information, such as data from pharmacodynamic studies of the drug in the pediatric population, data from other studies supporting the safety or effectiveness of the drug in pediatric patients, pertinent premarketing or postmarketing studies or experience, may be necessary to show that the drug can be used safely and effectively in pediatric patients. When a drug is approved for pediatric use based on adequate and well-controlled studies in adults with other information supporting pediatric use, the "Pediatric use" subsection of the labeling shall contain either the following statement, or a reasonable alternative: "The safety and effectiveness of (*drug name*) have been established in the age groups _ to _ (note any limitations, e.g., no data for pediatric patients under 2, or only applicable to certain indications approved in adults). Use of (*drug name*) in these age groups is supported by evidence from adequate and well-controlled studies of (*drug name*) in adults with additional data (insert wording that accurately describes the data submitted to support a finding of substantial evidence of effectiveness in the pediatric population)." Data summarized in the preceding prescribed statement in this subsection of the labeling shall be discussed in more detail, if appropriate, under the "Clinical Pharmacology" or the "Clinical Studies" section. For example, pediatric pharmacokinetic or pharmacodynamic studies and dose-response information should be described in the "Clinical Pharmacology" section. Pediatric dosing instructions shall be included in the "Dosage and Administration" section of the labeling. Any differences between pediatric and adult responses, need for specific monitoring, dosing adjustments, and any other information related to safe and effective use of the drug in pediatric patients shall be cited briefly in the "Pediatric use" subsection and, as appropriate, in the "Contraindications," "Warnings," "Precautions," and "Dosage and Administration" sections.

21 CFR Subpart B--Applications Sec. 314.55 Pediatric use information.

(a) *Required assessment.* Except as provided in paragraphs (b), (c), and (d) of this section, each application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration shall contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective. Where the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies. Studies may not be needed in each pediatric age group, if data from one age group can be extrapolated to another. Assessments of safety and effectiveness required under this section for a drug product that represents a meaningful therapeutic benefit over existing treatments for pediatric patients must be carried out using appropriate formulations for each age group(s) for which the assessment is required.

DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

COMPLETED DEC 1 6 2005

Division of Neurology Products, ODE-1

Date: 12/16/05

From: M.Walton, DNP/ODE1 12/16/05

Subject: Genzyme BLA STN 125141 / 0
Aglucosidase alfa for treatment of Pompe disease
Consult request

Through: R.Katz, Director, DNP/ODE1 12/16/05

To: Division of Gastrointestinal Products, ODE3

This consult review is in response to DGP requesting comment on the developmental milestone assessments and upon the primary endpoint of Genzyme's BLA for aglucosidase alfa for treatment of Pompe disease. This consult will focus upon Genzyme's study 1602 which is the key efficacy study in this application. This study enrolled patients with infantile onset severe disease in an open label treatment of patients with comparison made to a historical dataset as the control.

Primary Efficacy Endpoint

The primary endpoint of this study was an analysis of mortality using survival (time to event) methodology. The external control group was a subset of the full historical dataset with early onset, severe symptoms. There were 18 patients enrolled into the prospective study, and data for at least 1 year of study follow up are present in the BLA submissions. On the basis of this comparison between these non-randomized, non-concurrent groups, the treatment appears to be highly effective in delaying mortality. However, comparison to a non-randomized, historical control is a highly unusual basis for an outcome comparison to be deemed substantial evidence of efficacy. The underlying basis for the data used in this comparison should be examined closely prior to concluding that it provides rigorous evidence of efficacy. The following discussion addresses some of these issues. In addition to the content of the BLA submission of Genzyme, this consult review has been greatly aided by reliance upon the clinical review draft document of Dr. A. Pariser, DGP/ODE3 .

In 2002 Genzyme conducted a worldwide retrospective chart review of patients with Pompe disease at clinical centers they were able to identify and gain cooperation with. The details of this survey have been reviewed by Dr. Pariser, and need not be further described in this consult document. Data were collected to assess the certainty of diagnosis, the onset of clinically evident disease and the nature of the impairments leading to the diagnosis, major management modalities, and date of death or last follow-up. Methods for imputing minor missing data (e.g., day of event when month, but not exact date was recorded) were specified, but major data (e.g., data to permit confirmed

diagnosis) were not imputed. Of the 300 patients screened, 168 met the eligibility criteria and were included.

