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CLINICAL STUDIES

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Statistical Reviewer:	Lisa A. Kammerman, Ph.D. Lisa A Kammerman 4/27/06
Concurring Reviewers:	Stella Grosser, Ph.D. Stella Grosser 4/27/06
Medical Division:	Gastrointestinal Products, HFD-180
Clinical Team:	Anne Pariser, MD
Project Manager:	Cristi Stark

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Compared with the natural history of Pompe disease, the results from a dose-ranging, randomized study (Study AGLU01602) of two doses of Myozyme, indicate improved survival and improved invasive ventilator-free survival among patients with infantile-onset Pompe disease who received Myozyme. The results from eighteen subjects, who were randomized to one of two doses of Myozyme, were compared with a historical control group of subjects with infantile-onset Pompe disease who were not treated with Myozyme.

At the time of the major amendment (dated 12/30/05), two of eighteen subjects had died. The first death occurred at 14 months post-randomization and the second at 25 months. Sixteen subjects, who were alive at the time the study report was prepared, continue to be followed for survival status. Their times of follow-up ranged from 16 to 28 months.

Analyses of data from an historical control group of 62 untreated subjects, whose characteristics were similar to those enrolled in the Myozyme-treatment study, documented the poor survival of patients with infantile-onset Pompe disease. By the age of 18 months, only one patient was still alive.

Seven of the eighteen Myozyme-treated subjects, including the two who died, were placed on invasive ventilatory support. These two subjects started invasive ventilation 11 days and 7.5 months before their deaths at 14 and 25 months following randomization. The other five subjects were placed on invasive ventilatory support at 3, 7, 10, 13 and 17 months post-randomization.

The randomized study of the 18 patients with infantile-onset Pompe disease was open-label and subject to selection bias. The ages of the patients at the time of first infusion ranged from 1.2 months to 7.3 months. One additional subject, who was eligible for randomization, was excluded from the analyses. Intubation and ventilator support were started for this subject before randomization could take place.

The historical control group included all subjects whose clinical status was similar to the entry criteria for Study 1602.

Because the 18 subjects in Study 1602 did not enter the study at the time of birth, they had to have survived long enough to enter the study and to begin treatment. On the other hand, the historical control group included all subjects, including those who died within the first few months of life.

The implication, therefore, of surviving long enough to enter Study 1602 and, once entered into the study, surviving long enough to start treatment was a study sample that was "healthier" than the population included in the historical control group.

Sensitivity analyses, which attempted to account for selection of healthier subjects in Study 1602, support the finding of poor survival for patients with infantile-onset Pompe disease who were not treated with Myozyme.

The study design and analyses did not permit an appropriate, statistical comparison between Study 1602 and the historical controls: intervention for the Myozyme-treated subjects started between 1.2 and 7.3 months of age; there was no similar intervention for the historical control subgroup. The influence of Myozyme on survival started at the time of randomization; survival for the historical controls was measured from birth. The Kaplan-Meier analyses contained in the submission overstate the treatment effect of Myozyme.

The use of matched controls, if that was possible, would have permitted a more appropriate statistical analysis. For example, for each subject enrolled in Study 1602, a set of matched subjects possibly could have been selected from the historical control subgroup. These matched sets could be analyzed for a treatment effect.

Because of the lack of comparability between the Myozyme-treated subjects and the historical control subjects, I recommend deleting [redacted] from the proposed label and simply report the survival rates for the Myozyme-treated subjects through the last known date of contact. To provide evidence of the natural history of infantile-onset Pompe's disease and to give some context to the findings in the Myozyme-treated subjects, the label could include the survival rate at the age of 18 months among the historical controls.

1.2 Brief Overview of Clinical Studies

Study AGLU01602 is a randomized, open-label, multicenter, multinational, dose-ranging study of the safety, efficacy, PK, and PD of Myozyme treatment in patients with infantile-onset Pompe disease.

This submission constitutes (1) a planned interim report on 18 treated subjects, based on data collected until 26 weeks after the last patient began treatment, (2) an abridged 52 week clinical study report containing one-year follow-up data and (3) a major amendment submitted 12/30/05.

To be included in this study, patients were required to have endogenous GAA levels <1% of the mean of the normal range in skin fibroblasts or in peripheral blood mononuclear cells (PBMC). Subjects were randomized in a 1:1 ratio to receive an IV infusion of Myozyme at either 20 mg/kg or 40 mg/kg of body weight qow. The study will continue for 52 weeks after the last patient is randomized to treatment.

A historical control subgroup of 62 untreated patients was used as a comparator group. These subjects were selected from a retrospectively identified cohort of 168 patients with infantile-onset Pompe disease (AGLU-004-00). The selection of the subgroup was based on the entry criteria used for Study 1602.

A primary study objective was to estimate, using Kaplan-Meier methodology, the proportion of patients treated with Myozyme who were alive and free of invasive ventilator support at 12 months of age and 18 months of age. These estimates were compared to the outcome for the historical control subgroup.

Additionally, instruments that measure psychomotor and cognitive development were used to assess the Myozyme-treated subjects. These analyses constituted secondary endpoints.

1.3 Statistical Issues and Findings

The primary statistical issues include the primary endpoint used in the study, selection bias, inappropriate implementation of Kaplan-Meier methodologies, comparisons with historical controls and the validity of instruments used to measure mental and motor development.

The primary endpoint specified the estimate of proportions of ventilator-free survival and survival at prespecified ages, regardless of a subject's age at study entry or the length of time on study medication. A more appropriate endpoint is ventilator-free survival and survival at prespecified times following randomization. Randomization represents the start of study intervention and is a starting time that is common to all Myozyme-treated subjects.

Moreover, the proportions at prespecified ages were estimated by an inappropriate application of the Kaplan-Meier methodology. Instead of starting at the date of birth, the analyses need to start at the time of randomization.

Subjects who started invasive ventilator therapy drove the endpoint "ventilator-free survival", a composite endpoint. The two deaths occurred while the subjects were using invasive ventilator therapy; no deaths occurred prior to the start of ventilator therapy. Therefore, results for the outcome "ventilator-free survival" are actually the results for the outcome "ventilator-free".

The historical control subgroup contains data from subjects with birthdates covering over 20 years. The applicant's analyses of a larger cohort point to the potential for improved outcome over time due to more aggressive therapies and the better availability of the therapies in more diverse geographic regions. Because of small sample sizes, however, these analyses of the subgroup of 62 patients were not definitive.

Even in the presence of improved outcomes over time, the results from the historical control subgroup support the contention that the long-term survival of infantile-onset Pompe disease is poor. Only one of 62 subjects was still alive at the age of 18 months.

The quantification of a treatment difference between the Myozyme-treated subjects and the historical control subjects is almost impossible. Not only are there the issues of improved outcomes over time, however slight they may be, among the untreated subjects, but there remains the issue of selection bias among the Myozyme-treated subjects and the impact on the Kaplan-Meier estimates. For these reasons, even if the treatment effect could be estimated, it would likely be an overestimate.

The applicant's discussion of the development and validation of the instruments used to measure cognitive and psychomotor development was lacking. The use of the instruments in various cultures and the issue of translation were not described satisfactorily.

One major concern is the scoring of the subjects by therapists who were aware of the diagnosis and treatment status of each subject. Combined with the absence of a concurrent control group, it is possible the scores are higher than what might actually be the case.

The data suggest improved outcomes among subjects treated with Myozyme when compared with the natural history of subjects who go untreated. The historical control subgroup provided a description of the natural history.

2. INTRODUCTION

2.1 Overview

The primary basis for the applicant's claim of efficacy is the comparison of results from a randomized, open-label study (AGLU-01602) of 18 subjects randomized to one of two doses with the outcomes from a subgroup of 62 subjects selected from a retrospective cohort of 168 subjects diagnosed with infantile-onset Pompe disease (AGLU-004-00). Based on comparisons between the open-label study and the historical controls, the applicant asserts Myozyme prolongs survival among subjects presenting with infantile-onset Pompe disease.

2.1.1 Study AGLU-004-00: "Epidemiologic Study of the Natural History of Infantile Pompe Disease"

Study AGLU-004-00 was designed to characterize the natural history of disease progression in patients diagnosed with infantile Pompe disease. Through a retrospective review of 300 medical records, the study identified and collected data on a cohort of 168 subjects diagnosed with infantile-onset Pompe disease.

Subsequently, a subgroup of 62 patients from within the AGLU-004-00 cohort was selected based on screening criteria adapted from the inclusion and exclusion criteria of Study AGLU-01602 and was used as the control population for Study AGLU-01602.

Table 2.1 shows the countries represented in this study.

Table 2.1 Geographic Location of Patient Medical Records in Study AGLU-004-00 (n=168)

Country	No. of Subjects	Percent of Total
Total Europe	**36**	**21.4**
Austria	1	0.6
France	21	12.5
Italy	4	2.4
The Netherlands	4	2.4
UK	6	3.6
Total Middle East	**32**	**19.0**
Israel	32	19.0
Total Asia	**46**	**27.4**
Taiwan	46	27.4
Total North America	**54**	**32.1**
USA	51	30.4
Canada	3	1.8

Note: N = 168

Source: Table 10-2, AGLU-004-00 Study Report

Results of the exploratory analyses were reported for two groups of subjects and then compared. The groups were defined by age at death: died ≤12 months of age, died > 12 months of age.

Additionally, the applicant used Cox regression models to estimate hazard ratios for the risk of death, ventilator use or both. Analyses also included stepwise models to identify potential risk factors for each of these three outcomes.

The applicant found:

- *Subjects born since 1995 were less likely to die at any given time point than those who were born before 1995.* Univariate analysis for the risk of death indicates that patients with a year of birth > 1995 have a lower risk of death (RR 0.71, p=0.042) compared to those born earlier than 1995. According to the applicant, "this finding could reflect an earlier and more comprehensive start of supportive therapeutic modalities in more recent years, as well as wider availability of such therapies in different geographical areas"; (p. 107, AGLU-004-00 Study Report). Despite the finding of a lower risk of death, the report notes the upper limit of the 95% CI for median age at death in patients born after 1995 is less than a year.
- *The later the subjects presented with their first symptoms, the less likely they would die at any given time point.* Generally, the younger the age at which the symptoms first occurred, the higher the risk of death at any given time point.

