

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125291

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

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Brand Name	(b) (4) or Lumizyme (under review)
Generic Name	Alglucosidase alfa
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OCP Division	DCP 3
OND Division	ODE3/DGP
Sponsor	Genzyme Corporation
Relevant IND(s)	BB-IND 10,780
Submission Type	NME, priority review
Formulation; Strength(s)	Lyophilized cake or powder for reconstitution with sterile water for injection (5.0 mg/mL)
Proposed indication	Long-term use in patients with late-onset Pompe disease
Proposed Dosage and Administration	20 mg/kg body weight administered every 2 weeks as an intravenous infusion over approximately 4 hours.

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1 EXECUTIVE SUMMARY

Alglucosidase alfa is recombinant human acid alpha-glucosidase [rhGAA] produced from Chinese hamster ovary cells using recombinant DNA technology. RhGAA, manufactured at the 160 L scale (Myozyme[®], STN 125141), was approved for the treatment of infantile-onset Pompe disease on April 28, 2006.

The applicant has also developed a 2000 L manufacturing process and submitted clinical data obtained from a small group of infantile-onset patients, who were treated with both 160 L and 2000 L products, or solely with 2000 L product, in support of the 2000 L process for approval (BLA Supplement 125141/65 dated October 31, 2007). In response to the Supplement, the FDA informed that comparability had not been demonstrated between lots manufactured using **the 160 L and 2000 L processes. Based on the FDA's recommendation, the applicant submitted** this BLA with a new submission tracking number (STN 125291) with clinical data to support the licensure of the 2000 L product for use in patients with late-onset Pompe disease. The submission dated October 31, 2007, was recoded to this new BLA. The clinical data were collected from a double-blind, placebo-controlled study (referred to as "LOTS"; AGLU02704) performed in patients with late-onset Pompe disease who received only 2000L product in accordance with post-marketing commitment 1 for STN 125141.

Information relating to chemistry, manufacturing and controls (CMC), and nonclinical data in this application is cross-referenced to that in the submission dated October 31, 2007 in accordance with the discussion with FDA on April 25, 2008 regarding the content and format of BLA 125291. Except for the pharmacokinetic and immunogenicity data collected from Study AGLU02704, clinical pharmacology information is also cross-referenced to that in STN 125141. Thus, this review includes the clinical pharmacology information submitted since May 30, 2008. For the clinical pharmacology information submitted before May 30, 2008, please refer to the review completed on August 26, 2008 by the previous clinical pharmacology reviewer, Dr. Tien-Mien Chen.

The acceptability of the CMC, clinical efficacy and safety data, and approvability of this application were discussed in the Endocrinologic and Metabolic Drugs Advisory Committee meeting held on October 21, 2008. The committee recommended that post-marketing studies should be required to continue assessing the **updated rhGAA's effectiveness and safety. The** majority of committee members recommended a Subpart E accelerated approval (12 votes) using forced vital capacity as a surrogate endpoint over a regular approval (4 votes) based on 6-min walk test (1 vote for no approval). In consistent with the committee recommendation, the FDA is currently communicating with the applicant regarding a Subpart E verification study, and postmarketing requirement and commitment studies.

(b) (4) or Lumizyme was proposed as the brand name for rhGAA by 2000 L manufacturing process. The proposed brand name is still under review at the completion of this review. In this review, rhGAA refers to the 2000 L product while Myozyme[®] does the 160 L product approved previously.

1.1 Recommendation

The clinical pharmacology information included in this application is acceptable and supports the approval of the rhGAA product manufactured by 2000 L scale process for the treatment of adult patients with late-onset Pompe disease (studied age range, from 21 to 70 years old). The labeling comments need to be communicated to the applicant. Initial labeling recommendations for clinical pharmacology areas are in **Section 3 DETAILED LABELING RECOMMENDATIONS**.

However, the pharmacokinetics of rhGAA have not been characterized in patients with late-onset Pompe disease younger than 21 years old. The clinical pharmacology review team recommends collecting adequate pharmacokinetic data from pediatric patients with late-onset Pompe disease from the Subpart E verification study to be conducted (see **1.2 Postmarketing Commitments** below)

1.2 Phase 4 Commitment (Subpart E Verification Study)

Because the pharmacokinetics of rhGAA have not been characterized for the safe and effective use of rhGAA in pediatric patients with late-onset Pompe disease, the clinical pharmacology review team recommends evaluating the pharmacokinetics as a substudy of the Subpart E verification study.

The pharmacokinetic substudy needs to but should not be limited to include the following considerations:

- a. Sufficient number of patients (e.g., N = 20) representing the entire range of the suggested age group (i.e., 12 months - 8 years old)
- b. Sufficient number and adequate time points of pharmacokinetic blood sampling in order to fully characterize the pharmacokinetics (at least an entire dosing interval at steady state and adequately selected trough concentrations)
- c. Determination of exposure-response relationships and immunogenicity impact on pharmacokinetics
- d. Use of accurate, precise, and validated analytical method
- e. Submissions of the pharmacokinetic substudy protocol and final report at the time of main study protocol and report submissions

1.3 Summary of Clinical Pharmacology Findings

Pharmacokinetics

Table 1 below shows the multiple dose pharmacokinetic parameter values of rhGAA (2000 L scale product) estimated in 32 patients with late onset Pompe disease who received rhGAA 20 mg/kg body weight every other week using a 2-compartment linear pharmacokinetic model with a zero-order input in Study AGLU02704. The parameters appear to be comparable at Weeks 0, 12 and 52. The estimated effective half life seems to reflect more distribution half-life than elimination half-life due to relatively short pharmacokinetic sampling (up to 16 hours post dose). **Patient's age and sex** had no significant impact on the pharmacokinetic parameters.

C_{max}, Clearance (CL) and the central volume of distribution (V₁) were affected by body weight. However, weight did not affect the effective half-life of rhGAA.

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

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

V_{ss}, volume of distribution at steady state

Immunogenicity

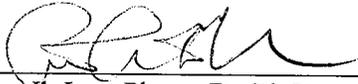
All patients in the rhGAA treatment group tested for post-exposure immunogenicity test in Study AGLU02704 developed anti-rhGAA IgG antibodies (binding antibodies) as assessed by enzyme-linked immunosorbent assay (ELISA) and confirmed by radioimmunoprecipitation assay (RIP). The median time to seroconversion was 4 weeks (range, 4 to 12 weeks) after the first rhGAA dose.

None of the 60 binding antibody positive patients tested positive for inhibition of enzyme activity in an rhGAA inhibition assay. However, 10 patients (16.9%) were positive, 8 (13.6%) were borderline positive, and 41 were negative for inhibition of rhGAA uptake into human fibroblast cells in a flow cytometry assay.

Both high anti-rhGAA IgG antibody titers and inhibitory antibody status (positive for uptake inhibition) are indicative of an impact on rhGAA pharmacokinetics. Inhibitory antibody status coincide with highest anti-rhGAA IgG antibody titers: 5 patients with the highest binding antibody titer also had positive inhibitory antibody status in Study AGLU02704. Those five patients had higher CL, lower C_{max}, and lower AUC than 29 patients with negative status.

The clinical significance of high antibody titers or positive uptake inhibition status is unclear. It appears that higher binding antibody titers in general indicate a greater change that the patient performs better in a 6-minute walk test (6MWT) in response to rhGAA therapy. Most of those patients with higher binding antibody titers had positive inhibitory antibody.

There was no apparent association between higher anti-rhGAA IgG antibody titers and occurrence of infusion associated reactions (IAR). Two patients (3.4%) among the 59 evaluated patients had positive anti-rhGAA IgE antibody status and experienced serious events of hypersensitivity.

for 

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2 QUESTION-BASED REVIEW

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Alglucosidase alfa (recombinant human acid alpha-glucosidase [rhGAA]) is produced from Chinese hamster ovary cells by recombinant DNA technology and is identical to a commonly occurring form of human GAA in amino acid sequence. RhGAA is a large protein ^{(b) (4)}

The calculated mass of rhGAA is 99,377 daltons for the polypeptide chain, and a total mass of approximately 109,000 daltons, including carbohydrates.

RhGAA formulation is lyophilized powder for solution for injection. The product is provided in a 20 mL vial containing 52.5 mg rhGAA, 210 mg mannitol, 0.5 mg polysorbate 80, 9.9 mg sodium phosphate dibasic heptahydrate and 31.2 mg sodium phosphate monobasic monohydrate. Each vial is intended for single use administration only. The contents of the vial should be reconstituted with 10.3 mL Water for Injection (USP). The reconstituted product contains rhGAA 5 mg/mL.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Acid alpha-glucosidase is a hydrolase that degrades lysosomal glycogen to glucose. During trafficking to the lysosome, acid alpha-glucosidase is proteolytically processed, resulting in the formation of an enzymatically active multi-subunit complex. Acid alpha-glucosidase degrades glycogen by catalyzing the hydrolysis of α -1,4- and α -1,6-glycosidic linkages of lysosomal glycogen.

Pompe disease (acid alpha-glucosidase deficiency) is a rare inherited disorder caused by a deficiency of acid alpha-glucosidase. Other names for Pompe disease include glycogen storage disease type II, acid maltase deficiency, and glycogenosis type II. Pompe disease is characterized by organelle bound (lysosomal) and extra-lysosomal accumulation of glycogen in many body tissues, as opposed to the exclusive cytoplasmic accumulation of glycogen that occurs in other glycogen storage disorders.

Myozyme[®], rhGAA manufactured at the 160 L scale (STN 125141), was approved for the treatment of Pompe disease on April 28, 2006. The approved indication in Myozyme[®] labeling is, “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.”

The proposed indication for rhGAA manufactured at the 2000 L scale (current application) is “for long-term use in patients with late-onset Pompe disease.”

2.1.3 What are the proposed dosage(s) and route(s) of administration?

RhGAA is intended for long-term use as an enzyme replacement therapy (ERT) for the treatment of patients with a confirmed diagnosis of Pompe disease. The proposed dosage is 20 mg/kg body weight administered every 2 weeks as an intravenous infusion. The total volume of **infusion is determined by the patient's body weight** and should be administered over approximately 4 hours. Infusions should be administered in a step-wise manner using an infusion pump. The initial infusion rate should be no more than 1 mg/kg/hr. The infusion rate may be increased by 2 mg/kg/hr every 30 minutes, after patient tolerance to the infusion rate is established, until a maximum rate of 7 mg/kg/hr is reached. Vital signs should be obtained at the end of each step. If the patient is stable, rhGAA may be administered at the maximum rate of 7 mg/kg/hr until the infusion is completed. The infusion rate may be slowed and/or temporarily stopped in the event of infusion-associated reactions.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

In order to support the claims in this submission, the applicant conducted Study AGLU02704 (also acknowledged as LOTS study), entitled “**A Randomized, Double-Blind, Multicenter, Multinational, Placebo-Controlled Study of the Safety, Efficacy, and Pharmacokinetics of Myozyme, Recombinant Human Acid alpha-Glucosidase, Treatment in Patients with Late-Onset Pompe Disease.**” The objective of the study was to evaluate the safety, efficacy and pharmacokinetics of rhGAA (2000 L product) in patients with late-onset Pompe disease as compared to placebo. A total of 90 patients were randomized to receive intravenous infusions (over approx. 4 hours) of either rhGAA (N = 60) at a dose of 20 mg/kg every other weeks or placebo (N = 30) in a step-wise manner from 1 to 7 mg/kg/hr. Eighty-one patients completed the study (55 in rhGAA group and 26 in placebo group). Mean age at the first infusion was 45.3 years (range, 15.9 - 70.0) in the rhGAA group.

Pharmacokinetic assessment was performed on a subgroup of 34 patients. Blood samples for the measurement of plasma rhGAA activity were collected at each of the following time points at Day 0, Week 12 and Week 52: 0 (before the start of the infusion), 1 and 2 hours after the start of infusion, end of the infusion, and then 0.25, 0.5, 1, 2, 3, 4, 8, 12, and 16 hours after the end of the infusion. RhGAA pharmacokinetics were characterized by a 2-compartmental model under a nonlinear mixed effects model paradigm. Covariates examined were age, weight, sex, antibody titer, presence/absence of anti-rhGAA antibodies, and inhibitory antibody status. The typical patient was 46.0 years old (range, 20.7 to 70.0 years) at the time of first infusion, weighed 77.4 kg (range, 42.5 to 118.8 kg), and received a dose of 1547 mg (range, 850 to 2376 mg).

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

The primary efficacy endpoints used in Study AGLU02704 include changes in six minute walk test (6MWT) and forced vital capacity (FVC) from baseline to 78 weeks of rhGAA treatment.

The 6MWT is a timed walk test that measures functional endurance. The 6MWT is regarded as an objective measure that is easy to administer, well tolerated by most patients and more reflective of the performance of activities of daily living than other functional endurance tests. The reliability, validity and responsiveness to change of the 6MWT have been established in chronic obstructive pulmonary disease, cystic fibrosis and heart failure. FVC is a pulmonary function test to quantify respiratory muscle weakness by measuring the maximal volume of air that can be exhaled with the patient breathing forcefully to obtain maximal airflow rates.

2.2.3 Are the active and or relevant moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic and pharmacodynamic parameters and exposure response relationships?

RhGAA in heparin plasma samples was assayed using an activity-based assay with fluorescence detection. The in-process performance of the assay method is acceptable (see 2.6 Analytical).

2.2.4 Exposure-Response

2.2.4.1 What are the characteristics of the exposure-response relationships for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

No exposure-efficacy relationship was observed within the available data in this application. The data was limited to one dose level and the range of exposure to the drug was limited because of the single dose level. A wider exposure range achieved by more dose levels may support an exposure-response relationship that was undetectable within this submission. As a result, there are no dose-adjustment related recommendations based on exposure-efficacy response relationships (see *Question 2.2.4.4*).

2.2.4.2 What are the characteristics of the exposure-response relationships for safety?

The exposure-safety response relationship was not characterized in this submission.

2.2.4.3 Does this drug prolong the QT or QTc interval?

No thorough clinical study has been conducted to determine the effect of rhGAA on QT/QTc interval. Based on the ECG monitoring in Study AGLU02704, ECG findings at baseline were abnormal for 28 (46.7%) of 60 patients in the rhGAA treatment group and 13 (44.8%) of 29 patients in the placebo treatment group. One patient in each treatment group had prolonged QT or QTc at baseline. During the study, 7 additional patients (4 and 3 in rhGAA and placebo groups) experienced prolongation of QT interval. In 2 patients, the QTc prolongation was considered clinically significant and was reported as an adverse event. These adverse events were assessed as possibly related in one patient in the rhGAA treatment group and remote/unlikely related in one patient in the placebo treatment group and both were assessed as non-serious and mild.

2.2.4.4 Is the dose and dosing regimen selected by the Sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Not applicable to this submission. The dose and dosing regimen has already been determined in the previous application (see Dr. Anil Rajpal's review for STN125141 Myozyme®). See also Question 2.2.4.1 above

2.2.5 What are the pharmacokinetic characteristics of the drug and its major metabolite?

2.2.5.1 What are the single dose and multiple dose pharmacokinetic parameters?

Table 1 in Section 1.3 Summary of Clinical Pharmacology Findings shows the multiple dose pharmacokinetic parameter values of rhGAA (2000 L manufacturing scale) estimated in 32 patients with late onset Pompe disease who received rhGAA 20 mg/kg body weight every other week using a 2-compartment linear pharmacokinetic model with a zero-order input under a nonlinear mixed effects model paradigm in Study AGLU02704. The parameter values appear to be comparable at Weeks 0, 12 and 52. The estimated effective half life (approx. 2.4 hours) appears to be distribution rather than elimination half-life. The estimated elimination half-life (approx. 214 hr) is not reliable since pharmacokinetic blood samples were collected only up to 16 hours post dose.

2.2.5.2 How do the pharmacokinetics in healthy volunteers compare to those in patients?

RhGAA pharmacokinetics have not been assessed in healthy volunteers in this application so that the pharmacokinetics cannot be compared between healthy volunteers and patients

2.2.5.3 What are the characteristics of drug absorption?

Not applicable to rhGAA that is administered intravenously.

