

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

BLA 125291/136

Trade Name: LUMIZYME

Generic Name: Alglucosidase Alfa

Sponsor: Genzyme Corporation

Approval Date: August 1, 2014

Indications: LUMIZYME® (alglucosidase alfa) is a hydrolytic lysosomal glycogen-specific enzyme indicated for patients with Pompe disease (acid α -glucosidase (GAA) deficiency).

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APPROVAL LETTER



BLA 125291/136

**SUPPLEMENT APPROVAL
RELEASE REMS REQUIREMENT**

Genzyme Corporation
Attention: Jennifer Eaddy
Associate Director, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Ms. Eaddy:

Please refer to your Supplemental Biologics License Application (sBLA), dated and received January 30, 2014, submitted under section 351(a) of the Public Health Service Act for Lumizyme (aglucosidase alfa).

We acknowledge receipt of your amendments dated April 02, 2014, April 04, 2014, April 14, 2014, May 19, 2014, May 23, 2014, May 30, 2014, June 20, 2014, June 23, 2014, June 25, 2014, July 17, 2014, July 21, 2014, July 30, 2014, July 31, 2014, August 01, 2014, and your risk evaluation and mitigation strategy (REMS) assessments dated May 23, 2014 and June 13, 2014.

This Prior Approval supplemental biologics application proposes to revise the indication for Lumizyme to extend the population to all patients with Pompe disease (acid α -glucosidase (GAA) deficiency), including infantile-onset and late-onset patients less than 8 years of age.

The revised indication will be Lumizyme (aglucosidase alfa) is a hydrolytic lysosomal glycogen-specific enzyme indicated for patients with Pompe disease (acid α -glucosidase (GAA) deficiency).

Additionally, this application proposes to eliminate the requirement for the approved Lumizyme REMS.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling (text for the package insert, text for the patient package insert) and include the labeling changes proposed in any pending “Changes Being Effectuated” (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this BLA, including pending “Changes Being Effectuated” (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because your application has orphan designation, you are exempt from this requirement.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Lumizyme (alglucosidase alfa) was originally approved on May 24, 2010, and the most recent REMS modification was approved on July 16, 2012. The REMS consists of a communication plan, elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments of the REMS.

You propose that FDA no longer require a REMS for Lumizyme (alglucosidase alfa).

Because the May 23, 2014, assessment demonstrates that the communication plan has been completed and has met its goals, we have determined that it is no longer necessary to include it as an element of the approved REMS to ensure that the benefits of the drug outweigh the risks.

Additionally, the approval of the expanded indication to include patients of any age eliminates the need for restricted distribution under the ETASU because it is no longer necessary to limit

the treatment with Lumizyme to use in patients with non-infantile onset Pompe disease who are greater than or equal to 8 years of age.

Therefore, we agree with your proposal, and a REMS for Lumizyme (alglucosidase alfa) is no longer required.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Kevin Bugin, Regulatory Project Manager, at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE(S):

Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DONNA J GRIEBEL
08/01/2014

**CENTER FOR DRUG EVALUATION AND
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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LUMIZYME safely and effectively. See full prescribing information for LUMIZYME.

LUMIZYME® (alglucosidase alfa), for injection, for intravenous use
Initial U.S. Approval: 2010

WARNING: RISK OF ANAPHYLAXIS, HYPERSENSITIVITY AND IMMUNE-MEDIATED REACTIONS, and RISK OF CARDIORESPIRATORY FAILURE

See full prescribing information for complete boxed warning.

- Life-threatening anaphylactic reactions and severe hypersensitivity reactions have occurred in some patients during and after alglucosidase alfa infusions. Immune-mediated reactions presenting as proteinuria, nephrotic syndrome, and necrotizing skin lesions have occurred in some patients following alglucosidase alfa treatment. Closely observe patients during and after alglucosidase alfa administration and be prepared to manage anaphylaxis and hypersensitivity reactions. Inform patients of the signs and symptoms of anaphylaxis, hypersensitivity reactions, and immune-mediated reactions and have them seek immediate medical care should signs and symptoms occur (5.1, 5.2).
- Infantile-onset Pompe disease patients with compromised cardiac or respiratory function may be at risk of serious acute exacerbation of their cardiac or respiratory compromise due to fluid overload, and require additional monitoring (5.3).

RECENT MAJOR CHANGES

- | | |
|--------------------------------|---------|
| • Boxed Warning | 08/2014 |
| • Indications and Usage (1) | 08/2014 |
| • Warnings and Precautions (5) | 08/2014 |

INDICATIONS AND USAGE

LUMIZYME® (alglucosidase alfa) is a hydrolytic lysosomal glycogen-specific enzyme indicated for patients with Pompe disease (GAA deficiency) (1).

DOSAGE AND ADMINISTRATION

- 20 mg per kg body weight administered every 2 weeks as an intravenous infusion (2).

DOSAGE FORMS AND STRENGTHS

- For injection: 50 mg of alglucosidase alfa as lyophilized powder in a single-use vial for reconstitution (3).

CONTRAINDICATIONS

- None (4).

WARNINGS AND PRECAUTIONS

- **Anaphylaxis and Hypersensitivity Reactions:** Life-threatening anaphylaxis and hypersensitivity reactions have been observed in some patients during and after treatment with alglucosidase alfa. Ensure that appropriate medical support measures, including cardiopulmonary resuscitation equipment, are readily available. If anaphylaxis or severe hypersensitivity reactions occur, immediately discontinue infusion and initiate appropriate medical treatment (5.1).
- **Immune-Mediated Reactions:** Monitor patients for the development of systemic immune-mediated reactions involving skin and other organs (5.2).
- **Risk of Acute Cardiorespiratory Failure:** Patients with compromised cardiac or respiratory function may be at risk of acute cardiorespiratory failure. Caution should be exercised when administering alglucosidase alfa to patients susceptible to fluid volume overload. Appropriate medical support and monitoring measures should be available during infusion (5.3).
- **Risk of Cardiac Arrhythmia and Sudden Cardiac Death during General Anesthesia for Central Venous Catheter Placement:** Caution should be used when administering general anesthesia for the placement of a central venous catheter intended for alglucosidase alfa infusion (5.4).

ADVERSE REACTIONS

- The most frequently reported adverse reactions (≥ 5%) in clinical trials were hypersensitivity reactions and included: anaphylaxis, rash, pyrexia, flushing/feeling hot, urticaria, headache, hyperhidrosis, nausea, cough, decreased oxygen saturation, tachycardia, tachypnea, chest discomfort, dizziness, muscle twitching, agitation, cyanosis, erythema, hypertension/increased blood pressure, pallor, rigors, tremor, vomiting, fatigue, and myalgia (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Genzyme at 1-800-745-4447 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm (8.1).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 08/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF ANAPHYLAXIS, HYPERSENSITIVITY AND IMMUNE-MEDIATED REACTIONS, AND RISK OF CARDIORESPIRATORY FAILURE

Life-threatening anaphylactic reactions and severe hypersensitivity reactions, presenting as respiratory distress, hypoxia, apnea, dyspnea, bradycardia, tachycardia, bronchospasm, throat tightness, hypotension, angioedema (including tongue or lip swelling, periorbital edema, and face edema), and urticaria, have occurred in some patients during and after alglucosidase alfa infusions. Immune-mediated reactions presenting as proteinuria, nephrotic syndrome, and necrotizing skin lesions have occurred in some patients following alglucosidase alfa treatment. Closely observe patients during and after alglucosidase alfa administration and be prepared to manage anaphylaxis and hypersensitivity reactions. Inform patients of the signs and symptoms of anaphylaxis, hypersensitivity reactions, and immune-mediated reactions and have them seek immediate medical care should signs and symptoms occur [see [Warnings and Precautions \(5.1, 5.2\)](#)].

Infantile-onset Pompe disease patients with compromised cardiac or respiratory function may be at risk of serious acute exacerbation of their cardiac or respiratory compromise due to fluid overload, and require additional monitoring [see [Warnings and Precautions \(5.3\)](#)].

1 INDICATIONS AND USAGE

LUMIZYME® (alglucosidase alfa) [see [Description \(11\)](#)] is a hydrolytic lysosomal glycogen-specific enzyme indicated for patients with Pompe disease (acid α -glucosidase (GAA) deficiency).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended dosage of alglucosidase alfa is 20 mg/kg body weight administered every 2 weeks as an intravenous infusion.

2.2 Instructions for Use

Alglucosidase alfa does not contain any preservatives. Vials are single-use only. Discard any unused product.

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, alglucosidase alfa may be administered at the maximum rate of 7 mg/kg/hr until the infusion is completed. The infusion rate may be slowed or temporarily stopped in the event of mild to moderate hypersensitivity reactions. In the event of anaphylaxis or severe hypersensitivity reaction, immediately discontinue administration of alglucosidase alfa, and initiate appropriate medical treatment. See *Table 1* below for the rate of infusion at each step, expressed as mL/hr based on the recommended infusion volume by patient weight.

Table 1: Recommended Infusion Volumes and Rates

Patient Weight Range (kg)	Total infusion volume (mL)	Step 1 1 mg/kg/hr (mL/hr)	Step 2 3 mg/kg/hr (mL/hr)	Step 3 5 mg/kg/hr (mL/hr)	Step 4 7 mg/kg/hr (mL/hr)
1.25 - 10	50	3	8	13	18
10.1 - 20	100	5	15	25	35
20.1 - 30	150	8	23	38	53
30.1 - 35	200	10	30	50	70
35.1 - 50	250	13	38	63	88
50.1 - 60	300	15	45	75	105
60.1 - 100	500	25	75	125	175
100.1 - 120	600	30	90	150	210
120.1 - 140	700	35	105	175	245
140.1 - 160	800	40	120	200	280
160.1 - 180	900	45	135	225	315
180.1 - 200	1,000	50	150	250	350

2.3 Reconstitution, Dilution, and Administration

Alglucosidase alfa should be reconstituted, diluted and administered by a healthcare professional. Use aseptic technique during preparation. Do not use filter needles during preparation.

- Determine the number of vials to be reconstituted based on the individual patient's weight and the recommended dose of 20 mg/kg.

Patient weight (kg) x dose (mg/kg) = patient dose (in mg)

Patient dose (in mg) divided by 50 mg/vial = number of vials to reconstitute. If the number of vials includes a fraction, round up to the next whole number.

Example: Patient weight (68 kg) x dose (20 mg/kg) = patient dose (1,360 mg)

1,360 mg divided by 50 mg/vial = 27.2 vials; therefore, 28 vials should be reconstituted.

Remove the required number of vials from the refrigerator and allow them to reach room temperature prior to reconstitution (approximately 30 minutes).

- Reconstitute each alglucosidase alfa vial by slowly injecting 10.3 mL of Sterile Water for Injection, USP to the inside wall of each vial. Each vial will yield a concentration of 5 mg/mL. The total extractable dose per vial is 50 mg per 10 mL. Avoid forceful impact of the water for injection on the powder and avoid foaming. This is done by slow drop-wise addition of the water for injection down the inside of the vial and not directly onto the lyophilized cake. Tilt

and roll each vial gently. Do not invert, swirl, or shake.

- c. The reconstituted alglucosidase alfa solution should be protected from light.
- d. Perform an immediate visual inspection on the reconstituted vials for particulate matter and discoloration. If upon immediate inspection opaque particles are observed or if the solution is discolored do not use. The reconstituted solution may occasionally contain some alglucosidase alfa particles (typically less than 10 in a vial) in the form of thin white strands or translucent fibers subsequent to the initial inspection. This may also happen following dilution for infusion. These particles have been shown to contain alglucosidase alfa and may appear after the initial reconstitution step and increase over time. Studies have shown that these particles are removed via in-line filtration without having a detectable effect on the purity or strength.
- e. Alglucosidase alfa should be diluted in 0.9% Sodium Chloride for Injection, USP, immediately after reconstitution, to a final alglucosidase alfa concentration of 0.5 to 4 mg/mL. See [Table 1](#) for the recommended total infusion volume based on patient weight.
- f. Slowly withdraw the reconstituted solution from each vial. Avoid foaming in the syringe.
- g. Remove airspace from the infusion bag to minimize particle formation due to the sensitivity of alglucosidase alfa to air-liquid interfaces.
- h. Add the reconstituted alglucosidase alfa solution slowly and directly into the sodium chloride solution. Do not add directly into airspace that may remain within the infusion bag. Avoid foaming in the infusion bag.
- i. Gently invert or massage the infusion bag to mix. Do not shake.
- j. Administer alglucosidase alfa using an in-line low protein binding 0.2 µm filter.
- k. Do not infuse alglucosidase alfa in the same intravenous line with other products.

The reconstituted and diluted solution should be administered without delay. If immediate use is not possible, the reconstituted and diluted solution is stable for up to 24 hours at 2°C to 8°C (36°F to 46°F). Storage of the reconstituted solution at room temperature is not recommended. The reconstituted and diluted alglucosidase alfa solution should be protected from light. Do not freeze or shake.

Alglucosidase alfa does not contain any preservatives. Vials are single-use only. Discard any unused product.

3 DOSAGE FORMS AND STRENGTHS

For injection: 50 mg of alglucosidase alfa is supplied as a sterile, nonpyrogenic, white to off-white, lyophilized cake or powder in a single-use vial for reconstitution. After reconstitution, the resultant solution concentration is 5 mg/mL.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis and Hypersensitivity Reactions

Anaphylaxis and hypersensitivity reactions have been observed in patients during and up to 3 hours after alglucosidase alfa infusion. Some of the reactions were life-threatening and included anaphylactic shock, cardiac arrest, respiratory arrest, respiratory distress, hypoxia, apnea, dyspnea, bradycardia, tachycardia, bronchospasm, throat tightness, hypotension, angioedema (including tongue or lip swelling, periorbital edema, and face edema), and urticaria. Other accompanying reactions included chest discomfort/pain, wheezing, tachypnea, cyanosis, decreased oxygen saturation, convulsions, pruritus, rash, hyperhidrosis, nausea, dizziness, hypertension/increased blood pressure, flushing/feeling hot, erythema, pyrexia, pallor, peripheral coldness, restlessness, nervousness, headache, back pain, and paresthesia. Some of these reactions were IgE-mediated.

If anaphylaxis or severe hypersensitivity reactions occur, immediately discontinue administration of alglucosidase alfa, and initiate appropriate medical treatment. Severe reactions are generally managed with infusion interruption, administration of antihistamines, corticosteroids, intravenous fluids, and/or oxygen, when clinically indicated. In some cases of anaphylaxis, epinephrine has been administered. Appropriate medical support, including cardiopulmonary resuscitation equipment, should be readily available when alglucosidase alfa is administered.

The risks and benefits of re-administering alglucosidase alfa following an anaphylactic or hypersensitivity reaction should be considered. Some patients have been rechallenged and have continued to receive alglucosidase alfa under close clinical supervision. Extreme care should be exercised, with appropriate resuscitation measures available, if the decision is made to re-administer the product [see [Adverse Reactions \(6.2\)](#)].

5.2 Immune-Mediated Reactions

Immune-mediated cutaneous reactions have been reported with alglucosidase alfa including necrotizing skin lesions [see [Adverse Reactions \(6.3\)](#)]. Systemic immune-mediated reactions, including possible type III immune-mediated reactions have been observed with alglucosidase alfa. These reactions occurred several weeks to 3 years after initiation of alglucosidase alfa infusions. Skin biopsy in one patient demonstrated deposition of anti-rhGAA antibodies in the lesion. Another patient developed severe inflammatory arthropathy in association with pyrexia and elevated erythrocyte sedimentation rate. Nephrotic syndrome secondary to membranous glomerulonephritis was observed in some Pompe disease patients treated with alglucosidase alfa who had persistently positive anti-rhGAA IgG antibody titers. In these patients, renal biopsy was consistent with immune complex deposition. Patients improved following treatment interruption. Therefore, patients receiving alglucosidase alfa should undergo periodic urinalysis [see [Adverse Reactions \(6.3\)](#)].

Patients should be monitored for the development of systemic immune-mediated reactions involving skin and other organs while receiving alglucosidase alfa. If immune-mediated reactions occur, consider discontinuation of the administration of alglucosidase alfa, and initiate appropriate

medical treatment. The risks and benefits of re-administering alglucosidase alfa following an immune-mediated reaction should be considered. Some patients have been able to be rechallenged and have continued to receive alglucosidase alfa under close clinical supervision.

5.3 Risk of Acute Cardiorespiratory Failure

Patients with acute underlying respiratory illness or compromised cardiac and/or respiratory function may be at risk of serious exacerbation of their cardiac or respiratory compromise during infusions. Appropriate medical support and monitoring measures should be readily available during alglucosidase alfa infusion, and some patients may require prolonged observation times that should be individualized based on the needs of the patient. Acute cardiorespiratory failure has been observed in infantile-onset Pompe disease patients with underlying cardiac hypertrophy, possibly associated with fluid overload with intravenous administration of alglucosidase alfa [see [Dosage and Administration \(2.2\)](#)].

5.4 Risk of Cardiac Arrhythmia and Sudden Cardiac Death During General Anesthesia for Central Venous Catheter Placement

Administration of general anesthesia can be complicated by the presence of severe cardiac and skeletal (including respiratory) muscle weakness. Therefore, caution should be used when administering general anesthesia. Ventricular arrhythmias and bradycardia, resulting in cardiac arrest or death, or requiring cardiac resuscitation or defibrillation have been observed in infantile-onset Pompe disease patients with cardiac hypertrophy during general anesthesia for central venous catheter placement.

5.5 Risk of Antibody Development

As with all therapeutic proteins, there is potential for immunogenicity. In clinical studies, the majority of patients developed IgG antibodies to alglucosidase alfa, typically within 3 months of treatment. There is evidence to suggest that some patients who develop high and sustained IgG antibody titers may experience reduced clinical efficacy to alglucosidase alfa treatment, such as loss of motor function, ventilator dependence, or death. The effect of antibody development on the long term efficacy of alglucosidase alfa is not fully understood.