- *The presence of pneumonia decreased the risk of death at any given time point by 40%.* Analyses showed the presence of pneumonia was highly associated with respiratory therapy.
- *The risk for death among subjects with respiratory therapy was less than the risk for those who did not have documented respiratory therapy* (Hazard ratio 0.62, p=.009).
- *Subjects with the following nutrition or therapy modalities had a lower risk of death at any given time point compared to those who did not have the corresponding nutrition or therapy.*
    - *High protein diet*
    - *CPAP/BiPAP*
    - *Physical therapy*
    - *Respiratory therapy*
    - *Early ventilator use*

Appendix 5.1 contains the results of the univariate analyses.

2.1.2 The Historical Control Subgroup Selected (n=62) from Study AGLU-004-00 and used as a Comparator for AGLU1602

A historical control subgroup of 62 untreated patients was selected from the AGLU-004-00 cohort and was used as a comparator population for the Myozyme-treated subjects in Study AGLU01602. Screening criteria adapted from Study AGLU01602 determined the selection of the historical control subgroup. These screening criteria included age at first symptoms, age at diagnosis, presence of cardiomyopathy by 26 weeks of age, GAA activity, and congenital abnormalities.

Patients with ventilator use ≤6 months of age were excluded from the historical control subgroup.

The distribution of countries in the historical control subgroup subjects resembled the distribution seen for the entire cohort (Table 2.2).

Table 2.2 Geographic Location of Medical Records for the Historical Control Subgroup (n=62)

Country	No. of Patients	Percent of Total
Total Europe	**20**	**32.2**
Austria	1	1.6
France	14	22.6
Italy	2	3.2
The Netherlands	2	3.2
UK	1	1.6
Total Middle East	**14**	**22.6**
Israel	14	22.6
Total Asia	**15**	**24.2**
Taiwan	15	24.2
Total North America	**13**	**21.0**
USA	12	19.4
Canada	1	1.6

Note: N = 62
Source: Table 4-2, "Analysis of a Historical Control Subgroup for AGLU01602

The year of birth covered 20 years, ranging from 1982 to 2002. Table 2.3 shows the demographics of the subjects.

Table 2.3 Summary of Demographics for the Historical Control Subgroup (n=62)

Variable	Summary Statistic	Overall
Total Number of Patients	N	62
Gender		
Male	n (%)	28 (45.2)
Female	n (%)	34 (54.8)
Ethnicity		
Caucasian	n (%)	31 (50.0)
Black	n (%)	4 (6.5)
Hispanic	n (%)	1 (1.6)
Asian	n (%)	18 (29.0)
Other	n (%)	1 (1.6)
Unknown	n (%)	7 (11.3)
Gestational Age at Birth (weeks)	n	50
	Mean	38.5
	Median	39.0
	Std. Dev.	2.23
	Min., Max.	32.0,42.0
Year of Birth		
2000 to present	n (%)	12 (19.4)
1995 to 1999	n (%)	20 (32.3)
1990 to 1994	n (%)	17 (27.4)
1985 to 1989	n (%)	9 (14.5)
Before 1985	n (%)	4 (6.5)
Source: Table 4-4, "Analysis of a Historical Control Subgroup for AGLU01602		

Analyses done for the entire cohort were repeated for the historical control subgroup; see *"Analysis of a Historical Control Subgroup for AGLU01602" (original submission).*

In this group of 62 subjects, 55 (89%) died, 6 (10%) had unknown status and one was still alive at the time of data collection (Table 2.4). Forty-five died at ≤12 months, 9 died at > 12 months and one subject had an unknown age at death.

Table 2.4 Summary of Patient Status-Overall

Category	Summary Statistic	Overall
Total Number of Patients	N	62
Number of Patients Died		
Yes	n (%)	55 (88.7)
No	n (%)	1 (1.6)
Unknown	n (%)	6 (9.7)
Not Available	n (%)	0
Age at Death (months)[1]		
Overall	n	61
	Mean	8.6
	Median (95% CI)	7.5 (6.7, 8.6)
	Std. Error	0.81
	Min., Max.	0.3, 43.9
Note: [1]Survival times (months) of patients not known to have died were right-censored. Kaplan-Meier methodology was used to compute non-parametric estimates of the survival distribution function. Reference: Table 14.1-6		

Source: Table 4-9, Analysis of a Historical Control Subgroup for AGLU01602

Although the analyses of the entire cohort of 168 subjects showed the risk of death decreased over time as represented by the year of birth, the sample sizes for the subgroup were too small to detect a similar effect over time (Table 2.5).

Similar to the results from the analyses of the entire cohort, oxygen therapy, and a high protein diet were associated with a decreased risk of death, while the use of carnitine was associated with an increased risk of death, early age of cardiomegaly or cardiomyopathy diagnosis and early age of failure to thrive[1]. Other factors associated with a decreased risk of death were later age of symptom onset, later age of diagnosis, and early age of first occurrence of pneumonia[2].

Physical therapy (yes/no), CPAP/BiPAP (yes/otherwise), respiratory therapy (yes/otherwise) and early age of first ventilator use were associated with a decreased risk for death in the full cohort but were not statistically significant in the historical control subgroup.

[1] Date of failure to thrive was recorded for only 33 patients.
[2] Date of pneumonia was recorded for only 25 patients.

Table 2.5 Summary of Survival Status for the Historical Control Subgroup, by Period of Death; for patients with known date of death (n=54)

Category	Summary Statistic	Overall
Number of Subjects Who Died	N	55
Number of Subjects with Known Date of Death	N	54
Mean age of Death (months) by Period[1]		
2000 to present	n	12
	Mean	8.5
	Median (95% CI)	8.2 (6.7, 9.4)
	Std. Error	0.98
	Min., Max.	4.1, 14.7
1995 to 1999	n	19
	Mean	10.1
	Median (95% CI)	7.8 (6.0, 9.4)
	Std. Error	2.03
	Min., Max.	3.5, 43.9
1990 to 1994	n	16
	Mean	7.6
	Median (95% CI)	6.5 (5.3, 9.9)
	Std. Error	0.81
	Min., Max.	4.1, 14.8
1985 to 1989	n	5
	Mean	5.2
	Median (95% CI)	5.8 (2.1, 7.8)
	Std. Error	1.07
	Min., Max.	2.1, 7.8
Before 1985	n	2
	Mean	8.4
	Median (95% CI)	8.4 (6.3, 10.5)
	Std. Error	2.09
	Min., Max.	6.3, 10.5

Note: [1] Of the 55 subjects who died, one had an unknown date of death.
Source: Table 4-10, "Analysis of a Historical Control Subgroup for AGLU01602

2.1.3 Study AGLU-01602: "A Randomized, Open-Label, Multicenter, Multinational, Dose-Ranging Study of the Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics or Recombinant Human Acid alpha-Glucosidase (rhGAA) Treatment in Patients ≤6 Months Old with Infantile-Onset Pompe Disease (Glycogen Storage Disease Type II)

Study AGLU01602 is a randomized, open-label, multicenter, multinational, dose-ranging study of the safety, efficacy, PK, and PD of Myozyme treatment in patients with infantile-onset Pompe disease.

To be included in this study, patients were required to have endogenous GAA levels <1% of the mean of the normal range in skin fibroblasts or in peripheral blood mononuclear cells (PBMC) and needed to be no older than 26 weeks ("adjusted for gestational age, if necessary")[3]. Subjects were randomized in a 1:1 ratio to receive an IV infusion of Myozyme at either 20 mg/kg or 40 mg/kg of body weight qow. The study continued for 52 weeks after the last patient was randomized to treatment.

The original protocol called for adaptive randomization to balance the two treatment groups with respect to ACE allele status. The plan called for simple randomization of the first four subjects. The algorithm for the adaptive assignment to treatment was to start with the fifth subject.

When the fifth subject (Subject 305) was enrolled, the ACE status was not available for the first four subjects. Because of the desire to start treatment for Subject 305 as soon as possible, simple randomization assigned this subject to one of the two treatment groups; the adaptive randomization algorithm was not used. Subject 305 was randomized on 9/17/03 and therapy was started on 9/19/2003. The protocol was changed to "simple randomization" (Amendment 4) on 10/8/03.

One additional subject (Subject 304) was enrolled but not treated because he experienced an AE that required ventilatory support during the baseline period prior to initiation of Myozyme treatment and, therefore, did not satisfy the entry criteria for the study.

Starting with Subject 306, subjects were randomized in blocks of two to either 20 mcg or 40 mcg; see (BLA 125141/0000); Clinical Study Report, Appendix 16.1.7 (Randomisation Scheme and Codes)[4].

An indwelling IV catheter was recommended for delivery of Myozyme. Placement, however, was at the discretion of the investigator. The length of infusion ranged from

[3] I could not find the definition of the phrase, "adjusted for gestational age, if necessary".

[4] The study report does not mention that Subject 306 was apparently randomized (9/24/03) prior to Amendment 4 (10/8/03) which eliminated adaptive randomization. This observation is based on the listing of randomization dates and assignments provided by the applicant in an email dated October 25, 2005 and submitted formally in Amendment 6 (BLA 125141/0006).

approximately 3.7 hours for 20 mg/kg to approximately 6.5 hours for 40 mg/kg. Infusions were scheduled at 2-week intervals.

The distribution of subjects by country is shown in Table 2.6:

Table 2.6 Geographic Location of Subjects in the Randomized Study (Study 1602, n=18)

Country	No. of Patients	Percent of Total
Total Europe	**5**	**28%**
France	3	17%
UK	2	11%
Total Middle East	**3**	**17%**
Israel	3	17%
Total Asia	**3**	**17%**
Taiwan	3	17%
Total North America	**7**	**39%**
USA	7	39%
Source: Constructed from Table 11-2, 26-week Interim Study Report AGLU01602		

2.2 Changes in Conduct of the Study

The study report states no patients were enrolled under the original protocol, which was issued 9/25/02. Patients, instead, were enrolled under five amendments:

Table 2.7 Protocol Amendments and changes potentially affecting statistical analyses and interpretation

Amendment #	Date	# of patients enrolled under amendment	Changes affecting statistical analysis
1	3/12/03	2	▪ Dose could be augmented after 6 months of treatment for lack of efficacy ▪ Extended primary efficacy analysis to include the survival probability and corresponding 95% CI at 12 and 18 months
2	8/20/03	2	▪ Increased study length to 52 weeks of treatment ▪ Modified primary efficacy endpoint to survival from birth (all causes of mortality) at 18 months of age for patients treated with Myozyme for 52 weeks as compared to a historical cohort ▪ Deleted lack of efficacy as a reason for dose adjustment ▪ Specified patients unable to tolerate a dose of 10 mg/kg per week would be discontinued from the study ▪ Deleted dose augmentation
3	9/23/03	1	▪ Permitted starting treatment based on lymphocyte assay prior to determination of endogenous GAA activity in cultured skin fibroblasts
4	10/8/03	10	▪ Allowed patient with GAA deficiency (as measured in PBMC) to be enrolled into the study ▪ Eliminated adaptive randomization based on ACE Marker Allele status. All patients in study were enrolled using simple randomization
5	5/18/04	3	▪ Changes to primary endpoint Measured by the Kaplan-Meier estimate of the proportion of patients treated with Myozyme who were alive and free of ventilator support at 18 months as compared to a historical cohort. Estimated at 18 months of age for patients treated until 52 weeks after the last patient was randomized to treatment. For the 26-week interim analysis: 12 months and 26 weeks were used. ▪ Changes to secondary endpoint Evaluate effect of treatment on time to ventilator-dependence or death from birth at 12 months of age. Estimated at 12 months of age for patients treated until 26 weeks after the last patient was randomized to treatment. This is identical to the primary efficacy variable used in the interim analysis. ▪ Specified quarterly reviews of safety data by the DSMB and revised make-up thereof.
Note: Appendix 16.1.1 of the study report contains copies of the original protocol and all amendments.			