2.2.5.4 What are the characteristics of drug distribution?

The steady-state volume of distribution (approx. 70 L) and plasma pharmacokinetics indicate the drug is distributed rapidly and is not limited to the central plasma. The central volume of distribution was correlated with body weight but not the peripheral volume parameter.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Not applicable to therapeutic protein products.

2.2.5.6 What are the characteristics of drug metabolism?

Not applicable to therapeutic protein products that are disintegrated to amino acids.

2.2.5.7 What are the characteristics of drug excretion?

Not applicable to rhGAA, a large molecular therapeutic protein product that is not expected to be excreted.

2.2.5.8 Based on pharmacokinetic parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The degree of linearity in dose-concentration relationship was not determined in this application.

2.2.5.9 How do the pharmacokinetic parameters change with time following chronic dosing?

Provided the patient does not develop high inhibitory antibody titer, the pharmacokinetics of rhGAA should remain time-invariant following chronic dosing (see Table 1). Increased anti-rhGAA antibody titer over time resulted in an increase in rhGAA clearance (see Section 2.3.3).

2.2.5.10 What is the inter- and intra-subject variability of pharmacokinetic parameters in volunteers and patients, and what are the major causes of variability?

The 2-compartment linear pharmacokinetic model with a zero-order input under a nonlinear mixed effects model paradigm was concise and captured the intra- and inter-subject variation in rhGAA pharmacokinetics well (Table 2). Intra-subject variation (IOV parameters, Table 2) on clearance (CL) and volume of distribution (V) was small with estimates of coefficients of variation (CV) of 14% and 18%, respectively. Inter-subject variation (BPV parameters, Table 2) was also fairly low for the central volume of distribution and inter-compartmental clearance. However, the highest inter-patient variation was found on the peripheral volume of distribution of rhGAA (CV, 107%). Clearance had CV 30% between patients.

Table 2: Inter- and intra-subject variability in rhGAA (2000L scale) pharmacokinetic parameters estimated in 32 patients with late onset Pompe disease using a 2-compartment linear pharmacokinetic model (Study AGLU02704)

<i>Parameter</i>	<i>Sponsor's Estimate</i>	<i>Sponsor's Standard Error</i>	<i>Reviewer's Estimate</i>	<i>Reviewer's Standard Error</i>
CL (mL/hr)	613	156	613	152
V ₁ (mL)	3400	133	3400	133
Q (mL/hr)	334	153	334	150
V ₂ (mL)	46900	44900	46800	44300
θ ₅	0.683	0.131	0.683	0.128
BPV (CL)	30.3%		29.6%	
BPV (V ₁)	20.4%		13.8%	
BPV (Q)	23.4%		25.7%	
BPV (V ₂)	107%		87.3%	
IOV (CL)	17.9%		17.8%	
IOV (V ₁)	14.2%		14.1%	
σ ²	19.9%		19.7%	

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The applicant claims that rhGAA pharmacokinetics are independent of anti-rhGAA antibody titers. Based on a population pharmacokinetic analysis of pharmacokinetic data obtained from 34 patients with late-onset Pompe disease by a 2-compartmental model under a nonlinear mixed effects model paradigm, patient's age and sex had no impact on rhGAA pharmacokinetics. Patient's weight was correlated with C_{max}, CL, and the central volume of distribution (V₁) of rhGAA (Table 3). Clearance varied the most between patients with CV of 25% for between subject variations.

Table 3 Impact of patient's body weight on pharmacokinetic parameters of rhGAA (2000L scale) estimated in 32 patients with late onset Pompe disease using a 2-compartment linear pharmacokinetic model (Study AGLU02704)

Parameter	L.S. Mean for 70 kg Patient	Between-Patient Variation
C _{max} (mcg/mL)	338	14%
Clearance (mL/hr)	576	25%
V ₁ (L)	3.2	17%

V₁, central volume of distribution

The impacts of anti-rhGAA and inhibitory antibodies on rhGAA exposure and efficacy and safety responses are addressed in Section 2.3.3 Immunogenicity.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

The currently available data are not sufficient to suggest that increasing dose will increase efficacy. There is a high degree of variation in clinical response to rhGAA treatment. Anti-rhGAA antibody titer does not greatly impact on the efficacy results (see Section 2.3.3 Immunogenicity). Thus, no dosing adjustments based on intrinsic factors are recommended.

2.3.2.1 Elderly

Study AGLU02704 submitted in this application did not include sufficient numbers (N = 4) of subjects aged 65 years or older to determine whether they respond differently to rhGAA treatment from younger subjects.

2.3.2.2 Pediatric Patients

Study AGLU02704 submitted in this application did not include sufficient numbers (N = 4, 2 of which were treated with rhGAA) of subjects aged 16 and younger to determine whether they respond differently from adult subjects.

2.3.2.3 Gender

In a population pharmacokinetic analysis, the difference in gender had no impact on the clinical pharmacology of rhGAA.

2.3.2.4 Race

No specific analysis was conducted to evaluate the effect of race on the clinical pharmacology of rhGAA.

2.3.2.5 Renal impairment

No specific analysis was conducted to evaluate the effect of renal impairment on the clinical pharmacology of rhGAA.

2.3.2.6 Hepatic impairment

No specific analysis was conducted to evaluate the effect of hepatic impairment on the clinical pharmacology of rhGAA.

2.3.2.7 What pregnancy and lactation use information is there in the application?

It is not known whether rhGAA is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when rhGAA is administered to a nursing woman. Nursing women are encouraged to enroll in the Pompe Registry.

2.3.3 Immunogenicity (applicable only to therapeutic proteins)

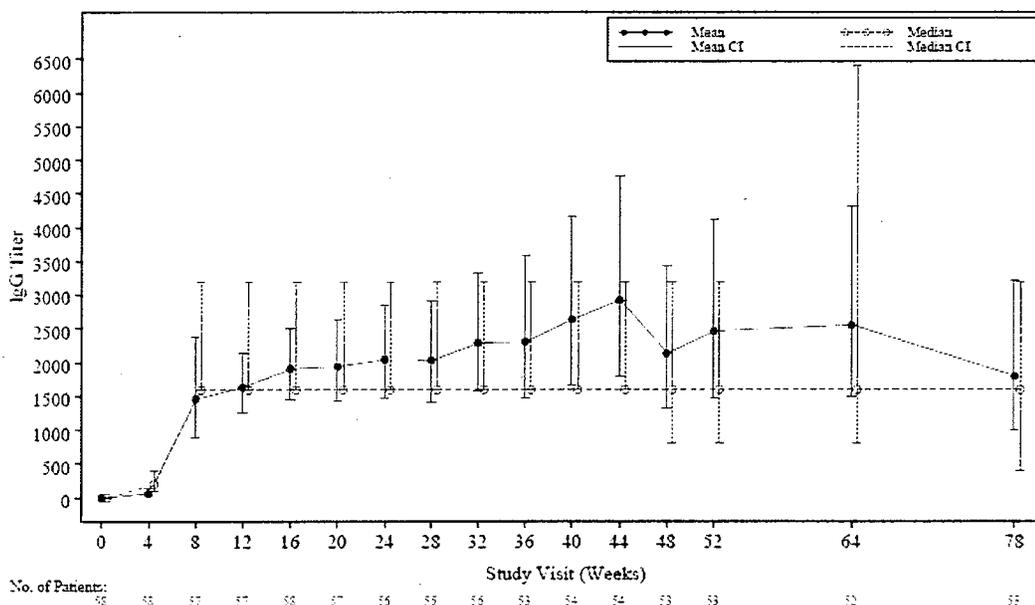
2.3.3.1 What is the incidence of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?

Serum samples for immunogenicity testing were obtained pre-infusion every four weeks. All patients in the rhGAA treatment group tested for post-exposure immunogenicity (Study AGLU02704) developed anti-rhGAA IgG antibodies (binding antibodies) as assessed by enzyme-linked immunosorbent assay (ELISA) and confirmed by radioimmunoprecipitation assay (RIP). The median time to seroconversion was 4 weeks (range, 4 to 12 weeks) after the first rhGAA dose. Of these patients, 39 (66.1%) patients seroconverted by the Week 4 Visit, 18 (30.5%) patients seroconverted by the Week 8 Visit, and the remaining 2 (3.4%) patients seroconverted by the Week 12 Visit. One patient dropped out of the study at week 2 and tested

IgE positive to rhGAA. The geometric mean and median titers of binding antibodies from baseline to the end of the study are plotted over time in Figure 1 below.

The mean titer increased to a maximum of 2,925 at Week 44 and thereafter declined. The median titer remained steady at 1,600 throughout most of the study. Analysis of individual patient titer showed approximately 61% of patients showed trends toward decreasing titers from peak to last observation with continued treatment. However, 9 of 59 (15%) of evaluable patients who developed positive IgG titers during the study had a persistently elevated IgG titer at the end of the study. The median peak titer was 6,400 (range 200 to 819,200) and the median last titer was 1,600.

Figure 1: Anti-rhGAA IgG antibody titers over time determined in patients with late-onset Pompe disease after initiation of rhGAA 20 mg every other week (Study AGLU02704)



2.3.3.2 Do the anti-product antibodies have neutralizing activity?

Inhibitory antibody status was assessed in patients the first time they tested positive for IgG antibodies to rhGAA (binding antibody) and approximately quarterly thereafter. Two assay methods were used, one to measure the inhibition of rhGAA enzymatic activity by binding antibodies and another to measure inhibition of the uptake of rhGAA into human fibroblast cells. In the cases that inhibitory antibody status do not match with the corresponding pharmacokinetic sampling dates, a window of ± 1 week was used to match inhibitory antibody status with corresponding pharmacokinetic samples.

None of the 59 evaluable patients tested positive for inhibition of enzyme activity. However, 18 patients (30%) were positive for inhibitory antibodies to enzyme activity, and 41 (69.5%) were negative for inhibition of enzyme uptake antibodies. Patients who tested positive for uptake inhibition had a mean time to first detection of inhibitory antibodies of 36 weeks after first infusion, or 30 weeks after first positive IgG titer. Patients classified with positive uptake

inhibition assay results generally had higher median peak IgG antibody titers (102,400) and higher median last IgG antibody titers (72,408) than patients who remained negative for uptake inhibition (median peak IgG antibody titer 3,200; median last IgG antibody titer 400).

2.3.3.3 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?

Both high binding antibody titers and inhibitory antibody status (positive for uptake inhibition) are indicative of an increased systemic clearance (CL) of rhGAA. Inhibitory antibody status coincide with highest binding antibody titers: 5 patients with the highest binding antibody titer also had positive inhibitory antibody status in Study AGLU02704.

As shown in Figure 2A, though the applicant claims no difference in rhGAA CL with antibody titers, there is a clear upslope in the smoothed trend line for CL estimate at binding antibody titers at or above 10,000, which suggests that clearance increases with higher binding antibody titers. Similarly, Figure 2B shows that rhGAA CL depicted as mean (blue dots) and median (solid red line across each bar) values was greater at the highest quartile of binding antibody titers. The highest quartile in 2B contains 6 subjects, of which 5 were positive for inhibitory antibody status. Those were the only 5 subjects with positive inhibitory antibody status at the time of pharmacokinetic sampling in the study.

Figure 2. Tendency of rhGAA clearance across anti-rhGAA IgG antibody titer

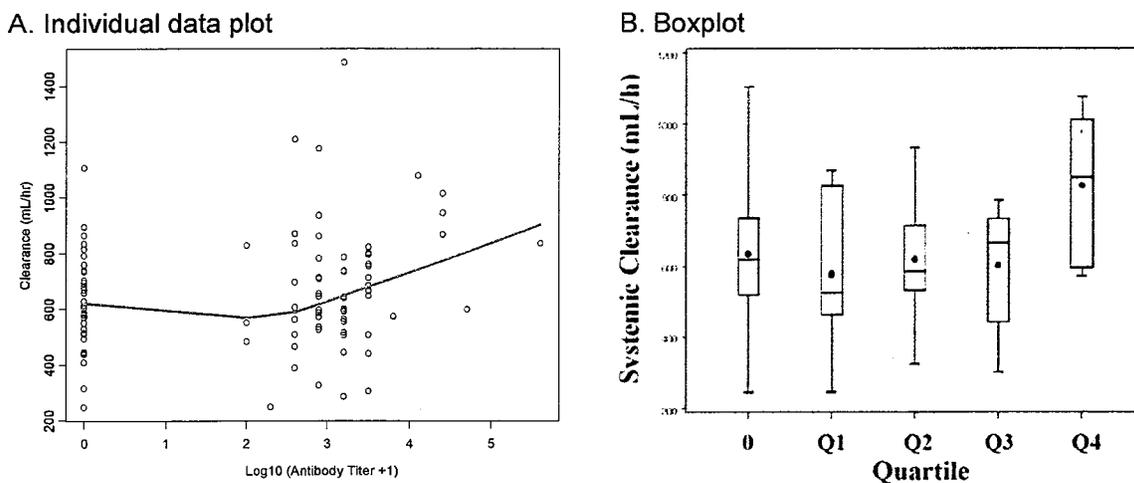
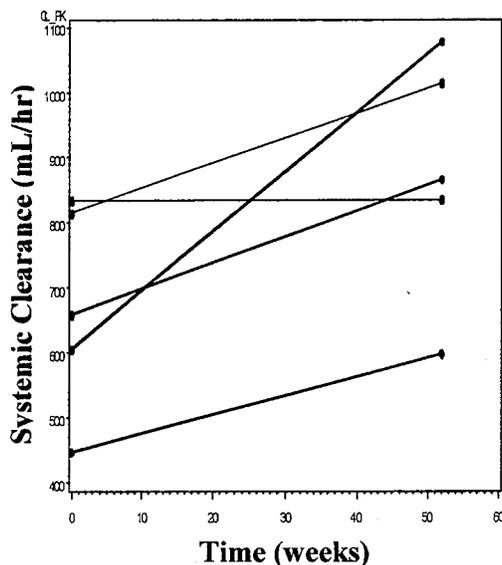


Figure 3 shows the changes in rhGAA CL over time in the 5 inhibitory antibody positive patients. There was a clear increase rhGAA CL in 4 patients between Week 0 and Week 52. In one patient, the clearance increased by as much as 100% (from approx. 600 to approx 1200 mL/hr). The results clearly indicate that the onset of inhibitory antibodies increases the clearance of rhGAA. Although the 5 inhibitory positive patients also had the highest IgG antibody titer in the study, it is unclear whether binding or inhibitory antibodies are the cause for increased clearance. It can only be stated that inhibitory antibody status coincides with high binding antibody titers.

Figure 3: Time Course of rhGAA Clearance in patients with high anti-rhGAA IgG antibody titers and positive inhibitory antibody status at Week 52.



Five patients with positive inhibitory antibody status had higher CL, lower AUC, and lower Cmax than 29 patients with negative status (Table 4).

Table 4: Comparison of pharmacokinetic parameters of rhGAA (2000L scale) between inhibitory antibody positive and negative patients with late onset Pompe disease who received rhGAA 20 mg/kg every other week (Study AGLU02704)

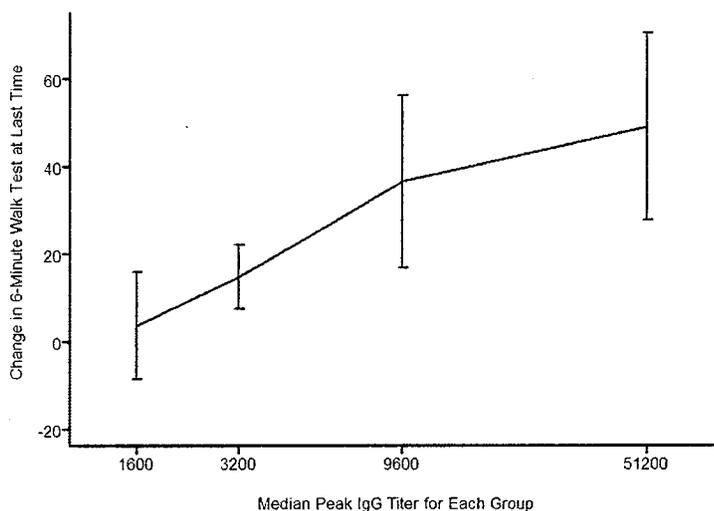
Parameter	Least Squares Mean		Mean Ratio (%)	90% Confidence Interval (%)
	Positive (N=5)	Negative (N=29)		
Cmax (mcg/mL)	300	363	82.7	71.3 - 95.9
AUCinf (mcg*hr/mL)	1951	2547	76.7	65.9 - 89.0
Clearance (mL/hr)	813	608	133.6	115.5 - 154.5
Vss (L)	48.9	48.4		
Effective half-life(hr)	2.25	2.46		

Vss, volume of distribution at steady state

2.3.3.4 What is the impact of anti-product antibodies on clinical efficacy?

The pharmacometrics review team explored the relationship between the change from baseline in 6MWT value and anti-rhGAA IgG antibody titer quartile at mean, peak or last observation in Study AGLU02704. It appears that higher antibody titers in general indicate a greater change that the patient will perform better in 6MWT in response to rhGAA therapy. As shown in Figure 4 below, there appears to be an upward trend in the median 6MWT values.