Patients should be monitored for IgG antibody formation every 3 months for 2 years and then annually thereafter. Testing for IgG titers may also be considered if patients develop hypersensitivity reactions, other immune-mediated reactions, or lose clinical response. Patients who experience reduced clinical response may also be tested for inhibitory antibody activity. Patients who experience anaphylactic or hypersensitivity reactions may also be tested for IgE antibodies to alglucosidase alfa and other mediators of anaphylaxis [see [Adverse Reactions \(6.2\)](#)].

There are currently no marketed tests for antibodies against alglucosidase alfa; however, a testing service is provided by Genzyme. Contact your local Genzyme representative or Genzyme Corporation at 1-800-745-4447 for information on testing and to obtain a sample collection box.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The following serious adverse reactions are described below and elsewhere in the labeling:

- Anaphylaxis and hypersensitivity reactions [see [Warnings and Precautions \(5.1\)](#)].

In clinical trials, the most common adverse reactions ($\geq 5\%$) following alglucosidase alfa treatment were hypersensitivity reactions, and included anaphylaxis, rash, pyrexia, flushing/feeling hot, urticaria, headache, hyperhidrosis, nausea, cough, decreased oxygen saturation, tachycardia, tachypnea, chest discomfort, dizziness, muscle twitching, agitation, cyanosis, erythema, hypertension/increased blood pressure, pallor, rigors, tremor, vomiting, fatigue, and myalgia.

Clinical Trials in Infantile-Onset and Juvenile-Onset Pompe Disease

Two multicenter, open-label clinical trials were conducted in 39 infantile-onset Pompe disease patients, ages 1 month to 3.5 years old. Approximately half of the patients (54%) were male. Patients were treated with alglucosidase alfa 20 or 40 mg/kg every other week for periods ranging from 1 to 106 weeks (mean: 61 weeks).

The most serious adverse reactions reported with alglucosidase alfa treatment included anaphylaxis and acute cardiorespiratory failure.

The most common adverse reactions requiring intervention in clinical trials were hypersensitivity reactions, occurring in 20 of 39 (51%) patients treated with alglucosidase alfa, and included rash, pyrexia, urticaria, flushing, decreased oxygen saturation, cough, tachypnea, tachycardia, hypertension/increased blood pressure, pallor, rigors, vomiting, cyanosis, agitation, and tremor. These reactions were more likely to occur with higher infusion rates. Some patients who were pre-treated with antihistamines, antipyretics and/or corticosteroids still experienced hypersensitivity reactions.

Table 2 summarizes all adverse reactions occurring in $\geq 5\%$ of patients (2 or more patients) treated with alglucosidase alfa in clinical trials described above.

Table 2: Adverse Reactions that Occurred in At Least 5% of Infantile-Onset Patients Treated with Alglucosidase Alfa in Clinical Trials

	Number of Patients (N=39) n (%)
Adverse Reaction	20 (51)
Rash (including rash erythematous, rash macular and maculo-papular)	7 (18)
Pyrexia	6 (15)
Urticaria	5 (13)
Flushing	5 (13)
Hypertension/Increased Blood Pressure	4 (10)
Decreased Oxygen Saturation	3 (8)
Cough	3 (8)
Tachypnea	3 (8)
Tachycardia	3 (8)

Erythema	2 (5)
Vomiting	2 (5)
Rigors	2 (5)
Pallor	2 (5)
Cyanosis	2 (5)
Agitation	2 (5)
Tremor	2 (5)

An open-label, single-center trial was conducted in 18 treatment-naïve infantile-onset Pompe disease patients who were treated exclusively with alglucosidase alfa. Adverse reactions observed in these patients were similar to infantile-onset Pompe disease patients who received alglucosidase alfa in other clinical trials.

Additional hypersensitivity reactions observed in infantile-onset Pompe disease patients treated in other clinical trials and expanded access programs with alglucosidase alfa included livedo reticularis, irritability, retching, increased lacrimation, ventricular extrasystoles, nodal rhythm, rales, respiratory tract irritation, and cold sweat.

Safety was also evaluated in 99 patients (51 male, 48 females) with Pompe disease in an ongoing, open-label, prospective study in patients 12 months of age and older who were previously treated with the 160 L scale of alglucosidase alfa and switched to the 4000 L scale of alglucosidase alfa. Patients were aged 1 to 18 years with a median duration of treatment of 437 days (range 13 to 466 days). No new safety findings were observed following the switch to 4000 L scale of alglucosidase alfa.

Clinical Trials in Late-Onset Pompe Disease

Assessment of adverse reactions in patients with late-onset Pompe disease is based on the exposure of 90 patients (45 male, 45 female), aged 10 to 70 years, to 20 mg/kg alglucosidase alfa or placebo in a randomized, double-blind, placebo-controlled trial. The youngest alglucosidase alfa-treated patient was 16 years of age, and the youngest placebo-treated patient was 10 years of age. All patients were naïve to enzyme replacement therapy. Patients were randomized in a 2:1 ratio and received alglucosidase alfa or placebo every other week for 78 weeks (18 months). The study population included 34 males and 26 females (n=60) in the alglucosidase alfa group and 11 males and 19 females (n=30) in the placebo group. Two patients receiving alglucosidase alfa discontinued the trial due to anaphylactic reactions.

Serious adverse reactions reported with alglucosidase alfa included anaphylaxis, which presented as angioedema, throat tightness and chest pain/discomfort. One patient with a history of Wolff-Parkinson-White syndrome experienced a serious adverse reaction of supraventricular tachycardia.

The most common adverse reactions ($\geq 3\%$; 2 or more patients) observed in alglucosidase alfa-treated patients were hypersensitivity reactions and included anaphylaxis, headache, nausea, urticaria, dizziness, chest discomfort, vomiting, hyperhidrosis, flushing/feeling hot, increased blood pressure, paresthesia, pyrexia, local swelling, diarrhea, pruritus, rash, and throat tightness.

Delayed-onset reactions, defined as adverse reactions occurring 2 - 48 hours after completion of alglucosidase alfa infusion, that were observed in $\geq 3\%$ more patients in the alglucosidase alfa-treated group compared to patients in the placebo-treated group in the controlled trial, included hyperhidrosis. Additional delayed-onset reactions occurring in alglucosidase alfa-treated patients

included fatigue, myalgia, and nausea. Patients should be counseled about the possibility of delayed-onset hypersensitivity reactions and given proper follow-up instructions.

Table 3 summarizes the most common adverse reactions that occurred in at least 3% of alglucosidase alfa-treated patients and with a higher incidence than the placebo-treated patients during the randomized, double-blind, placebo-controlled study described above.

Table 3: Adverse Reactions Occurring in at Least 3% of Alglucosidase Alfa-Treated Late-Onset Patients and with a Higher Incidence than the Placebo-Treated Patients

Adverse Reaction	Alglucosidase Alfa n=60 N (%)	Placebo n=30 N (%)
Hyperhidrosis	5 (8.3)	0 (0)
Urticaria	5 (8.3)	0 (0)
Anaphylaxis	4 (6.7)	0 (0)
Chest Discomfort	4 (6.7)	1 (3.3)
Muscle Twitching	4 (6.7)	1 (3.3)
Myalgia	3 (5.0)	1 (3.3)
Flushing/Feeling Hot	3 (5.0)	0 (0)
Increased Blood Pressure	3 (5.0)	0 (0)
Vomiting	3 (5.0)	0 (0)
Edema, Peripheral	2 (3.3)	0 (0)
Pruritus	2 (3.3)	0 (0)
Rash Papular	2 (3.3)	0 (0)
Throat Tightness	2 (3.3)	0 (0)

In clinical trials, anaphylaxis and hypersensitivity reactions were managed with infusion interruption, decreased infusion rate, administration of antihistamines, corticosteroids, intravenous fluids, and/or oxygen, when clinically indicated. In some cases of anaphylactic reactions, epinephrine was administered. Patients who have experienced anaphylaxis or hypersensitivity reactions should be treated with caution when they are re-administered alglucosidase alfa.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The data reflect the percentage of patients whose test results were considered positive for antibodies to alglucosidase alfa using an enzyme-linked immunosorbent assay (ELISA) and confirmed by a radioimmunoprecipitation (RIP) assay for alglucosidase alfa-specific IgG antibodies.

In the two clinical trials in infantile-onset patients, the majority of patients (34 of 38; 89%) tested positive for IgG antibodies to alglucosidase alfa. There is evidence to suggest that some patients who develop high sustained titers of anti-alglucosidase alfa antibodies may experience reduced clinical efficacy to alglucosidase alfa treatment [see [Warnings and Precautions \(5.5\)](#)]. Some IgG-positive patients in clinical trials who were retrospectively evaluated for the presence of inhibitory antibodies tested positive for inhibition of enzyme activity and/or uptake in *in vitro* assays. Furthermore, CRIM-negative infants have shown reduced clinical effect in the presence of high sustained IgG antibody titers with inhibitory activity. Alglucosidase alfa-treated patients who

experience a decrease in motor function should be tested for the presence of inhibitory antibodies that neutralize enzyme uptake or activity.

In the randomized, double-blind, placebo-controlled trial in late-onset patients, all alglucosidase alfa-treated patients with available samples (N=59, 100%) developed IgG antibodies to alglucosidase alfa. Most patients who developed IgG antibodies did so within the first 3 months of exposure (median time to seroconversion was 4 weeks). There was no apparent association between mean or peak IgG antibody titers and the occurrence of adverse reactions.

None of the 59 evaluable patients tested positive for inhibition of enzyme activity. Antibody titers for cellular uptake inhibition were present in 18 of 59 (31%) patients by Week 78. All other patients tested negative for inhibition of cellular uptake. Patients who tested positive for uptake inhibition tended to have higher IgG titers than patients who tested negative for uptake inhibition. Among the 32 patients with evaluable pharmacokinetic (PK) samples, 5 patients tested positive for uptake inhibition. The clinical relevance of this *in vitro* inhibition is not fully understood. The clearance values for 4 of these 5 patients were approximately 1.2- to 1.8-fold greater in the presence of inhibitory antibodies (Week 52) as compared to in the absence of inhibitory antibodies (Week 0) [see [Clinical Pharmacology \(12.3\)](#)].

Some patients in the clinical studies or in the postmarketing setting have undergone testing for alglucosidase alfa-specific IgE antibodies. Testing was performed in patients who experienced moderate to severe or recurrent hypersensitivity reactions, for which mast-cell activation was suspected. Some of the patients who tested positive for alglucosidase alfa-specific IgE antibodies experienced anaphylactic reactions [see [Boxed Warning and Warnings and Precautions \(5.1\)](#)].

Some patients who tested positive for alglucosidase alfa-specific IgE antibodies and experienced hypersensitivity reactions were able to be rechallenged with alglucosidase alfa using a slower infusion rate at lower starting doses and have continued to receive treatment under close clinical supervision [see [Warnings and Precautions \(5.1\)](#)]. Since patients who develop IgE antibodies to alglucosidase alfa appear to be at a higher risk for developing anaphylaxis and hypersensitivity reactions, these patients should be monitored more closely during administration of alglucosidase alfa.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to alglucosidase alfa with the incidence of antibodies to other products may be misleading.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post approval use of alglucosidase alfa. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. In postmarketing experience with alglucosidase alfa, serious adverse reactions have been reported,

including anaphylaxis [see [Boxed Warning and Warnings and Precautions \(5.1\)](#)]. Acute cardiorespiratory failure, possibly associated with fluid overload, has been reported in infantile-onset Pompe disease patients with pre-existing hypertrophic cardiomyopathy [see [Boxed Warning and Warning and Precautions \(5.3\)](#)].

Recurrent reactions consisting of flu-like illness or a combination of events such as pyrexia, chills, myalgia, arthralgia, pain, or fatigue occurring after completion of infusions and lasting usually for 1 - 3 days have been observed in some patients treated with alglucosidase alfa. The majority of patients were able to be rechallenged with alglucosidase alfa using lower doses and/or pretreatment with anti-inflammatory drugs and/or corticosteroids and were able to continue treatment under close clinical supervision.

In addition to the hypersensitivity reactions reported in clinical trials [see [Adverse Reactions \(6.1\)](#)], the following hypersensitivity reactions have been reported in at least 2 patients and included: anaphylactic shock, respiratory failure, respiratory arrest, cardiac arrest, hypoxia, dyspnea, wheezing, convulsions, peripheral coldness, restlessness, nervousness, back pain, stridor, pharyngeal edema, abdominal pain, apnea, muscle spasm, and conjunctivitis. In addition, one case of hyperparathyroidism has been reported.

Systemic and cutaneous immune-mediated reactions, including proteinuria and nephrotic syndrome secondary to membranous glomerulonephritis, and necrotizing skin lesions have been reported in postmarketing safety experience with alglucosidase alfa [see [Warnings and Precautions \(5.2\)](#)].

7 DRUG INTERACTIONS

7.1 Interference with Other Drugs

No drug interaction or *in vitro* metabolism studies were performed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There is a registry for Pompe disease patients that monitors the outcomes of women and their offspring exposed to alglucosidase alfa during pregnancy. Patients or their physicians should call 1-800-745-4447 or visit www.pompregistry.com to enroll [see [Patient Counseling Information \(17\)](#)].

Risk Summary

There are no studies of alglucosidase alfa in pregnant women. In animal reproduction studies, no effects on embryo-fetal development were observed in mice or rabbits given daily administration of alglucosidase alfa up to 0.4 or 0.5 times the human steady-state AUC (area under the plasma concentration-time curve), respectively, at the recommended human bi-weekly dose during the period of organogenesis. An increase in pup mortality was observed when alglucosidase alfa was administered every other day in mice during the period of organogenesis through lactation at a dose 0.4 times the human steady-state AUC at the recommended human bi-weekly dose. Alglucosidase

alfa should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

All reproductive studies included pre-treatment with diphenhydramine to prevent or minimize hypersensitivity reactions. The effects of alglucosidase alfa were evaluated based on comparison to a control group treated with diphenhydramine alone. Daily intravenous (IV) administration of alglucosidase alfa up to 40 mg/kg in mice and rabbits (0.4 and 0.5 times the human steady-state AUC, respectively, at the recommended bi-weekly dose) during the period of organogenesis had no effects on embryo-fetal development. Administration of 40 mg/kg IV every other day in mice (0.4 times the human steady-state AUC at the recommended bi-weekly dose) during the period of organogenesis through lactation produced an increase in mortality of offspring during the lactation period.

8.3 Nursing Mothers

Alglucosidase alfa is present in human milk. In one case report, the enzymatic activity of alglucosidase alfa was detected in the breast milk of a lactating woman up to 24 hours after the end of intravenous alglucosidase alfa administration. To minimize infant exposure to alglucosidase alfa, a nursing mother may temporarily pump and discard breast milk produced during the 24 hours after administration of alglucosidase alfa. Exercise caution when administering alglucosidase alfa to a nursing mother.

8.4 Pediatric Use

The safety and effectiveness of alglucosidase alfa have been established in pediatric patients with Pompe disease.

The safety and effectiveness of alglucosidase alfa were assessed in 57 treatment-naïve infantile-onset Pompe disease patients, aged 0.2 month to 3.5 years at first infusion, in three separate clinical trials [see [Clinical Studies \(14.1\)](#)].

The safety and effectiveness of alglucosidase alfa were assessed in pediatric patients with late (non-infantile) onset Pompe disease in a randomized, double-blind, placebo-controlled study in 90 patients, including 2 patients 16 years of age or less [see [Clinical Studies \(14.2\)](#)].

Anaphylaxis, hypersensitivity reactions, and acute cardiorespiratory failure have occurred in pediatric patients [see [Boxed Warning, Warnings and Precautions \(5.1, 5.3\)](#)]. Additionally, cardiac arrhythmia and sudden cardiac death have occurred in pediatric patients during general anesthesia for central venous catheter placement [see [Warnings and Precautions \(5.4\)](#)].

8.5 Geriatric Use

The randomized, double-blind, placebo-controlled study of alglucosidase alfa did not include sufficient numbers (n=4) of patients aged 65 years and over to determine whether they respond differently from younger patients [see [Clinical Studies \(14.1\)](#)].

11 DESCRIPTION

Alglucosidase alfa is a hydrolytic lysosomal glycogen-specific enzyme encoded by the predominant of nine observed haplotypes of the human acid α -glucosidase (GAA) gene. Alglucosidase alfa is produced by recombinant DNA technology in a Chinese hamster ovary cell line. Alglucosidase alfa degrades glycogen by catalyzing the hydrolysis of α -1,4- and α -1,6- glycosidic linkages of lysosomal glycogen.

Alglucosidase alfa is a glycoprotein with a calculated mass of 99,377 daltons for the polypeptide chain, and a total mass of approximately 109,000 daltons, including carbohydrates. Alglucosidase alfa has a specific activity of 3.6 to 5.4 units/mg (one unit is defined as that amount of activity that results in the hydrolysis of 1 micromole of synthetic substrate per minute under specified assay conditions). Alglucosidase alfa is intended for intravenous infusion. It is supplied as a sterile, nonpyrogenic, white to off-white, lyophilized cake or powder for reconstitution with 10.3 mL Sterile Water for Injection, USP. Each 50 mg vial contains 52.5 mg alglucosidase alfa, 210 mg mannitol, 0.5 mg polysorbate 80, 9.9 mg sodium phosphate dibasic heptahydrate, 31.2 mg sodium phosphate monobasic monohydrate. Following reconstitution as directed, each vial contains 10.5 mL reconstituted solution and a total extractable volume of 10 mL at 5 mg/mL alglucosidase alfa. Alglucosidase alfa does not contain preservatives; each vial is for single use only.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pompe disease (acid maltase deficiency, glycogen storage disease type II, GSD II, glycogenosis type II) is an inherited disorder of glycogen metabolism caused by the absence or marked deficiency of the lysosomal enzyme GAA.

Alglucosidase alfa provides an exogenous source of GAA. Binding to mannose-6-phosphate receptors on the cell surface has been shown to occur via carbohydrate groups on the GAA molecule, after which it is internalized and transported into lysosomes, where it undergoes proteolytic cleavage that results in increased enzymatic activity. It then exerts enzymatic activity in cleaving glycogen.