2.3 Applicant's Analyses

For the 52-week analysis, the proportion of Myozyme-treated patients who were alive and free of invasive ventilation at 12 months of age were compared to the proportion of survivors at 12 months of age in the historical control subgroup. Patients who had not reached 12 months of age were censored from the analysis. These analyses were repeated for these endpoints at 18 months of age. Table 2.8 and Figure 1, taken from the clinical study report, summarize the results.

Note that the confidence intervals for the Myozyme-treated subjects are not accurate. Because of the small number of subjects enrolled in the study, an exact confidence interval is more appropriate. Section 3.7 of my review discusses this in further detail.

Table 2.8 Comparison of Invasive Ventilator-Free Survival in Myozyme-Treated Patients to Survival in Historical Control Reference Group at 12 and 18 Months of Age

		Proportion of Patients Alive and Free of Invasive Ventilator Support in AGLU01602					Proportion of Patients Alive in Historical Control Subgroup		
Age (months)	Dose Group	N	Patients Alive and Invasive Ventilator -Free	Patients Censored[1]	Patients Failed[2]	Proportion Estimate and 95% CI[3]	N[4]	Number of Patients Alive	Proportion Estimate and 95% CI[5]
12	Overall	18	16	0	2	89% (74, 100)	61	9	16.8% (6.8, 26.8)
12	20 mg/kg	9	8	0	1	89% (68, 100)			
12	40 mg/kg	9	8	0	1	89% (68, 100)			
18	Overall	18	13	2	3	83% (66, 100)	61	1	1.9% (0, 5.5)
18	20 mg/kg	9	8	0	1	89% (68, 100)			
18	40 mg/kg	9	5	2	2	78% (50, 100)			

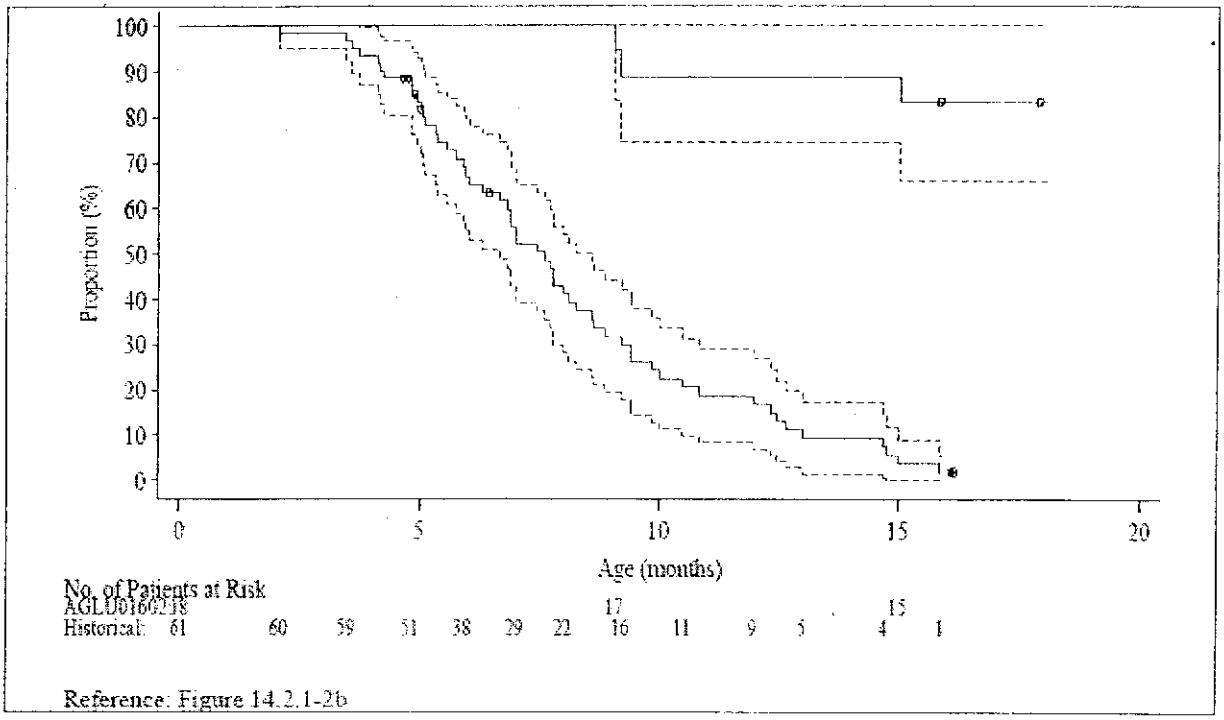
Reference: Table 14.2.1-2, AGLU-004-00 CSR.
[1] Patients censored refers to patients who did not yet achieve milestone age of 18 months, but were not invasively ventilated at the end of the study. Patient 315 was censored at the age of 15.9 months and Patient 318 was censored at the age of 17.9 months.
[2] Failed refers to patients who were invasively ventilated before the milestone age.
[3] Proportions are from Kaplan-Meier analysis of time to invasive ventilation or death.
[4] One patient was excluded from this analysis as date of death was unknown.
[5] Proportions are from Kaplan-Meier analysis of time to death.

Source: Table 11-1, AGLU01602 Abridged Final 52-Week Clinical Study Report (BLA 125141/0002)

In the analyses of the data from the historical control subgroup, six patients with unknown dates of death were censored at the date of last contact that was entered into the medical records[5].

[5] In an e-mail dated 3/13/2006, the applicant confirmed that the Kaplan-Meier analyses censored six subjects at the age at last known visit. These subjects had an unknown date of death.

Figure 1 Kaplan-Meier Estimate of Time to Invasive Ventilation or Death from Date of Birth to 18 Months of Age (Comparison to Historical Control Subgroup)



The solid line at the top shows the Kaplan-Meier estimate of the proportion of patients in Study AGLO01602 alive and free of invasive ventilation as a function of age; the dashed line shows the 95% confidence interval for this estimate. The solid line at the bottom shows the Kaplan-Meier estimate of the proportion of patients in the historical control subgroup alive as a function of age; the dashed line shows the 95% confidence interval for this estimate. Circles indicate censored observations (Patients 315 and 318). Three patients failed this endpoint because they required invasive ventilatory support (Patient 301 at the age of 15.0 months [Week 43], Patient 319 at the age of 9.1 months [Week 32], and Patient 317 at the age of 9.2 months [Week 13]).

*Asterisk indicates that 1 patient from the historical control group remained alive at 18 months of age; this patient died at age 44 months.

Source: Figure 11-1, AGLU01602 Abridged Final 52-Week Clinical Study Report (BLA 125141/0002)

2.4 Selection Bias

To enter Study 1602, subjects had to survive long enough to enroll (median age of 5.7 months; range 1.2 to 7.3 months)[6]. The Kaplan-Meier analyses of the data from the historical controls start at the date of birth, regardless of survival status. Because the subjects in the historical control subgroup were untreated, selection bias with respect to survival was not an issue for the subgroup.

The comparison between the two groups would likely favor the treated patients, if a selection bias existed. To explore this possibility, the applicant compared survival rates with historical

[6] These are the chronological ages at first infusion for the 18 subjects who were randomized. *Source: Table 10-3 Summary of Myozyme Administration and Cutoff Dates for Interim Analysis*

control subgroups in which patients that died prior to 3, 4, 5, or 6 months of age were removed (Source: Table 14.2.1-2, AGLU01602 Abridged Final 52-Week Clinical Study Report (BLA 125141/0002)):

Table 2.9 Sensitivity Analysis: Excluding Subjects from Historical Control Subgroup who died prior to 3, 4, 5, or 6 months of age. Comparison of Invasive Ventilator-free Survival.

AGLU01602 Invasive Ventilator-Free Survival			AGLU01602 Historical Control Subgroup Survival		
Assessment Age	N	Proportion Estimate and 95% CI[1]	Age Milestone Subset[2]	N[3]	Proportion Estimate and 95% CI[4]
12 Months	18	89 (74, 100)	All Patients	61	16.8 (6.8, 26.8)
			3 months	60	17.1 (7.0, 27.2)
			4 months	57	18 (7.4, 28.6)
			5 months	45	20.6 (8.6, 32.6)
			6 months	37	25.0 (10.9, 39.2)
18 Months	18	83 (66, 100.0)	All Patients	61	1.9 (0.0, 5.5)
			3 months	60	1.9 (0.0, 5.6)
			4 months	57	2.0 (0.0, 5.9)
			5 months	45	2.3 (0.0, 6.7)
			6 months	37	2.8 (0.0, 8.2)

[1] Proportions are from Kaplan-Meier analysis of time to invasive ventilation or death

[2] AGLU01602 historical control subgroup age milestone subsets were formed by including only those subjects who survived to the denoted age in each row.

[3] While the number of subjects in the historical control subgroup is 62, 1 subject was excluded from the analysis as date of death was unknown.

[4] Proportions are from Kaplan-Meier analysis of time to death.

Source: Tables 11-2 and 14.2.1-2; AGLU01602 Abridged Final 52-Week Clinical Study Report (BLA 125141/0002)

(The confidence intervals for the Myozyme-treated subjects are too wide, due to a calculation error; see 3.7 Confidence Intervals for a discussion.)