Figure 4: Relationship between the mean change from baseline in 6-minute walk test at the last observation and anti-rhGAA IgG antibody titer quartile observed in patients with late onset Pompe disease who received rhGAA 20 mg/kg every other week (Study AGLU02704)



Patients with positive inhibitory antibody status also trended upward compared to patients with negative inhibitory antibody status (Figure 5). The trend is visually clear; however, the data is not sufficiently precise to conclude statistical difference between both groups. The data are also in agreement with the upward trend observed for Efficacy with Peak IgG titer. Since inhibitory antibody status is associated with greater IgG titer values, it is expected that inhibitory antibody status will be correlated with increased efficacy because peak IgG titer is.

Figure 5: Inhibitory antibody status might indicate increased efficacy

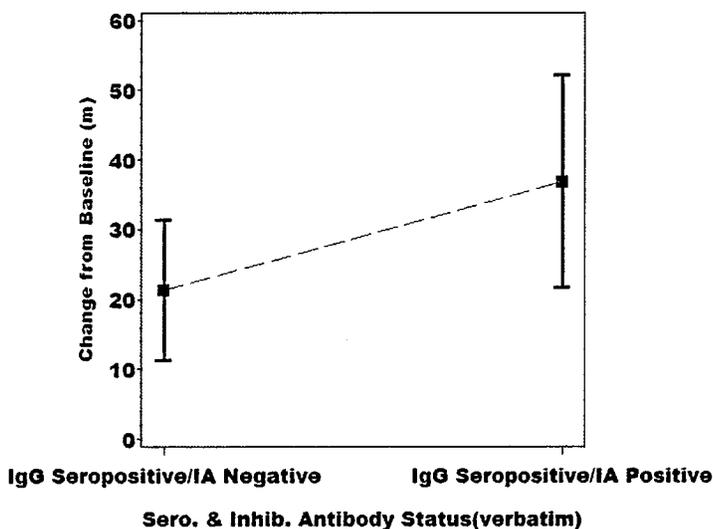


Table 5 shows the applicant's analysis on the relationships between uptake inhibition status and co-primary efficacy endpoints including 6MWT and FVC.

Table 5: Relationship between anti-rhGAA antibody titers, uptake inhibition status, and co-primary efficacy endpoints observed in patients with late onset Pompe disease who received rhGAA 20 mg/kg every other week (Study AGLU02704)

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

The clinical significance of high antibody titers or positive uptake inhibition status is unclear. Higher peak titers were observed among those with positive uptake inhibition. The sponsor claims there is no consistent effect on either co-primary efficacy endpoint (6MWT or FVC) when patients are stratified according to mean titer quartiles, whereas we find there to be an apparent trend in the mean efficacy at the last observation time. The sponsor also concludes the results of 6MWT do not show any consistent effect when patients are stratified by inhibitory antibody status; in fact, patients classified in the positive inhibition subset improved their mean distance walked over baseline by 57.5 meters while those who were inhibition negative only improved by 21.4 meters. The large degree of variation limits the ability to detect a statistical difference between the patients with positive and negative inhibitory antibody status. However, there appears to be greater mean change in the 6-minute walk test in the patient group that developed inhibitory antibodies, possibly resulting from the correlation between inhibitory antibody status and high IgG titer.

When considering the secondary endpoint FVC, no effects of immunogenicity on efficacy were observed. Patients classified in the positive inhibition subset showed less improvement in FVC % predicted (mean 0.2% [SD = 5.53]) than inhibition negative patients (mean 1.8% [SD = 5.48]), while patients who were classified as borderline positive showed less improvement in FVC than either positive or negative patients.

2.3.3.5 What is the impact of anti-product antibodies on clinical safety? (e.g., infusion-associated reactions, hypersensitivity reactions, cross-reactivity to endogenous counterparts, etc.)?

The Applicant reports that in the Myozyme treatment group, 236 (79.2%) of 298 treatment-related events, occurring in 17 patients (28.3%) were characterized as IARs. In the Placebo

treatment group, 73 (50.7%) of 144 treatment-related events, occurring in 7 patients (23.3%), were characterized as IARs. However, upon review and reclassification of these events by the clinical review team, 29 patients in the rhGAA treatment group experienced infusion associated reactions (IAR), and in the placebo treatment group, all of whom tested seronegative, 15 patients experienced IARs. Six patients experienced the first IAR with the first infusion, before seroconversion. Eight patients experienced the first IAR from 8 weeks to 52 weeks after seroconversion. Thus, there was no consistent relationship between time to seroconversion and onset of IARs. There was no apparent association between higher anti-rhGAA IgG antibody titers and occurrence of IARs. However, the types of AEs differed between the 2000 L treatment group and placebo group. Notable differences between the 2000 L and placebo group included the presence of hypersensitivity (allergic) reactions, skin reactions, including urticaria, and paresthesias that were not present in the placebo group. Headache and nausea, the most common IARs in the placebo group were also noted in the 2000 L treatment group.

Forty-six% of the IARs in the rhGAA treatment group were experienced by an IgE positive patient (Patient 18713) who underwent desensitization procedure, including weekly administration of rhGAA. The patient experienced serious hypersensitivity reaction consisting of symptoms of serious non-cardiac chest pain and non-serious events of chest discomfort, urticaria, feeling hot, flushing, local swelling (focal swelling of scalp), pruritus, lip swelling, and macular rash during the 14th infusion at study Week 28. Treatment was interrupted and the patient recovered. Anti-rhGAA IgE antibody status was positive on 7 of 13 occasions beginning at Week 30, complement activation was positive on 1 of 9 occasions and serum tryptase was within normal limits on all 9 occasions tested. The patient remained in the study but study drug infusions were continued under close clinical supervision using a desensitization procedure, incrementally increasing dose from 10 mg/kg per week for 6 consecutive weeks followed by a 7th week of 15 mg/kg before resuming the protocol specified dose of 20 mg/kg. **The patient's anti-rhGAA IgG antibody titer on the day of the event was 3,200, after a peak titer of 12,800 at Week 16.**

One patient (Patient 16709) also experienced serious events of hypersensitivity, chest discomfort, and throat tightness and non-serious events of urticaria, increased blood pressure, flushing, nausea, decreased oxygen saturation, papular rash, pruritus, sinus tachycardia, wheezing, and headache at study Week 2 (second infusion). The patient recovered without sequelae. The patient tested positive for anti-rhGAA IgE antibodies and complement activation and had tryptase elevated to 23.7 mcg/L. The patient was discontinued from study.

Upon medical review, an additional adverse event suggestive of hypersensitivity reaction was identified in a third patient. Patient 90701 experienced severe angioneurotic edema after completing the 3rd infusion at study Week 4 and the patient recovered the same day. The patient was discontinued from the study. Anti-rhGAA IgE antibodies and complement activation were negative and serum tryptase was within normal limits. Testing for anti-rhGAA IgG antibodies was performed retrospectively and the titer on the day of the event was 3,200.

Additionally, the medical review team uncovered one additional patient (29708) who met the definition of anaphylaxis based on a standard clinical definition for anaphylaxis. The patient developed chest discomfort, oral pruritis, hypotension, dizziness, tightness in chest requiring use of an inhaler during at least one infusion. This patient tested negative for anti-rhGAA

antibodies and serum tryptase was within normal limits, but tested positive for complement activation. Peak IgG titer for this patient was 3200.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

No specific analysis was conducted to evaluate the effect of the extrinsic factors on the clinical pharmacology of rhGAA.

2.4.2 Drug-drug interactions

No drug-drug interaction studies were conducted.

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

No studies related to dose, dosing regimens, or administration were conducted for this application.

2.5 General Biopharmaceutics

Only Question 2.5.10 is applicable to therapeutic protein products.

2.5.10 What is the pharmacokinetic and/or pharmacodynamic comparability of the proposed to-be-marketed formulation to the pivotal clinical trial? (Applicable to therapeutic proteins only)

Not applicable to this submission. All studies were conducted using to be marketed formulation.

2.6 Analytical

Questions from 2.6.1 to 2.6.4 are not applicable to therapeutic proteins.

2.6.5 What bioanalytical methods are used to assess therapeutic protein concentrations? Briefly describe the methods and summarize the assay performance.

(b) (4)

Patient sample results were reported if the following acceptance criteria were met for each plate: the r^2 value of the standard curve was \geq (b) (4), the obtained values for each of the rhGAA and 4-MU controls were within established limits (see below), the results for each patient sample were valid if the CV% between the relative fluorescence unit (RFU) values of duplicate wells is \leq (b) (4) when sample fluorescence is greater than 10 RFU.

The table below contains a summary of the precision of interpolated 4MU and rhGAA quality control values across 4 time periods during the course of clinical testing for Study AGLU02704.

Date Range	Control Sample	Lot#	Assays	Mean (ng/mL)	Intra-assay Precision		Inter-assay Precision	
					SD (ng/mL)	CV%	SD (ng/mL)	CV%
11/4/05 to 11/28/05	rhGAA	13152-177b	4	9.7	0.5	5.2	1.6	16.5
11/4/05 to 11/28/05	4MU	13580-136	4	278.1	2.7	1.0	20.6	7.4
12/21/05 to 03/01/06	rhGAA	15021-38	18	295.1	6.9	2.3	20.0	6.8
12/21/05 to 03/01/06	4MU	15021-39	18	9.6	0.3	3.1	1.2	12.5
03/15/06 to 11/19/07	rhGAA	15021-38	92	297.4	11.8	4.0	26.6	8.9
03/15/06 to 11/14/06	4MU	15021-39	50	9.5	0.4	4.2	1.9	20.0
12/28/06 to 11/19/07	4MU	16325-164	42	9.1	0.5	5.5	1.4	15.4

The table below contains a summary of inter-assay precision, intra-assay precision, and relative error (i.e., accuracy) estimates for interpolated (back-fit) rhGAA values from 114 standard curves from passing assays only. Intra-assay precision is defined as the degree of agreement of standard curve interpolated rhGAA back-fit replicate values within individual assay plates. Inter-assay precision is defined as the degree of agreement of standard curve interpolated rhGAA back-fit replicate values across assay plates. Relative error (%) of each interpolated

standard curve point is defined as (interpolated rhGAA concentration - standard rhGAA concentration)/standard rhGAA concentration x 100.

N= 114 standard curves		Intra-Assay Precision		Inter-Assay Precision		Relative Error (RE)	
Standard (ng/mL)	Measured Mean (ng/mL)	SD (ng/mL)	CV%	SD (ng/mL)	CV%	RE (ng/mL)	RE (%)
500	500.1	14.3	2.9	0.8	0.2	0.1	0.0
250	249.6	10.3	4.1	3.6	1.4	-0.4	-0.2
100	100.7	3.8	3.8	4.5	4.5	0.7	0.7
50	50.0	2.4	4.8	2.9	5.8	0.0	0.0
10	10.0	0.7	7.0	1.1	11.0	0.0	0.0
5	4.8	0.4	8.3	1.3	27.1	-0.2	-4.2
2.5	2.4	0.4	16.7	1.3	54.2	-0.1	-4.2

2.6.6 What bioanalytical methods are used to assess the formation of the anti-product antibodies? Briefly describe the methods and assay performance including sensitivity, specificity, precision, cut point, interference and matrix, etc.

The immunogenicity data in this application were generated from the following 5 assays for which final validation reports were previously submitted and reviewed under STN 125141/0:

1. rhGAA IgG Enzyme Linked Immunosorbent Assay (ELISA)
2. rhGAA IgG Radioimmunoprecipitation (RIP) Assay
3. rhGAA IgE Assay
4. rhGAA Inhibition Assay (enzyme activity)
5. Flow Cytometry Assay for Inhibition of GAA Uptake

Reports detailing in-process performance of these assays during Study AGLU02704 are not available at completion of this review. The applicant proposed to provide technical reports containing the in-process performance data as part of a post-marketing commitment (PMC) for BLA 125291. The Division of Therapeutic Proteins (DTP) accepted the applicant's proposal.

2.6.6.1 What is the performance of the binding assay(s)?

IgG antibody binding to rhGAA was analyzed by ELISA and confirmed by RIP. The performance of the assays are to be received as a PMC as accepted by DTP.

2.6.6.2 What is the performance of the neutralizing assay(s)?

Based on the description in the clinical study report (AGLU02704), the amount of enzyme inhibition was quantified by measuring rhGAA enzyme activity. The assay limit of detection (defined as the lowest percent inhibition that could be discriminated from serum background) was set at 20%. Patient samples with percentage inhibition greater than 20% at any sera dilution were considered positive by inhibitory antibody assay.

A flow cytometry based assay was also developed to evaluate whether patient antibodies interfered with uptake of rhGAA by human fibroblast cells in culture. Different dilutions of

patient serum were pre-incubated with GAA conjugated to a fluorescent marker and added to the fibroblast cells. Cells were harvested and analyzed by flow cytometry. Serum samples that had enzyme uptake inhibition greater than 20% at two or more sera dilutions were considered to be positive at that time point. Patients were considered positive for uptake inhibition if they demonstrated an end point titer 40 or greater at 2 or more consecutive time points. Patients who demonstrate an end point titer 40 or greater at only 1 time point or at non-consecutive time points, and patients who show inhibition below the 1/40 dilution only, are classified as borderline positive for uptake inhibition. The performance of the assays are to be received as a PMC as accepted by DTP.

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4 APPENDICES

4.1 Package Insert (Proposed and Annotated)

Please refer to \\cbsap58\M\EDR Submissions\2007
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4.2 Summary of Individual Studies

See the attached Pharmacometric Review by Dr. Justin Earp.

4.3 Consult Reviews

See the attached Pharmacometric Review by Dr. Justin Earp.

End of Document

OFFICE OF CLINICAL PHARMACOLOGY:

PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

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

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

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

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

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

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

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

1.1.4 Is there an exposure-efficacy relationship?

No exposure-efficacy relationship was observed within the available data. The data was limited to one dose level and the range of exposure to the drug was limited because of this. A wider exposure range achieved by more dose levels may support an exposure-response relationship that was undetectable within this submission. As a result there are no dose-adjustment related recommendations.