12.2 Pharmacodynamics

Clinical pharmacodynamic studies have not been conducted for alglucosidase alfa.

12.3 Pharmacokinetics

The pharmacokinetics of alglucosidase alfa were evaluated in 13 patients with infantile-onset Pompe disease, aged 1 month to 7 months, who received 20 mg/kg (approximately as a 4-hour infusion) or 40 mg/kg (approximately as a 6.5-hour infusion) of alglucosidase alfa every 2 weeks. The measurement of alglucosidase alfa plasma concentration was based on an activity assay using an artificial substrate. Systemic exposure was approximately dose proportional between the 20 and 40 mg/kg doses. Based on the pharmacokinetic blood samples collected for 12 hours after a 4-hour intravenous infusion of 20 mg/kg (n=5), the estimated mean AUC was 811 mcg•hr/mL with 17%

coefficient of variation [CV], C_{\max} was 162 mcg/mL with 19% CV, clearance was 25 mL/hr/kg with 16% CV, and half-life was 2.3 hours with 17% CV.

The pharmacokinetics of alglucosidase alfa were also evaluated in a separate trial of 14 patients with infantile-onset Pompe disease, aged 6 months to 3.5 years, who received 20 mg/kg of alglucosidase alfa as a 4-hour infusion every 2 weeks. The pharmacokinetic parameters were similar to those observed for the infantile-onset Pompe disease patients aged 1 month to 7 months who received the 20 mg/kg dose.

Nineteen of 21 patients who received treatment with alglucosidase alfa and had pharmacokinetics and antibody titer data available at Week 12 developed antibodies to alglucosidase alfa. Five patients with antibody titers $\geq 12,800$ at Week 12 had an average increase in clearance of 50% (range 5% to 90%) from Week 1 to Week 12. The other 14 patients with antibody titers $< 12,800$ at Week 12 had similar average clearance values at Week 1 and Week 12.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate carcinogenic potential or studies to evaluate mutagenic potential have not been performed with alglucosidase alfa.

Intravenous administration of alglucosidase alfa every other day in mice at doses up to 40 mg/kg (0.4 times the human AUC at the recommended bi-weekly dose) had no effect on fertility and reproductive performance.

14 CLINICAL STUDIES

14.1 Clinical Trials in Infantile-Onset Pompe Disease

The safety and efficacy of alglucosidase alfa were assessed in 57 treatment-naïve infantile-onset Pompe disease patients, aged 0.2 month to 3.5 years at first infusion, in three separate clinical trials.

Study 1 was an international, multicenter, open-label, clinical trial of 18 infantile-onset Pompe disease patients. This study was conducted between 2003 and 2005. Patients were randomized 1:1 to receive either 20 mg/kg or 40 mg/kg alglucosidase alfa every two weeks, with length of treatment ranging from 52 to 106 weeks. Enrollment was restricted to patients 7 months of age or younger at first infusion with clinical signs of Pompe disease and cardiac hypertrophy, and who did not require ventilatory support at study entry. Fourteen patients were Cross Reactive Immunologic Material (CRIM) positive and 4 patients were CRIM-negative.

Efficacy was assessed by comparing the proportions of alglucosidase alfa-treated patients who died or needed invasive ventilator support at 18 months of age with the mortality experience of a historical cohort of untreated infantile-onset Pompe disease patients with similar age and disease severity. In the historical cohort, 61 untreated patients with infantile-onset Pompe disease diagnosed by age 6 months, born between 1982 and 2002, were identified by a retrospective review of medical charts. By 18 months of age, 15 of 18 (83%) alglucosidase alfa-treated patients were alive without invasive ventilatory support and 3 (17%) required invasive ventilator support,

whereas only one of the 61 (2%) historical control patients was alive. No differences in outcome were observed between patients who received 20 mg/kg versus 40 mg/kg.

Other outcome measures in this study included unblinded assessments of motor function by the Alberta Infant Motor Scale (AIMS), a measure of infant motor performance that assesses motor maturation of the infant through age 18 months. Although gains in motor function were noted in 13 patients, the motor function was substantially delayed compared to normal infants of comparable age in the majority of patients. Two of 9 patients who had initially demonstrated gains in motor function after 12 months of alglucosidase alfa treatment regressed despite continued treatment.

Changes from baseline to Month 12 in left ventricular mass index (LVMI), a measure of pharmacodynamic effect, were evaluated by echocardiography. Fifteen patients who underwent both baseline and Month 12 echocardiograms demonstrated decreases from baseline in LVMI (mean decrease 118 g/m², range 45 to 193 g/m²). However, the magnitude of the decrease in LVMI did not correlate with the clinical outcome measure of ventilator-free survival.

Study 2 was an international, multicenter, non-randomized, open-label clinical trial that enrolled 21 infantile-onset patients aged 3 months to 3.5 years at first infusion. Eighteen patients were CRIM-positive and 3 patients were CRIM-negative. All patients received 20 mg/kg alglucosidase alfa every other week for up to 104 weeks. Five of 21 patients were receiving invasive ventilatory support at the time of first infusion.

The primary outcome measure was the proportion of patients alive at the conclusion of treatment. At the 52-week interim analysis, 16 of 21 patients were alive. Sixteen patients were free of invasive ventilatory support at the time of first infusion; of these, 4 died, 2 required invasive ventilatory support, and 10 were free of invasive ventilatory support after 52 weeks of treatment. For the 5 patients who were receiving invasive ventilatory support at baseline, 1 died, and 4 remained on invasive ventilatory support at Week 52.

Study 3 was an open-label, single-center trial in 18 infantile-onset Pompe disease patients who had a confirmed diagnosis of Pompe disease as identified through a newborn screening program. All patients were CRIM-positive. Patients were treated with alglucosidase alfa prior to 6 months of age (0.2 to 5.8 months at first infusion). Sixteen patients reached 18 months of age at the time of analysis, and all (100%) were alive without invasive ventilator support.

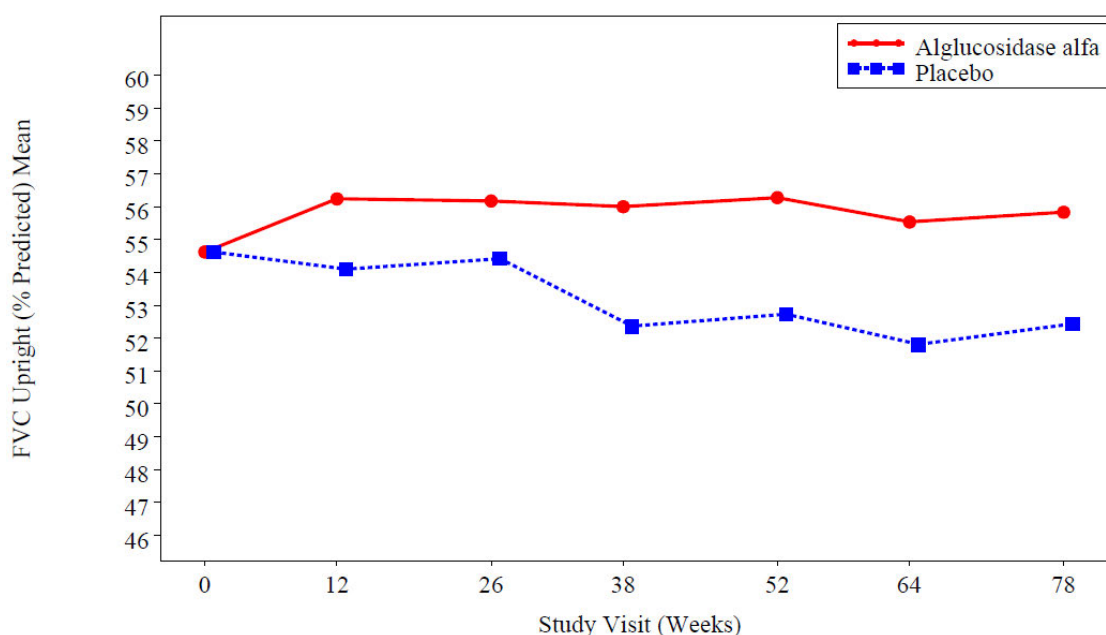
14.2 Clinical Trials in Late-Onset Pompe Disease

The safety and efficacy of alglucosidase alfa were assessed in 90 patients with late-onset Pompe disease, aged 10 to 70 years, in a randomized, double-blind, placebo-controlled trial. The youngest alglucosidase alfa-treated patient was 16 years of age, and the youngest placebo-treated patient was 10 years of age. All patients were naïve to enzyme replacement therapy. Patients were allocated in a 2:1 ratio and received 20 mg/kg alglucosidase alfa (n=60) or placebo (n=30) every other week for 78 weeks (18 months). The study population included 34 males and 26 females (n=60) in the alglucosidase alfa group and 11 males and 19 females (n=30) in the placebo group. At baseline, all patients were ambulatory (some required assistive walking devices), did not require invasive ventilator support or non-invasive ventilation while awake and sitting upright, and had a forced vital capacity (FVC) between 30 and 79% of predicted in the sitting position. Patients who could not walk 40 meters in 6 minutes or were unable to perform appropriate pulmonary and muscle function testing were excluded from the study.

A total of 81 of 90 patients completed the trial. Of the 9 patients who discontinued, 5 were in the alglucosidase alfa group and 4 were in the placebo group. Three patients discontinued the study due to an adverse event, two patients were in the alglucosidase alfa treatment group and one patient was in placebo group.

At study entry, the mean % predicted FVC in the sitting position among all patients was about 55%. After 78 weeks, the mean % predicted FVC increased to 56.2% for alglucosidase alfa-treated patients and decreased to 52.8% for placebo-treated patients indicating an alglucosidase alfa treatment effect of 3.4% (95% confidence interval: [1.3% to 5.5%]; $p=0.004$). Stabilization of % predicted FVC in the alglucosidase alfa-treated patients was observed (see [Figure 1](#)).

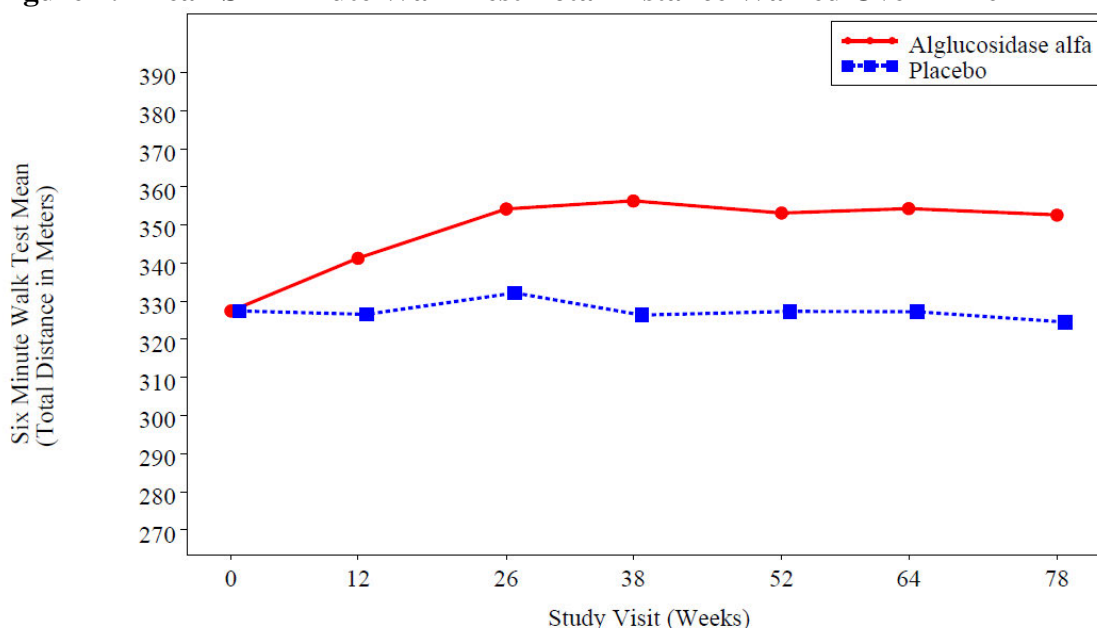
Figure 1: Mean FVC Upright (% Predicted) Over Time



Note: ANCOVA least squares means adjusting for baseline values

At study entry, the mean 6 minute walk test (6MWT) among all patients was about 330 meters. After 78 weeks, the mean 6MWT increased by 25 meters for alglucosidase alfa-treated patients and decreased by 3 meters for placebo-treated patients indicating an alglucosidase alfa treatment effect of 28 meters (95% confidence interval: [-1 to 52 meters]; $p=0.06$) (see [Figure 2](#)).

Figure 2: Mean Six Minute Walk Test Total Distance Walked Over Time



Note: ANCOVA least squares means adjusting for baseline values

16 HOW SUPPLIED/STORAGE AND HANDLING

LUMIZYME 50 mg vials are supplied as a sterile, nonpyrogenic, white to off-white lyophilized cake or powder in single-use vials.

NDC 58468-0160-1 (Carton of one single-use vial)

NDC 58468-0160-2 (Carton of ten single-use vials)

Store LUMIZYME under refrigeration between 2°C to 8°C (36°F to 46°F). Do not use LUMIZYME after the expiration date on the vial.

17 PATIENT COUNSELING INFORMATION

Anaphylaxis, Hypersensitivity and Immune-Mediated Reactions

Advise the patients and caregivers that reactions related to administration and infusion may occur during and after alglucosidase alfa treatment, including life-threatening anaphylaxis, hypersensitivity reactions, and immune-mediated reactions. Patients who have experienced anaphylaxis or hypersensitivity reactions may require close observation during and after alglucosidase alfa administration. Inform patients of the signs and symptoms of anaphylaxis, hypersensitivity reactions, and immune-mediated reactions and have them seek medical care should signs and symptoms occur.

Risk of Acute Cardiorespiratory Failure

Advise patients and caregivers that patients with underlying respiratory illness or compromised cardiac or respiratory function may be at risk of acute cardiorespiratory failure. Patients with

compromised cardiac or respiratory function may require close observation during and after
alglucosidase alfa administration.

Pompe Registry

Inform patients and their caregivers that the Pompe Registry has been established in order to better understand the variability and progression of Pompe disease, and to continue to monitor and evaluate long-term treatment effects of alglucosidase alfa. The Pompe Registry will also monitor the effect of alglucosidase alfa on pregnant women and their offspring [see *Use in Specific Populations (8)*]. Patients and their caregivers should be encouraged to participate in the Pompe Registry and advised that their participation is voluntary and may involve long-term follow-up. For more information regarding the registry program, visit www.pomperegistry.com or call 1-800-745-4447.

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
BLA 125291/136

OFFICER/EMPLOYEE LIST

Officer/Employee List

Application: 125291/136

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

Name	Title
Joyce Korvick	Deputy Director for Safety
Jessica Lee	Clinical Team Leader
Juli Tomaino	Clinical Reviewer
David Joseph	Nonclinical Team Leader
Christopher Downey	Quality Reviewer
Cecilia Tami	Immunogenicity Reviewer
Justin Earp	Pharmacometrics Reviewer
Jibril Abdus-Samad	Quality Labeling Reviewer
Lubna Merchant	DMEPA Team Leader
Sherly Abraham	DMEPA Reviewer
Jamie Wilkins Parker	DRISK Team Leader
Robert Pratt	DRISK Reviewer
Hari Sachs	PMHS Team Leader
Jeanine Best	PMHS Team Leader
Kevin Bugin	Senior Regulatory Project Manager
Yow-Ming Wang	Clinical Pharmacology Team Leader
Christine Hon	Clinical Pharmacology Reviewer

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
BLA 125291/136

OFFICE DIRECTOR MEMO

Division Director Review

Date	(electronic stamp)
From	Donna J. Griebel, MD
Subject	Division Director Summary Review
NDA/BLA #	BLA 125291
Supplement #	Supplement 136
Applicant Name	Genzyme
Date of Submission	January 300, 2014
PDUFA Goal Date	August 1, 2014
Proprietary Name / Established (USAN) Name	LUMIZYME /alglucosidase alfa
Dosage Forms / Strength	Lyophilized cake or powder in single-use vials/50 mg
Proposed Indication(s)	For treatment of patients with Pompe disease (acid α -glucosidase deficiency)
Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
Medical Officer Review	Juli Tomaino, MD
Statistical Review	Freda Cooner, PhD/Stephen E. Wilson, Dr. PH
Pharmacology Toxicology Review	Fang Cai, PhD/David Joseph, PhD
CMC/DTP/OBP Review	Christopher Downey, PhD/Juhong Liu, PhD/Susan Kirshner, PhD Maria Cecilia Tami, PhD/Susan Kirshner, PhD
Clinical Pharmacology Review	Christine Hon, PharmD/Yow-Ming Wang, PhD
OSI	Susan Leibenhaut, MD/Susan Thompson, MD/Kassa Ayalew, MD, MPH
CDTL Review	Jessica Lee, MD
OSE/DRISK	Bob Pratt, PharmD/Jamie Wilkins-Parker, PharmD/Reema Mehta, Pharm D, MPH
PMHS	Alyson Karesh, MD/Hari C. Sachs, MD Tamara Johnson, MD,

OND=Office of New Drugs
 OSE= Office of Surveillance and Epidemiology
 OSI=Office of Scientific Investigations
 DRISK=Division of Risk Management
 CDTL=Cross-Discipline Team Leader

Division Director Review

1. Introduction

In this supplemental biologics application (sBLA), Genzyme proposes to expand the Lumizyme (alglucosidase alfa) indication for Pompe disease to all Pompe disease patients, including infantile-onset patients and late (non-infantile) onset patients less than 8 years of age, with no limitations related to presence of cardiac hypertrophy. The current approved indication is:

“for patients 8 years and older with late (non-infantile) onset Pompe disease (acid α -glucosidase deficiency) who do not have evidence of cardiac hypertrophy. The safety and efficacy of Lumizyme have not been evaluated in controlled clinical trials in infantile-onset patients, or in late (non-infantile) onset patients less than 8 years of age.”