In order for comparisons to historical datasets to be considered rigorous a number of aspects need to be considered. A highly important one is the comparability of the compared groups. For purposes of comparison to the Study 1602 population a subset of the historical dataset was selected based upon having data that indicated that at onset of clinically symptomatic disease the patient would have met the eligibility criteria for study 1602. It appears that Genzyme was able to ensure eligibility on the important criteria, with one possible exception. One criterion where confidence in comparability may be difficult is that for Study 1602 screened patients could be excluded for evidence of respiratory insufficiency based upon oxygen saturation limits or carbon dioxide limits, or by a history of prior ventilator use. For most patients in the historical dataset no blood gas values were available to confirm non-exclusion and only ventilator use history could be relied upon. However, outside of this criterion Genzyme was able to apply the same criteria. There were 62 patients that were retained in the historical comparator subset. Analysis of this subset reiterated the very early mortality of these patients that was the pre-existing general impression in the clinical field.

It is interesting to note that although the qualitative understanding of this disease was confirmed, the concrete data have altered the prior impressions in quantitative terms. It had been proposed by some in this clinical area that mortality in patients with true infantile onset Pompe disease occurs soon after diagnosis and that no infants survive to month 12. However, within this historical subset, designed to select reliably severe cases with symptoms at or before age 6 months, the Kaplan-Meier estimate of survival at age 12 months was approximately 20%, and 1 of the 62 patients was known to survive past age 18 months. Thus while confirming the near universal mortality of this disorder, the concrete data have shifted the estimate of maximal likely survival to somewhat older ages. This underscores the importance of having a rigorous quantitative dataset when quantitative historical comparisons are proposed, even if the disease outcome is considered by the "field in general" to be highly reliably known.

Included among the critical features to support historical comparisons is the robustness of the historical dataset. This may be considered in two aspects; quantity of data and quality of the data. With respect to quantity of the data, Genzyme has identified a large number (for this disease) of infantile onset Pompe patients, forming the largest known collected pool of such patients. From these collected patients they have then culled down to a set of patients who largely share the same characteristics used as eligibility criteria for the prospective study. In doing so, Genzyme is still left with a substantial number of patients relative to annual US incidence, for example, as well as to the sample size of the prospective study. This contributes to supporting belief that the historical comparator dataset is not likely to be a skewed group in some unknown manner, and is reasonably likely to be representative of the true natural history of this disorder for the patients who meet these criteria.

In regard to the quality of the data, reliability of ascertainment of the specified outcome is a critical aspect. Genzyme has used mortality as the outcome for comparison. This has the substantial advantage that it can be reliably ascertained (outside of loss to follow up patients) at all clinical sites with out special training, and is likely to be recorded. Mortality as an outcome measure may be

nearly unique in this characteristic, and is unlike outcomes such as specialized functional ability scales which may be precise, but are often not performed at all centers which see patients with any particular type of disorder, general function level assessments which may be haphazardly recorded and may be assessed in substantially different manners by different physicians, or even laboratory measures, which may be done with different assays or procedures at different clinical sites leading to inconsistency. Thus, Genzyme's dataset gains in rigor from the reliability of ascertainment.