1.1.5 Does the IgG- or inhibitory-antibody titer affect the efficacy of recombinant alglucosidase alpha?

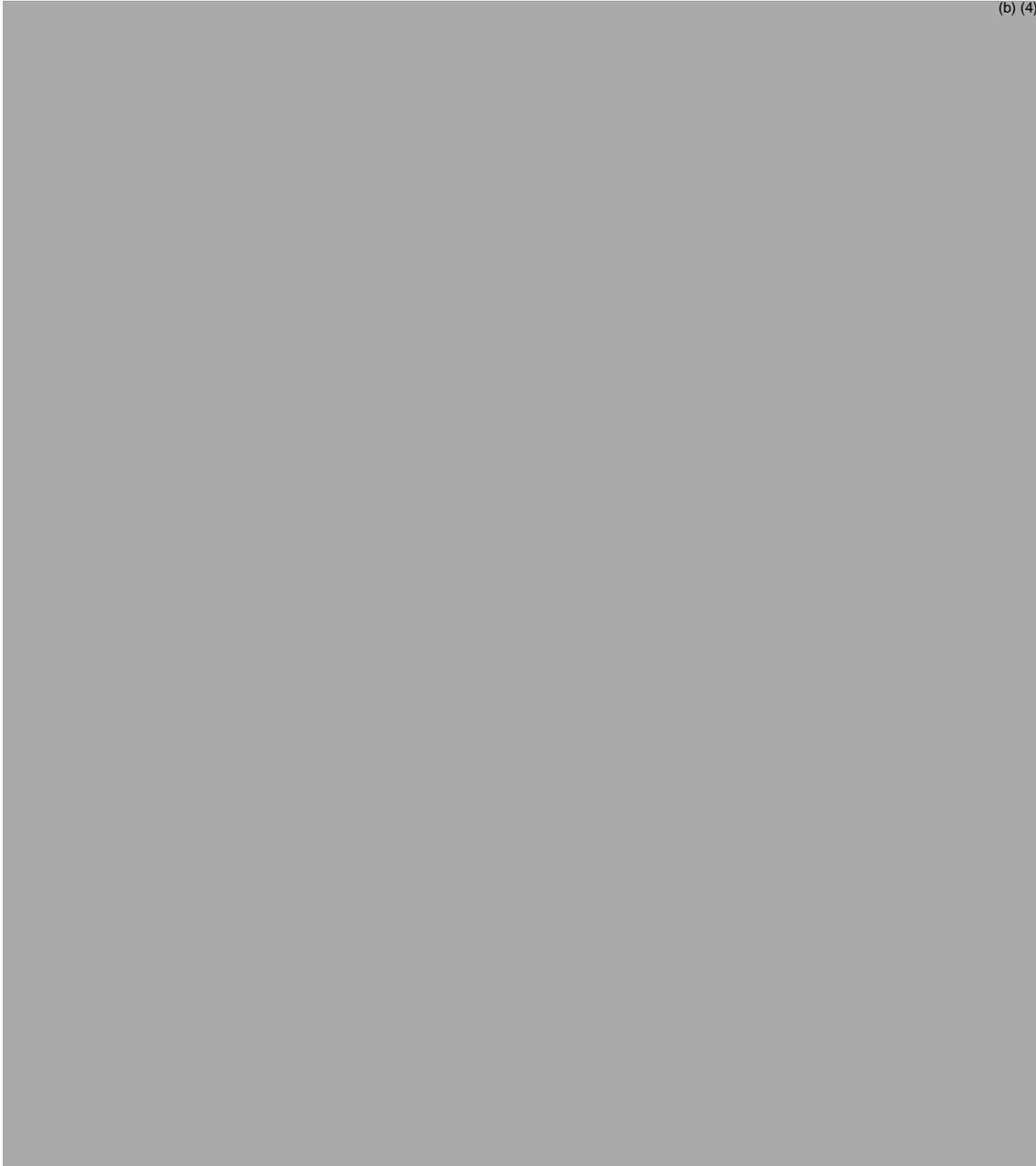
Higher peak antibody titers indicate a higher chance that the individual will respond better in the 6-minute walk test to the drug. However, immunogenic responses are varied between subjects and there is inter-subject variation in the data. While, there is no guarantee that if an individual develops antibodies he/she will perform better, individuals with inhibitory antibodies and high IgG antibody titer showed the greatest improvements.

1.2 Recommendations

The Pharmacometrics Section of the Office of Clinical Pharmacology has reviewed the pharmacokinetics of alglucosidase alpha and has identified necessary adjustments to the label.

1.3 Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.



2 PERTINENT REGULATORY BACKGROUND

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

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Pharmacokinetics

3.1.1 Study Design

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

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

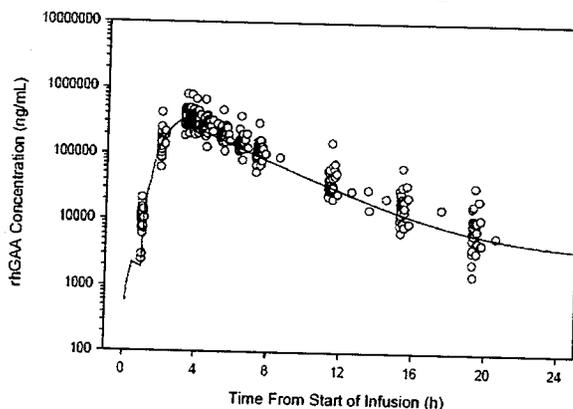
“Assessment of pharmacokinetics was performed on a subgroup of patients. The subgroup of patients for whom pharmacokinetic samples were obtained was based on those study sites that could accommodate pharmacokinetic sampling needs. Blood samples for the measurement of plasma rhGAA activity were collected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

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

3.1.2 Pharmacokinetic Model

The sponsor applied a 2-compartment linear pharmacokinetic model with a zero-order input that was calculated based on the individual's **alglucosidase alpha infusion rate**. In general, the model described the data well (Figure 1). The model fitting for each individual was then used to determine the individual's Clearance values (Table 1) from which AUC was calculated. Observed concentrations were used to determine the C_{max} . Non-compartmental analysis was not used to present the pharmacokinetic parameters of the individuals in the population studied.

Figure 1. Sponsor's Final Pharmacokinetic Model Fitting at Week 0.



(Source: Sponsor's Pharmacokinetic Report)

Table 1. Alglucosidase Alpha Model-Based Pharmacokinetic Parameters

(b) (4)

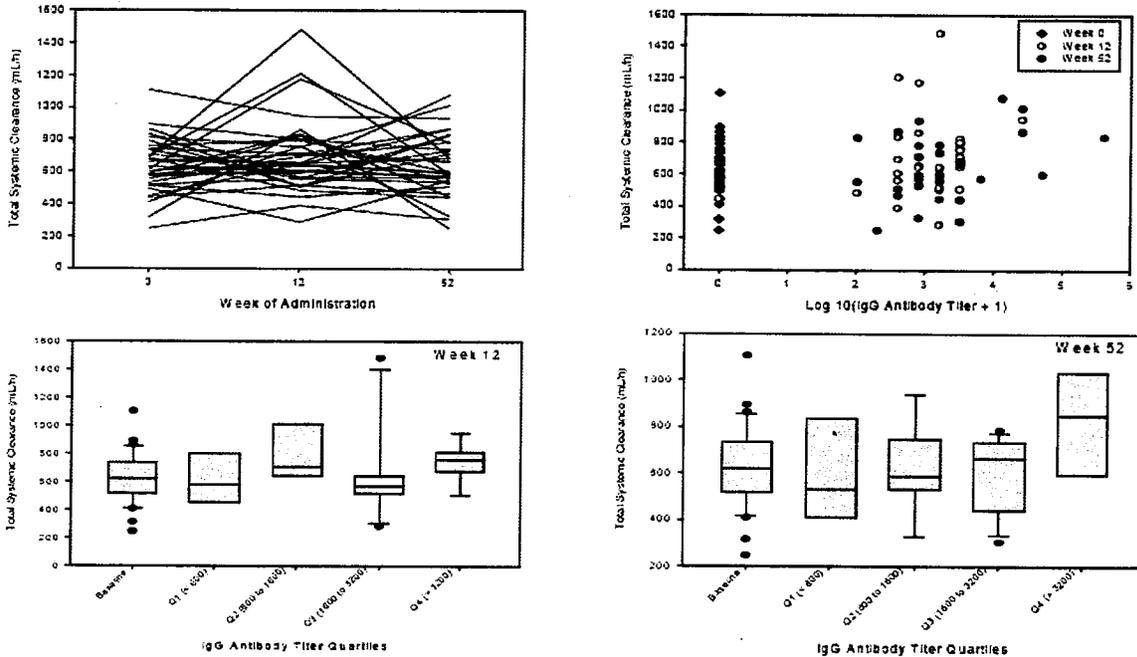


(Source: Sponsor's Proposed Label Document)

3.1.3 Do IgG antibodies Change the Clearance of Alglucosidase Alpha?

Based on the graphs in Figure 2, Genzyme suggests that clearance is not affected by the individual's IgG antibody titer.

Figure 2. Sponsor's Presentation of IgG antibody Impact on Systemic Clearance.

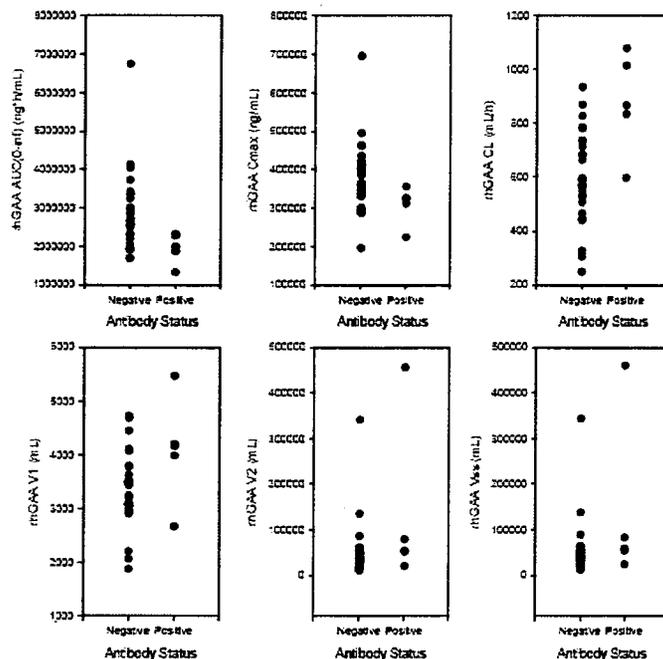


(Source: Sponsor's Pharmacokinetic Report)

Reviewer's Comments: Although the sponsor claims no difference in systemic clearance with antibody titer, clearance appears to increase at much higher antibody titer concentrations. This is most visible at week 52 in the 4th quartile -- there is a higher median. In the log₁₀ antibody titer versus systemic clearance plot, clearance appears to increase at the higher antibody titer amounts. There is no apparent difference in AUC across the weeks and across different amounts of antibody titer. However, AUC should not be used as a secondary parameter as dosing is weight and tolerance dependent and not all individuals are expected to have the same AUC following dosing and across different weeks.

The sponsor goes on to show that the pharmacokinetics of the 5 patients that tested positive for inhibitory antibodies have lower AUC and higher clearance values than in the population that tested negative (Figure 3).

Figure 3. Week 52 Pharmacokinetics in Patients who Tested Negative or Positive for Inhibitory Antibodies.



(Source: Sponsor’s Pharmacokinetic Report)

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

3.2 Efficacy

3.2.1 Is there an exposure-efficacy relationship?

The sponsor did not present an analysis of the relationship or lack of relationship between exposure to alglucosidase alpha and efficacy.

3.2.2 Does the IgG- or inhibitory-antibody titer affect the efficacy of recombinant alglucosidase alpha?

The sponsor concludes that there was no consistent effect on either co-primary efficacy endpoint when patients were stratified by mean IgG titer quartiles. The IgG titer data from study Aglu2704 was divided into four quartiles dependent on titer value. Both the mean (Table 2) and peak (Table 3) titer values were used to test if there was a difference in efficacy between groups.

Table 2. Summary of Safety and Efficacy in Myozyme Treated Patients by Mean IgG Titer Quartiles

Parameter	Mean IgG Titer Category for Myozyme Patients who Seroconverted (N = 59)			
	Quartile 1 124.1-581.0	Quartile 2 729.4-1449.2	Quartile 3 1458.8-3736.8	Quartile 4 4098.6-135117.6
Number of Patients n (%)	14 (23.7)	15 (25.4)	15 (25.4)	15 (25.4)
Number of Patients with any AE n (%)	14 (100.0)	15 (100.0)	15 (100.0)	15 (100.0)
Number of Patients with any SAE n (%)	4 (28.6)	2 (13.3)	4 (26.7)	2 (13.3)
Number of Patients with any IAR n (%)	2 (14.3)	7 (46.7)	3 (20.0)	4 (26.7)
6MWT change in meters walked from Baseline to last observation	-6.9±48.15 median -8.0	25.2±41.61 median 17.0	24.2±46.18 median 16.0	59.7±94.17 median 23.0
FVC change in % predicted from Baseline to last observation	-0.6±4.96 median -1.0	2.4±5.72 median 2.0	1.5±5.18 median 1.0	1.7±6.33 median 0.0

Source: Sponsor's Final Clinical Study Report, Table 12-14.

The change in meters walked in the 6-minute walk test in Table 2 indicates there is an increase in efficacy in patients with higher IgG titers.

Table 3. Summary of Safety and Efficacy in Myozyme Treated Patients by Peak IgG Titer Quartiles

Parameter	Peak IgG Titer Category for Myozyme Patients who Seroconverted (N = 59)			
	Quartile 1 200-1600	Quartile 2 3200-3200	Quartile 3 6400-12800	Quartile 4 25600-819200
Number of Patients n (%)	17 (28.8)	12 (20.3)	16 (27.1)	14 (23.7)
Number of Patients with any AE n (%)	17 (100.0)	12 (100.0)	16 (100.0)	14 (100.0)
Number of Patients with any SAE n (%)	5 (29.4)	2 (16.7)	4 (25.0)	1 (7.1)
Number of Patients with any IAR n (%)	6 (35.3)	2 (16.7)	5 (31.3)	3 (21.4)
6MWT change in meters walked from Baseline to last observation	6.1±53.67 median 5.0	16.0±24.98 median 9.0	34.8±76.60 median 16.5	49.1±79.91 median 19.5
FVC change in % predicted from Baseline to last observation	0.8±5.68 median 0.0	1.8±5.29 median 3.0	1.5±5.73 median 0.5	1.1±5.95 median 0.0

Source: Sponsor's Final Clinical Study Report, Table 12-15.

Similarly, the change in meters walked in the 6-minute walk test in Table 3 indicates there is an increase in efficacy in patients with higher IgG titers. The trend is clearer in Table 3; however, the sponsor concludes no effect because of the large inter-subject variation that exists in both Table 2 and Table 3. Further, the FVC endpoint does not appear to exhibit a trend or change between mean or peak IgG titer quartiles.

The sponsor also claimed that no consistent difference was observed in efficacy between patients with positive and negative inhibitory uptake antibody status (Table 4).

Table 4. Summary of Efficacy by Inhibitory Antibody Status.

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

Source: Sponsor's Final Clinical Study Report, Table 12-17.

Reviewer's Comments: While the sponsor's tables, report did not suggest there was a consistent correlation between the presence of antibodies and increased efficacy, the mean change in the 6-minute walk test at the last observation consistently increased with higher antibody titers and in patients considered positive for uptake inhibition.

4 REVIEWER'S ANALYSIS

4.1 Introduction

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

4.2 Objectives

Analysis objectives are:

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

4.3 Methods

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

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

4.3.1 Data Sets

Data sets used are summarized in Table 5.

Table 5. Analysis Data Sets

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

4.3.2 Software

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

4.4 Results

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

The final parameter estimates from both the sponsor's and agency's NONMEM fittings are shown in Table 6. There was no apparent difference in the parameter estimates though slight differences were noted in the estimates of the parameter and inter-occasion variances.

Table 6. Comparison of Sponsor's and Reviewers Pharmacokinetic Estimates.

Parameter	Sponsor's Estimate	Sponsor's Standard Error	Reviewer's Estimate	Reviewer's Standard Error
CL (mL/hr)	613	156	613	152
V ₁ (mL)	3400	133	3400	133
Q (mL/hr)	334	153	334	150
V ₂ (mL)	46900	44900	46800	44300
θ ₅	0.683	0.131	0.683	0.128
BPV (CL)	30.3%		29.6%	
BPV (V ₁)	20.4%		13.8%	
BPV (Q)	23.4%		25.7%	
BPV (V ₂)	107%		87.3%	
IOV (CL)	17.9%		17.8%	
IOV (V ₁)	14.2%		14.1%	
σ ²	19.9%		19.7%	

The model adequately described the observed pharmacokinetics data. Determination of clearance from the model is reasonable. The kinetics appeared stationary for the entire population. However, for biologics the development of immunogenicity against the drug is always of concern. Immunogenicity is different between individuals and kinetics in one person may vary greatly from what the population predicts. The remainder of the pharmacokinetic review attempts to address the impact of high antibody titer on the clearance of alglucosidase alpha.