Consistent with the proposed broader indication, the applicant also requested elimination of the Lumizyme REMS that restricts its use to patients 8 years of age and older to mitigate the potential risk of rapid disease progression in infantile-onset patients and to communicate the risks of anaphylaxis and severe allergic reactions to patients and prescribers. The REMS assures that patients with infantile onset Pompe disease and patients with late (non-infantile) onset disease who are less than 8 years of age receive Myozyme instead of Lumizyme.

To support the proposed expansion of the population and the attendant elimination of the REMS, the applicant submitted information to establish the comparability of Lumizyme to Myozyme, which are both alglucosidase alfa products produced from the same cell line by the applicant. Lumizyme is produced at a 4000L scale, whereas Myozyme is produced on a smaller fermentation scale, 160L. The key information submitted was the analytical (i.e., biochemical, physical and in vitro biological) comparability evaluation between the two scales. In addition, the applicant submitted safety and efficacy data from patients with infantile-onset Pompe disease enrolled in an open label study underway in Taiwan, as well as data from pediatric patients older than 12 months of age who had been switched from Myozyme to Lumizyme during a drug shortage of Myozyme (see below). These clinical data ultimately were considered merely supportive, as the DTP reviewers found that the two product scales were analytically comparable. In meetings between the applicant and FDA, during the planning phase for the sBLA submission, the FDA had strongly recommended submission of these clinical data to provide an essential source of support should unresolved questions regarding analytical comparability remain after s-BLA review.

Given the ongoing drug shortage of Myozyme, the FDA reviewers conducted the review of this BLA supplement under a Priority review clock. As stated above, the REMS was intended to assure that children with Pompe disease under the age of 8 years of age are treated with Myozyme; however, beginning in March 2012, a shortage of Myozyme has necessitated further limiting treatment with Myozyme to an even younger subset of patients, i.e., infants 12 months of age and younger. In light of the existence of the Lumizyme REMS, substitution of

Lumizyme for Myozyme for treatment of children between 12 months and 8 years of age during the Myozyme shortage could only occur under an IND study. The latter study, ADVANCE (AGLU09411), included monitoring of safety and efficacy outcomes.

All review disciplines have recommended approval of this sBLA. In addition, the REMS Oversight Committee concurred with the reviewers' recommendation to eliminate the REMS. My review will summarize the review highlights. The reader should refer to the CDTL review for a more comprehensive summary.

2. Background

In this section, I have provided key information regarding the regulatory history relevant to the safety and efficacy review issues described above. In summary, the applicant has two separate BLA's for two different bioreactor scales of their alglucosidase alfa product (160L and 4000L). There are two separate BLA's due to concerns about the comparability of the originally approved 160L product to the initially proposed larger bioreactor scale product, a 2000L product, i.e., concerns that the drug substance from the different manufacturing scales differed in critical quality attributes. When approval of the 2000L scale product was precluded due to persistent compliance issues at the 2000L product's manufacturing site, the manufacturing sites were withdrawn from the BLA and the manufacturing sites that produced a linear scale-up of the 2000L manufacturing process to a larger 4000L scale were substituted. Ultimately, the product approved in the Lumizyme BLA was the 4000L scale product. The manufacturing sites of the 4000L scale passed inspection, and data were reviewed that established the analytical comparability of the 4000L and 2000L products. However, at that time, data had not been submitted for review to establish comparability of the 4000L product to the original 160L scale (Myozyme) product. I will describe this series of events in more detail in this section. The absence of information to establish comparability of the 4000L product to the 160L product (and previous evidence that the 2000L product was not analytically comparable to the 160L product) led to the REMS that restricted use of Lumizyme to a Pompe disease population with a less aggressive disease phenotype. Refer to the CDTL and Clinical reviews for a comprehensive summary of the relevant regulatory history.

Pompe disease is a rare, autosomal recessive disorder of glycogen metabolism caused by the absence or deficiency of the lysosomal enzyme acid α -glucosidase or alglucosidase alfa (GAA). This deficiency results in glycogen accumulation in tissues, including cardiac and skeletal muscles, which leads to progressive muscle weakness, cardiomyopathy, and impairment of respiratory function. There are two main phenotypes of Pompe disease: early-onset (infantile) and late-onset (juvenile or adult). The infantile form of the disease is more rapidly progressive. Without enzyme replacement treatment, infants with Pompe disease die by 1-2 years of age. Infants develop failure to thrive, hypotonia, hypertrophic cardiomyopathy, hepatomegaly, and hearing difficulties. Patients with juvenile- or adult-onset Pompe disease have symptoms related to skeletal and respiratory muscle weakness, which result in impaired

mobility and respiration.¹ Respiratory failure is the underlying cause of death in all forms of Pompe disease.

Lumizyme and **Myozyme** (both alglucosidase alfa) are the only two enzyme replacement therapies approved for treatment of Pompe disease in the U.S. They are both human enzyme acid α -glucosidase produced by recombinant DNA technology in a Chinese hamster ovary cell line by the same applicant, Genzyme; however, they are produced in two different bioreactor scales. Myozyme, the first approved, is produced at the smallest scale, 160L. It was approved in April 2006, under BLA 125141, based on the following clinical data:

- 1) A clinical trial (Study AGLU01602) that demonstrated improved ventilator-free survival in 18 patients with infantile-onset Pompe disease who were ≤ 7 months of age at the time of first infusion. The historical control was a group of age-matched, untreated patients with infantile-onset Pompe disease (from Study AGLU00400).
- 2) Case narratives from an uncontrolled series of patients with juvenile- and adult-onset disease patients that suggested disease stabilization. Disease stabilization is difficult to establish without a control arm in the setting of these phenotypes, which have a slower, more indolent rate of progression.

Myozyme was approved with an indication that did not specifically limit its use to infantile onset disease; however, it provided information on the limitations of the evidence supporting efficacy and safety in patients with a different phenotype of the disease, as shown below:

“Myozyme (alglucosidase alfa) is.....**indicated for use in patients with Pompe disease**....Myozyme has been shown to improve ventilator-free survival in patients with infantile-onset Pompe disease....., whereas use of Myozyme in patients with other forms of Pompe disease has not been adequately studied to assure safety and efficacy...”

At the time of Myozyme’s approval, an ongoing placebo, controlled trial was evaluating treatment of patients with non-infantile onset disease (the Late Onset Treatment Study [LOTS trial], AGLU02704). The efficacy endpoints included changes in six minute walk test (6-MWT) and percentage predicted forced vital capacity (FVC). The 2000L scale alglucosidase alfa product was used in this trial. It should be noted that the original Myozyme BLA (125141) submission included both the 160L and 2000L production scales; however, during the course of the review the Agency found that the submitted data did not establish comparability of the two production scale products, and the applicant withdrew the 2000L scale product from the BLA. After receiving approval for the 160L Myozyme product in April 2006, the applicant submitted a supplement to the same BLA with data intended to establish comparability of the two scales (160L and 2000L) in October 2007, and FDA reviewers again determined that the products were not analytically comparable. The reviewers were specifically concerned that differences in certain attributes in the 2000L product vs. the 160L scale product might decrease the potency/efficacy of the 2000L product. The Agency concluded that alglucosidase alfa manufactured using the 2000L scale should be classified a different product based on

¹ Hirschhorn R, et al. (2001). Glycogen Storage Disease Type II: Acid Alpha-Glucosidase (Acid Maltase) Deficiency. In C. Scriver, et al. (Eds.), *The Metabolic and Molecular Bases of Inherited Disease* (pp. 3389-3420). New York, NY: McGraw-Hill.

measurable differences in some critical quality attributes. The applicant was advised (in April 2008) to submit the clinical data available to support the efficacy and safety of the 2000L scale from the LOTS trial to a new BLA, for separate licensure. The new BLA (125291) for the 2000L product was submitted in May 2008, and the trade name accepted was “Lumizyme”. (In the meantime, the 2000L scale product was approved ex-US with the name “Myozyme”.)

The Myozyme 160L production scale was insufficient to meet US and world-wide demand from the time of its approval in the US, and the applicant began limiting its access in the U.S. to patients less than 18 years of age. They made the unapproved (unapproved in the US; approved ex-US) 2000L scale product available to US adult patients, on a case by case basis, through a temporary access program administered under IND 10780. The applicant ended this access program just before it submitted the new BLA for the 2000L product in April 2008. The LOTS data included a statistically significant change in FVC; however, the change in 6MWT (28.1 meters between Lumizyme and placebo groups at 78 weeks) was not statistically significant at $p=0.06$ (ANCOVA, with re-randomization inference). The application was presented to open and closed sessions of the Endocrinologic and Metabolic Drugs Advisory Committee on October 15, 2008. The Committee recommended accelerated approval (Subpart E) based on FVC and recommended a REMS to ensure Lumizyme’s safe use.

In light of the AC recommendation for accelerated approval, the Clinical reviewers carefully considered the age for which the risk/benefit associated with the larger scale product could be justified. They ultimately recommended using the LOTS trial’s eligibility criteria to define the indicated age range for Lumizyme, i.e., patients greater than or equal to 8 years of age, as long as the patient had no evidence of cardiac hypertrophy. They recommended a REMS to assure that children less than 8 years of age, who would be expected to have more rapidly progressive disease, are treated with the product that had been shown to be effective in infantile onset disease, i.e., Myozyme (160L). However, the 2000L product BLA was not ultimately approved because of manufacturing issues at the applicant’s Allston facility, which led to issuance of an FDA Form 483 in October 2008, followed by a Warning Letter on February 27, 2009. A Complete Response letter was issued on the same day, February 27, 2009, which cited deficiencies in the manufacturing facilities, CMC issues and clinical deficiencies. The latter included: 1) inability to agree upon a verification study required for Subpart E approval and 2) inability to agree upon a complete Risk Evaluation and Mitigation Strategy (REMS).

Of note, just prior to issuance of the CR letter, the applicant received approval of an even larger scale product (4000L) in the European Union. The applicant informed FDA that it intended to seek approval for that product in the US, sometime during 2009.

A Complete Response resubmission was submitted by the applicant in May 15, 2009. The applicant and Agency had met in the interim between issuance of the Complete Response letter and the resubmission, and the Agency had agreed that the applicant could submit clinical outcome data (overall survival and 18 month survival) from infantile onset disease patients treated with the 2000L product who were registered in the Pompe Registry (an international registry) for review to support regular approval of the product (as opposed to accelerated approval). The applicant identified 48 patients in the Pompe registry who had infantile onset disease and matched inclusion criteria for the trial that led to Myozyme’s approval

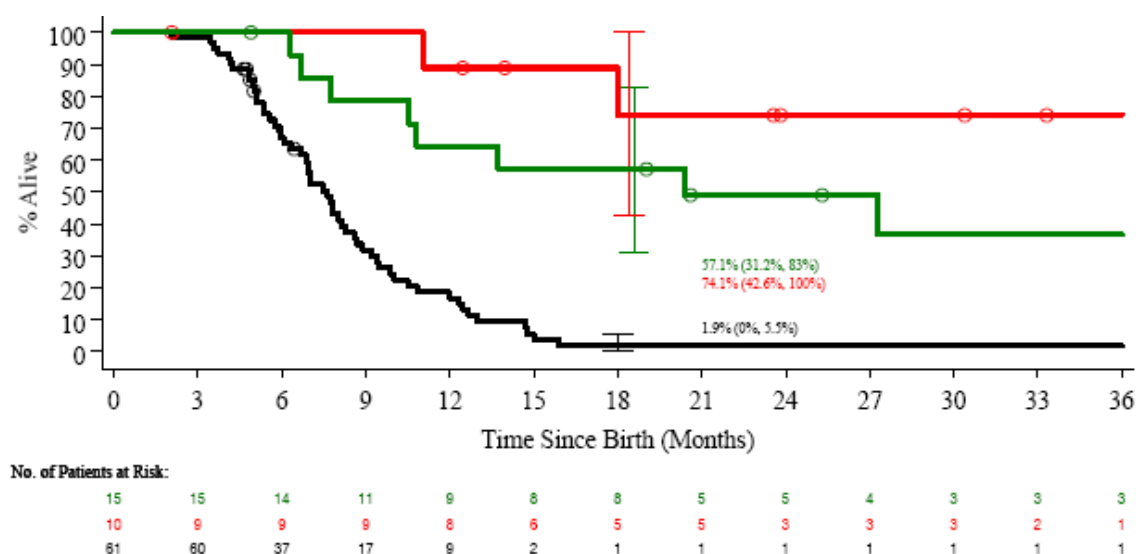
(AGLU1602). Only 15/48 (all ex-US) had received the 2000L product exclusively. Ten US infantile onset patients in the registry had received Myozyme exclusively. These groups were compared to the historical control population relied upon for Myozyme's approval. The following table, reproduced from the CDTL review from the resubmission summarizes the overall survival data for the two Registry subpopulations and the Historical Control. Ventilator-free survival could not be assessed due to insufficient patient numbers.

Table 1: Overall Survival

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

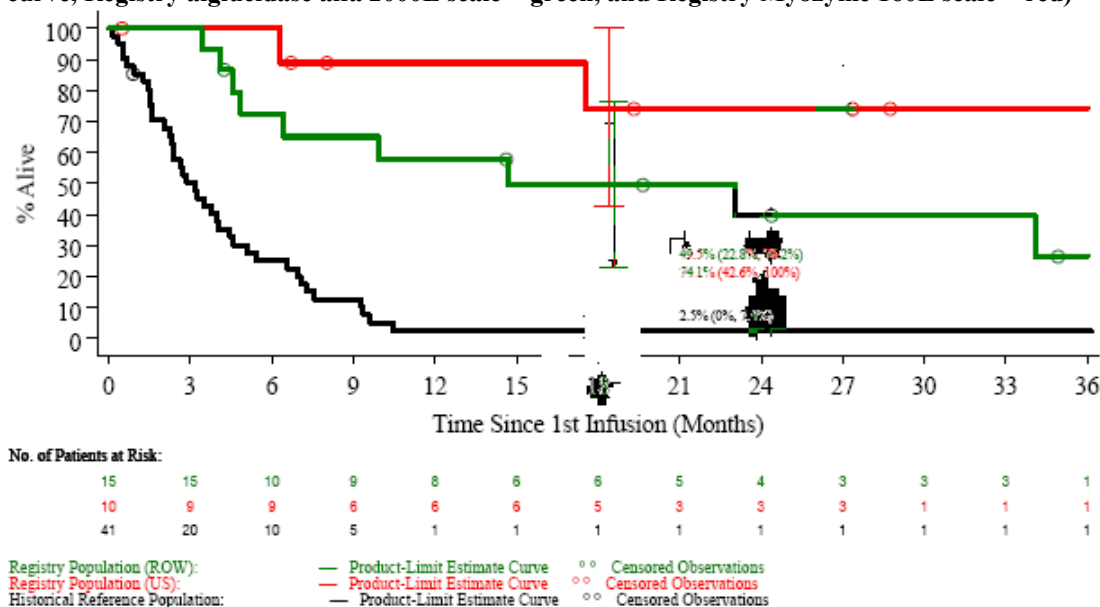
The following figure, reproduced from the CDTL review, shows that overall survival from date of birth in patients treated with either product was higher than the historical control. The confidence intervals at 18 months for the two products overlapped at 18 months.

Figure 1: Kaplan-Meier estimate of time to death from date of birth (Historical control = black curve, Registry alglucidase alfa 2000L scale = green, and Registry Myozyme 160L scale = red)



The K-M estimate of time to death from date of first infusion analysis is shown below, and demonstrates similar relative survivals.

Figure 2: Kaplan-Meier estimate of time to death from date of first infusion (Historical control = black curve, Registry alglucidase alfa 2000L scale = green, and Registry Myozyme 160L scale = red)



The CDTL for the resubmission stated in her review, “The overall survival and survival at 18 months in Lumizyme-treated patients compares favorably with an age-matched, disease-matched historical control group. Eighteen month survival for Lumizyme-treated patients was 57% compared with 1.9% in the historical control group.” She concluded that these data supported considering regular approval instead of accelerated approval; however, she stated the limitations of the Pompe Registry data precluded recommending Lumizyme for all ages. She recommended approving Lumizyme for patients 8 years and above, based on the entry criteria for the LOTS trial. The applicant’s revised, proposed REMS was reviewed and agreement was reached on the REMS. The reviewers determined the clinical deficiencies from the CR letter had been adequately addressed; however, again the manufacturing issues remained unresolved. The Office of Compliance recommended withholding approval of the BLA due to unacceptable compliance at the Allston Landing, MA manufacturing facility. The second CR letter for the 2000L product BLA was issued on November 13, 2009.

During the course of the various reviews of the 2000L production scale product, the applicant had developed and achieved ex-US marketing approval (February 2009, in Europe) of a linear scale up of the 2000L scale manufacturing process to a 4000L production scale (also marketed with the name “Myozyme” outside the US). The drug substance was manufactured in Geel Belgium and the drug product was manufactured in Waterford, Ireland. Shortly after issuance of the FDA’s November 2009 CR letter, the applicant submitted its second Complete Response Resubmission on December 16, 2009. In this resubmission, it withdrew request for licensure of the Allston Landing facility where the 2000L scale product was made and requested licensure of the Genzyme Flanders and Waterford facilities, which manufactured the 4000L product. This necessitated establishing comparability between the 2000L and 4000L scale products, since the BLA had been initially submitted for the 2000L scale product. The

submitted CMC data established analytical comparability between the products, and the CDTL review of the second resubmission stated, “Additionally, there appear to be improvements in the 4000L product in several attributes critical for product quality.” Inspections of the Waterford Ireland and Flanders facilities found both in compliance with CGMP. All disciplines recommended approval; however, the concerns regarding Lumizyme’s risk/benefit in patients with infantile onset disease remained.