Other sensitivity analyses excluded subjects based on the age of first infusion and adjustments for presence of congenital anomalies.

From the results of these sensitivity analyses, the applicant concluded the treatment effect was seen regardless of factors that could account for selection bias.

2.5 Data Sources

My review is based on the following documents submitted by the applicant to the BLA.

Original submission (BLA 125141/0000):

- 26-Week Interim Report: A Randomized, Open-Label, Multicenter, Multinational, Dose-Ranging Study of the Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of Recombinant Human Acid alpha-Glucosidase (rhGAA) Treatment in Patients _ 6 Months Old with Infantile-Onset Pompe Disease (Glycogen Storage Disease Type II) interim report to 26 weeks (\\cbsap58\M\eCTD_Submissions\DSTN125141\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pompe\5351-stud-rep-contr)

  Annotated CRF: m5\datasets\aglu01602\listings\blankcrf.pdf

- Epidemiologic Study of the Natural History of Infantile Pompe Disease (\\cbsap58\M\eCTD_Submissions\DSTN125141\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pompe\5354-other-stud-rep\aglu00400-final)

- Analysis of Patients with Infantile-Onset Pompe Disease Selected from Genzyme's Natural History Database Based on Screening Criteria from Study AGLU01602 (\\cbsap58\M\eCTD_Submissions\DSTN125141\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pompe\5354-other-stud-rep\aglu00400-hist-cntrl)

Amendment 2 (BLA 125141/0002):

- The AGLU01602 Abridged Final 52-Week Clinical Study Report (dated 10/13/2005)

Amendment 6 (BLA 125141/0006):

- Randomization dates and assignments (originally provided by email on October 25, 2005)

Major Amendment, Submitted 12/30/05; Amendment 8 (BLA 125141/0008)

- Module 1: Administrative and Prescribing Information; Efficacy Information Amendment

E-mail dated 3/13/2006

- Information on subjects in the historical controls who were missing date of death

3. STATISTICAL EVALUATION

My review addresses the efficacy results from Study 1602. The Medical Officer's review considers the safety issues of Myozyme that emerged not only in Study 1602 but in other clinical studies as well.

The original submission's description of the design of Study 1602 and its conduct were incomplete and, in certain instances, internally inconsistent. We sent information requests for the items needed to complete an informed review of the efficacy of Myozyme in the infantile-

onset population; see *Information Request dated 11/18/05* and *Appendix 5.3: Information Request dated 12/5/05.*

The applicant's responses constituted a major amendment, (BLA 125141/0008), which was submitted on 12/30/05.

Major review issues discussed in subsequent sections include:

- Inappropriate application of the Kaplan-Meier methodology to estimate survival
- Selection bias
- Study endpoint

A major statistical issue is the inappropriate application of the Kaplan-Meier methodology to the survival data. The appropriate analysis is time to death or invasive ventilator support, starting at the date of randomization. Instead, the applicant's analyses use date of birth for the baseline and estimate proportions alive at specific ages (12 months and 18 months). My review discusses other approaches to determining the efficacy of Myozyme.

The submissions' descriptions of the study protocol and study conduct suggest the strong possibility of selection bias, leading to the treatment of "healthier" subjects with infantile-onset Pompe's disease.

The following sections describe these issues and others.

3.1 Historical Control Subgroup

3.1.1 Time trends in patient outcomes

The applicant's analyses of the entire cohort indicated subjects born since 1995 were less likely to die at any given time point than those who were born before 1995. The report concludes, "This finding could reflect an earlier and more comprehensive start of supportive therapeutic modalities in more recent years, as well as wider availability of such therapies in different geographical areas"; see p. 107, AGLU-004-00 Study Report.

The sample sizes for the subgroup of historical controls were too small to detect a time trend of increased survival.

If a time trend does exist for the historical control subjects, the implication is an overstatement of the efficacy of Myozyme when compared with the historical control subjects.

3.1.2 Unknown survival status for six subjects in the historical control subgroup

Survival status was unknown for six of the 62 subjects, and one subject was still alive at the time of data collection.

The six subjects with unknown survival status were censored at the age at last known visit[7].

The subject (23-05-806) who was known to be alive on the date of diagnosis was excluded from the Kaplan-Meier analyses because the subject was missing a date of death. Although there is no follow-up information for this subject, it is not clear why this subject was excluded from the applicant's analyses, since the Kaplan-Meier analyses started at the date of birth.

However, including this subject would not have changed the interpretation of the study results.

3.2 Potential Sources of Selection Bias

The submission does not state when randomization was to take place. Generally, study protocols specify a fixed timeline for screenings leading to randomization and specify when randomization and treatment take place. In this study, however, the timing of randomization and the timing of the first infusion, relative to the date of randomization, are not stated.

Any delay in the randomization and the start of therapy, combined with the open-label study design, could have resulted in the selection of "healthier" subjects.

3.2.1 Timing of first infusion is unknown

Neither the study protocol nor the study report state when therapy was to start. Inspection of the Screening Log shows the first infusion could have started as early as the day of randomization (Subject 319) or as long as 17 days after randomization (Subject 315); see *Table 3.1 Dates for Skin Biopsy, Informed Consent, Qualified, Randomization and First Infusion* and *Screening Log*.

Compounding the unspecified time of first infusion is the unknown timing of randomization. Because the date of randomization was not included in the original submission, we requested this information. On 10/25/2005, the applicant emailed this information as a text document and formally submitted the document with an amendment to the BLA, Amendment 6 (BLA 125141/0006).

I compared the dates of randomization with the information in the screening log; see *Table 3.1 Dates for Skin Biopsy, Informed Consent, Qualified, Randomization and First Infusion* and *Screening Log*. Several subjects were randomized on the day they completed all the screening procedures and were qualified for the study. The maximum time between qualification for the study and randomization was eight days (Subject 302).

The screening log indicates one subject (Subject 303) was randomized prior to informed consent and prior to completing the screening procedures. Although the informed

[7] In an e-mail dated 3/13/2006, the applicant confirmed that the Kaplan-Meier analyses censored six subjects at the age at last known visit. These subjects had an unknown date of death.

consent procedures appear to have been violated, this patient was hospitalized in Israel while the patient's parents were in the — and were unable to travel to — due to border disputes. The parents gave oral approval and subsequently gave written approval when they arrived in Israel.

One subject (#304) was enrolled but never randomized because the subject needed invasive ventilatory support prior to the time of randomization. Therefore, the subject's outcome was not captured in the applicant's analyses, which was limited to eighteen subjects.

Table 3.1 Dates for Skin Biopsy, Informed Consent, Qualified, Randomization and First Infusion

Patient ID	Date of Skin Biopsy	Date of Informed Consent	Screening Procedures Completed and Qualified	Date of Randomization*	Date of First Infusion*
301		5/19/03	5/19/03	5/19/03	
302		8/10/03	8/11/03	8/11/03	
303		9/2/03	9/3/03	8/29/03	
304		9/8/03	9/10/03	N/A	
305		9/10/03	9/12/03	9/17/03	
306		9/17/03	9/17/03	9/24/03	
307		10/26/03	10/27/03	10/30/03	
308		N/A	11/10/03	11/14/03	
309		11/20/03	11/24/03	11/25/03	
310		12/11/03	12/12/03	12/12/03	
311		12/09/03	12/11/03	12/15/03	
312		1/23/04	1/23/04	1/28/04	
313		12/17/03	1/29/04	1/30/04	
314		1/27/04	1/27/04	2/2/04	
315		3/1/04	3/6/04	3/8/04	
316		4/05/04	4/7/04	4/9/04	
317		5/17/04	5/18/04	5/19/04	
318		5/10/04	5/24/04	5/26/04	
319		5/31/04	6/2/04	6/3/04	

Source: Dates for Skin Biopsy, Informed Consent and Screening – Amendment 16.2.1, Screening Log for Protocol AGLU01602

* The dates for Randomization and First Infusion were submitted as part of Amendment 6 (BLA 125141/0006).

The study report defines baseline as "Baseline assessment is defined as the last measurement prior to the first infusion (Day 0) in these analyses"; Section 9.6.8.2 of Study Report. However, the date of baseline is not summarized for the subjects.

3.2.2 Screened but not randomized or treated

Of the 27 subjects screened, 19 were assigned a patient identification number, one of whom (#304) was not randomized; see Screening Log. Among the eight not entered into the study, two died and one was placed on a ventilator.

Because the study was open-label, randomization potentially could have been delayed for the more fragile subjects, resulting in the exclusion of these subjects. In that case, the rates of survival for the Myozyme-treated subjects would be overestimates.

3.3 Impact of Selection Bias on the Kaplan-Meier Estimates

For all the reasons discussed here, "selection bias" affected the applicant's Kaplan-Meier analyses of survival and the interpretation of the results.

3.3.1 Inappropriate baseline date

The analyses submitted with the original submission used date of birth as the baseline. Because intervention did not start until randomization and subjects needed to survival long enough to enroll, the use of date of birth as the baseline is inappropriate

Due to selection bias – needing to survive long enough to enroll -- the use of date of birth as baseline creates a long, initial, horizontal line on the Kaplan-Meier curve, which inappropriately conveys that all patients treated with Myozyme survived at least 7.2 months – see Figure 1, page 18 – the maximum age at which treatment started for the eighteen subjects. In fact, much of the 7.2 months represents the time a subject did not receive any treatment.

The applicant cites Kaplan and Meier (1957) to support their approach to obtaining product-limit estimates of proportions. However, the implementation of the Kaplan-Meir analyses is not consistent with the article.

The assumption for a product-limit estimate is a random sample of size N. The N observed lifetimes are listed and labeled in order of increasing magnitude so that:

$$0 \leq t_1' \leq t_2' \leq \cdots t_N'$$

In the context of the application, the applicant defines lifetime as the time from birth to death (or other outcome of interest). The observed lifetimes as used in the application, however, are the sum of a fixed amount (age at randomization) and a random variable (time from randomization to death).

For example:

- If *Subject 1* is randomized at 1 month of age and dies at 2 months of age, the observed lifetime equals 2 months: age at randomization plus 1 month on study.
- If *Subject 2* is randomized at 12 months of age and dies at 13 months of age, the observed lifetime equals 13 months: age at randomization plus 1 month on study.