Concern also exists regarding the potential for adjunctive treatments to have been applied differently between the patients in the historical dataset and the prospective study. This could occur either through different choices made in the historical period versus the current study, or due to changes in the specific adjunctive treatments available. However, because the outcome of concern for these patients is mortality, except for terminal ventilatory support it is likely that as much supportive care was provided to these infants as was feasible even in the historical period. The second concern is that advances in adjunctive therapy have altered the course of the disease between the historical period and the period when the prospective study is conducted. However, there have been no advances in any disease specific treatment during this period for Pompe disease, and there are no changes in general supportive care that are known to have had any impact upon these patients survival, outside of ventilatory support. Thus ventilatory support remains the one adjunctive treatment that could have been utilized differently between the historical cohort and the prospective cohort and influenced age at death. In the historical cohort, knowing that that severely debilitated infants with definite diagnoses of Pompe disease had no prospects for extended survival may have limited decision-making to temporarily prolong life through artificial ventilation. However, in the prospective study, knowing that the infants were for the first time receiving a treatment that theoretically had potential to alter substantially the disease course, greater willingness to apply mechanical ventilatory support may have occurred. The importance of this issue was recognized in advance, and addressed in the Genzyme study. Recognizing that choices regarding ventilatory support may have been different, application of mechanical ventilation was regarded as indicating the endpoint event in the study 1602 cohort. This endpoint rule thus makes the analysis more conservative, as if there had been excessive opting for ventilatory support that prolonged avoidance of actual death, the study would have appeared to show decreased survival in the study analysis. Consequently, the study comparison retained rigor.

Overall, Genzyme's submission provides a solid basis for acceptance of the historical comparison in this specific case. In interpreting these data it should not be forgotten that this remains a historical comparison, and uncertainties of patient group comparability always remain and cannot be entirely eliminated. These uncertainties are not reflected in any p-value that is calculated from numerical analysis of the data, thus conclusions based upon study results need to consider strength of the data in a larger perspective. Reaching a firm conclusion in favor of efficacy is generally better supported when the treatment effect size is substantial. In the initially submitted analysis with age 12 months data the treatment effect is of limited robustness because the residual uncertainties in the comparability of the groups could call into question the small number of months for which mortality might be delayed. However, subsequent analysis of longer term data show that the treatment effect persists to older ages. The analysis to age 18 months depicts a treatment effect size that substantially larger in length of mortality avoidance. This long an avoidance of mortality is unlikely to be attributable to modest non-comparability concerns.

In summary, the data submitted by Genzyme appear to support regarding this as one of the uncommon circumstances in which a historical comparison is capable of being regarded as rigorous evidence of efficacy. This comparison indicates a notable difference in the mortality of patients who receive enzyme treatment as compared to the historical dataset patients who did not.

Developmental Milestone Assessments

Study 1602 collected data on a number of growth and development assessments. In addition to height and weight , the study employed the Alberta Infantile Motor Scale (AIMS), Peabody Developmental Motor Scale-2 (PPDMS-2), Pediatric Evaluation of Disability Inventory (PEDI) and a specially Pompe disease modified form (Pompe PEDI), Motor Development Milestones (MDM), and Modified Bayley Scale of Infant Development II (BSID-II). These were administered at baseline and several times during the study.

There are many infant and child development assessment tools available. The nature of these scales are quite varied. The intended goal of these types of assessment tools, from which the specific tools used in this study were selected, range from an intent to assess physical function and independent mobility of the infant to an assessment of cognitive function. Some are standardized scales which have been used in large numbers of healthy children and have been applied as screening tools to distinguish children developing within normal ranges and those who are sufficiently atypical to warrant further detailed evaluation to try to diagnose the cause of the developmental delay. This was not the purpose for use in this study, as all study subjects were known Pompe disease patients, and further diagnosis was unnecessary. Other scales have been used in disabled children to characterize the disability and assist in developing child-specific assistance plans. Again, this was not the purpose in study 1602. Other assessment tools, the Pompe-PEDI and MDM were newly devised during the course of this development program with the intent of providing sensitivity to the types of impairments common in Pompe disease patients. Little validation and no widespread experience is available with these newly devised tools.

However, for Study 1602 these assessments were not intended as "validated" outcome tools to support a claim of efficacy. This is clearly indicated by the fact that these tools were included only as tertiary endpoints in this study. This was a historically controlled study, and there is no significant amount of data available on patients with Pompe disease for these tools with which to form a comparison. Instead these tools were intended for descriptive purposes. Since the study enrolled patients who would be expected to die without an effective treatment, and the treatment goal was to prevent mortality, if the treatment is effective there would occur a group of severe, early onset Pompe disease patients surviving to ages never before observed. Having achieved an increase in life span, the next question is to assess what the quality of life is for these infants. These assessments were intended to assist with this description, and were intended to be used only for descriptive purposes.