Data reviewed in the second resubmission established the comparability of the 2000L and 4000L products; however, data to establish comparability of the 4000L scale product and 160L scale Myozyme were not provided for review in the resubmission. The Pompe Registry data did not alleviate concerns that differences in key physicochemical attributes might result in reduced efficacy in the infantile onset disease setting. The Lumizyme BLA for the 4000L scale product was approved with labeling and a REMS that addressed reviewers’ concerns about the risk/benefit of the larger scale product in patients with infantile onset disease, a phenotype with rapidly progressive disease. In keeping with the concerns that differences between the Lumizyme and Myozyme products which might lead to reduced efficacy for Lumizyme, which could be devastating in children with rapidly progressing disease, the following Indication and Boxed Warning were included in the Lumizyme label:

Lumizyme Indication: “...indicated for patients 8 years and older with late (non-infantile) onset Pompe disease.....who do not have evidence of cardiac hypertrophy. The safety and efficacy of Lumizyme have not been evaluated in controlled clinical trials in infantile-onset patients, or in late (non-infantile) onset patients less than 8 years of age....”

Boxed Warning: Anaphylaxis and Restricted Distribution Program. In addition to a warning regarding life-threatening anaphylactic reactions, severe allergic reactions and immune mediated reactions, the box states the following: “Because of the potential risk of rapid disease progression in Pompe disease patients less than 8 years of age, Lumizyme is available only through a restricted distribution program called the Lumizyme ACE Program. Only prescribers and healthcare facilities enrolled in the program may prescribe, dispense or administer Lumizyme. Lumizyme may be administered only to patients who are enrolled in and meet all the conditions of the Lumizyme ACE program. To enroll in the Lumizyme ACE Program call....”

Section 14 Clinical Studies of the Lumizyme product label presents the FVC and 6MWT data from the LOTS trial. Under Section 14.2 “Uncontrolled Studies”, the Pompe Registry data that provided the support to approve Lumizyme under regular approval, instead of accelerated approval, are presented, as follows: “The effectiveness of Lumizyme has not been established in infantile-onset patients. Descriptive data from infantile-onset patients who have received Lumizyme commercially outside the US have been collected in the Pompe Registry..... Descriptive clinical data from patients with infantile-onset Pompe disease in the Pompe Registry were used to verify the overall effectiveness of Lumizyme for patients 8 years and older with late-onset Pompe disease.”

A REMS (known as the Lumizyme Alglucosidase Alfa Control and Education Program) was established that consists of a communication plan (CP); elements to assure safe use (ETASU) that include prescriber special certification, healthcare facility special certification, and documentation of safe use conditions to ensure that patients are enrolled in the program; an implementation system; and a timetable for submission of assessments. The REMS goals were to mitigate the potential risk of rapid disease progression in infantile-onset Pompe disease patients and patients with late (non-infantile) onset disease less than 8 years of age (because efficacy had not been established in those patients), and to ensure that the known risks of anaphylaxis and severe allergic reactions, and potential risks of severe cutaneous and systemic immune mediated reactions are communicated to prescribers and patients. The following table, reproduced from the Division of Risk Management's REMS Modification Review dated July 18, 2014, is an abbreviated summary of the REMS.

Table 2. Abbreviated Summary of Lumizyme REMS

REMS Goals	To mitigate the potential risk of rapid disease progression in infantile-onset Pompe disease patients and patients with late (non-infantile) onset disease less than 8 years of age for whom the safety and effectiveness of Lumizyme have not been evaluated.
	To ensure that the known risks of anaphylaxis and severe allergic reactions associated with the use of Lumizyme are communicated to patients and prescribers, and to ensure that the potential risks of severe cutaneous and systemic immune mediated reactions to Lumizyme are communicated to patients and prescribers.
REMS Elements	CP consisting of a Prescriber Introductory Letter and a Healthcare Professional Introductory Letter distributed at product launch.
	ETASU A – Special certification of HCPs who prescribe Lumizyme: Completion of prescriber training and enrollment.
	ETASU B – Special certification of healthcare facilities that dispense Lumizyme: Completion of healthcare facility training and enrollment; confirmation of infusion administration.
	ETASU D – Safe-use condition: Enrollment of patients and patient/caregiver acknowledgement of having received information and counseling from the prescriber.
Implementation System	Monitor compliance with enrollment, product distribution, and use of enrollment forms and other forms.
Timetable for submission of assessments	REMS assessments were to be submitted to FDA at 6 months and 1 year from the date of approval (May 24, 2010), then annually thereafter.

Current Lumizyme sBLA. The applicant has now submitted data to establish that the 4000L scale product (Lumizyme) is analytically comparable to the 160L scale product (Myozyme). The FDA and applicant met prior to submission to reach agreement on the data that would be submitted to support this supplement. At the time of those discussions, the Myozyme supplies were inadequate to meet the needs of the U.S. Pompe population for which the product was specifically required, (for which Lumizyme had specifically not been approved and its REMS precluded treatment), i.e., patients less than 8 years of age. Due to the Myozyme shortage, patients greater than 12 months of age and <8 years of age had to be treated with Lumizyme under an IND access study (ADVANCE; AGLU09411).

In a February 19, 2013 Type C meeting, the FDA stated that the key data to be submitted to achieve extension of the Lumizyme indication to children less than 8 years of age were CMC data

that established the analytical comparability of the two product scales. The clinical reviewers also recommended that the applicant submit clinical efficacy and safety data on patients with infantile onset disease who were treated with the 4000L product. This request was intended to assure adequate supportive clinical data, should there be residual concerns regarding specific aspects of comparability. The Division stated Taiwan study data analysis should focus on infants who would have met the inclusion criteria for the clinical trial that supported Myozyme's approval (AGLU01602) and that these data would need to establish that Lumizyme "is associated with ventilator-free survival".


In FDA's July 3, 2013 written response to questions from the applicant, the FDA and applicant agreed that the supportive clinical data would include survival and safety data from a single-center, open label study in Taiwan (Taiwan01), in addition to safety data from the ADVANCE study (in which patients were switched from Myozyme to Lumizyme due to Myozyme drug shortage). Available outcome data on survival beyond 18 months were requested. The FDA recommended submission of available data on patient genotype and CRIM status, in addition to an assessment of impact of anti-drug antibody titers on the safety and efficacy of the 4000L product scale, with a comparison to the results of patients who received the 160L scale exclusively (from Study AGLU01602 and the extension study AGLU02403). The FDA stated it agreed with the applicant's plan to compare proportions of patients alive at 18 months of age and comparing the proportions of subjects alive at 18 months of age and free of invasive ventilator support. The Agency stated the study report should include an outcome comparison between the Taiwan patients treated with a larger scale product, patients treated with the 160L product from Study AGLU01602/AGLU02403, and untreated patients from the natural history study (AGLU00400). With regard to the ADVANCE study, the Agency requested a comparison of the impact of antibody response on safety before and after switching from the 160L to the 4000L product.

3. CMC


I concur with the conclusions reached by the Division of Therapeutic Proteins (DTP) reviewers. They concluded that Lumizyme manufactured at a 4000L scale is comparable in terms of activity and most structural attributes to Myozyme, manufactured at a 160L scale. As stated by the CDTL in her review, "Although the 160 L and 4000 L products are currently marketed in the U.S. under different licenses, the DTP reviewers approached this submission as a comparability exercise as described in *ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process*, since the same manufacturer has complete control of the manufacturing processes, cell lines, and analytical testing for both production scales and also has a knowledge of the product development history." They evaluated a head-to head comparison of the drug substance, compared historical release results and compared stability data of the two production scales. The following summary statements about each of these 3 comparisons are reproduced from Dr. Christopher Downey's CMC review:

"The first is a comparison of 3 lots each of 160 L- and 4000 L-process drug substance tested side-by-side in a variety of assays. This study yielded highly comparable results for the two scales for critical quality attributes, including specific activity (*i.e.* potency), enzymatic kinetic parameters, primary, secondary, and tertiary structure, and levels of product-related impurities. The content of mannose-6- phosphate (M6P) (b) (4)


which are post-translational modifications of the enzyme required for cellular targeting and uptake, were also comparable. Several test results suggest that (b) (4)



The second component of the analytical data is a comparison of release and extended characterization data for all previous drug substance and drug product lots produced from the two process scales. These data include release test results from more than 100 lots each of drug substance from both scales. The results show the materials from the two scales to be highly comparable for most attributes. (b) (4)



The third component of the analytical data is a comparison of historical stability data for the two process scales. Genzyme provided stability data for all relevant drug substance and drug product lots stored under long-term storage conditions (5°C) and for drug product stored under accelerated conditions (25 °C). The data for the long-term conditions show little change over time in most tests for materials manufactured at both 160 L and 4000 L scales. Aggregation measurably increases over time for a majority of the long-term lots. The rates of increase do not differ significantly between lots from the two manufacturing scales. The data from accelerated stability are also comparable for most attributes, including specific activity, protein concentration, and purity. (b) (4)



After the CMC review was completed,

(b) (4)

CMC Immunogenicity Review. A CMC Immunogenicity review filed by Dr. Maria Cecilia Tami, PhD included evaluation of the relative immunogenicity profiles of CRIM-positive infantile-onset Pompe disease patients treated with Lumizyme in Taiwan 01 and the infantile onset disease patients treated with Myozyme in the study that supported its approval, AGLU01602/02403. The reviewers found no persuasive evidence of different antibody responses to Lumizyme relative to Myozyme in CRIM-positive infantile-onset Pompe disease patients. The review summary stated, “CRIM positive early onset patients exclusively receiving Lumizyme (Taiwan study) showed a better immunogenicity profile when compared to CRIM positive early onset patients who exclusively received Myozyme (Study AGLU01602/2403) in that no patients developed high sustained antibody titers, peak IgG titers were lower, and time to seroconversion was longer. Moreover, unlike the studies to support Myozyme, no correlation was observed between IgG titers and incidence of serious adverse events or clinical outcome, including invasive ventilator and survival in the Taiwan study.” The reviewers acknowledged that the patient numbers available for this cross-study comparison were limited (in both studies).

Immunogenicity data from the cross-over patients followed in the ADVANCE study (cross over from Myozyme to Lumizyme) were also evaluated for evidence of increased seroconversion or increasing antibody titers in patients with the change to Lumizyme. The Immunogenicity review states, “Data from the ADVANCE study show that antibody responses before and after switching from Myozyme to Lumizyme are comparable or better.”

The reviewers concluded the data “support comparable immunogenicity profiles in infantile-onset patients who received the 4000 L product (Taiwan 01 study) and patients who received 160 L product exclusively (in AGLU01602/02403). Further, data from the switch over study [ADVANCE] support similar impact of antibody response on safety before and after switching.”

Compliance. Ultimately, Compliance recommended the BLA could be approved from the standpoint of its evaluation of manufacturing and testing sites. Issues with an alternate sterility testing site listed in the BLA were resolved through withdrawal of this site from the BLA. The applicant stated that it has not used this site, even as an alternative. In the letter withdrawing the site, they stated there is “currently no drug product sterility testing performed” at the site. A recent supplement for a different alternate sterility testing site has been approved.

Summary. I concur with the reviewers' determination of analytical comparability of the two production scales, 160L and 4000L. I concur with the reviewers' approval recommendation..

4. Nonclinical Pharmacology/Toxicology

No new nonclinical data were submitted in this supplemental BLA. The nonclinical reviewers evaluated the proposed labeling and concluded the original Pregnancy Category of "B" was not appropriate, based on their evaluation of the results of a pre- and postnatal developmental (Segment 3) study in mice that had been previously reviewed in September of 2008. The nonclinical reviewers noted that the previously reviewed Segment 3 study showed a significant increase in number of pup deaths in the high-dose group of dams treated with alglucosidase alfa during pregnancy and lactation, relative to the vehicle+saline control group, as well as the vehicle+diphenhydramine group (diphenhydramine was administered to the mothers during pregnancy and lactation to prevent or minimize hypersensitivity reactions to alglucosidase alfa). The applicant agreed to revise the Lumizyme Pregnancy category from "B" to "C".

Given the comparability of the two product scales (4000L and 160L), the change in the Pregnancy category for Lumizyme (4000L) should be applied to the Myozyme label. The applicant stated they do not plan to manufacture more Myozyme (160L) and the remaining available product will be sold until supplies run out (expected in August 2015). They stated that the Myozyme product labels are already printed and packaged with the product waiting for distribution. The pragmatics of requesting removal of the associated labels and replacement with newly printed labels for the sole purpose of changing the Pregnancy Category were considered, in light of the fact that the 160L product is generally only used (based on longstanding shortage over the years) in infants and children under the age of 8 years (and most recently, only under the age of 12 months). Pregnancy is not an issue for this age group and the change would be irrelevant to the population actually treated with the 160L product, based on well-established practice patterns. The regulatory action for the Myozyme label was under discussion at the completion of this review.

The nonclinical reviewers also worked with the reviewers from the Maternal Health Team of the Pediatric and Maternal Health Staff to revise Section 8.1 of the proposed label to conform with the format of the Proposed Pregnancy and Lactation labeling Rule.

I concur with the labeling recommendations of the Nonclinical reviewers.

5. Clinical Pharmacology

The Applicant did not submit any new Clinical Pharmacology data with this efficacy supplement. PK studies to assess comparability between Myozyme (160 L scale) and Lumizyme (4000 L scale) were not necessary because the CMC data submitted were adequate to establish analytical comparability between the two product scales. The reviewers noted that PK data in the previously approved Lumizyme label (for the 4000L scale) are actually data

obtained from PK testing in patients with late onset Pompe disease who were being treated with another alglucosidase alfa product scale, the 2000L scale studied in the LOTS trial (the scale originally proposed in the Lumizyme BLA; see Section 2 Background). Inclusion of the PK data for the 2000L scale in the 4000L scale product label (Lumizyme) was appropriate at the time of Lumizyme's initial approval because the CMC data provided adequate evidence of analytical comparability between the 2000L scale product and the 4000L scale product. However, the reason that the 2000L scale product was submitted under a different BLA from the Myozyme (160L) product was that FDA had determined that the 2000L scale should be classified a different product from the 160L product, based on measurable differences in some critical quality attributes. In addition, in a previous BLA review of PK data, the Clinical Pharmacology reviewers had determined that the 160L scale product and the 2000L scale product were not comparable; however, they noted that the small sample size and sequential design were significant limitations of the study.

(b) (4)



(b) (4)



(b) (4)



(b) (4)



The Clinical Pharmacology reviewers also conducted a review of the immunogenicity data presented in this BLA and, similar to the DTP immunogenicity reviewers, they concluded that “there appeared to be no notable difference in the immunogenicity impact on efficacy between Lumizyme in the Taiwan01 study and Myozyme in the AGLU01602/2403 trial.” In addition, with regard to the switch over study (ADVANCE), they concluded, “There appears to be no noticeable difference in ADA titers before and after the switch over from Myozyme to Lumizyme in the ADVANCE trial.” They also stated, “There appeared to be no difference in immunogenicity impact on efficacy after the switch over from Myozyme to Lumizyme in the ADVANCE trial.”

I concur with the Clinical Pharmacology review findings and recommendations.

6. Clinical Microbiology

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

7. Clinical/Statistical-Efficacy

The Clinical reviewers, including the CDTL, have recommended approval of this supplemental BLA. I concur with their recommendations. As stated earlier in my review, the applicant was advised to include clinical data in this supplement to provide additional support of efficacy and safety of the 4000L product in patients with infantile onset Pompe disease or children less than 8 years of age with Pompe disease. Ultimately, the reviewers found that the products made in the two scales are analytically comparable. The clinical data that were submitted in this supplement will be included in the product label as additional supportive

data; however, these data were not critical to the decision to approve the product, in light of the analytical comparability of the scales. These clinical data were also considered as part of the decisional process for removing the Lumizyme REMS.

The clinical data submitted included information on 18 patients treated in Taiwan 01, an ongoing, investigator-sponsored, open-label, single-center, observational study that was developed to assess outcomes of Pompe disease patients identified through the national Taiwan University Hospital newborn screening program. Patients in this study were treated with Genzyme's 2000L scale product until October 2009, when treatment with the 4000L scale product was started in the study. The applicant identified 18 patients in the Taiwan 01 study who met the same key inclusion criteria as the patients who were enrolled in the infantile disease Pompe study (AGLU01602), with its extension (AGLU2403), that supported marketing approval of Myozyme (the 160L product). As noted by the Statistical reviewer, the patients identified from these studies (Taiwan01, AGLU01602/02403, and the natural history cohort) were "mostly comparable," with the exception that "age of first infusion was younger in the Taiwan study (median 1.0 month) than in Study AGLU01602/02403 (median 5.6 months)." In addition, differences in CRIM status and exposures to varying alglucosidase alfa fermentation scales were noted, which will be discussed below.

Ventilator-free survival in these 18 patients in the Taiwan 01 study was compared to that observed in the Myozyme 160L study (AGLU01602/02403), as well as the natural history cohort (AGLU00400), which was the historical comparator source for establishing efficacy observed in AGLU01602/02403. The reviewers have noted that these cross study comparisons demonstrated similar favorable survival outcome for patients treated in the Taiwan 01 study. Although not all of the 18 patients in the Taiwan study were treated with the 4000 L product exclusively (only 7/18 received the 4000L product exclusively), the others had been treated with either the 2000L scale product exclusively (n=2) or a combination of the 2000L and 4000L scales. I concur with the CDTL that the outcomes observed, even with inclusion of the 2000L scale exposures, are reassuring, since the FDA's previous findings of lack of comparability of the 2000L and 160L scale products had raised concerns about a potential decrement in efficacy with the 2000L product. Another difference in the trials was the distribution of CRIM status, i.e., all the Taiwan 01 study patients were CRIM positive, whereas 4/18 of the AGLU01602/02403 patients were CRIM negative.

The applicant's primary analysis, which examined ventilator free survival from time of birth and showed similar favorable outcome to the observations in AGLU01602/02403, was replicated by the Statistical reviewer. The Statistical reviewer also performed a Kaplan-Meier analysis using onset of treatment (instead of birth) as the starting point of the analysis to avoid selection bias that could arise from having had to survive long enough to get into the trial and to account for the earlier onset of treatment that might come with a newborn screening program used to identify patients for the Taiwan01 study. This re-analysis had its greatest impact on the AGLU01602/02403 results, and also favorably supported the clinical outcomes observed with larger volume scale product. Kaplan Meier curves generated by the Statistical reviewer (with confidence interval bands) for these two analyses are reproduced below.