The observed lifetimes, as calculated by the sponsor, have a lower bound that differs for each subject, namely the age at time of randomization. Because a subject cannot die before they were randomized, they earliest they can die is at the age of randomization. This is not consistent with the requirement that each lifetime can be as small as zero for each subject.

For example:

- For the sample of N=2 (*Subject 1* and *Subject 2*), the earliest possible time of death is 1 month – Subject 1's age at randomization.
- For Subject 2, however, the earliest possible time of death is 12 months – Subject 2's age at randomization.

If, however, the fixed amount (age at randomization) is subtracted from the observed lifetimes calculated by the applicant, we are left with "time from randomization to death". With this formulation, the smallest observed time of death could be as small as zero for the entire sample. This would hold for each individual as well.

For example:

- The observed lifetime for Subject 1 becomes 1 month: (2 months minus 1 month). Under this scheme, the earliest possible time of death is zero – the time of randomization.
- The observed lifetime for Subject 2 becomes 1 month: (13 months minus 12 months). The earliest possible time of death for this subject is zero – the time of randomization.

Another way of looking at the applicant's definition of observed lifetime is the observation the Kaplan-Meier survival curves do not account for time on therapy. For example, consider two patients with the same chronological age.

As calculated by the applicant, the first part of the observed lifetime – from date of birth to randomization – is conditional on a subject surviving until the time of randomization. By definition, this interval excludes subjects who died before the start of treatment. Therefore, this interval is not representative of all subjects born with infantile-onset Pompe disease and treated with Myozyme.

What can be generalized is the time from randomization to the time of death (or other outcome).

For these reasons, the Kaplan-Meier estimates need to start at the date of randomization. For further details, see Kaplan and Meier (1957).

3.3.2 Screened but not randomized or treated

Potentially, randomization could have been delayed for the more fragile subjects, who subsequently experienced an event that disqualified them from the study before they could be randomized. In such a situation, the sample would overrepresent the proportion of survivors. Moreover, the sample would be skewed towards subjects who are more robust.

3.4 Comparisons between Myozyme-treated subjects and the historical control subgroup

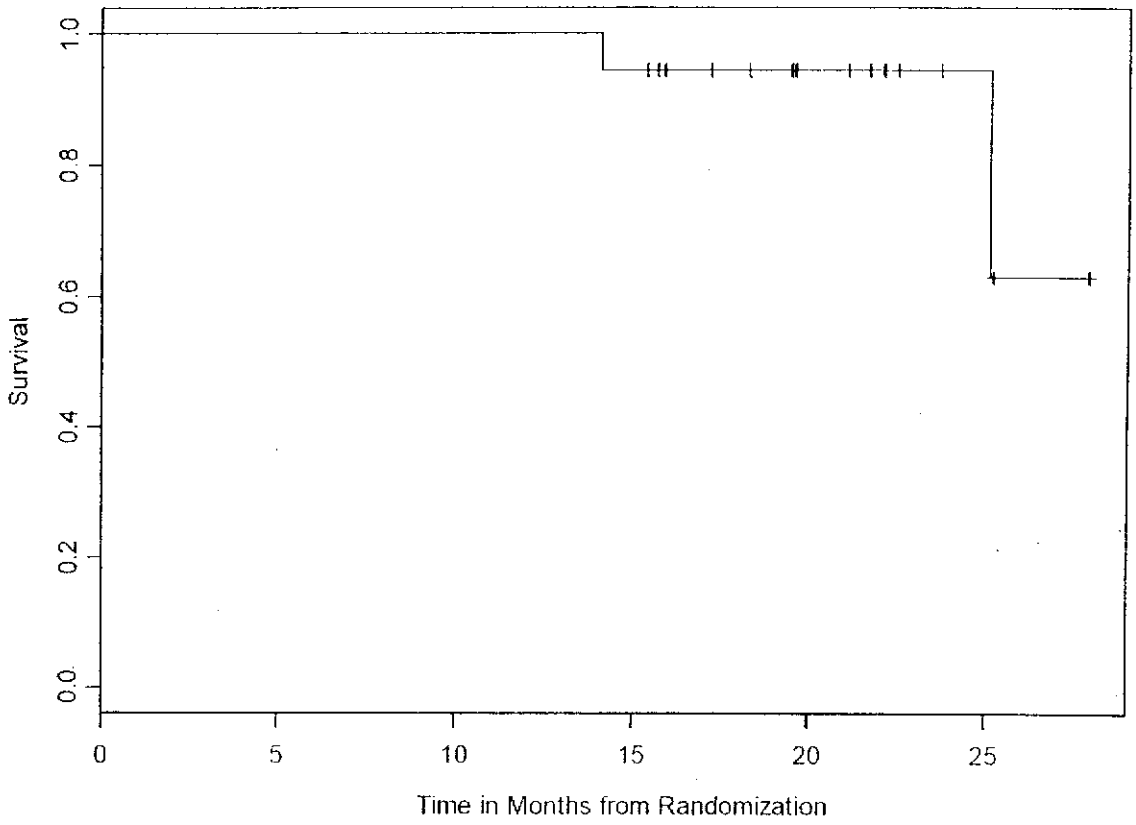
Because of selection bias and the use of date of birth as baseline, the visual comparison between Myozyme-treated subjects and the historical controls conveys the impression that Myozyme is much more effective than it actually is. To address these concerns and the issues raised by the Kaplan-Meir methodology used in the original submission, the applicant provided the following information in response to our Information Requests.

3.4.1 Additional Kaplan-Meier Analyses Submitted with the Major Amendment

3.4.1.1 Survival, using Date of Randomization as Baseline

The Kaplan-Meir analyses of survival, starting at the time of randomization, shows the first of two deaths occurred at 14 months after randomization; the other at 25 months. One subject was alive at a follow-up time of 28 months.

Figure 2 Survival in months from randomization



Source: Figure 1, Module 1, Major Amendment

The remaining sixteen subjects were alive at the time the study report was prepared. They are being followed for survival status. At last contact, the survival times ranged from 16 to 28 months. Four subjects had survival times between 17 and 23 months, the interquartile range.

3.4.1.2 Invasive ventilatory support

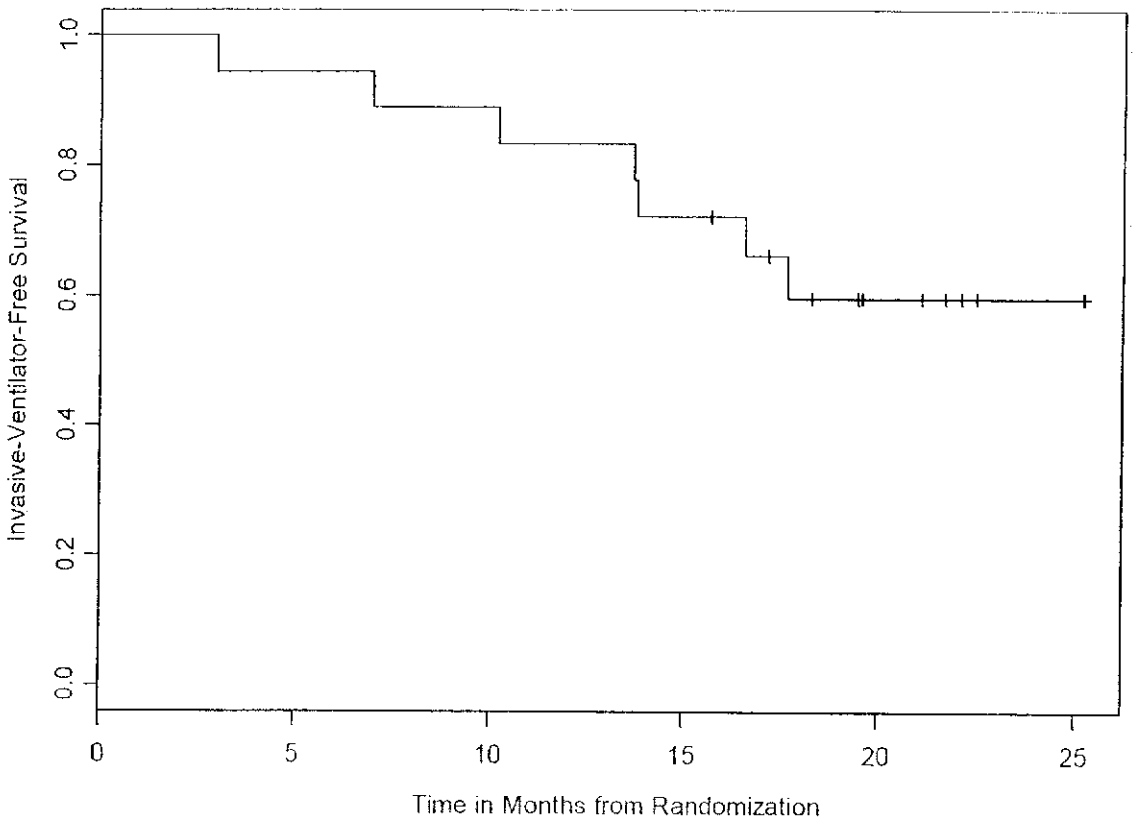
Seven subjects, including the two who died, received invasive ventilatory support. The two subjects who died started invasive ventilatory support at 14 months (11 days before death) and 18 months (7.5 months before death). The other five subjects, who were alive at the time of this submission, started invasive ventilatory support at 3, 7, 10, 13 and 17 months post-randomization.

Because the two patients who died received invasive ventilatory support prior to dying, all analyses reporting time to invasive ventilation or death are simply analyses of time to invasive ventilation.

A visual comparison of *Figure 3 Kaplan-Meier estimates of invasive ventilation for Myozyme-treated subjects, starting at the date of randomization* and *Figure 1 Kaplan-*

Meier Estimate of Time to Invasive Ventilation or Death from Date of Birth to 18 Months of Age (Comparison to Historical Control Subgroup) shows ventilator-free survival from the time of randomization is not as impressive as ventilator-free survival from the date of birth. For example, within the first 8 months, *Figure 3 Kaplan-Meier estimates of invasive ventilation for Myozyme-treated subjects, starting at the date of randomization* shows two subjects were placed on invasive ventilation compared with none as suggested by the graph starting at date of birth.

Figure 3 Kaplan-Meier estimates of invasive ventilation for Myozyme-treated subjects, starting at the date of randomization



Source: Figure 2, Module 1, Major Amendment

3.5 Sensitivity Analyses

To explore the bias of selecting Myozyme-treated subjects surviving long enough to be randomized, a so-called landmark analysis was submitted in the major amendment.