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

The sponsor's plot of clearance versus antibody titer (Figure 2) was remade with a smoothed trend line through the data (Figure 4) to better show the clearance-antibody titer relationship. There is a clear upslope in the clearance estimate at antibody titers at or above 10000. This would suggest that clearance increases with higher antibody titers.

Figure 4. Smoothed Trend Line Depicts the Tendency of Clearance to Increase with Antibody Titer.

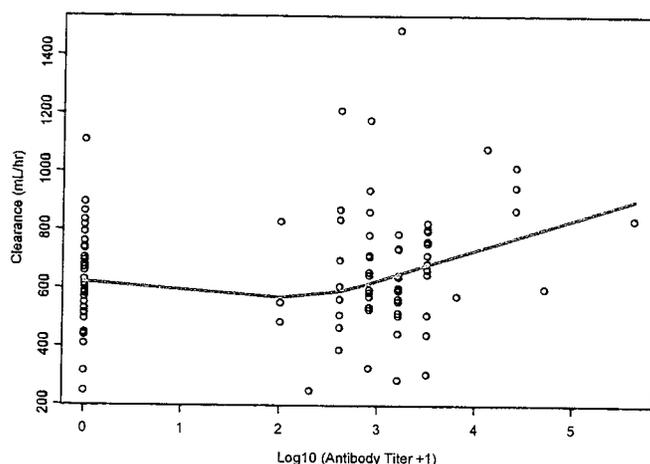
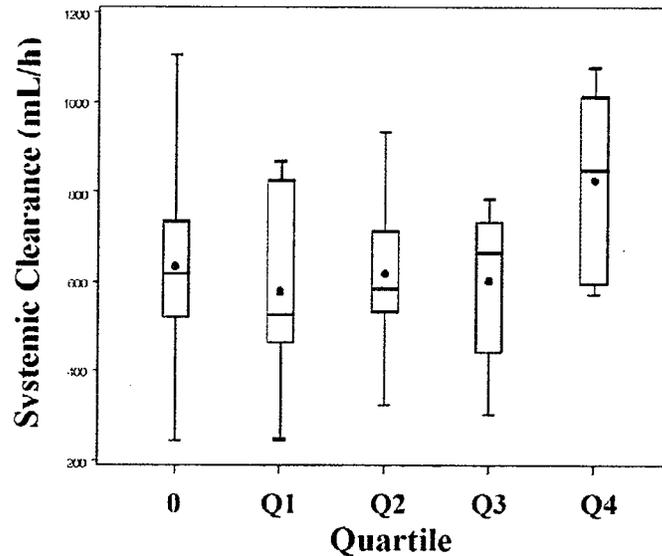


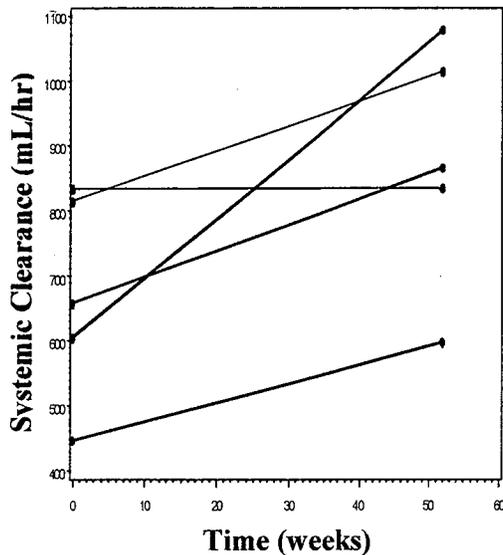
Figure 5 is similar to Figure 4 and the sponsor's depiction of the data (Figure 2). Here the mean (blue dots) is shown in addition to the median (solid red line across each bar) for each quartile of antibody titer. Clearance appears to be greater at the higher quartile.

Figure 5. Systemic Clearance versus Antibody Titer Quartile.



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

Figure 6. Time Course of Clearance for Individuals with High IgG Antibody Titer and Positive Inhibitory Antibody Status at Week 52.

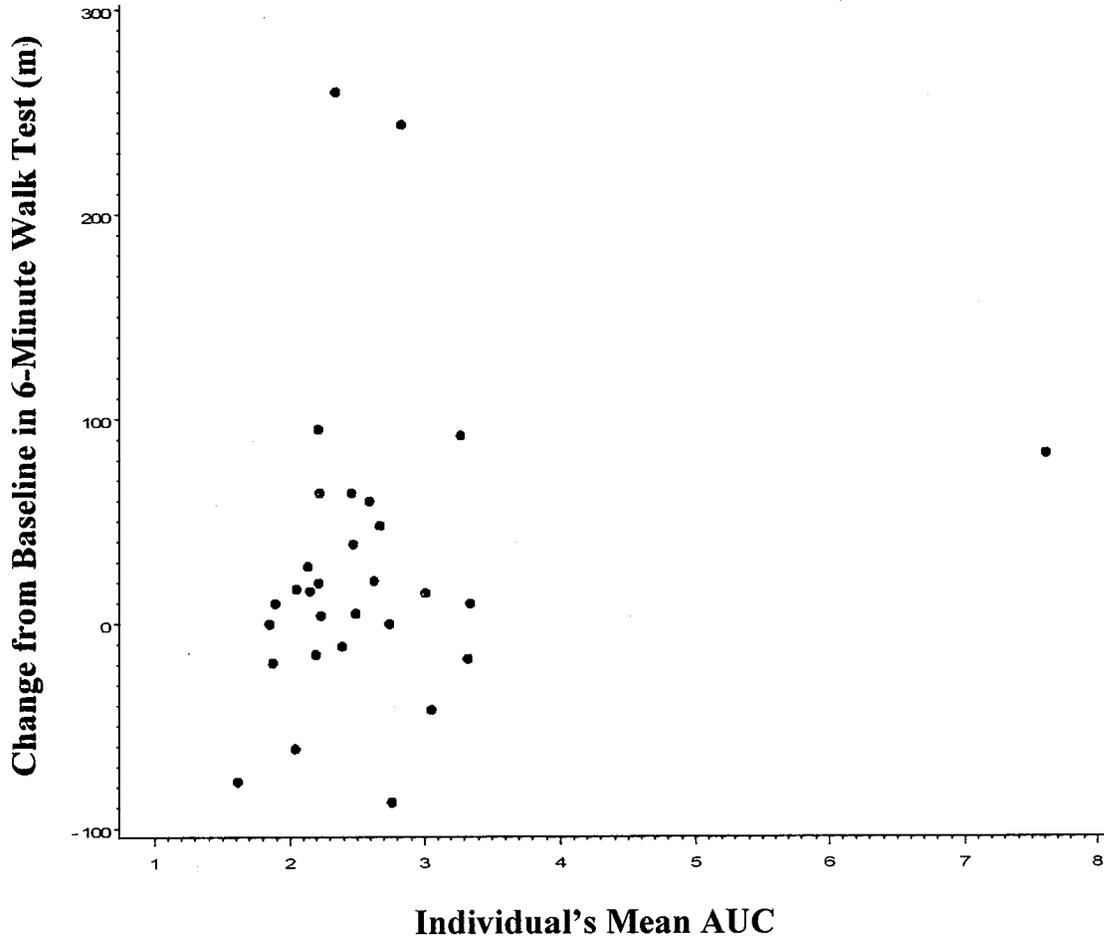


The results in Figure 6 clearly indicate that the onset of inhibitory antibodies increases the clearance of alglucosidase alpha. It should also be noted that the 5 inhibitory positive individuals also had the highest IgG antibody titer in the study. This second observation makes it unclear whether IgG antibodies or inhibitory antibodies are the cause for increased clearance. It can only be stated then that inhibitory antibody status appears to coincide with high IgG antibody titer.

4.4.3 Is there an exposure-efficacy relationship.

Figure 7 shows the change from baseline in the 6-minute walk test at week 78 compared to the individual's mean exposure (as indicated by AUC) across weeks 0, 12, and 52. The range of mean AUC values is limited given only one dose-level was administered. Within this data it is difficult to see a consistent trend in response across the range of exposures to alglucosidase alpha.

Figure 7. There is no clear exposure-response relationship within the studied dose level.



As there is a limited exposure range, no recommendations regarding dose adjustment can be made.

4.4.4 Does the IgG- or inhibitory-antibody titer affect the efficacy of recombinant alglucosidase alpha?

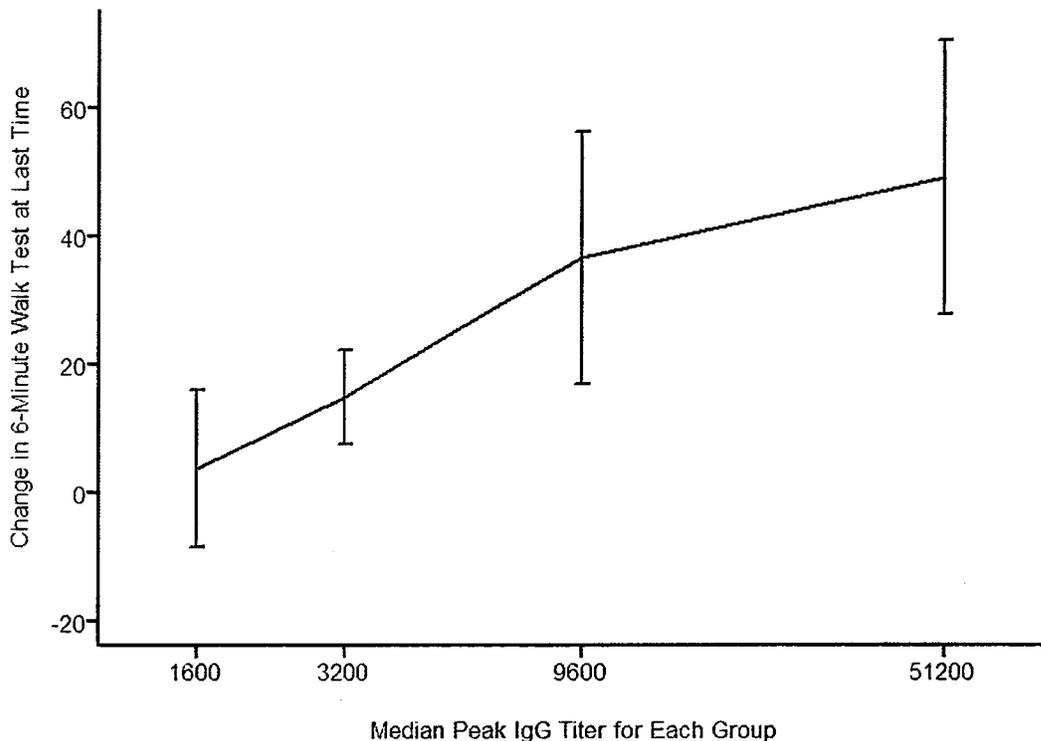
The effect of IgG and inhibitory antibody titers on the efficacy of alglucosidase alpha was evaluated with the mean change from baseline dependent on four quartiles of IgG antibody titer or the patient's inhibitory antibody status. The sponsor's approach divides individuals responses into quartiles depending on their mean or peak IgG titer and compares this with the change from baseline at the last observation for that individual.

Quartiles were constructed based on the value of the titer rather than by an equal number of subjects in each group. Grouping by values is more appropriate given the discrete nature of the titer values and the logarithmic range of the data. If the grouping was done by number of subjects than individuals with a peak titer of 3200 would be divided among two different groups.

Both the sponsor and this reviewer concluded the data showed an increasing trend in efficacy with increasing IgG antibody titer.

The means and standard errors for efficacy at the last observation dependent on peaks IgG titer are shown in Figure 8. In Figure 8 it appears that higher antibody titers in general indicate a higher chance that the individual will perform better in response to the drug.

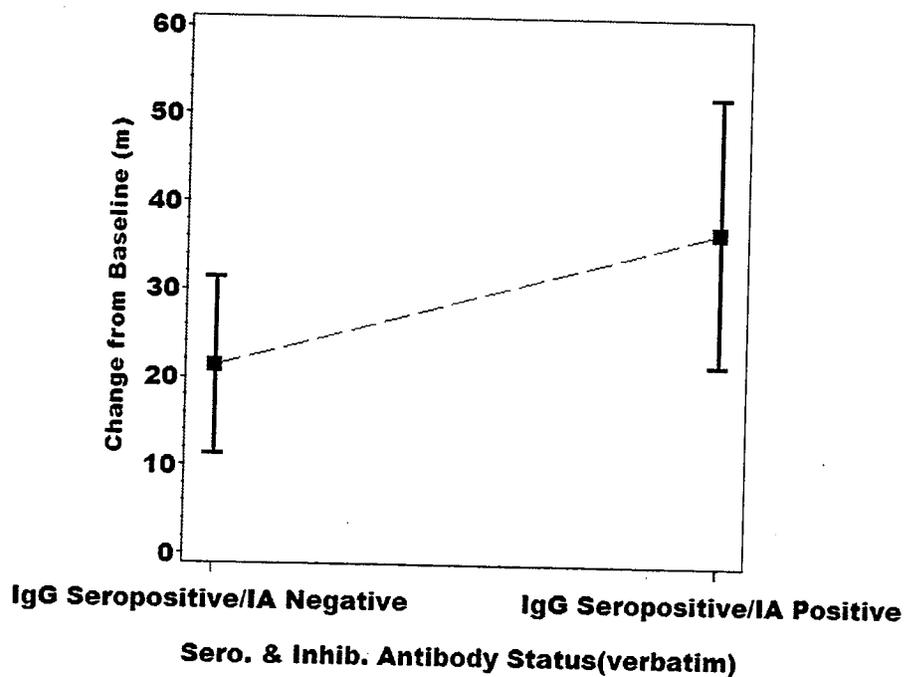
Figure 8. Data Show Upward Trend in Efficacy with Increasing IgG Antibody Titer*



*While no titer value of 9600 was present, the third group was evenly divided by individuals with a peak titer of 6400 and 12800.

Patients with positive inhibitory antibody status also trended upward compared to patients with negative inhibitory antibody status (Figure 9). The trend is visually clear; however, the data is not sufficiently precise to conclude statistical difference between both groups. The data are also in agreement with the upward trend observed for Efficacy with Peak IgG titer. Since inhibitory antibody status is associated with greater IgG titer values, it is expected that inhibitory antibody status will be correlated with increased efficacy because peak IgG titer is.

Figure 9. Inhibitory Antibody Status Might Indicate Increased Efficacy.



5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
pkpd.sas	SAS Code for Figure 7	\\cdsnas\PHARMACOMETRICS\Aglucosidase Alpha\Reviewer
PD6MWT.csv	PD Dataset	\\cdsnas\PHARMACOMETRICS\Aglucosidase Alpha\Reviewer
Myozyme.ctf	Sponsor's PK NONMEM CODE	\\cdsnas\PHARMACOMETRICS\Aglucosidase Alpha\Reviewer\PK NONMEM Files
	Reviewer's PK Output	\\cdsnas\PHARMACOMETRICS\Aglucosidase Alpha\Reviewer\PK NONMEM Files
	Sponsor's PK Dataset	\\cdsnas\PHARMACOMETRICS\Aglucosidase Alpha\Reviewer\Aglucosidase Alpha NONMEM

Clinical Pharmacology Review

BLA:	125141/65
Brand Name:	Myozyme
Generic Name:	Alglucosidase alfa, recombinant human acid alpha-glucosidase [rhGAA]
Dosage form and Strength:	Lyophilized cake or powder for reconstitution with sterile water for injection (5.0 mg/mL)
Route of administration:	Intravenous (IV) Infusion
Indication:	For use in patients with infantile-onset Pompe disease
Sponsor:	Genzyme Corporation
Type of submission:	Efficacy Supplement
Clinical Division:	Division of Gastroenterology Products (HFD-180)
OCP Division:	DCP III
Priority:	Priority (6 months)
Submission dates:	10/31/07, 01/15/08, and 02/07/08
Reviewer:	Tien-Mien Chen, Ph.D.
Team leader:	Sue-Chih Lee, Ph.D.