Figure 3: Kaplan-Meier Estimates of Ventilator-Free Survival From Birth to 36 Months of Age (Estimated Percentage at 18 Months with Confidence Interval Bands) in Infantile-Onset Pompe Disease Patients

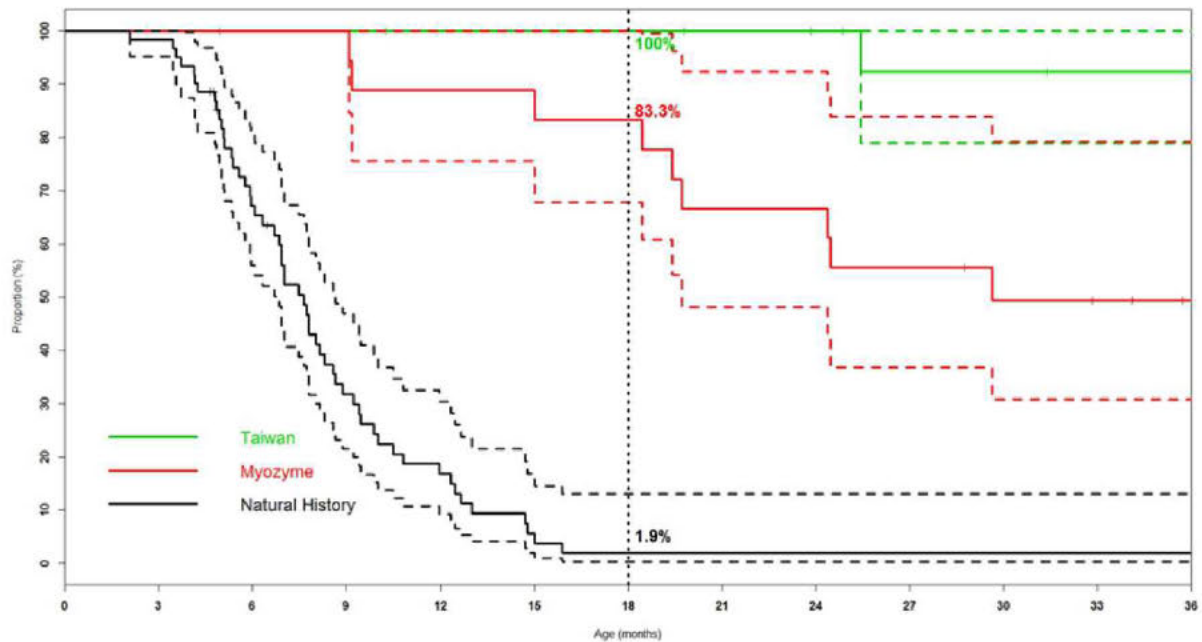
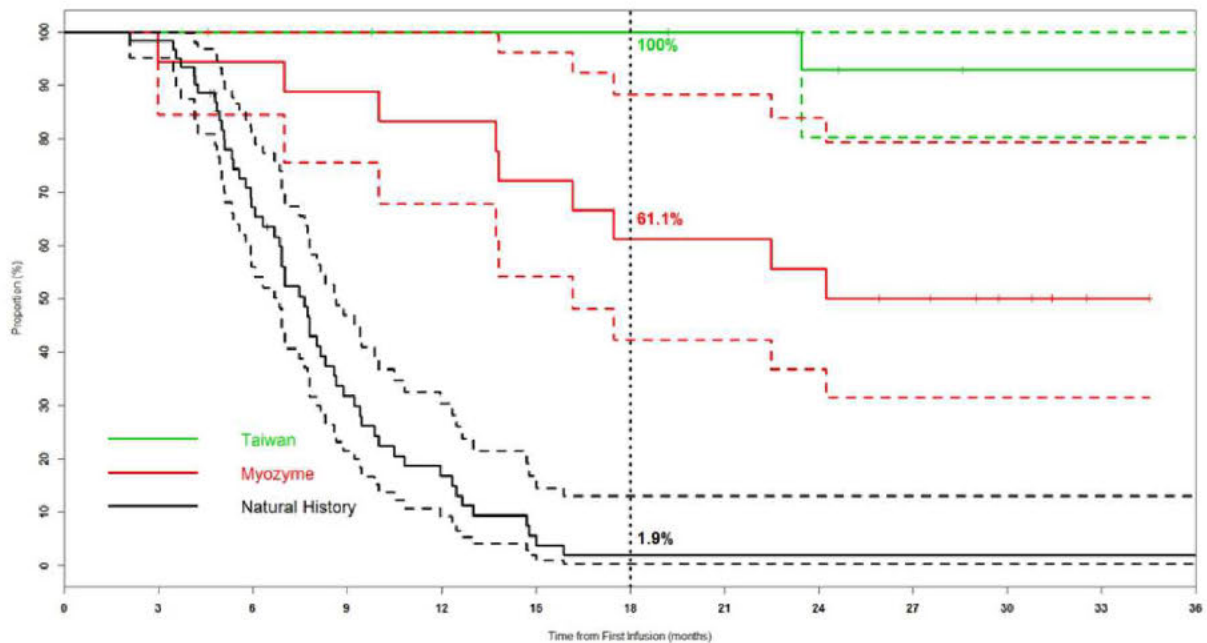


Figure 4: Kaplan-Meier Estimates of Ventilator-Free Survival From First Infusion to 36 Months of Age (Estimated Percentage at 18 Months with Confidence Interval Bands) in Infantile-Onset Pompe Disease Patients



(b) (4)

(b) (4)

descriptive information was included in Section 14 of the label, under Section 14.1 Clinical Trials in Infantile-Onset Pompe Disease, as follows:

Study 3 was an open-label, single-center trial in 18 infantile-onset Pompe disease patients who had a confirmed diagnosis of Pompe disease as identified through a newborn screening program. All patients were CRIM-positive. Patients were treated with alglucosidase alfa prior to 6 months of age (0.2 to 5.8 months at first infusion). Sixteen patients reached 18 months of age at the time of analysis, and all (100%) were alive without invasive ventilator support.

The reviewers explored the impact of CRIM status on survival in these datasets, as poorer clinical outcomes in CRIM-negative Pompe disease patients treated with enzyme replacement have been attributed to development of high sustained anti-drug antibodies. As stated above, none of the Taiwan 01 patients were CRIM negative, whereas 4 patients in AGLU01602/2403 were CRIM negative. Inclusion of these poor prognosis patients could lead to outcomes on the 160L study that appear less favorable than those for the larger scale product. (See the Clinical review and CDTL review for details.) When the CRIM negative patients were removed from the analysis of ventilator free survival in AGLU01602/2403, the ventilator free survival at 18 months of age increased from 83% to 92.9% in that study.

Given the absence of CRIM negative infantile onset disease data from the Taiwan study, the Clinical reviewers requested information on CRIM negative patients treated with the 4000L product in the Pompe registry. Only 4 patients were identified, and it was difficult to draw any conclusions from such small patient numbers. CRIM negative patients treated initially with the 160L scale product who were switched to the 4000L scale product in the ADVANCE study were also identified (patients had to be older than 12 months of age to switch). Of the 34 infantile-onset patients in ADVANCE, 10 were CRIM negative. Five of those 10 were on ventilator support by the time they were switched to the 4000L scale product, and none of the remaining 5 had ventilator support initiated after the switch (as of April 2014).

The impact of immunogenicity on efficacy was explored in the Taiwan01 dataset. A clear relationship between IgG titers and outcome could not be identified in this small dataset. The CDTL notes in her review the published literature reports that high sustained IgG titers are associated with poorer clinical outcome, and this information is currently reported in the Myozyme (160L) product label. The reviewers recommended inclusion of this information in the Lumizyme label. I concur. The label Sections 5.5 Risk of Antibody Development and Section 6.2 Immunogenicity will provide this information.

In summary, the clinical data were not necessary to support approval of this efficacy supplement that extends the Lumizyme indication to include treatment of infantile onset

Pompe disease, given that the applicant has established the analytical comparability of the 160L and 4000L scale products. Review of these supportive clinical data identified no evidence to suggest differences in efficacy might be expected between the two product scales in this particularly vulnerable infantile onset disease population, who have rapidly progressive disease. The Lumizyme indication in product labeling will be revised to the following:

LUMIZYME® (alglucosidase alfa) [see [Description \(11\)](#)] is a hydrolytic lysosomal glycogen-specific enzyme indicated for patients with Pompe disease (acid α -glucosidase (GAA) deficiency).

8. Safety

The Clinical Reviewer and CDTL concluded that “adverse reactions reported from patients who were treated with Lumizyme (4000 L scale product) in Taiwan01 and ADVANCE studies were similar to those observed during the trial that supported approval of Myozyme (160 L scale product). No new or unexpected adverse reactions were identified from the data provided.” Anaphylaxis and hypersensitivity reactions were observed, and review of these new safety data identified no evidence warranting labeling changes in the Lumizyme label regarding these reactions. As shown below, the currently approved Boxed Warning language regarding these reactions in the Lumizyme and Myozyme labels is identical, which is relevant to the discussion that follows regarding to the decisional process for eliminating the REMS, concurrent with the approval of a broader Lumizyme indication. As stated in Section 2 Background of this review, one of the Lumizyme REMS objectives is to ensure that the known risks of anaphylaxis and severe allergic reactions associated with the use of Lumizyme are communicated to patients and prescribers, and to ensure that the potential risks of severe cutaneous and systemic immune mediated reactions to Lumizyme are communicated to patients and prescriber.

The Lumizyme boxed warning:

Life-threatening anaphylactic reactions, severe allergic reactions and immune mediated reactions have been observed in some patients during LUMIZYME infusions. Therefore, appropriate medical support should be readily available when LUMIZYME is administered (5.1, 5.2).

The Myozyme boxed warning:

Life-threatening anaphylactic reactions, severe allergic reactions and immune mediated reactions have been observed in some patients during MYOZYME infusions. Therefore, appropriate medical support should be readily available when MYOZYME is administered

Assessment of proposed REMS modification to eliminate the Lumizyme REMS. (See also the Risk Evaluation and Mitigation Strategy Memorandum REMS Elimination Memo dated August 1, 2014) A REMS was established for Lumizyme, as a condition of approval that consisted of a communication plan (CP); elements to assure safe use (ETASU) that include prescriber special certification, healthcare facility special certification, and documentation of safe use conditions to ensure that patients are enrolled in the program; an

implementation system; and a timetable for submission of assessments. The goals of the REMS were to mitigate the potential risk of rapid disease progression in infantile-onset Pompe disease patients and patients with late (non-infantile) onset disease less than 8 years of age (because efficacy had not been established in those patients), and to ensure that the known risks of anaphylaxis and severe allergic reactions, and potential risks of severe cutaneous and systemic immune mediated reactions are communicated to prescribers and patients. (See the Lumizyme Summary Table in the Background section of this review.)

The major impetus for establishing the REMS was the analytical comparability of the 4000L scale product (Lumizyme) to the 160L scale product (Myozyme) had not been established. The infantile onset form of Pompe disease progresses rapidly and there was concern about the potential use of Lumizyme in this disease phenotype, in which the smaller scale product (Myozyme) had been shown to prolong survival/ventilator free survival. Note that the Lumizyme Boxed Warning specifically stated, “Because of the potential risk of rapid disease progression.... Lumizyme is available only through a restricted distribution program....” It doesn’t state that because of the anaphylactic reactions, Lumizyme is available only through a restricted distribution program. See the Boxed warning language from the Highlights section of the label, reproduced below:

LUMIZYME® (alglucosidase alfa)
Injectable for intravenous infusion
Initial U.S. Approval: 2010

WARNING: ANAPHYLAXIS and RESTRICTED DISTRIBUTION PROGRAM

- Life-threatening anaphylactic reactions, severe allergic reactions and immune mediated reactions have been observed in some patients during LUMIZYME® infusions. Therefore, appropriate medical support should be readily available when LUMIZYME is administered (5.1, 5.2).
- Because of the potential risk of rapid disease progression in Pompe disease patients less than 8 years of age, LUMIZYME is available only through a restricted distribution program called the LUMIZYME ACE Program®. Only prescribers and healthcare facilities enrolled in the program may prescribe, dispense or administer LUMIZYME. LUMIZYME may be administered only to patients who are enrolled in and meet all the conditions of the LUMIZYME ACE Program. To enroll in the LUMIZYME ACE Program call 1-800-745-4447 (5.3).

The DTP review of this sBLA has concluded that the products from the two scales (4000L and 160L) are analytically comparable. Therefore, I agree with the reviewers’ recommendation that the existing REMS should be released at the time of approval of this supplement. The approval will extend the indication of Lumizyme to the population that the REMS was designed to assure would not be treated with Lumizyme. Establishment of analytical comparability makes restricting distribution unnecessary. Retaining this component of the REMS would contradict the new expanded indication.

The REMS includes a second goal to ensure that the known risks of anaphylaxis and severe allergic reactions, and potential risks of severe cutaneous and systemic immune mediated reactions are communicated to prescribers and patients. The decisional process for determining whether to eliminate the REMS in its entirety required that FDA determine whether the REMS components in place to address this goal are still necessary. I will summarize that process below. See also CDTL and DRISK reviews.

The DRISK REMS Modification Review, dated July 18, 2014, states that in the DRISK evaluator of the 4-Year REMS Assessment Report concluded that “the survey results indicate

prescribers have a reasonable understanding of the risk of Lumizyme and overall high knowledge scores regarding its safe use.The survey results from patients/caregivers have shown a good understanding of the risks of severe allergic reactions, but relatively poor understanding of immune mediated reactions; however, patients and caregivers know the appropriate actions to take if experiencing these reactions". The DRISK REMS Modification Review summarized the conclusions regarding this component of the REMS as follows, "although the second goal of the REMS has been met only in part because of relatively poor understanding of severe immune mediated reactions on the part of patients and caregivers, DRISK believes the risk message and survey questions related to these reactions may have been too complex for patients, compared to what patients and prescribers need to know to ensure safe use of the product. Therefore, this isolated finding reported in the REMS assessments does not preclude elimination of the second goal of the REMS." The DRISK reviewers pointed to the fact that Myozyme shares the same risks of severe allergic reactions but does not have a REMS, and noted that product labeling communicates these risks. Therefore, the prescriber can meet the needs of providing this risk information to patients and caregivers through routine patient counseling. In light of this and because the extended indication eliminates the need for one of the goals of the REMS, they recommended release from the REMS requirement for Lumizyme.

Furthermore, the communication plan associated with the REMS was determined to be complete. It consisted of a Prescriber Introductory Letter and Healthcare Professional Introductory Letter, which were mailed at product launch and were intended to disseminate risk information about rapid disease progression in infantile-onset Pompe disease patients and patients with late (non-infantile) onset disease less than 8 years of age, in addition to risk of anaphylaxis, severe allergic reactions and severe cutaneous and systemic immune mediated reacts associated with use of Lumizyme. The assessment of this communication plan was presented in the applicant's 6-month REMS Assessment Report, which indicated that the prescriber survey respondents received and reported reading the Prescriber Introductory Letter. Survey results indicated that prescribers have a reasonable understanding of the risk of Lumizyme and overall high knowledge scores regarding its safe use. No other communication plan activities were required under the REMS and the prescriber assessment data were considered sufficient to ensure the communication plan met its goal.

In light of the analytical comparability of the two product scales, the safety and effectiveness of Myozyme and Lumizyme can be expected to be the same. Myozyme does not have a REMS with a goal to ensure that the known risks of anaphylaxis and severe allergic reactions, and potential risks of severe cutaneous and systemic immune mediated reactions are communicated to prescribers and patients. Risks of these reactions are managed with product labeling. One of the Lumizyme REMS ETASU, healthcare facility certification (which includes home infusion agencies), required that healthcare facilities attest that they have measures in place for appropriate patient monitoring and that they are prepared to treat patients who experience severe allergic reactions including anaphylaxis. These measures are standard operating procedure for hospitals and ambulatory infusion centers, and home infusion agencies also have accreditation standards requiring policies and procedures that address these measures. Therefore, it is not necessary to continue this certification measure to ensure the benefits outweigh the risks.

After consultation with Office of Surveillance and Epidemiology (OSE), the Division determined that the REMS for Lumizyme is no longer necessary to ensure the benefits of the drug outweigh the risks. The REMS Oversight Committee met on June 4, 2014 to consider elimination of the REMS and agreed with the reviewers.

The DRISK reviewers recommended an external communication strategy to stakeholders to notify stakeholders of the release from the REMS requirement “to ensure there are no unnecessary delays in patient access to Lumizyme as a result of the change in the distribution model for Lumizyme.” The Division has worked with the FDA Communications staff in this regard. A press release has been developed. OCHA will send an email from their centralized mailbox to patient organizations that support and physicians that treat Pompe disease. The Division also spoke with Genzyme about the applicant’s plans to educate health care providers and patients about the new indication and elimination of the REMS. They reported developing an educational strategy for providers and patients regarding the changes and submitted a summary of their plans. The DRISK reviewer evaluated it and considered it adequate; however, he suggested the applicant should specify that patients, prescribers and facilities that are currently enrolled in the ACE program are not required to take any further actions in the program to continue use of the product. This was conveyed to the applicant.

Safety labeling. With regard to labeling, the Boxed Warning will be retained; however, the information on the REMS and previous information in the Lumizyme Boxed Warning regarding risk for rapid progression of disease in infantile onset disease patients will be removed. Because the indication will now be extended to include patients with infantile onset disease, the Lumizyme Boxed Warning was revised to warn about the risk of serious acute exacerbation of cardiac or respiratory compromise due to fluid overload in infantile-onset Pompe patients. The revised Boxed Warning is reproduced below:

WARNING: RISK OF ANAPHYLAXIS, HYPERSENSITIVITY AND IMMUNE-MEDIATED REACTIONS, AND RISK OF CARDIORESPIRATORY FAILURE

Life-threatening anaphylactic reactions and severe hypersensitivity reactions, presenting as respiratory distress, hypoxia, apnea, dyspnea, bradycardia, tachycardia, bronchospasm, throat tightness, hypotension, angioedema (including tongue or lip swelling, periorbital edema, and face edema), and urticaria, have occurred in some patients during and after alglucosidase alfa infusions. Immune-mediated reactions presenting as proteinuria, nephrotic syndrome, and necrotizing skin lesions have occurred in some patients following alglucosidase alfa treatment. Closely observe patients during and after alglucosidase alfa administration and be prepared to manage anaphylaxis and hypersensitivity reactions. Inform patients of the signs and symptoms of anaphylaxis, hypersensitivity reactions, and immune-mediated reactions and have them seek immediate medical care should signs and symptoms occur. [see *Warnings and Precautions* (5.1, 5.2)].