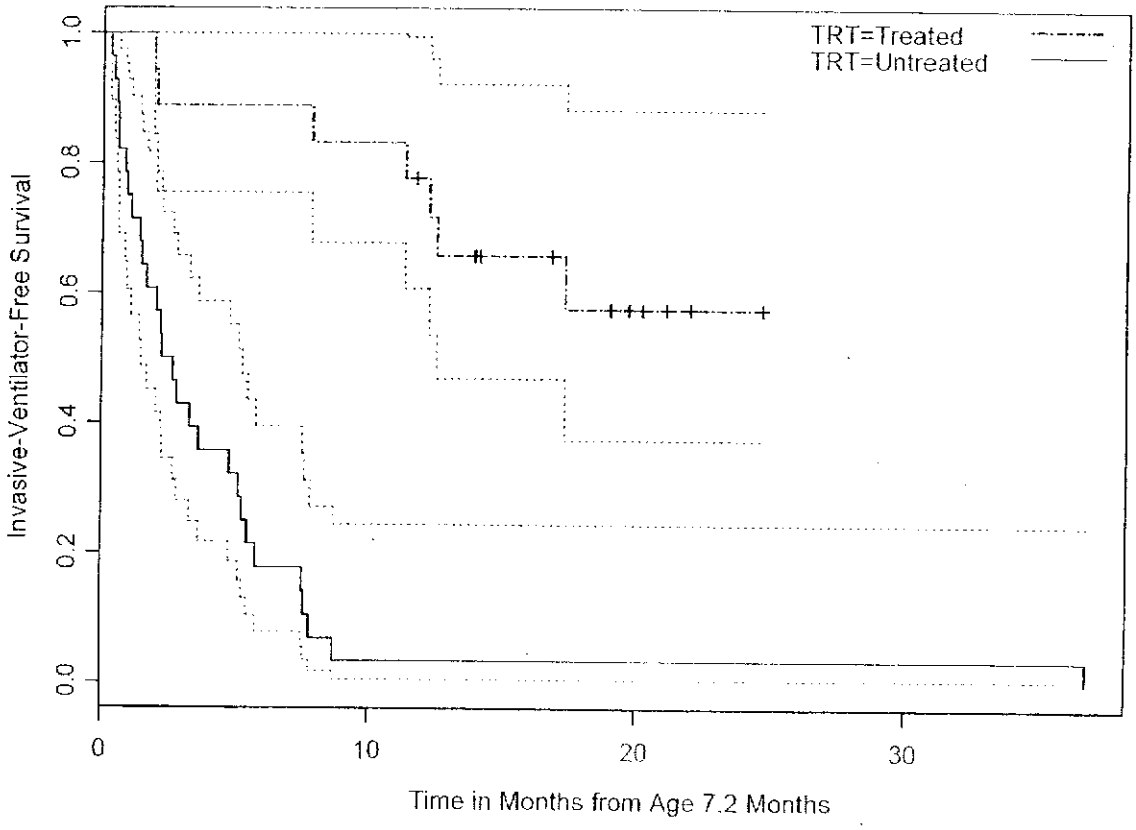
The analysis is a Kaplan-Meier analysis that started at the maximum age of randomization among the Myozyme-treated subjects. The analysis excludes data from the untreated

subjects who died before 7.2[8] months, the maximum age at randomization. The untreated subjects who were alive at the age of 7.2 would be counted as if being randomized at that age.

For the Myozyme-treated subjects, the maximum age of randomization was used as the baseline for all subjects. For example, if a subject was randomized at the age of two months, the study experience between randomization and 7.2 months was ignored. The individual's contribution to the Kaplan-Meier analysis started at the age of 7.2 months.

This sensitivity analysis reinforces the impression that Myozyme-treated subjects fair better than those who are untreated *(Figure 4 Invasive ventilator-free survival in months from 7.2 months of age)*:

Figure 4 Invasive ventilator-free survival in months from 7.2 months of age



Source: Figure 5, Module 1, Major Amendment

[8] This was calculated by the applicant; see page 25 (of 6390); Module 1: Administrative and Prescribing Information, Efficacy Information Amendment;

3.6 Dose Response

The Kaplan-Meier analyses, using date of randomization as the baseline, were repeated for each dose group. Although the doses do not appear different, the sample sizes are too small to draw any conclusions about the lack of a dose response.

3.7 Confidence Intervals

The applicant's confidence intervals for survival and for invasive ventilatory therapy were calculated under the assumption that a binomial distribution can be approximated by a normal distribution.

Because of the small number of subjects, however, the assumption does not hold. Using StatXact V5.0, I calculated the following Clopper Pearson exact, two-sided 95% confidence interval for ventilator use at 52 weeks following randomization: [4%, 41%].

This interval would be somewhat larger if adjusted for interim analyses.

3.8 Study Conduct

My review of the study identified many issues related to the conduct of the study. These include the timing of informed consent; lack of clarity on the timing of randomization, screen and baseline events; and data inconsistencies. The Information Requests (see Appendix 5.2 and Appendix 5.4) and the Medical Officer's review identify many of these issues.

The study used instruments to measure cognitive and physical function. However, no information was provided regarding cross-cultural and translation issues. No information regarding the training of the raters and the assurance of inter-rater reliability is provided.

3.9 Comparisons between the Historical Control Subgroup and the Randomized Study (1602)

The applicant's analyses of the entire cohort indicated subjects born since 1995 were less likely to die at any given time point than those who were born before 1995. The report concludes, "this finding could reflect an earlier and more comprehensive start of supportive therapeutic modalities in more recent years, as well as wider availability of such therapies in different geographical areas"; (p. 107, AGLU-004-00 Study Report). The sample sizes for the subgroup of historical controls were too small to detect a similar effect over time.

If a time trend does exist for the historical control subjects, the implication is an overestimate of the treatment effect estimated from comparisons between the subjects in 1602 and the historical control subjects.

An analysis of survival status in the large cohort, by geographic location, may have given further information about the time trend.

3.10 Interim Analyses

Contrary to the following statement in the statistical analysis plan, the analyses need to be adjusted for an interim look:

> "It should be noted that no adjustment will be made in the overall Type I error rate, as there is no plan to terminate the study prematurely based on the outcome from this analysis." (from Section 3.3 of the statistical analysis plan for Study AGLU01602).

Even though the applicant did not expect to terminate the study, an examination of the data at interim analyses opens the door for that possibility. Interim analyses could have revealed one dose was superior to the other, a finding that likely would have resulted in the termination of one of the treatment arms. In another scenario, the treatment could have been shown worse than the historical controls, which would have resulted in early termination of the study.

3.11 Development and Implementation of Instruments Used to Measure Cognitive and Psychomotor Development

Background information on the development, reliability and validity of the instruments was minimal. To understand the reliability and validity of the instruments, we requested information on the process used to validate the instruments for use in the cultures and languages encountered in the studies.

The applicant's response stated that all participating physical therapists were fluent in English and, therefore, the need for translations was limited. The response cites numerous articles to support the use of the instruments in various countries and cultures.

This response is less than adequate. Many forms of English exist throughout the world and each has its own idioms. Even if all therapists were fluent in English, this does not mean all questions and items were interpreted in the same way.

To understand the development of the Pompe PEDI requires the submission of the complete documentation of the development process, including how items were selected, the use of focus groups and iterative steps taken to refine the instrument. The citation of articles does not meet the level of evidence needed.

The response, "the need for translations was limited", seems to suggest that some instruments were translated. The applicant did not provide any further details for us to review.

Of concern are the open-label nature of the study and the lack of a concurrent comparator. Because all observers were aware of the subjects' diagnosis and that all were receiving Myozyme, it is possible the scores would tend to be higher than the "truth".

3.12 Gender and Ethnicity Subgroups

Subgroup analyses by gender and ethnicity were not possible because of the small sample size of 18 subjects.

4. SUMMARY AND CONCLUSIONS

4.1 Statistical Issues and Collective Evidence

A major design issue is the choice of time represented in the study endpoint for the Myozyme-treated subjects: 12 months, 18 months, 24 months of age. A more appropriate endpoint is the proportions at prespecified times following randomization.

The proportions at prespecified ages cannot be used, because they were estimated by an inappropriate use of the Kaplan-Meier methodology. The Kaplan-Meier analyses need to start at the time of randomization, not at the date of birth.

The historical control subgroup contains data from subjects with birthdates covering over 20 years. The applicant's analyses point to the potential for improved outcome over time due to more aggressive therapy and the better availability of the therapies in more diverse geographic regions.

The results from the cohort, however, support the contention that the long-term survival of patients with infantile-onset Pompe disease, who are not treated with Myozyme, is poor.

The comparison of data between the historical control subgroup and the Myozyme-treated subjects does suggest a treatment effect. This observation is not based on statistical conclusions, per se, but more so on the visual inspection of the results in the Myozyme-treated subjects compared with results in the historical control subgroup.

The quantification of the treatment difference is almost impossible. Not only are there the issues of improved outcomes, however slight they may be, over time among the untreated subjects, but there remains the issue of selection bias among the Myozyme-treated subjects. For these reasons, even if the treatment effect could be estimated, it would likely be an over estimate.

The applicant's discussion of the development and validation of the instruments used to measure cognitive and psychomotor development was lacking. The use of the instruments in various cultures and the issue of translation was not satisfactorily described.

One major concern is the scoring of the subjects by therapists who were aware of the diagnosis and treatment status of each subject. Combined with the absence of a concurrent control group, it is possible the scores are higher than what might actually be the case.

4.2 Conclusions and Recommendations

The data suggest improved outcomes among subjects treated with Myozyme when compared with the natural history of subjects who go untreated. The historical control subgroup provided a description of the natural history.

Because of concerns with selection bias and the inability to do an appropriate statistical comparison between Myozyme-treated subjects and the historical control data, the label cannot :

Subjects who started invasive ventilator therapy drove the endpoint "ventilator-free survival". The two deaths occurred while the subjects were using invasive ventilator therapy; no deaths occurred prior to the start of ventilator therapy. Labeling needs to indicate this.

At most, the label can report that Myozyme prolongs ventilator-free survival in subjects with infantile-onset Pompe disease when compared with the natural history of the disease as documented in an historical control group of untreated subjects with infantile-onset disease. Preferably, the label reports the results for invasive ventilator use separately from the survival outcomes, because invasive ventilator use drove the analysis of the composite endpoint.