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1. Executive Summary

The sponsor submitted this BLA supplement on 10/31/07 to seek approval of use of Myozyme manufactured at the 2000 L scale in patients with infantile-onset Pompe disease. This is the scope of this clinical pharmacology review. The purpose of this submission was changed in April 2008 [REDACTED] (b) (4) [REDACTED] to the use in late-onset patients. Evaluation of the data in support of this new indication will be made by Dr. Ike Lee of OCP. As such, this review is for documentation purpose only.

1.1 Comments

- A. Based on the PK data provided for Study AGLU02403, the sponsor has not demonstrated that the proposed 2000 L scale lots are bioequivalent to the approved 160 L scale lots. It should be noted that the sponsor did not provide the in-process assay performance report for determination of plasma GAA in this study. If the PK data generated from this study are to be used for other purposes, the above assay performance report should be provided.
- B. It is not clear how the immunogenicity profile for the 2000L lots compares to that for the 160L lots since immunogenicity data for the 2000L lots following long term treatment are lacking. (Note: Immunogenicity data were obtained for a median time period of 29.0 weeks for the 2000 L lots vs. 108.1 weeks for the 160 L lots.) Again, the sponsor did not provide the in-process assay performance report for determination of anti-GAA antibody in the study. If these immunogenicity data are to be used for other purposes, the above assay performance report should be provided.

08/26/08

Tien-Mien Chen, Ph.D.
OCP/DCP3 reviewer

Team Leader: Sue-Chih Lee, Ph.D.

 8/26/08

1.2 Summary of Clinical Pharmacology and Biopharmaceutics Findings

BACKGROUND:

Pompe disease is a rare, autosomal recessive disease caused by the deficiency of lysosomal GAA (alglucosidase alfa, acid alpha-glucosidase), an enzyme that degrades lysosomal glycogen. In patients with Pompe disease, glycogen builds up abnormally in cells resulting in accumulation of glycogen in body tissues, especially cardiac, respiratory, and skeletal muscle, disrupts the architecture and function of affected cells leading to multisystemic pathology and death. Infantile-onset Pompe disease is

characterized by the early onset of symptoms, severe cardiac involvement, and early death due to cardiac and/or respiratory failure.

Myozyme® (recombinant human GAA [rhGAA]) is labeled for use as an enzyme replacement therapy (ERT) for patients with infantile-onset Pompe disease. Market approval was granted on 04/28/06 for Myozyme manufactured at the 160 L scale with an approved dosing regimen of 20 mg/kg (given by IV infusion for about 4 hrs) every other week (qow). The 2000L lots were not approved at the time because the data provided were inadequate to support the 2000 L scale product.

The original BLA submission included a pivotal clinical trial (Study AGLU01602) among others. In this pivotal trial, 18 patients with infantile-onset Pompe disease were enrolled and 160 L scale lots and two dose levels, 20 mg/kg (n=9) and 40 mg/kg (n=9), were studied. At 18 months, 83.3% of patients were alive and not on the ventilation, while in the historical control at 18 months, only 1 out of 61 patients (1.6%) was alive and not on the ventilation.

Under this BLA supplement (BLA125141/65), several clinical studies (see Table 1 and Note #1 beneath the table) were submitted in addition to the *in vitro* testing results to support the comparability between 160 L and 2000 L scale lots. The primary clinical data were obtained from Study AGLU02403 and Study AGLU01702.

Study AGLU02403 was an open-label, extension study for patients previously enrolled in the above pivotal clinical trial AGLU01602. This study assessed ventilator-free survival, safety, immunogenicity, pharmacokinetics (PK) and pharmacodynamics (PD; motor status) of the 160 L and 2000 L scale lots. In addition, the effect of different dosages of Myozyme (20 or 40 mg/kg qow) on safety and efficacy outcomes were also evaluated.

Study AGLU01702 was also submitted to original BLA to support the 160 L lot. It provided data on pharmacokinetics (PK), immunogenicity, and pharmacodynamics (PD, e.g., muscle GAA and glycogen content and plasma and urine oligosaccharide levels). It should be noted that the PD measures evaluated by the sponsor are considered exploratory in nature and none of the measures is deemed to be a qualified marker for efficacy at this time.

Comparative PK data between 160 L and 2000 L scale lots was also provided in the original BLA, but was obtained from GAA knockout mice (Animal Study 05-0414). It was concluded by the previous CP reviewer that the 2000L scale product had a 30% lower plasma AUC than that of the 160 L scale product and therefore, comparability was not demonstrated. The sponsor later withdrew the 2000 L scale product from the original BLA submission.

Preliminary human PK data in 5 patients (age range 5-15 years) with late-onset Pompe disease for the 2000 L scale lots (Study AGLU02804) was submitted later in an amendment to the original BLA, but it was concluded that comparability could not be made due to limited number of patients and different patient population.

In total, 31 patients in Studies AGLU01602/2403 (n=16) and AGLU01702 (n=15) who switched from 160 L lots to 2000 L lots received a median of 108.1 weeks (range of 70.0 to 143.2 weeks) of Myozyme treatment with 160 L lots. Exposure to 2000 L lots was shorter (median, 29.0 weeks) among patients who switched.

Pharmacokinetics:

In Study AGLU02403, PK blood samples were collected in one occasion for the 160L lots and in two occasions separated by 12 weeks for the 2000L lots. Plasma GAA levels after IV infusion were fitted using a one-compartment open model. Peak level (C_{max}) and area under the curve ($AUC_{0-\infty}$) were estimated based on modeling. The observed C_{max} levels were also obtained at the end of infusion. A total of 12 patients had comparative PK data, seven (7) in the 20 mg/kg cohort and five (5) in the 40 mg/kg cohort.

The geometric mean ratios for the PK parameters (for the 20 and 40 mg/kg doses combined) and their 90% confidence intervals are presented in the table below. Based on the bioequivalence (BE) acceptance criteria, the 2000 L scale lot has not been demonstrated to be bioequivalent to the currently approved 160 L lot in terms of C_{max} and $AUC_{0-\infty}$. This, however, does not necessarily mean that the scale-up lot (2000 L) was not bioequivalent to the 160 L lot in PK, since there were limitations in the study design (e.g., a sequential design, not a crossover design, and a small sample size). It is noted that the PK parameters for the 2000 L lots determined at two different occasions (12 weeks apart) were not shown to be bioequivalent. Again, one has to bear in mind the limitations in the study design as stated above.

Sponsor's Results of BE Assessment between 160 L and 2000 L lots (Study AGLU02403)

Comparison	Test/Ref Ratio	90% CIs
2000 L (Test) vs. 160 L (Ref)		
C_{max}	1.40	1.16 – 1.70
$AUC_{0-\infty}$	1.24	1.04 – 1.46
2000 L Repeat (Test) vs. 160 L (Ref)		
C_{max}	1.09	0.89 – 1.32
$AUC_{0-\infty}$	1.02	0.86 – 1.20
2000 L Repeat (Test) vs. 2,000 L (Ref)		
C_{max}	0.774	0.633 – 0.946
$AUC_{0-\infty}$	0.824	0.686 – 0.989
2000 L Combined (Test) vs. 160 L (Ref)		
C_{max}	1.23	1.05 – 1.45
$AUC_{0-\infty}$	1.12	0.97 – 1.29

Immunogenicity: Anti-rhGAA IgG antibody titers in switched patients treated with rhGAA lots manufactured at the 2 scales were compared for Studies AGLU01602/2403 and AGLU01702. The results showed that median IgG titers were similar before and after switching from the 160L scale lot to the 2000 L scale lot. However, the treatment period for the 2000L lots was too short (a median of 29.0 weeks for the 2000 L lots vs. 108.1 weeks for the 160 L lots). As such, the comparability of immunogenicity after 29 weeks in patients switched to 2000 L lot is unknown.

Nearly all Naïve Patients exposed to Myozyme exhibited seroconversion, including 35 (89.7%) of the 39 Naïve patients receiving 160 L lot in Studies AGLU01602/2403 and

AGLU01702, and 9 (90%) of the 10 Naïve patients receiving 2000 L lots in Study AGLU02203. These results are consistent with previous myozyme data analysis.

Pharmacodynamics:

Biomarkers: Several biomarkers had been explored for exposure-response (E-R) relationships for Myozyme in the original BLA submission. In the review of the original BLA submission, it was concluded that the muscle GAA activity increased with time, however, no clear trend was appreciated for the decrease in skeletal muscle glycogen content with the increase in GAA activity. Plasma and urinary oligosaccharide levels might be useful as a biomarker and urinary oligosaccharide level would be a better, non-invasive marker. None of these biomarkers are qualified and none were measured in the extension study AGLU02403. Therefore, there is paucity of biomarker data for comparison between 160 L and 2000 L scale lots.

Motor development: In the current submission, motor development status was explored as supportive clinical efficacy endpoint using several observational measures of infant motor development to evaluate normal patterns of motor movement that evolve from birth through 18 months of age. The motor status appears to be predictive of ventilator-free survival. However, due to the sequential design and small sample size, the data are inadequate for comparison between the 160L and 2000L batches.

The sponsor also provided other PD data, e.g., LVMI (left ventricular mass index). These data were reviewed in details by Dr. Ku of DGP. According to Dr. Ku, no conclusions could be reached because there were only a few data points collected during the 2000L experience for these parameters.

CONCLUSION:

This reviewer focused on PK and immunogenicity data as part of the comparability assessment for the proposed 2000L lots relative to the approved 160L lots. Both the PK and immunogenicity data as submitted by the sponsor do not support the comparability of the product between the two batch sizes.

2. Question Based Review

2.1. General Attributes

Drug Substance:

Myozyme® (alglucosidase alfa), a recombinant human acid alph alglucosidase (rhGAA), was developed by Genzyme from one of its own Chinese hamster ovary (CHO) cell lines. No changes to the drug manufacturing processes were made when the batch was scaled up from 160L to 2000L, however, some manufacturing specifications are different between the two different scale lots which may impact the efficacy.

Formulations:

Myozyme is supplied as a sterile, nonpyrogenic, white to off-white, lyophilized cake or powder for reconstitution with sterile water for injection for IV infusion. After reconstitution, each 50-mg vial contains 10 mL solution at 5.0 mg/mL of GAA. The currently approved formulation was used.

Mechanism of Action:

Pompe disease is a rare, autosomal recessive disease caused by the deficiency of lysosomal GAA, an enzyme that degrades lysosomal glycogen by catalyzing the hydrolysis of α -1,4 and α -1,6 glycosidic linkages. In patients with Pompe disease, glycogen builds up abnormally in cells resulting in accumulation of glycogen in body tissues, especially cardiac, respiratory, and skeletal muscle, disrupts the architecture and function of affected cells leading to multisystemic pathology and death. In addition to being a lysosomal storage disorder (LSD), Pompe disease is also considered a neuromuscular disease, a metabolic myopathy, and a glycogen storage disorder. Infantile-onset Pompe disease is characterized by the early onset of symptoms, severe cardiac involvement, and early death due to cardiac and/or respiratory failure.

Myozyme is intended to target to lysosomes to provide an exogenous source of GAA. It binds to mannose-6-phosphate receptors on the cell surface via carbohydrate groups on the GAA molecules. After binding to receptors, GAA is internalized and transported into lysosomes. In the lysosomes, GAA undergoes proteolysis to higher affinity form; digesting glycogen, releasing glucose, and preventing buildup of insoluble glycogen inclusions in Pompe's patients.

Indication:

Myozyme is indicated for use in patients with Pompe disease (GAA deficiency) to improve ventilator-free survival in patients with infantile-onset Pompe disease. No new target population was proposed.

Dosing Regimen:

The currently approved dosage regimen is 20 mg/kg body weight (BW) given by IV infusion qow. The total volume of infusion is determined by the patient's BW and should be administered over approximately 4 hrs. Infusion should be given in a step-wise manner using an infusion pump. The initial infusion rate should be no more than 1 mg/kg/hr and then infusion rate may be increased by 2 mg/kg/hr every 30 min, after patient tolerance to the infusion rate is established, until a maximum rate of 7 mg/kg/hr is reached. No new dosing regimen is proposed.

2.2. General Clinical Pharmacology**Q1. How was the comparative PK data obtained?**

A1. Study AGLU01602, a pivotal clinical trial, was submitted under original BLA submission for approval. It had been reviewed by OCP previously. This study

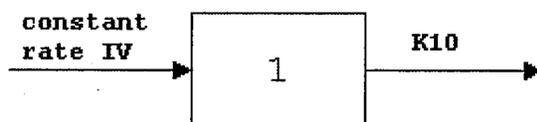
evaluated the PK, PD, efficacy, and safety of Myozyme in 18 patients (11M+7F) with the most rapidly progressing form of infantile-onset Pompe disease: patients who were diagnosed at ≤ 6 months of age and exhibited severe GAA deficiency (in skin and muscle tissues) and evidence of cardiomyopathy. Patients were randomly assigned in a 1:1 ratio to receive IV infusions of Myozyme at a dose of either 20 mg/kg qow (n=9) or 40 mg/kg qow (n=9) using 160 L scale lot. Myozyme was administered in a step-wise manner with the duration of the infusion dependent upon the dose. In general, patients received the infusion in four (4) steps with an increasing rate per step as the patient demonstrated tolerability to the enzyme; there were, however, some instances where the infusion was administered in more than four steps. Within each step, the rate of administration was constant. Fifteen of 18 patients had skeletal muscle GAA levels below quantifiable levels at Baseline ($< 1\%$ of the normal mean).

Study AGLU02403 is an open-label, long-term continuation, extension study for patients previously enrolled in the above pivotal Study AGLU01602. This extension study was designed to evaluate safety, ventilator-free survival, PK/PD, and the effect of different dosages of Myozyme (20 or 40 mg/kg qow) on safety and efficacy outcomes. The final report of Study AGLU02403 includes data collected under the initial study, AGLU01602.

The objective of the PK analysis was to evaluate the bioequivalence of GAA of 160 L and 2000 L scale lots after administration of a single lot of GAA manufactured at the 160 L scale and lots manufactured at the 2000 L scale lots. Sixteen (out of 18 in Study AGLU01602) received treatment in this extension study. Patients were treated with Myozyme produced at the 160 L scale lot in Study AGLU01602 and were subsequently transitioned to lots produced at the 2000 L scale during the Study AGLU02403. Therefore, this is not a crossover study.

Blood samples were drawn before the start of the infusion, at the end of the infusion, and 0.5, 1, 3, 6, and 12 hours after the end of the infusion. Plasma concentrations were determined after administration of the last dose from a 160 L scale lot and at the time of the first or second dose from a 2000 L scale lot. An additional set of blood samples was obtained after a patient had received another treatment with 2000 L scale lot for a minimum of 12 weeks apart (referred to as the 2000 L Repeat group).

Based on previous experience, the PK parameters were estimated by fitting to a 1-compartment open model with a constant rate of infusion by the sponsor as shown below:



The model was parameterized in terms of the elimination rate constant (K_{10}) and volume of distribution (V_d). Data were treated as a multiple-dose administration to account for multiple infusion steps. Additional parameters calculated from the fitted parameters were total plasma clearance (CL), maximum plasma concentration (C_{max}), area under the curve to infinity ($AUC_{0-\infty}$), and elimination half-life ($T_{1/2}$) as shown below:

$$CL = K_{10} \cdot V_d$$

C_{max} : estimated by curve-fitting to one-compartment open model

$AUC_{0-\infty} = \text{Infused Dose}/CL$ (using WinNonlin)

$$T_{1/2} = 0.693/K_{10}$$

The observed C_{max} levels were also obtained at the end of IV infusion.

Note: Study AGLU1702 had been submitted in the original BLA and the PK and PD data for 160 L lot were already reviewed previously by OCP. It was also submitted to this BLA supplement for additional efficacy and safety comparisons between the 2000 L and 160 L scale lots, but no additional PK data was obtained for the 2000 L scale lot for PK comparisons in this target population, i.e., infantile-onset Pompe disease.

Q2. Did the proposed Myozyme 2000 L scale lot show BE to the approved 160 L in terms of PK?