Infantile-onset Pompe patients with compromised cardiac or respiratory function may be at risk of serious acute exacerbation of their cardiac or respiratory compromise due to fluid overload, and require additional monitoring [see *Warnings and Precautions* (5.3)].

Postmarketing Requirements (PMRs). There were no new safety issues identified during this review that necessitated requiring studies or clinical trials to evaluate safety. The reviewers did not recommend PMRs. I concur with their conclusions and recommendations.

6. Advisory Committee Meeting

There was no Advisory Committee meeting for this application as there were no decisional issues that required input from the Advisory Committee.

7. Pediatrics

With this supplement, Lumizyme will be labeled across the full pediatric age range, including treatment of the infantile onset disease and juvenile onset disease populations. Pediatric Equity in Research Act (PREA) did not apply to this product because recombinant human acid alpha-glucosidase was granted orphan product designation in 1997.

Pediatrics and Maternal Health Staff (PMHS) labeling recommendations were incorporated.

8. Other Relevant Regulatory Issues

Financial Disclosures

The Clinical reviewer noted that there were no investigators or sub-investigators who participated in the Taiwan01 study with disclosable financial interest as defined in 21 CFR 54.2. (b) (4)

I agree with the Clinical reviewers that it is important to note that “the Taiwan01 study/newborn screening program was developed and initiated prior to the Division’s suggestion to use its data to further support physicochemical comparability in this sBLA.” (b) (4)

, of which (b) (6)

The Office of Scientific Investigations also investigated this site during the course of this review (see next). I agree with the Clinical reviewers that these arrangements do not raise concerns over the integrity of the data. It is also important to consider that these data were not relied upon to establish comparability of the two products to support extension of the Lumizyme indication to patients with infantile onset disease. Analytical comparability was established by DTP review.

Office of Scientific Investigations

The Division requested inspection of the clinical site conducting the Taiwan01 study, since the primary clinical data were collected from this single site. When the request was made DTP

had not yet definitively determined the two product scales were analytically comparable. The field investigator verified efficacy data and found no evidence of under-reporting of adverse events. The OSI reviewer stated “the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.”

(b) (4)

9. Labeling

Refer to the CDTL review for details of labeling negotiations and decisions regarding specific labeling changes.

In light of the findings of analytical comparability of Lumizyme and Myozyme, the Lumizyme indication was revised to encompass the full scope of Pompe disease (not limited by specific phenotype). Information, including clinical trial data, from the Myozyme label was incorporated into the Lumizyme label. (b) (4)

(b) (4) description of the cross over study (ADVANCE) in Section 6.1 Clinical Trials Experience, in the subsection called “Clinical Trials in Infantile-Onset and Juvenile-Onset Pompe Disease”. Provision of the manufacturing scales for this study was considered relevant here because the purpose of collecting the data was to compare adverse reactions associated with switching from one scale (160L) to the other (4000L) in this population. Use of the name “Lumizyme” will be limited to Section 1 Indications and Usage and Section 16 How Supplied/Storage and Handling.

The Boxed Warning was revised to remove the reference to the REMS program that restricted use of the product to a specific age range, and the information regarding the risk of cardiorespiratory failure in infantile-onset Pompe disease patients with compromised cardiac and respiratory function due to fluid overload was added.

As discussed in Section 4 of this review, the Pregnancy category was changed from “B” to “C”.

See Section 5 Clinical Pharmacology regarding the labeling decision to remove the PK data found in the currently approved label, which were obtained in patients treated with the 2000L scale product.

10. Decision/Action/Risk Benefit Assessment

- Regulatory Action - Approval
- Risk Benefit Assessment – The reviewers have recommended approval of this supplemental BLA, which extends the indication for Lumizyme to children with infantile onset Pompe disease, including children less than 8 years of age. I concur. When the BLA was originally approved, CMC data that established analytical comparability of Lumizyme and Myozyme had not been provided, and FDA determined that there were inadequate data to assure that Lumizyme would be effective in a more rapidly progressive disease phenotype, such as infantile onset disease. The BLA was approved with a REMS to assure that Lumizyme would not be used to treat patients with infantile onset of disease and children less than 8 years of age, and that those patients would be treated with Myozyme instead. (Myozyme had established efficacy in the infantile onset disease phenotype.) Now that analytical comparability of Myozyme and Lumizyme, Genzyme's two manufacturing scales (160L and 4000L) of alglucosidase alfa from the same cell lines, has been established, the Lumizyme indication limitations can be removed and the REMS can be eliminated. This CMC evidence shows that the risk/benefit of Lumizyme is favorable for the infantile onset Pompe disease patients, and in patients under the age of 8 years of age. It is not necessary for the two manufacturing scales to be marketed under two different names; however, they were approved under two different BLA's due to insufficient evidence to establish comparability of different manufacturing scales when the applicant had originally proposed submitting their alglucosidase alfa product scales under one BLA (see Background section of this review). The applicant plans to change the trade name of Lumizyme to Myozyme when the remaining Myozyme supplies have been exhausted.
- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies – As described in this review, the REMS that was a condition of the initial approval of Lumizyme will be eliminated on the basis of the information reviewed in this supplemental BLA. The REMS is no longer necessary to assure that the benefits of the product outweigh the risks. The product labeling (Warnings and Precautions and a Boxed Warning) is adequate to communicate the potential safety risks of anaphylaxis and severe allergic reactions, including severe cutaneous and systemic immune mediated reactions. This information was also present in the Myozyme product labeling, but without a REMS. The information in the labels has been adequate to communicate the risk to ensure that the benefits of the product outweigh the risks.
- Recommendation for other Postmarketing Requirements and Commitments
There were no PMRs or PMCs recommended by the reviewers. I concur that the information submitted in this supplemental BLA did not reveal a safety or efficacy issue that necessitate a PMR or PMC as a condition for approval.

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/s/

DONNA J GRIEBEL
08/01/2014

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

BLA 125291/136

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	July 22, 2014
From	Jessica J. Lee, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	BLA 125291
Supplement#	Supplement 136
Applicant	Genzyme
Date of Submission	January 30, 2014
PDUFA Goal Date	August 1, 2014
Proprietary Name / Established (USAN) names	LUMIZYME / alglucosidase alfa
Dosage forms / Strength	20 mg/kg every other week
Proposed Indication(s)	Patients with Pompe disease
Recommended:	<i>Approval</i>

1. Introduction

On January 30, 2014, Genzyme (the Applicant) submitted a supplemental biologics application (sBLA 125291/136) to support expansion of the Lumizyme indication to all Pompe disease patients, including the infantile-onset patients and late (non-infantile) onset patients less than 8 years of age. In this submission, the Applicant also included a request to eliminate the REMS that currently restricts the use of Lumizyme to patients 8 years of age and older to mitigate the potential risk of rapid disease progression in the infantile-onset patients and to communicate the risks of anaphylaxis and severe allergic reactions to patients and prescribers. The review of this application was conducted as Priority review in light of ongoing drug shortage of Myozyme and, if approved, the potential for Lumizyme to treat infantile-onset Pompe disease patients as well as patients with late (non-infantile) onset disease less than 8 years of age.

Currently, the Applicant manufactures two recombinant alglucosidase alfa enzyme replacement therapies, Myozyme and Lumizyme, in the United States for the treatment of Pompe disease. Myozyme and Lumizyme are manufactured from the same cell line at different production scales. Myozyme, manufactured at the 160 L scale and approved in the U.S. in 2006, is indicated for use in all patients with Pompe disease. The approval of Myozyme was based on a clinical trial in 18 patients with infantile-onset Pompe disease who demonstrated improved ventilator-free survival compared to an untreated historical cohort. Lumizyme, manufactured at the 4000 L scale and approved in 2010, is indicated for treatment of Pompe disease patients 8 years and older. The approval of Lumizyme (4000 L scale product) was based on clinical data from the Late-Onset Treatment Study or "LOTS" (AGLU02704) using the 2000 L scale product and demonstration of analytical comparability of the critical product quality attributes between the 2000 L and 4000 L scale products.

It should be noted that the Applicant had initially sought marketing approval of the 2000 L bioreactor scale as a post-licensing manufacturing supplement under Myozyme BLA 125141,

but the Agency determined that the drug substance from the 160 L and 2000 L processes differed in critical quality attributes and, therefore, the drug substances were not physicochemically comparable. This determination led to the Agency recommending the Applicant to submit efficacy and safety data to support a separate licensure of the 2000 L product. On May 30, 2008, the Applicant submitted a new BLA (125291) for the 2000 L product, seeking an indication for treatment of late (non-infantile) onset Pompe disease based on the Late-Onset Treatment Study (LOTS). However, this BLA was subject to two Complete Response actions (on February 27, 2009 and November 13, 2009) due to persistent deficiencies noted at the Allston Landing, MA facility, where the 2000 L product was being manufactured. It should be noted that in parallel with the submission of BLA 125291, the Applicant had been developing a linear scale-up of the 2000 L scale manufacturing process to a 4000 L scale. Based on persistent deficiencies noted at the Allston Landing, MA facility, the Agency recommended that the Applicant pursue marketing approval of the 4000 L scale product that was being manufactured at the Genzyme Flanders facility in Geel, Belgium. An inspection of this facility in September 2009 revealed that it was in compliance with CGMP requirements and there were no pending compliance actions that would prevent the approval of the BLA.

On December 16, 2009, the Applicant submitted a response to the second Complete Response letter to support marketing approval of Lumizyme. In this response, the applicant proposed the 4000 L product manufactured at the Geel, Belgium facility as the product to be marketed under the BLA, instead of the 2000 L scale product. The submission included data that demonstrated physicochemical comparability between the 2000 L and 4000 L products. Since the overall safety and effectiveness of the 2000 L product was demonstrated in data submitted in the two previous review cycles, the review team determined that additional clinical data were not required. Since the 160 L product (i.e., Myozyme) and the 2000L product had been deemed to be different products and data to establish the analytical comparability between the 160 L and 4000L products had not yet been submitted and reviewed, the 4000 L product was approved under the trade name “Lumizyme” with an indication limited to treatment of patients 8 years of age and older with late (non-infantile) onset Pompe disease who do not have evidence of cardiac hypertrophy. A REMS was required at the time of Lumizyme approval to restrict it from use in infantile-onset Pompe disease patients and patients with late (non-infantile) onset disease less than 8 years of age, since the safety and effectiveness of Lumizyme had not been established in this patient population. The REMS assured that patients with the infantile-onset form of Pompe disease were treated with Myozyme. An additional goal of the REMS was to ensure that the known risks of anaphylaxis and severe allergic reactions, and the potential risks of severe cutaneous and systemic immune-mediated reactions to Lumizyme are communicated to patients and prescribers.

Due to the drug shortage and manufacturing challenges for Myozyme, the Applicant began restricting Myozyme in March 2012 to treatment of patients less than 12 months of age. Based on FDA recommendations, the Applicant launched the ADVANCE protocol (AGLU09411) to allow enrollment of patients older than 12 months of age to treatment with Lumizyme (4000 L product) and to monitor safety and efficacy outcomes, since the existing REMS restricts the use of Lumizyme in infantile-onset Pompe disease patients and patients less than 8 years of age. Since then, the Applicant and the Agency held several meetings to discuss the ongoing

supply and manufacturing capacity constraints for Myozyme and data that would be required to support expansion of the indication to all Pompe disease patients.

As agreed upon during a Type C meeting held on February 19, 2013, the Applicant included the following information to support comparability between Myozyme (160 L scale product) and Lumizyme (4000 L scale product) so that the Lumizyme indication could be expanded to all Pompe disease patients:

- 1) Analytical comparability evaluation between the two scales of alglucosidase alfa (i.e., Myozyme manufactured at the 160 L scale and Lumizyme manufactured at the 4000 L scale).
- 2) Safety and efficacy data collected from an investigator-sponsored, single-center, open-label study in Taiwan (Taiwan01) that evaluated ventilator-free survival in infantile-onset Pompe disease patients treated with Lumizyme. The clinical data were requested in the event that CMC data left residual concerns regarding comparability between the two products.
- 3) Safety data collected from the ongoing AGLU09411 (ADVANCE) study in Pompe disease patients 12 months of age and older previously treated with Myozyme and switched to Lumizyme.

All the review disciplines recommend in favor of approval, and I agree with their recommendations. The product quality data presented support analytical comparability (i.e., comparable results from chemical, biochemical, and *in vitro* biologic testing) of the 4000 L scale product to the 160 L scale product, and clinical data further support the overall safety and effectiveness of Lumizyme (4000 L scale product) for the treatment of infantile-onset Pompe disease patients.

This memorandum summarizes the information contained in sBLA 125291/136 and discusses the recommendations made by each review discipline.

2. Background

Clinical Background

Pompe disease, also known as glycogen storage disease Type II (GSD II), is a rare, autosomal recessive disorder of glycogen metabolism caused by the absence or marked deficiency of the lysosomal enzyme acid α -glucosidase or alglucosidase alfa (GAA). Deficiency of GAA results in accumulation of glycogen in various tissues, particularly the cardiac and skeletal muscles; consequently, affected patients experience severe and progressive muscle weakness, cardiomyopathy, and impairment of respiratory function. The estimated frequency of Pompe disease is 1 in every 40,000 births.¹

There are two main phenotypes of Pompe disease: early-onset (infantile) where there is total or almost total absence of GAA, and late-onset (juvenile or adult) where there is deficiency of GAA (up to 30% of normal levels) but not complete absence of the enzyme. Symptoms of

¹ <http://www.ninds.nih.gov/disorders/pompe/pompe.htm>

affected infants include failure to thrive, hypotonia, hypertrophic cardiomyopathy, hepatomegaly, and hearing difficulties. Historically, infants with Pompe disease died by 1-2 years of age, but since the advent of recombinant enzyme replacement therapy (ERT), survival is improving. Juvenile- or adult-onset (collectively known as “late-onset”) Pompe disease progresses more slowly, and symptoms are predominantly related to skeletal and respiratory muscle weakness, resulting in fatigue, muscle weakness and cramps, and difficulty with mobility and respiration.² Death in all forms of Pompe disease is usually a result of respiratory failure.

The amount of GAA enzyme, measured through visualization of GAA proteins by western blot analysis, determines cross reactive immunologic material (CRIM) status. Complete absence or <1% of normal levels of GAA (negative western blot) is considered CRIM negative, whereas presence of a GAA band on western blot is considered CRIM positive. The majority of patients develop anti-drug antibodies (ADA) regardless of CRIM status. CRIM-negative and CRIM-positive patients who develop high sustained ADA titers have been shown to have poorer prognosis than CRIM-positive patients with low antibody titers.³

Alglucosidase alfa, recombinant human acid- α -glucosidase (rhGAA), is a purified analog of the naturally occurring, endogenous lysosomal GAA. After intravenous administration, alglucosidase alfa is internalized by cells via cellular membrane mannose-6-phosphate (M6P) receptors binding to enzyme M6P residues. The enzyme is then taken up by lysosomes and undergoes proteolytic cleavage resulting in increased enzymatic activity. It then exerts enzymatic activity in cleaving glycogen present in lysosomes.

There are currently two approved enzyme replacement therapies in the U.S. for treatment of Pompe disease: Myozyme and Lumizyme. Both are recombinant human lysosomal glycogen-specific enzyme, acid α -glucosidase or alglucosidase alfa (rhGAA), manufactured by the Applicant, but made on two different bioreactor scales (160 L and 4000 L). Myozyme is indicated for treatment of Pompe disease, and the approved indication does not limit its use to a specific sub-population of Pompe disease. However, Lumizyme’s current indication is limited to treatment of patients 8 years of age and older with late (non-infantile) onset Pompe disease who do not have evidence of cardiac hypertrophy.

Regulatory Background

Pertinent regulatory issues and meetings are summarized chronologically below. For more complete information, the reader is referred to the Clinical review by Dr. Juli Tomaino, dated July 8, 2014.

- April 28, 2006: Myozyme (manufactured on a 160 L bioreactor scale), under BLA 125141, was approved for treatment of Pompe disease based on a single clinical trial (n=18) that demonstrated improved ventilator-free survival in patients with infantile-

² Hirschhorn R, et al. (2001). Glycogen Storage Disease Type II: Acid Alpha-Glucosidase (Acid Maltase) Deficiency. In C. Scriver, et al. (Eds.), *The Metabolic and Molecular Bases of Inherited Disease* (pp. 3389-3420). New York, NY: McGraw-Hill.

³ Banugarua S, et al. The impact of antibodies in clinical outcomes in diseases treated with therapeutic protein: Lessons learned from infantile Pompe disease. *Genet Med* 2011;13:729-736.

onset Pompe disease (age \leq 7 months at the time of first infusion) as compared to an age-matched, untreated historical control. Limited data (obtained primarily from case narratives and not from controlled studies) in juvenile- and adult-onset patients were suggestive of disease stabilization, but they were difficult to interpret in the absence of a placebo-treated control group. The indication statement in the approved label did not limit the use of Myozyme to a specific sub-population of Pompe disease. However, the label indicated that the use of Myozyme in patients with other forms of Pompe disease have not been adequately studied to assure safety and efficacy, since the Applicant had not provided data from controlled trials that evaluated the efficacy and safety of Myozyme in other forms of Pompe disease patients. At the time of Myozyme BLA approval, controlled data on the efficacy and safety of Myozyme in late (non-infantile) onset patients were being collected in ongoing AGLU02704 (LOTS) study and the results were expected to be submitted to the Agency in 2008.