5. APPENDICES

5.1 Study AGLU-004-00, "EPIDEMIOLOGIC STUDY OF THE NATURAL HISTORY OF INFANTILE POMPE DISEASE", Applicant's Results: Cox Regression Analyses of Risk of Death

Table 10-37 Risk of Death

Variable	Risk Ratio (95% CI)	p-value
Year of Birth ≥ 1995	0.71 (0.51, 0.99)	0.042
Age at First Symptoms		
per month increase	0.88 (0.82, 0.94)	< 0.001
≤ 6 months vs > 6 months	2.89 (1.58, 5.29)	< 0.001
Age at Diagnosis		
per month increase	0.92 (0.88, 0.96)	< 0.001
≤ 6 months vs > 6 months	2.13 (1.47, 3.08)	< 0.001
Reference: Appendix 16.1-9		

Source: Table 10-37, AGLU-004-00, "Epidemiologic Study of the Natural History of Infantile Pompe Disease"

Table 10-38 Risk of Death – Age of Cardiomegaly or Cardiomyopathy First Identified

Variable	Risk Ratio (95% CI)	p-value
Cardiomegaly		
per month increase	0.91 (0.87, 0.97)	0.001
≤ 6 months vs Otherwise	2.02 (1.40, 2.92)	< 0.001
Cardiomyopathy		
per month increase	0.89 (0.85, 0.94)	< 0.001
≤ 6 months vs Otherwise	1.93 (1.34, 2.78)	< 0.001
Reference: Appendix 16.1-9		

Source: Table 10-38, AGLU-004-00, "Epidemiologic Study of the Natural History of Infantile Pompe Disease"

Table 10-39 Risk of Death, Age at First Clinical Symptom Occurrence

Variable	Risk Ratio (95% CI)	p-value
Congestive Heart Failure		
per month increase	0.82 (0.74, 0.92)	0.001
≤ 6 months vs Otherwise	1.66 (1.18, 2.34)	0.004
Hypotonia/ Muscle Weakness		
per month increase	0.84 (0.79, 0.91)	< 0.001
≤ 6 months vs Otherwise	2.53 (1.61, 3.99)	< 0.001
Respiratory Distress		
per month increase	0.95 (0.90, 0.99)	0.027
≤ 6 months vs Otherwise	1.95 (1.36, 2.80)	< 0.001
Failure to Thrive		
per month increase	0.86 (0.79, 0.93)	< 0.001
≤ 6 months vs Otherwise	1.45 (1.03, 2.03)	0.032
Reference: Appendix 16.1-9		

Source: Table 10-39, AGLU-004-00, "Epidemiologic Study of the Natural History of Infantile Pompe Disease"

Table 10-40 Risk of Death, First Occurrence of Pneumonia, Gastroesophageal Reflux or Feeding Difficulties

Variable	Risk Ratio (95% CI)	p-value
Pneumonia		
Yes/No	0.61 (0.38, 0.99)	0.044
Yes/Otherwise	0.60 (0.43, 0.85)	0.004
Age at Pneumonia		
per month increase	0.92 (0.87, 0.97)	0.002
Age at Gastroesophageal Reflux/ Feeding Difficulties		
per month increase	0.86 (0.79, 0.93)	< 0.001
≤ 6 months vs Otherwise	1.68 (1.20, 2.35)	0.003
Reference: Appendix 16.1-9		

Source: Table 10-40, AGLU-004-00, "Epidemiologic Study of the Natural History of Infantile Pompe Disease"

Table 10-41 Risk of Death, Use of Treatments and Therapies

Variable	Risk Ratio (95% CI)	p-value
High Protein Diet (Yes/Otherwise)	0.43 (0.27, 0.68)	< 0.001
CPAP/BiPAP (Yes/Otherwise)	0.49 (0.29, 0.84)	0.010
Physical Therapy (Yes/Otherwise)	0.51 (0.34, 0.78)	0.002
Respiratory Therapy (Yes/Otherwise)	0.63 (0.45, 0.89)	0.009
Age at First Ventilator Use		
per month increase	0.91 (0.84, 0.98)	0.009
Reference: Appendix 16.1-9		

Source: Table 10-41, AGLU-004-00, "Epidemiologic Study of the Natural History of Infantile Pompe Disease"

Table 10-44 Adjusted Risk Ratio of Death, All Major Variables Considered

Category	Adjusted Risk Ratio (95% CI)	p-value
Age at First Symptoms	0.90 (0.83, 0.97)	0.006
Age at Confirmed Diagnosis	0.95 (0.91, 0.99)	0.013
High Protein Diet (Yes/Otherwise)	0.49 (0.31, 0.79)	0.003
Respiratory Therapy (Yes/Otherwise)	0.62 (0.43, 0.89)	0.009
Note: n =158, 136/158 died, percent censored 14% Reference: Appendix 16.1-9		

Source: Table 10-44, AGLU-004-00, "Epidemiologic Study of the Natural History of Infantile Pompe Disease"

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Table 10-46 Adjusted Risk Ratio of First Ventilator Use or Death

	Risk Ratio (95% CI)	p-value
Age at 1st Symptoms	0.90 (0.83, 0.97)	0.008
Age at Confirmed Diagnosis	0.96 (0.92, 1.00)	0.048
Congenital Abnormalities		
Yes/Otherwise	2.91 (1.59, 5.35)	0.001
Age at 1st Occurrence of Respiratory Distress		
≤ 6 months vs Otherwise	1.49 (1.01, 2.19)	0.045

Source: Table 10-46, AGLU-004-00, "Epidemiologic Study of the Natural History of Infantile Pompe Disease",

5.2 Information Request dated 11/18/05

(Note: Only the Clinical/statistical comments are included here)

Our STN: BL 125141/0

Genzyme Corporation
Attention: Alexander Kuta, Ph.D.
Vice President, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Dr. Kuta:

This letter is in regard to your biologics license application submitted under Section 351 of the Public Health Service Act.

We have reviewed the clinical; chemistry, manufacturing, and controls (CMC); clinical pharmacology; and pharmacology/toxicology section(s) of your application dated July 29, 2005, for Myozyme and have determined that the following information is necessary to take a complete action on your application:

Clinical/Statistical

1. For Study 1602, confirm whether or not the following personnel were blinded to patient and to study timepoint:
    a) central cardiologist reading ECGs and echocardiograms
    b) pathologist evaluating tissue samples for histopathological, biochemical and gene expression analyses.

2. In Study 1602, describe procedures used to "standardize" or "quality control" the performance of the pathologists and cardiologists. For example, were they also given "normal" samples as a means to quality control their performance, or were the samples all from study subjects? Describe any training they may have received.

3. In Study 1602, the AIMS assessments was performed by trained personnel at study sites and raw scores were centrally scored by a trained clinician. Were the personnel performing the AIMS test and the central scorer blinded to dose? Was the central scorer blinded to patient and sequence?

4. Describe the training given to the AIMS and Pompe PEDI evaluators and discuss procedures used to maintain consistency across study sites.

5. In Study 1602, describe blinding procedures used for the BSID-II and measures used across sites to maintain consistency.

6. Discuss the process used to translate the instruments into different languages. Describe the procedures used to validate the AIMS, Pompe PEDI and BSID-II instruments for use in the cultures and languages encountered in the studies.

7. In Study 1602, describe blinding techniques, if any, used for respiratory and radiology assessments.

8. In Study 1602, blinding for the central cardiologist was stopped after the first year of treatment. Is this also true for any other assessments after the first year?

9. For Study 1702, "single-blind interpretation" was noted for cardiology parameters - clarify exactly what blinding procedures were used (e.g., blinded to patient, to treatment, or to sequence), and what blinding procedures, if any, were used for any of the other study assessments, including motor and mental development, respiratory function, pathology, and radiology assessments.

10. For Study 1602,
    a) Clarify what happened to subjects, beginning with screening, through randomization and first infusion, i.e., provide explicit timelines for each patient from screening → to randomization → and then to first infusion.
    b) Describe what was supposed to occur, including a description of when the first infusion was to take place once a subject was randomized(e.g., randomized and treatment/first infusion within 24 to 48 hours).
    c) Provide explanations for subjects who started treatment after the time window specified in your answer to b.
    d) For Subject 304, who was not randomized, identify the amount of time that elapsed between the date of informed consent and the date the patient was placed on ventilation.

11. In Study 1602, it appears that there was one screening failure in addition to the one subject randomized but not treated (Subject 304). Supply screening failure information on this patient and any other screening failure patients. Were screening failures entered into any other treatment protocols?

12. For Study 1602, supply copies of medical records from all four patients entered at the Taiwan site (304, 305, 306 and 310) and the patient entered at the Cincinnati site (316), beginning with pre-screening/screening information leading to patient identification and entry into the study. Also, supply the English translation for the Taiwanese patients, if the records are not in English.

13. For Study 1702, the study was conducted March 17, 2003, through unknown (52-week treatment study). The data collected to the cut-off date of September 3, 2004, as well as the corresponding Study Report were noted to be "interim". At the time of data cut-off, efficacy data through study completion were provided on

the first 15 of 21 enrolled patients and on the remaining six patients up to Week 12, and safety data to September 3, 2004, were supplied on all 21 patients. The synopsis of the protocol states "A final analysis and report will describe all data from all 21 patients who were treated in the study." As this study has been completed, submit the following:

a) All efficacy and safety datasets for all 21 subjects treated through Week 52.
b) For patients receiving ongoing treatment, provide an updated status (survival and ventilator status) on these patients current to within 3 months.

14. Provide all data on all patients treated with rhGAA at doses greater than 40 mg/kg.

15. For Study 1602, provide an electronic dataset that contains the date of randomization for each subject.

16. For Study 1602, provide an electronic dataset that contains a censoring variable (1=event, 0=censored) and date of event for each of the time to event endpoints. Calculate these variables for each subject based on the subject's last available information.

17. For Study 1602, redo the time-to-event analyses using date of randomization as the baseline.

18. Provide landmark analyses to compare the results from Study 1602 with the historical controls. Use a cutoff age of 6 months for both Study 1602 and the historical controls. Repeat the time-to-event analyses using the cutoff age as the baseline. Provide Kaplan-Meier graphs of the results.

19. Submit results summarized by treatment group based on the date of randomization. Discuss your findings.

20. For Subject 8101313:
    a) Explain why 45 days elapsed between the date of informed consent and the date of randomization
    b) Explain why 10 days elapsed between the date of randomization and the start of infusion

21. For Subject 6003315, explain why 17 days elapsed between the date of randomization and the start of infusion.

22. As shown in the following table, four of the study sites evaluated only one of the doses. Discuss how these imbalances may have affected the results and their interpretation, including the lack of a dose response finding.