A2. From Study AGLU01602/2403, 12 patients had PK data for both the 160L and 2000L lots, seven in the 20 mg/kg cohort and five in the 40 mg/kg cohort. Based on the Agency's BE acceptance criteria, BE between the 2000 L scale lot and the currently approved 160 L lot has not been demonstrated. Blood sampling was repeated 12 weeks later for the 2000 L scale lot which again did not demonstrate BE to the currently approved 160 L lot either. However, this does not necessarily mean that the scale-up lots (2000 L) are not bioequivalent to the 160 L lots in PK, since there were limitations in the study design (e.g., small sample size, a sequential design not a crossover design). The PK parameters obtained are shown below in Table 2:

Table 2. Mean PK Parameters Obtained From Study No. AGLU02403

Manufacturing Scales	160 L Lot	2,000 L Lot	2,000 L Lot (Repeat) ¹
Parameters\Dose	20 mg/kg (n=7)		
Weight (kg)	12.6 ± 1.4 ²	12.9 ± 1.2	12.9 ± 1.5
C_{max} (ng/mL)	168,096 ± 96,968	269,269 ± 232,608	176,119 ± 71,640
$AUC_{0-\infty}$ (ng-hr/mL)	815,347 ± 418,759	1,238,280 ± 619,243	777,156 ± 284,476
CL (mL/kg)	37.4 ± 34.1	19.5 ± 9.6	31.9 ± 21.4
$T_{1/2}$ (hr)	2.36 ± 0.56	2.53 ± 0.64	2.21 ± 0.46
Observed C_{max} (ng/mL)	199,710 ± 97,001	275,409 ± 230,443	216,247 ± 79,055
Parameters\Dose	40 mg/kg (n=5)		
Weight (kg)	13.0 ± 2.6	13.0 ± 2.6	13.3 ± 2.6

C_{max} (ng/mL)	268,512 ± 88,454	291,130 ± 56,283	254,288 ± 42,055
$AUC_{0-\infty}$ (ng-hr/mL)	1,796,195 ± 566,697	1,806,667 ± 200,625	1,678,773 ± 246,453
CL (mL/kg)	25.8 ± 13.5	22.3 ± 2.5	24.3 ± 3.8
$T_{1/2}$ (hr)	2.08 ± 0.39	2.19 ± 0.36	1.95 ± 0.25
Observed C_{max} (ng/mL)	307,065 ± 46,220	297,564 ± 61,060	284,679 ± 60,726

1. Additional set of PK data was obtained 12 weeks later using 2,000 L Lot for infusion.

2. Standard deviation (SD)

Blue: Simulated data based on modeling.

Burgundy: Observed data, i.e., at the end of infusion.

The BE assessments between 160 L and 2000 L scale lots and 90% confidence intervals (CIs) are shown below in Table 3:

Table 3. Results of BE Assessment between 160 L and 2000 L lots (Study AGLU02403)

Comparison	Test/Ref Ratio	90% CIs
2000 L (Test) vs. 160 L (Ref)		
C_{max}	1.40	1.16 – 1.70
AUC_{0-x}	1.24	1.04 – 1.46
2000 L Repeat (Test) vs. 160 L (Ref)		
C_{max}	1.09	0.89 – 1.32
AUC_{0-x}	1.02	0.86 – 1.20
2000 L Repeat (Test) vs. 2,000 L (Ref)		
C_{max}	0.774	0.633 – 0.946
AUC_{0-x}	0.824	0.686 – 0.989
2000 L Combined (Test) vs. 160 L (Ref)		
C_{max}	1.23	1.05 – 1.45
AUC_{0-x}	1.12	0.97 – 1.29

The estimated C_{max} levels based on modeling were lower than that of the observed ones (an average of 15% lower). The BE assessments based on the observed C_{max} values (at the end of infusion) are also shown below in Table 4:

Table 4. Results of Comparability Assessment on Observed C_{max} between 160 L and 2000 L lots (Study AGLU02403)

Comparison	Test/Ref Ratio	90% CIs
2000 L (Test) vs. 160 L (Ref)		
Observed C_{max}	1.11	0.96 – 1.29
2000 L Repeat (Test) vs. 160 L (Ref)		
Observed C_{max}	1.17	0.98 – 1.39
2000 L Repeat (Test) vs. 2,000 L (Ref)		
Observed C_{max}	1.06	0.89 – 1.27
2000 L Combined (Test) vs. 160 L (Ref)		
Observed C_{max}	0.911	0.76 – 1.09

Compared to the PK data obtained from the 160 L lot based on the model fitting results:

1. The 2,000 L lot showed higher mean C_{max} (40% ↑ in point estimate) and $AUC_{0-\infty}$ (24% ↑ in point estimate) values (Table 3).

- The repeated 2,000 L lot, however, showed closer mean C_{max} (0.89 – 1.32) and $AUC_{0-\infty}$ (0.86 – 1.20.) values after a repeated IV infusion 12 weeks later (Table 2), although the mean C_{max} still failed to meet the BE criteria.
- The 20 mg/kg dose showed much higher mean C_{max} and $AUC_{0-\infty}$ values for the 2,000 L lot, while 40 mg/kg dose showed more comparable C_{max} and $AUC_{0-\infty}$ values for the 2,000L Lot (Table 2).
- The mean observed C_{max} levels (at the end of infusion) showed consistent conclusions for the comparisons to the 2000 L scale lot (Table 4).

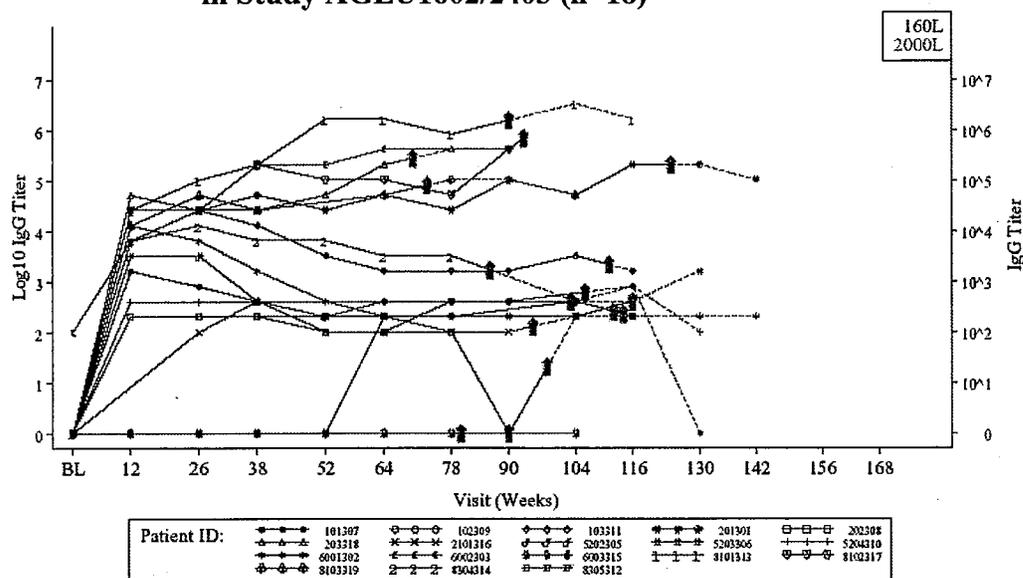
It is noted that 1) the comparison between the 2,000 L and repeated 2,000 L lots did not show BE and 2) even the 2,000 L lots combined, it is not bioequivalent to the currently approved 160 L Lot either. However, it should be noted that one can not combine 2000 L and 2000 L Repeat data for a BE assessment without a modification of the bioequivalence test because they involved the same subjects.

Immunogenicity

Q3. Are there differences in the effect of antibody on Myozyme between 160 L and 2000 L scale lots?

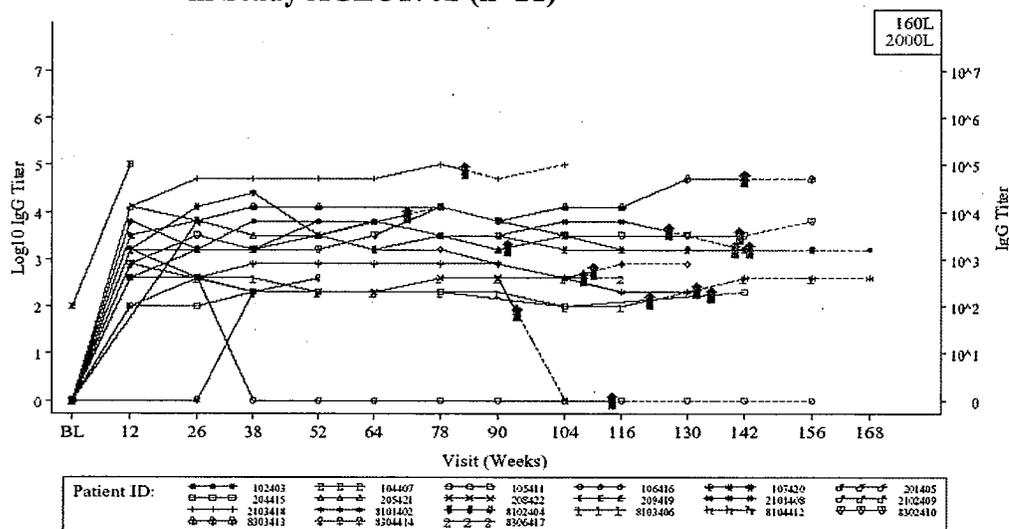
A3. The formation of anti-rhGAA IgG antibodies was evaluated as part of routine immunosurveillance in clinical studies of rhGAA. To compare anti-rhGAA IgG antibody titers in patients treated with rhGAA lots manufactured at the 2 scales, analyses were conducted in 160-L and 2000-L Switched Patients (Figures 1 & 2).

Figure 1. Individual Patient's IgG Titer Over Time (Before and After Switch) in Study AGLU1602/2403 (n=18)



Note: Red arrow (↑) depicted the time of switch from 160 L to 2000 L.

Figure 2. Individual Patient's IgG Titer Over Time (Before and After Switch) in Study AGLU1702 (n=21)



For “Switched” patients, median IgG titers did not appear to change after the switch. It should be noted that the patients switched from 160 L lots to 2000 L lots received a median of 108.1 weeks (range of 70.0 to 143.2 weeks) of 160-L Myozyme treatment, whereas, the exposure to 2000 L lots was shorter (median 29.0 weeks) among patients who switched. Therefore, the immunogenicity after exposure to 2000 L longer than 29 weeks in switched patients is not known.

Nearly all Naïve patients exposed to Myozyme exhibited seroconversion, including 35 (89.7%) of the 39 Naïve patients receiving 160 L lots in Studies AGLU01602/2403 and AGLU01702, and 9 (90%) of the 10 Naïve patients receiving 2000 L lots in Study AGLU02203.

The cross-reactive immunologic material (CRIM) levels were also evaluated. The CRIM negative, CRIM(-), patients are at greater risk of developing a higher, more sustained immunological response against rhGAA than CRIM (+) patients, and potentially, a more limited duration of clinical benefit after Myozyme administration. CRIM (-) patients generally have higher antibody titers than CRIM (+) patients. Among 6 out of 31 Switched patients (AGLU01602/2403 and AGLU01072) who showed CRIM (-), 2 died before switch, 2 died and 2 survived after switch from 160 L to 2000 L scale lots.

Q4. What pharmacodynamic measures have been explored for Myozyme?

A4. (i): Motor Status:

In AGLU01602/2403 and AGLU01702, motor status was assessed as supportive clinical efficacy endpoint using several observational measures of infant motor development (20 and 40 mg/kg combined) to evaluate normal patterns of motor movement that evolve from birth through 18 months of age. It included the AIMS (Alberta Infant Motor Scale), a checklist for the number of motor

development milestones achieved, and the PDMS-2 (Peabody Development Motor Scale 2nd Edition). Functional status was assessed using the Pompe PEDI (Pediatric Evaluation of Disability Inventory). The achievement of motor milestones leading up to independent ambulation, the acquisition of gross and fine motor skills, and the development of functional independence skills related to self-care, mobility, and social function were considered to be indicative of a positive motor response to treatment.

This reviewer compared the Motor Status for the 160 L and 2000 L scale lots as shown below in Table 5. Due to the limited sample size and sequential design, no conclusion could be made regarding the comparability in ventilator-free survival rate or motor status between the 160L and 2000L lots. However, the motor status appears to be a good predictor for the ventilator-free survival.

Table 5. Clinical Outcomes at the End of 160 L and 2000 L Treatments

Study No.	160L and 2000L Exposure Periods (160 L → 2000 L Scale Lots)							
	160 L Lot (N= 18)				2000 L Lot (N= 17)			
Motor Status	Non-Resp/Unkwn (n=6)		Responder (n=12)		Non-Resp/Unkwn (n= 5)		Responder (n= 12)	
	Deceased	Alive	Deceased	Alive	Deceased	Alive	Deceased	Alive
n =	1	5 ¹ (83%)	0	12 ² (100%)	2	3 ⁵ (60%)	2	10 ⁶ (83%)
1702	160 L Lot (N= 21)				2000 L Lot (N= 15)			
Motor Status	Non-Resp/Unkwn (n= 8)		Responder (n= 13)		Non-Resp/Unkwn (n= 3)		Responder (n= 12)	
	Deceased	Alive	Deceased	Alive	Deceased	Alive	Deceased	Alive
n =	5	3 ³ (38%)	0	13 ⁴ (100%)	0	3 ³ (100%)	1	11 ⁷ (92%)

Number of patients on invasive ventilator: ¹. (5); ². (1); ³. (3); ⁴. (4); ⁵. (3); ⁶. (1); ⁷. (5)

The sponsor provided other PD data, e.g., VLMI, which was reviewed by Dr. Joanna Ku of DGP. These data were reviewed in details by Dr. Ku of DGP while this reviewer examined the data only for the comparability purposes. According to Dr. Ku, no conclusions could be reached as additional information because there were only a few data points collected during the 2000L experience for these parameters.

(ii). Muscle GAA and Glycogen Content:

No new comparative data on muscle GAA and muscle glycogen content were obtained for the 160L lot and 2000L lots in this BLA supplement. Biomarker results from 2 supportive studies submitted in this BLA supplement were examined by this reviewer. Data obtained from the supportive Study No.

AGLU01202-04 (n=4 for Infantile receiving 15-40 mg/kg qow) for muscle GAA (nmol/mg protein/hr) and muscle glycogen content ($\mu\text{g}/\text{mg}$ protein) by study week in Infantile-onset Pompe patients are presented in Tables 6 and 7 and data from the supportive Study No. AGLU01205-02 in Table 8. These results showed that muscle GAA levels and muscle glycogen levels did not correlate well, which is consistent with previous observations. In addition, it is not clear how good the measurements represent the actual tissues levels.

Table 6. Muscle GAA Levels (Study No. AGLU01202-04)

Study Week	Patient 001 ¹	Patient 002 ¹	Patient 003 ²	Patient 004 ³
Baseline	(b) (4)			
Week 12				
Week 24				
Week 33				
Week 72				
Reference: Listing 16.2.3-2				
ND: Not done				
¹ These patients changed from the starting dose of 15 mg/kg to 30 mg/kg at Week 22 and to 40 mg/kg at Week 24				
² This patient changed from the starting dose of 20 mg/kg to 40 mg/kg at Week 17				
³ This patient changed from the starting dose of 20 mg/kg to 40 mg/kg at Week 15				
Normal reference value: 8-40 nmol/mg protein/hour				

Table 7. Muscle Glycogen Content (Study No. AGLU01202-04)

Study Week	Patient 001 ¹	Patient 002 ¹	Patient 003 ²	Patient 004 ³
Baseline	(b) (4)			
Week 12				
Week 24				
Week 33				
Week 72				
Reference: Listing 16.2.3-2				
ND: Not done				
¹ These patients changed from the starting dose of 15 mg/kg to 30 mg/kg at Week 22 and to 40 mg/kg at Week 24				
² This patient changed from the starting dose of 20 mg/kg to 40 mg/kg at Week 17				
³ This patient changed from the starting dose of 20 mg/kg to 40 mg/kg at Week 15				
Normal reference value: 30-180 $\mu\text{g}/\text{mg}$ protein				

Table 8. Muscle GAA and Glycogen Content (Study No. AGLU01205-02)

Study Week	GAA activity (nmol/g tissue/hr)		Glycogen content (mg/g tissue)	
	Patient 101	Patient 103	Patient 101	Patient 103
baseline	ND	ND	70.0	63.4
12	192.1	115.7	31.2	91.3
24	115.5	97.2	44.1	79.5
36	191.7	210.8	60.6	69.3
48	236.9	139.1	29.0	77.9
Reference: Listing muscle_0 (Section 16.2)				
ND = Not done.				