There are no validated, widely employed assessment tools for severe Pompe disease patients. Consequently Genzyme selected a range of existing tools, and modified two existing tools, that were intended to as a group be comprehensive in assessing the functional abilities of these infants.

To that end this appears to have been a reasonable selection of tools. In combination they have a broad range of assessments. These tools' sensitivity to various functions, however, may have a different neurological and musculo-skeletal basis in these infants than in the infants for whom there exists extensive prior experience (i.e., either healthy infants or infants disabled from other causes). Therefore, the interpretation of the meaning specific components of these assessments should be done with caution.

Understanding the specific limits in function of these infants does require examination of the individual test components. Worth noting is that some of these tests are designed to produce numeric combined summary scores. Although this may be a simple method of describing the result of the assessment, it is not a readily interpretable guide for the actual abilities of these patients.

Nonetheless, an important question is what are the functional capabilities of these Pompe infants with enzyme treatment as they grow older. The data from these assessments indicate that the functional abilities of the infants do not remain fixed at the level of impairment present at enrollment, but do show some advancement over the course of the study. However, advancement in abilities is an expected process in infants. The observed advancement cannot be interpreted as evidence that the treatment has permitted the infants to begin to develop along a more normal course. The interpretation can be only that for many of the infants, at least some advancement in ability occurs during the period of enzyme treatment and into the period when death would have been expected to have already occurred. Even with enzyme treatment the patients remain severely impaired infants, and do not approach the median of normal infant level of function. This will be an important perspective to provide to physicians and parents to assist them in considerations regarding use of this product.

Because a broad range of scales were selected for this study, there is the beginning of good basis for evaluating the growth and development of patients with severe Pompe disease receiving enzyme treatment. It will be valuable to follow these patients over time as they continue to receive enzyme treatment to continue to the descriptive value of these data.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: DNP/ODEI	FROM*(Division/Office)* DGP/ODEIII

DATE:	IND NO.	NDA NO.	TYPE OF DOCUMENT:	DATE OF DOCUMENTS:
10/18/05		STN 125141/0	original BLA (NME)	7/28/05

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE:
Myozyme	priority	cytokine	12/5/05

NAME OF FIRM: Genzyme Corporation

COMPLETED DEC 1 6 2005

REASON FOR REQUEST

I. GENERAL

- [ ] NEW PROTOCOL
- [ ] PROGRESS REPORT
- [ ] NEW CORRESPONDENCE
- [ ] DRUG ADVERTISING
- [ ] ADVERSE REACTION REPORT
- [ ] MANUFACTURING CHANGE/ADDITION
- [ ] MEETING PLANNED BY
- [ ] PRE--NDA MEETING
- [ ] END OF PHASE II MEETING
- [ ] RESUBMISSION
- [ ] SAFETY
- [ ] PAPER NDA
- [ ] CONTROL SUPPLEMENT
- [ ] RESPONSE TO DEFICIENCY LETTER
- [ ] FINAL PRINTED LABELING
- [ ] LABELING REVISION
- [ ] ORIGINAL NEW CORRESPONDENCE
- [ ] FORMULATIVE REVIEW
- [x] OTHER *(SPECIFY BELOW)*:

neuro developmental milestones

COMMENTS/SPECIAL INSTRUCTIONS:
This is an original BLA (priority and orphan). Please review the developmental milestones and let us know if the sponsor had asked valid questions and if the data indeed meets the primary endpoint.

SIGNATURE OF REQUESTER: Cristi L Stark
Validity unknown
Digitally signed by Cristi L Stark
DN: cn=Cristi L Stark, o=FDA, c=US
Date: 2005.10.18 15:30:41 -04'00'

METHOD OF DELIVERY (Check one)
- [x] MAIL
- [ ] FACSIMILE

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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On Original