	Site 10	*Site 20*	*Site 21*	*Site 52*	*Site 60*	*Site 81*	*Site 83*
20 mg/kg	1	-	1	3	1	1	2
40 mg/kg	2	3	-	-	2	2	-
	3	3	1	3	3	3	2

5.3 Appendix 5.3: Information Request dated 12/5/05

Our STN: BL 125141/0

Genzyme Corporation
Attention: Alexander Kuta, Ph.D.
Vice President, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Dr. Kuta:

This letter is in regard to your biologics license application submitted under Section 351 of the Public Health Service Act.

We have reviewed the clinical; chemistry, manufacturing, and controls (CMC); clinical pharmacology; and pharmacology/toxicology section(s) of your application dated July 29, 2005, for Myozyme and have determined that the following additional information is necessary to take a complete action on your application:

1. In Study 1602, it appears that patients may have undergone at least some study-related screening procedures, especially skin biopsies, prior to the parent's signing of the study Informed Consent Form (ICF).

    a. Provide documentation of the timing of all screening and baseline procedures and the signing of the study ICF for all patients, regardless of whether patients were randomized or received treatment.

    b. In any case where a patient received any study-related procedure or test prior to the study ICF being signed, explain why the procedure or test occurred prior to obtaining study informed consent.

    c. In any case where a patient underwent a test prior to the study ICF being signed and for which Genzyme's central laboratory was used, explain why that laboratory was used.

    d. In instances where Genzyme had any involvement in a patient's care prior to study entry and prior to obtaining study informed consent, describe the nature of Genzyme's involvement, provide documentation as to why this was necessary, and explain how it related to the conduct of the study.

    e. Provide an explanation and supporting documentation for any instance where a central catheter was placed or a muscle biopsy was performed prior to obtaining study informed consent. Not all patients have baseline catheter placement dates in the ivx_0.xpt dataset. Provide baseline catheter placement dates for patients 303, 305, 306, 308 and 314.

2. In Study 1602, patient 303 was randomized prior to the study ICF being signed. This was justified by time differences between the United States and Israel, and by concerns about a time delay through the weekend that could have resulted in patient ineligibility due to the age of the patient approaching six months. However, five days elapsed between randomization and the first infusion. Explain the necessity for the urgent randomization prior to obtaining study informed consent in light of the delay in giving treatment.

3. Provide more details on the process used to randomize subjects. Your explanation of why Subject 303 was randomized prior to the signing of the study ICF raises the question of whether the United States personnel responsible for randomizing the subjects were available on weekends. Clarify why the start of the week was

problematic for the Israeli site, but not for other sites. If a subject was eligible for randomization on a Saturday or Sunday, discuss whether randomization was delayed until Monday. Provide documentation.

4. Clearly describe when the first infusion was supposed to occur, relative to the time of randomization. The study protocol suggests the start of therapy was at least 24 hours and as long as 30 days after randomization took place, as evidenced by the following:

   "Baseline must be completed within 30 days of first infusion"; see Footnote 1 to Table 9-1 "Initial Treatment Module", study protocol.

   "Placement of an indwelling catheter is at the discretion of the Investigator. Catheter placement should occur during the same episode of anesthesia as the muscle biopsy, at least 24 hours prior to the first infusion of study drug"; see Footnote 2 to Table 9-1 "Initial Treatment Module", study protocol.

5. Two patients died prior to completing screening procedures (T-1 and DAD on screening log), and one patient became ineligible after study entry and before first infusion due to respiratory deterioration. We are concerned that delays in completion of screening procedures could have provided an opportunity for selection bias toward healthier patients. Please comment and discuss.

6. Information about protocol deviations and violations was not included with the datasets nor with the study report in the amendments submitted to the BLA with the updated 52-week study data. Protocol deviation and violation listings are necessary to adequately assess data integrity. Submit the protocol deviations and violations listings to the BLA.

7. Provide the screen log information in a SAS dataset.

8. Provide a dataset that contains the following dates:

   Randomization
   Birth
   First symptoms
   Diagnosis
   Informed consent
   Skin biopsy
   Shipment of cells
   Results received
   Blood draw for GAA analysis
   Shipment of blood
   Results received
   Screening procedures completed
   Baseline procedures completed
   Muscle biopsy
   Placement of catheter
   First infusion

9. Provide the following sensitivity analyses to help address the issue of selection bias:

   Using the data from Study 1602, calculate the maximum chronological age at the time of randomization.

   From the historical control cohort, select the subset of subjects who were alive at the maximum chronological age calculated from Study 1602.

Use Kaplan-Meier analyses and graphs to compare the combined treatment groups from Study 1602 with the subset of historical controls. The analyses are based on the maximum chronological age at the time of randomization:

a. For each subject in 1602, truncate data at age of randomization or maximum chronological age, whichever is greater. Use this as the baseline.

b. For each subject in the historical controls, truncate data at the maximum chronological age. Use this as the baseline. If someone has not reached the maximum chronological due to death or other reasons, that person's data will not be included in this analysis.

10. Provide copies of all DSMB meeting minutes and copies of all communications between Genzyme and the DSMB.

It is requested that you promptly submit a complete response to the items enumerated above. Failure to respond in a timely manner or submission of a partial response may result in a determination that your application is not approvable. If your response to this information request is determined to constitute a major amendment, you will be notified of this decision in writing. Receipt of a major amendment during the last 90 days of the review period extends the review period by an additional 90 days.

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions.

Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please contact the Regulatory Project Manager, Cristi Stark, at (301) 796-1007.

Sincerely,

Brian E. Harvey, M.D., Ph.D.
Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

5.4 Screening Log

Potential Patient Initials	Date of Birth	Hometown (City, State, Country)	Gender	Consented for Skin Biopsy/ Ship Cells (date) If Applicable	Date of Skin Biopsy	Screen #	GAA Results Received (date)	GAA Results	Consented for 016 (date)	Screening Procedures Completed and Qualified? (date)	Enrollment Number	Comments
		France	M	17-Mar-03		02-02	12-May-03	0.25%	19-May-03	19-May-03	02-01-301	
		MA	M	NA		01-19	NA	NA	NA	NA	NA	12Jun03: parents did not consent to trial
		France	UNK	9-Apr-03		02-04	NA	NA	NA	NA	NA	Patient is heterozygous
		MS	M	29-May-03		01-22	8-Jul-03	16.12%	NA	NA	NA	GAA too high
		Israel	UNK	11May03		83-02	9-Jul-03	0.53%	NA	NA	NA	pt. is deceased prior to completing screening procedures
		ZA	F	17-Jun-03		01-24	NA	NA	NA	NA	NA	patient died prior to skin biopsy/GAA activity analysis
		Israel (Dr. Mandel)	M	NA		83-03	30-Jul-03	0.40%	10-Aug-03	11-Aug-03	60-01-302	Has COA - Jami Levine to evaluate - not a congenital abnormality/Patient 6 weeks premature
		Palestine	F	2-Jul-03		83-01	28-Aug-03	0.58%	2-Sep-03	3-Sep-03	60-02-303	Pt. is 5 weeks premature
		Taiwan	F	15-Aug-03		01-25	5-Sep-03	0.53%	8-Sep-03	10-Sep-03	52-01-304	Patient discontinued 1602 due to ventilation at BL. Transitioned to Expanded Access
		Taiwan	F	15-Aug-03		01-26	5-Sep-03	0.40%	10-Sep-03	12-Sep-03	52-02-305	
		Taiwan	M	21-Aug-03		01-27	5-Sep-03	0.90%	17-Sep-03	17-Sep-03	52-03-306	
		America, GA	M	10/14/2003		01-01	3-Nov-03	0.32%	26-Oct-03	27-Oct-03	01-01-307	Patient is 4 weeks premature
		Italy	M	11/6/2003		02-02	UNK	0.38%	N/A	10-Nov-03	02-02-308	Qualified via PBMC
		Peru	F	NA		01-02	24Nov03 0.28% - fibroblasts	PBMC	20Nov03	24Nov03	01-02-309	Qualified via PBMC
		Taiwan	M	NA		52-04	16Dec03 0.49% - fibroblasts	PBMC 0.57	11Dec03	12Dec03	52-04-310	Qualified via PBMC
		NC	M	NA		01-03	23Dec03	0.59%	09Dec03	11Dec03	01-03-311	Qualified via PBMC
		GA	F	NA		81-01	0.32% - fibroblasts	PBMC OK	17Dec03	29Jan04	81-01-313	Qualified via PBMC
		The Netherlands	M	NA		83-04	0.76% - fibroblasts	PBMC OK	27Jan04	27Jan04	83-04-314	Qualified via PBMC

Potential Patient Initials	Date of Birth	Hometown (City, State, Country)	Gender	Consented for Skin Biopsy/ Ship Cells (date) If Applicable	Date of Skin Biopsy	Screen #	GAA Results Received (date)	GAA Results	Consented for 016 (date)	Screening Procedures Completed and Qualified? (date)	Enrollment Number	Comments
		Germany	F	NA		83-05	0.50% - fibroblasts	PBMC OK	23Jan04	23Jan04	83-05-312	Qualified via PBMC
		Israel	M	N/A		60-03		0% PBMC	1-Mar-04	6-Mar-04	60-03-315	GAA activity via skin fibroblasts: 0.72%
			F	NA		21-01	0.28% - fibroblasts	PBMC OK	05Apr04	07Apr04	21-01-316	Qualified via PBMC
		Virginia	F	NA		01-07	NA	NA	NA	NA	NA	Due to respiratory status (patient on CPAP and BiPap), pt not screened for 1602, but moved to AGLU01702.
		Israel	F	NA		60-04	8Apr04	78% via PBMC	05Apr04	NA	NA	Patient did not have Pompe disease
		Israel	F	NA		60-05	NA	NA	NA	NA	NA	Parents did not consent to trial
		British Virgin Islands	M	NA		81-02	0.82% - fibroblasts	PBMC OK	17May04	18May04	81-02-317	Qualified via PBMC
		France	M	NA		02-03	0.22% - fibroblasts	PBMC OK	10May04	24/May004	02-03-318	Qualified via PBMC
		AL	F	NA		81-03	0.58% - fibroblasts	PBMC OK	31May04	02Jun2004	81-03-319	Qualified via PBMC