(iii). Plasma and Urine Oligosaccharide Level:

An oligosaccharide, a degradant of glycogen, was released into the circulation by the enzyme amylase. The previous OCP review concluded that plasma or urinary oligosaccharide level appeared to decrease with time (baseline, week4, week12, and week26) and was associated with the degree of glycogen accumulation in tissues of patients, but no clear difference between the 20 and 40 mg/kg dosing groups was appreciated. Urinary oligosaccharide level may be useful as a better, non-invasive biomarker of the clinical response to ERT in this disease. However, no comparative data on plasma or urinary oligosaccharide levels were available to compare the 160L and 2000L lots.

2.3. Intrinsic Factors: Data not available

2.4. Extrinsic Factors: Data not available nor was drug-drug interaction study conducted.

2.5. General Biopharmaceutics:

Q5. What are the differences between the 160 L and 2000 L scale products?

A5. The formulation for the 2000L lots is the same as that of the currently approved 160L lots and no changes to the formulation are proposed. However, there are differences in manufacturing specifications between these two scale lots. Per chemist's comments, the above differences could impact the efficacy.

The following table was obtained from the reviewing chemist, Dr. Frederick Mills, showing differences in specifications between 160 L and 2000 L material (b) (4)

Table 9. Results of *In vitro* Determination and specifications of Myozyme 160 L and 2000 L Lots

(b) (4)



Genzyme previously described 3 manufacturing scales for rhGAA in the original BLA submission defined by the bioreactor working volume at each scale (b) (4), 160 L, and 2000 L). Material from all 3 scales has been used in clinical trials and the 160 L process was used to generate lots administered in the majority of clinical studies described in the application, including Studies AGLU01602 and its extension (AGLU02403), AGLU01702, and AGLU02203, and the EAP (International Expanded Access Program).

The sponsor reported that both the validated 160 L scale and 2000 L scale manufacturing processes were described fully in the original BLA. However, only the 160 L process was approved due to inadequate data available to support the approval of the 2000 L process at that time.

2.6. Analytical Section

Q6. Are assay methods used acceptable?

A6. The assay methods and validation results for plasma GAA levels and anti-GAA antibody were reviewed and found acceptable previously for the original BLA submission (see below). However, the in-process assay performance results are lacking.

GAA Assay:

The activity of GAA in human plasma was measured using 4-methylumbelliferylalphan-D-glucopyranoside (4-MUG; 5 $\mu\text{mol/L}$) as the substrate and was quantitated relative to the activity of rhGAA standard curve prepared from a dilution series of reference GAA. Briefly, plasma samples were diluted a minimum of 1/5 in acetate/potassium chloride buffer, pH 4.3, and incubated with the 4-MUG substrate for 2 hours at 37°C. The reaction was terminated with the addition of carbonate/bicarbonate buffer, pH 10.65. Fluorescence produced in samples was read at the 355/460 nm wavelength pair in a fluorometer. The concentration (ng/mL) of rhGAA in the sample was determined by interpolation from an eight-point second order polynomial standard curve.

The above same GAA assay method had been used, validated, reviewed, and found acceptable previously for the original BLA submission. The linear range of the method was 2.5 to 500 ng/mL with a limit of quantification (LOQ) of 12.5 ng/mL. Intra-assay precision (coefficient variation; CV%) for QC samples within a assay ranged from 2.6% to 4.2 %. Inter-assay precision between assays ranged from 1.2 to 8.2 % for the standard curve and from 2.8 to 17.0% for QC samples. The % recovery of GAA activity ranged from 94.2 to 116%. However, for this BLA supplement, the results of assay performance specifically for determination of GAA plasma levels (Study AGLU02403) are not found.

Anti-GAA Antibody:

(b) (4)

The above assay method for anti-GAA antibody had been used, validated, reviewed, and found acceptable previously for the original BLA submission. The linear range of the method was 0 to 2.5 µg/mL with a LOQ of 0.0375 µg/mL (1:100 dilution). Intra-assay CV% for QC samples within an assay ranged from 1.4% to 7.7 %. Inter-assay precision between assays ranged from 0.9% to 15.9% for QC samples. The % recovery of anti-GAA antibody ranged from 89.0% to 114%. However, for this BLA supplement, the results of assay performance specifically for determination of anti-GAA antibody plasma levels in Study AGLU02403 are not found.

3. Appendices

- 3.1. Proposed Package Insert (currently approved)
Note: The sponsor did not propose any change in the package insert.
- 3.2. Individual Study Review
- 3.3. Cover Sheet and OCPB Filing/Review Form

17 pp withheld in full immed. after this page as (b) (4) Draft
Labeling

**BLA125141/65 for Myozyme (Alglucosidase alfa,
recombinant human acid alpha-glucosidase
[rhGAA])**

Appendix 3.2

Review of PK Study No. AGLU2043

Introduction:

Study AGLU01602, a pivotal clinical trial, was submitted under original BLA submission and was reviewed by OCP previously. This study evaluated the PK, PD, efficacy, and safety of Myozyme in 18 patients (11M+7F) with the most rapidly progressing form of infantile-onset Pompe disease: patients who were diagnosed at ≤ 6 months of age and exhibited severe GAA deficiency (in skin and muscle tissues) and evidence of cardiomyopathy. Patients were randomly assigned in a 1:1 ratio to receive IV infusions of Myozyme at a dose of either 20 mg/kg qow (n=9) or 40 mg/kg qow (n=9) using 160 L scale lot. Myozyme was administered in a step-wise manner with the duration of the infusion dependent upon the dose. In general, patients received the infusion in four (4) steps with an increasing rate per step as the patient demonstrated tolerability to the enzyme; there were, however, some instances where the infusion was administered in more than four steps. Within each step, the rate of administration was constant. Fifteen of 18 patients had skeletal muscle GAA levels below quantifiable levels at Baseline ($< 1\%$ of the normal mean).

Study Design:

Study AGLU02403 is an open-label, long-term continuation, extension study for patients previously enrolled in the above pivotal Study AGLU01602. This extension study was designed to evaluate safety, ventilator-free survival, PK/PD, and the effect of different dosages of Myozyme (20 or 40 mg/kg qow) on safety and efficacy outcomes. The final report of Study AGLU02403 includes data collected under the initial study, AGLU01602.

Objective:

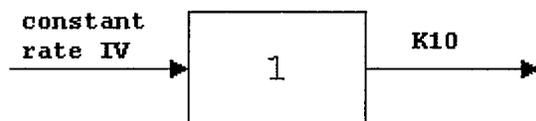
One objective of the study was to compare the PK of GAA of 160 L and 2000 L scale lots after administration of a single lot of GAA manufactured at the 160 L scale and lots manufactured at the 2000 L scale. Sixteen (out of 18 in Study AGLU01602) received treatment in this extension study. Patients were treated with Myozyme produced at the 160 L scale lot in Study AGLU01602 and were subsequently transitioned to lots produced at the 2000 L scale lot during the Study AGLU02403. However, this is not a 2x2 crossover study.

Blood Sampling:

Blood samples were drawn before the start of the infusion, at the end of the infusion, and 0.5, 1, 3, 6, and 12 hours after the end of the infusion. Plasma concentrations were determined after administration of the last dose from a 160 L scale lot and at the time of the first or second dose from a 2000 L scale lot. An additional set of blood samples was obtained after a patient had received another treatment with 2000 L scale lot for a minimum of 12 weeks apart (referred to as the 2000 L Repeat group).

PK Analysis and Modeling:

Based on previous experience, the PK parameters were estimated by fitting to a 1-compartment open model with a constant rate of infusion by the sponsor as shown below:



The model was parameterized in terms of the elimination rate constant (K_{10}) and volume of distribution (V_d). Data were treated as a multiple-dose administration to account for multiple infusion steps. Additional parameters calculated from the fitted parameters were total plasma clearance (CL), maximum plasma concentration (C_{max}), area under the curve to infinity ($AUC_{0-\infty}$), and elimination half-life ($T_{1/2}$) as shown below:

$$CL = K_{10} \cdot V_d$$

C_{max} : estimated by curve-fitting to one-compartment open model

$$AUC_{0-\infty} = \text{Infused Dose}/CL \text{ (using WinNonlin)}$$

$$T_{1/2} = 0.693/K_{10}$$

The observed C_{max} levels were also obtained at the end of IV infusion.

Results:

Pharmacokinetic Parameters for Myozyme after Intravenous Administration of 160 L and 2000 L Lots in Study AGLU02403

Parameter ¹	160 L	2000 L	2000 L Repeat
20 mg/kg (n=7)			
Weight (kg)	12.6 ± 1.43 (7)	12.9 ± 1.16 (6)	12.9 ± 1.48 (6)
K_{10} (h^{-1})	0.307 ± 0.066 (7)	0.288 ± 0.073 (5)	0.325 ± 0.061 (6)
V (mL)	1430 ± 1015 (7)	870 ± 377 (5)	1347 ± 1064 (6)
(mL/kg)	111 ± 74.1 (7)	67.3 ± 27.3 (5)	103.6 ± 77.2 (6)
CL (mL/h)	483 ± 461 (7)	254 ± 131 (5)	416 ± 297 (6)
(mL/h/kg)	37.4 ± 34.1 (7)	19.5 ± 9.56 (5)	31.9 ± 21.4 (6)
AUC_{∞} (h·ng/mL)	815,347 ± 418,759 (7)	1,238,280 ± 619,243 (5)	777,156 ± 284,476 (6)
C_{max} (ng/mL)	168,096 ± 96,968 (7)	269,269 ± 232,608 (6)	176,119 ± 71,640 (6)
MRT (h)	3.28 ± 0.56 (7)	3.31 ± 0.58 (5)	2.96 ± 0.34 (6)
$t_{1/2}$ (h)	2.36 ± 0.56 (7)	2.53 ± 0.64 (5)	2.21 ± 0.46 (6)
C_{max} Observed (ng/mL)	199,710 ± 97,001 (7)	275,409 ± 230,443 (6)	216,247 ± 79,055 (6)
40 mg/kg (n=5)			
Weight (kg)	13.0 ± 2.55 (5)	13.0 ± 2.57 (5)	13.3 ± 2.59 (5)
K_{10} (h^{-1})	0.344 ± 0.068 (5)	0.323 ± 0.047 (4)	0.361 ± 0.052 (5)
V (mL)	1016 ± 660 (5)	844 ± 195 (4)	919 ± 299 (5)
(mL/kg)	81.3 ± 57.2 (5)	69.9 ± 9.06 (4)	68.8 ± 17.9 (5)
CL (mL/h)	329 ± 158 (5)	266 ± 35.0 (4)	324 ± 88.1 (5)
(mL/h/kg)	25.8 ± 13.5 (5)	22.3 ± 2.5 (4)	24.3 ± 3.84 (5)
AUC_{∞} (h·ng/mL)	1,796,195 ± 566,697 (5)	1,806,667 ± 200,625 (4)	1,678,773 ± 246,453 (5)
C_{max} (ng/mL)	268,512 ± 88,454 (5)	291,130 ± 56,283 (5)	254,288 ± 42,055 (5)
MRT (h)	2.99 ± 0.57 (5)	3.15 ± 0.51 (4)	2.81 ± 0.37 (5)
$t_{1/2}$ (h)	2.08 ± 0.39 (5)	2.19 ± 0.36 (4)	1.95 ± 0.25 (5)
C_{max} Observed (ng/mL)	307,065 ± 46,220 (5)	297,564 ± 61,060 (5)	284,679 ± 60,726 (5)

¹ Presented as arithmetic mean ± standard deviation (n).

Reference: AGLU02403 Pharmacokinetic and Statistical Analyses Report, Table 1.

Statistical Analysis of Pharmacokinetic Parameters for Myozyme after Intravenous Administration of 160 L and 2000 L Lots in Study AGLU02403

Parameter	Geometric Mean Ratio ¹		Within Subject CV(%)	p-value ^{1,2,3}
	Estimate	90% CI		
2000 L (combined) vs. 160 L				
AUC _∞	112.1	(97.1, 129.4)	22.6	0.1846
C _{max}	123.3	(104.5, 145.5)	27.1	0.0414
2000 L vs. 160 L				
AUC _∞	123.5	(103.5, 147.4)	22.6	0.0530
C _{max}	140.2	(115.5, 170.1)	27.1	0.0070
2000 L Repeat vs. 160 L				
AUC _∞	101.7	(86.4, 119.8)	22.6	0.8576
C _{max}	108.5	(89.4, 131.6)	27.1	0.4775
2000 L Repeat vs. 2000 L				
AUC _∞	82.4	(68.6, 98.9)	22.6	0.0828
C _{max}	77.4	(63.3, 94.6)	27.1	0.0392

¹ Based on analysis of natural log-transformed data.

² Both doses were combined for the analysis.

³ p-value for comparison of the value of the contrast to 0.

Reference: AGLU02403 Pharmacokinetic and Statistical Analyses Report, Tables 2 and 3.

Statistical Analysis of the Observed C_{max} for rhGAA after Intravenous Administration of 160 L and 2000 L Lots in Study AGLU02403

Comparison	Geometric Mean Ratio ¹		Within Subject CV(%)
	Estimate	90% CI	
2000 L (combined) vs. 160 L	111.2	(95.7, 129.2)	24.4
2000 L vs. 160 L	116.5	(97.7, 138.8)	24.4
2000 L Repeat vs. 160 L	106.1	(89.1, 126.5)	24.4
2000 L Repeat vs. 2000 L	91.1	(76.0, 109.3)	24.4

¹ Based on analysis of natural log-transformed data.

Reference: Table 5 in the AGLU02403 Pharmacokinetic and Statistical Analyses Report.

Reviewer's comment:

Based on the pharmacokinetic data provided, the sponsor has not demonstrated that the proposed 2000 L scale lots are bioequivalent to the approved 160 L scale lots. It should be noted that the sponsor did not provide the assay report for this study.

**BLA125141/65 for Myozyme (Alglucosidase alfa,
recombinant human acid alpha-glucosidase
[rhGAA])**

Appendix 3.3

Cover Sheet and OCP Filing/Review Form

Office of Clinical Pharmacology

Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
BLA Number	125141/65	Brand Name	Myozyme
OCP Division (I, II, III)	DCP III	Generic Name	Recombinant human acid alpha-glucosidase
Medical Division	GI	Drug Class	Lysosomal enzyme
OCP Reviewer	Tien-Mien Chen, Ph.D.	Indication(s)	(b) (4)
OCP Team Leader	Sue-Chih Lee, Ph.D.	Dosage Form	Lyophilized powder for reconstitution
		Dosing Regimen	20 mg/kg every other week
Date of Submission	10/31/07	Route of Administration	Intravenous infusion
Estimated Due Date of OCP Review	03/10/08	Sponsor	Genzyme
Medical Division Due Date	N/A	Priority Classification	P
PDUFA Due Date	N/A (See Executive Summary)		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
HEALTHY VOLUNTEERS-				
single dose:				
multiple dose:				
Patients-				
single dose:				a BE-type PK study
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				

pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				Sequential design
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Immunogenicity	x	2	2	
Total Number of Studies		2	2	
Filability and QBR comments				
	"X" if yes	<i>Comments</i>		
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)	Is the proposed 2000 L scale lot bioequivalent to the approved 160 L in patients?			
Other comments or information not included above				
Primary reviewer Signature and Date	Tien-Mien Chen, Ph.D.			
Secondary reviewer Signature and Date	Sue-Chih Lee, Ph.D.			