- May 30, 2008: The Applicant submitted a new BLA (125291) seeking the approval of the 2000 L alglucosidase alfa product because the drug substance from the 160 L and 2000 L processes differed in critical quality attributes to support its review under the Myozyme BLA. The submission included one multicenter, randomized, double-blind, placebo-controlled trial of 90 late-onset Pompe disease patients (Late-Onset Treatment Study or LOTS). The trial data did not demonstrate a statistically significant difference between Lumizyme and placebo in the pre-specified primary endpoint (6-minute walk test [6MWT]), but the Clinical reviewer noted a trend toward improvement in the Lumizyme group. There was a statistically significant difference in the % predicted forced vital capacity (FVC), although the clinical significance of a treatment effect of 3% in the predicted FVC was unclear. Given the totality of the evidence, and also in the context of the drug shortage of Myozyme in the U.S., the Clinical reviewer recommended approval of Lumizyme under Accelerated Approval (21 CFR 601 Subpart E) based on the change in % FVC as a surrogate endpoint that is reasonably likely to predict clinical benefit.
- October 21, 2008: An Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) meeting was convened to discuss the adequacy of BLA 125291 to support marketing approval. The Advisory Committee voted 16-1 that the effectiveness of Lumizyme had been demonstrated in LOTS; however, the majority of members recommended accelerated approval under 21 CFR 601 Subpart E, based on improvement in the % predicted FVC for treatment of patients with late-onset Pompe disease ages \geq 8 years and older who do not have evidence of cardiac hypertrophy. Although some AC members recommended regular approval based on the 6MWT (primary endpoint) findings in LOTS, this approach was not in favor due to issues related to the Applicant's statistical analysis plan and a lack of demonstration of statistical significance on this endpoint. The Committee also recommended a REMS and post-marketing safety studies to further evaluate the risk of anaphylaxis, the impact of immunogenicity and potential immune-mediated reactions. The Committee also recommended that a REMS be required to ensure the safe use of Lumizyme in the approved population. However, due to manufacturing issues that arose after the AC meeting, the 2000 L product was not approved.

- February 27, 2009: A Complete Response (CR) action was taken, and the Office of Compliance issued a warning letter for CGMP deficiencies identified during the 2008 inspection of the Allston Landing, MA manufacturing facility.
- November 13, 2009: Second CR action was taken as deficiencies were noted again during the inspection. FDA recommended the Applicant to submit CMC information on the 4000 L product since the 4000 L product was manufactured in the Geel, Belgium facility, not in the Allston Landing, MA facility with recurrent deficiencies. A response to the second CR letter was submitted to the FDA on December 16, 2009.
- May 24, 2010: Lumizyme, manufactured on a 4000 L bioreactor scale, was approved for patients with late-onset Pompe disease 8 years and older, based on demonstration of physicochemical comparability between the 2000 L and 4000 L products. The review team felt that overall safety and effectiveness of the 2000 L product had been demonstrated in data presented in the two previous review cycles, and recommended regular approval. In addition to controlled data from the LOTS trial, the Applicant had submitted requested clinical outcome data from the Pompe Registry to support regular approval for the 2000 L product. Since physicochemical comparability between the 2000 L and 4000 L products had been established, the additional clinical data were not required during this review cycle to establish the effectiveness of the 4000 L product in late-onset Pompe disease. However, the safety and efficacy had not been demonstrated in patients with infantile-onset Pompe disease or late-onset patients who are less than 8 years of age. Therefore, a REMS was implemented to restrict the use of Lumizyme to treatment of patients with non-infantile onset Pompe disease who are at least 8 years of age to mitigate the potential risk of rapid disease progression in the infantile-onset patients and to communicate the risks of anaphylaxis and severe allergic reactions to prescribers and patients. The REMS assured that patients with the infantile-onset form of Pompe disease were treated with Myozyme (160 L product).
- November 17, 2010: A Type C meeting was held to discuss expanding the Lumizyme indication to patients younger than 8 years of age. The Agency did not agree that data from the Pompe Registry *alone* would be sufficient to demonstrate efficacy in this population. Since clinical data on survival of infantile-onset patients treated with Lumizyme (4000 L) had not been collected outside of the Pompe Registry, the Agency recommended a randomized, double-blind, parallel-dose study comparing the safety and efficacy of Myozyme (160 L) and Lumizyme (4000 L) in treatment-naïve infant-onset and late-onset patients less than 8 years of age.
- March 30, 2012: The drug shortage of the 160 L product led to restriction of 160 L to patients < 12 months of age. All Pompe disease patients ≥ 12 months of age previously treated with the 160 L product were switched to the 4000 L product under AGLU09411 (ADVANCE) study.
- February 19, 2013: A Type C meeting was held to discuss a path forward to expand the indication of Lumizyme to all patients with Pompe, given the ongoing drug

shortage of Myozyme (160 L). The Division recommended that the Applicant submit data that establish analytical comparability between the 160 L and 4000 L products, in addition to clinical data collected on classic infantile-onset Pompe disease patients in Taiwan that demonstrate that Lumizyme is associated with comparable ventilator-free survival relative to patients treated with Myozyme in the clinical trial that supported approval of Myozyme (AGLU01602). The Division indicated that infants in the Taiwan study should have the same inclusion criteria as those in the AGLU01602 study.

- July 9, 2013: At the request of the Applicant, the Division provided written responses to the pre-BLA meeting questions. The Division provided recommendations on the content of the efficacy supplement that might be adequate to support expansion of the Lumizyme indication.
- January 30, 2014: The Applicant submitted a supplemental BLA to support expansion of the Lumizyme indication to all Pompe disease patients.

It should be noted that alglucosidase alfa that is manufactured at the 4000 L scale is approved for the treatment of Pompe disease, regardless of phenotype, in over 70 countries outside of the United States. Myozyme is the trade name for the 4000 L product outside of the United States.

Submission and Review

The supplemental BLA was received electronically on January 30, 2014, and the application was granted a Priority Review status.

All of the relevant review disciplines have written review documents. The primary review documents relied upon in my CDTL memo are listed below:

Review discipline	Name(s) of reviewers
Product Quality (DTP/OBP)	C. Downey, Ph.D., dated 7/14/2014
Immunogenicity (DTP/OBP)	C. Tami, Ph.D., dated 7/17/2014
Nonclinical (DGIEP)	F. Cai, Ph.D., dated 7/8/2014
Clinical Pharmacology (OCP/DCP3)	C. Hon, Pharm.D., dated 7/8/2014
Clinical (DGIEP)	J. Tomaino, M.D., dated 7/8/2014
Statistics (DB III)	F. Cooner, Ph.D., dated 7/18/2014
Clinical site inspections (OSI/DGCPC)	S. Leibenhaut, M.D., dated 6/27/2014
Consultation review (PMHS) • Maternal Health Team	T. Johnson, M.D., dated 6/30/2014
4-Year REMS Assessment review (OSE/DRISK)	I. Cerny, Pharm.D., dated 7/2/2014
REMS Modification review (OSE/DRISK)	R. Pratt, Pharm. D., dated 7/20/2014
Labeling review (DMEPA)	S. Abraham, R.Ph., dated 6/20/2014
Labeling review (DTP/OBP)	J. Abdus-Samad, Pharm.D., dated 6/23/2014
Labeling review (OPDP)	A. Adeleye, Pharm.D., dated 7/16/2014

DTP, Division of Therapeutic Proteins; OBP, Office of Biotechnology Products; DGIEP, Division of Gastroenterology and Inborn Errors Products; OCP, Office of Clinical Pharmacology; DCP 3, Division of Clinical Pharmacology 3; DB III, Division of Biometrics III; OSI, Office of Scientific Investigations; DGCPC, Division of Good Clinical Practice Compliance; PMHS, Pediatric and Maternal Health Staff; REMS, Risk Evaluation and Mitigation Strategies; OSE, Office of Surveillance and Epidemiology; DRISK, Division of Risk Management; DMEPA, Division of Medical Error Prevention and Analysis; OPDP, Office of Prescription Drug Promotion

3. CMC

Lumizyme (alglucosidase alfa) is a hydrolytic lysosomal glycogen-specific enzyme produced by recombinant DNA technology in a Chinese hamster ovary cell line. Lumizyme is supplied as single-use vials containing 50 mg of alglucosidase alfa as lyophilized power for reconstitution. Dose strength is 5 mg/mL. The dosage of Lumizyme is 20 mg/kg/dose given intravenously (IV) every other week. The product labeling states that Lumizyme should be stored under refrigeration between 2°C to 8°C (36°F to 26°F) and protected from light.

The Division of Therapeutic Proteins (DTP) reviewers have recommended approval of the efficacy supplement to expand the Lumizyme indication to all Pompe disease patients, and I agree with their recommendation. I have summarized the key review findings below.

CMC/Product Quality Review


The reader is referred to the Product Quality review by Dr. C. Downey, dated July 14, 2014, for complete information.

In order to support expansion of Lumizyme indication to all Pompe disease patients, the Applicant submitted analytical comparability data for Myozyme (160 L) and Lumizyme (4000 L) to demonstrate that these two products are physicochemically comparable. Specifically, the

Applicant provided data that compared the following aspects of the 160 L and 4000 L scale materials:

- 1) Head-to-head comparison of the drug substance
- 2) Comparison of historical release results
- 3) Comparison of stability data


It should be noted that the 4000 L product underwent an important manufacturing change since the approval of Lumizyme in May 2010. (b) (4)



Although the 160 L and 4000 L products are currently marketed in the U.S. under different licenses, the DTP reviewers approached this submission as a comparability exercise as described in *ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process*, since the same manufacturer has complete control of the manufacturing processes, cell lines, and analytical testing for both production scales and also has a knowledge of the product development history.

Head-to-head comparison of 160 L- and 4000 L-process drug substance:

According to Dr. Downey, a side-to-side comparison of 3 lots each of 160 L and 4000 L (b) (4) drug substance yielded comparable results for the two scales in the following critical quality attributes: specific activity (i.e., potency); enzymatic kinetic parameters; primary, secondary, and tertiary structure; and levels of product-related impurities. The Quality reviewer considered the method of selecting lots for testing appropriate without concerns of introducing bias. Dr. Downey also noted (b) (4)



Comparison of historical release results

(b) (4)

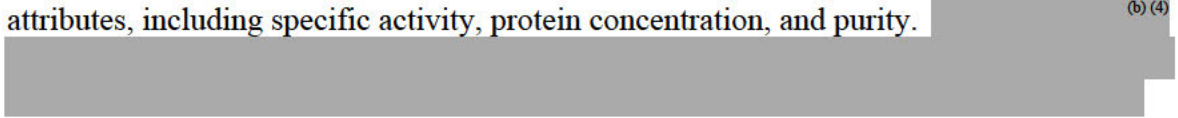


(b) (4)



Comparison of real time and accelerated stability data

Dr. Downey stated that long-term stability data (stored in 5°C) showed little change over time in most tests for materials manufactured at both 160 L and 4000 L scales. Although aggregation increases measurably over time, the rates of increase did not differ significantly between lots from the two manufacturing scales. In addition, the data collected from drug product lots stored under accelerated conditions (25°C) showed comparable results for most attributes, including specific activity, protein concentration, and purity. (b) (4)



In summary, Dr. Downey has concluded that Lumizyme, manufactured at a 4000 L scale, is comparable in terms of activity and most structural attributes to Myozyme, manufactured at a 160 L scale. Therefore, he recommends approval of this efficacy supplement. I concur with his recommendation.

The Quality reviewer has not recommended PMRs or PMCs.

Facilities Review/Inspection

A final Therapeutics Biological Establishment Evaluation Request (TB-EER) was submitted to the Office of Compliance, Division of Manufacturing and Product Quality on July 1, 2014 to evaluate all facilities involved in the manufacturing of alglucosidase alfa. A final TB-EER Form has not been completed at the time of completion of this review.

CMC/ Immunogenicity Review

The reader is referred to the Immunogenicity review by Dr. C. Tami, dated July 17, 2014, for complete information.

According to the Immunogenicity reviewer, all assays used to assess for the presence of binding anti-rhGAA IgG antibodies and anti-rhGAA antibodies that are able to inhibit enzyme uptake or activity have been validated.

To allow for the evaluation of the immunogenicity profile of Lumizyme (4000 L scale), FDA requested that the Applicant provide the following information:

For Taiwan01 study,

- Assessment of the association between clinical outcome and CRIM status, antibody response (binding and neutralizing), genetic mutations and enzyme activity level in patients who received 4000 L product.
- Assessment of the impact of anti-drug antibody titers in the safety and efficacy of the 4000 L product and comparison of the results to those from patients who received the 160 L product exclusively in the clinical trial that supported marketing approval of Myozyme (AGLU01602 and its extension AGLU02403).

For AGLU09411 (ADVANCE) study,

- Comparison of the impact of antibody responses on safety before and after switching from the 160 L (Myozyme) to the 4000L (Lumizyme) product.

In this section, I will summarize Dr. Tami's findings on immunogenicity profiles of patients treated with the 4000 L product in Taiwan01 and ADVANCE studies. The reader is referred to Sections 7 and 8 for discussion of the impact of immunogenicity on efficacy and safety, respectively.

Taiwan01

Taiwan01 is an ongoing open-label, investigator-sponsored study that is developed to monitor cases of Pompe disease identified through the National Taiwan University Hospital (NTUH) newborn screening program, and to compare their prognosis to the clinically identified cases in Taiwan. The Applicant submitted interim data from 25 Pompe disease patients enrolled and treated in the study, 18 of whom met the inclusion criteria for the trial that supported approval of Myozyme. These 18 patients were included in the analyses for this submission. To provide clinical support for chemical comparability between the 160 L and 4000 L products, the Applicant evaluated the survival estimates of these 18 infantile-onset Pompe disease patients treated with Lumizyme in Taiwan01 who are alive and free of invasive ventilator support at 18 months of age, and compared the estimates to patients who participated in the trial that supported marketing approval of Myozyme (AGLU01602 and its extension AGLU02403) and the natural historical cohort (AGLU00400).

Immunogenicity data were available in 17 of 18 infantile-onset disease patients who participated in the Taiwan01 study and met the inclusion criteria for the AGLU01602/02403 study. Of the 17 patients with available immunogenicity data, 16 (94.1%) patients seroconverted during Lumizyme treatment. According to the Immunogenicity reviewer, CRIM-positive infantile-onset Pompe disease patients who received Lumizyme exclusively in Taiwan01 demonstrated a similar or possibly better immunogenicity profile than CRIM-positive infantile-onset patients who received Myozyme exclusively in AGLU01602/2403, since (1) the peak IgG titers were lower, (2) time to seroconversion was longer, and (3) no patients in Taiwan01 developed high sustained antibody titers (defined by the Applicant as having a peak titer $\geq 25,600$ and the last titer equaling to the peak titer or 1 dilution level lower). According to the principal investigator, none of the patients in the Taiwan01 study received immune tolerance induction treatment. Table 1 compares the immunogenicity profile

of CRIM-positive infantile-onset Pompe disease patients who received Lumizyme in Taiwan01 and Myozyme in AGLU01602/02403.

Table 1: Comparison of Immunogenicity Profile of CRIM-positive Infantile-Onset Pompe Disease Patients Who Received Lumizyme in Taiwan01 and Myozyme in AGLU01602/02403

		Taiwan01 (N = 18)	AGLU01602/02403 (N = 18)
Number of CRIM Positive patients in the study	n (%)	18 (100)	14 (77.8)
Number of CRIM-positive patients with immunogenicity data	n	17	14
Number of patients seroconverted	n (%)	16 (94.1)	12 (85.7)
Number of days to seroconversion	Median Range	84 27-1,547	28 0-448
Peak titer	Median Range	1,600 0-12,800	2400 0-409,600
Last titer*	Median Range	400 0-12,800	200 0- 409,600
Number of patients tested positive for inhibition of enzyme uptake or activity (n) / Total number of patients tested (n)		0/3**	0/12

*Measured at a median of 180 (32 - 369) weeks in Taiwan01 and at a median of 116 (52 – 142) weeks in AGLU01602/02403.

** In Taiwan01, testing for inhibitory antibodies was performed only on patients whose adverse event was suggestive of antibody-mediated inhibition.

Source: Adapted from the Immunogenicity review by Dr. C. Tami, dated July 17, 2014, Appendix 1.

Based on a review of the submitted data, the Immunogenicity reviewer concluded that antibody responses to Lumizyme do not appear to be notably different from that to Myozyme for CRIM-positive infantile-onset Pompe disease patients.

AGLU09411 (ADVANCE)

AGLU09411 (ADVANCE) is an ongoing, phase 4, open-label, prospective, 52-week study to evaluate the efficacy and safety of alglucosidase alfa produced at the 4000 L scale (Lumizyme) in Pompe disease patients previously treated with the 160 L scale (Myozyme). The interim report submitted with this efficacy supplement included available immunogenicity data from 99 enrolled patients (based on a data cut-off date of June 30, 2013).

At the time of switching from 160 L to 4000 L alglucosidase alfa, 31 of the 99 patients were seronegative and 68 of the 99 patients were seropositive. Ten of 31 patients who were seronegative at baseline seroconverted after receiving Lumizyme. Twenty one patients remained seronegative. In the trial that supported marketing approval of Myozyme (AGLU01602 and its extension AGLU02403), 34 (89%) of 38 patients developed anti-drug antibodies (ADA). The observations that 31 patients were seronegative at time of switching and 21 of the patients remained seronegative suggest that those patients may have tolerized to alglucosidase alfa during treatment. This is consistent with the observation that ADA titers

decline in many patients over time. See Dr. Tami's review dated, July 17, 2014, for details. The median time for IgG conversion from date of first Lumizyme infusion was 61 days (range: 21 to 224 days), and the median titer at seroconversion was 100 (range: 100 to 1,600). A higher number of patients in the ADVANCE study remained seronegative (21 of 99), as compared to those who participated in Taiwan01 (1 of 17 evaluated) or AGLU01602/02403 (2 of 18). Based on these data, switching from Myozyme to Lumizyme does not appear to negatively impact anti-drug antibody responses.

In summary, Dr. Tami has concluded that submitted data support a comparable immunogenicity profile between infantile-onset Pompe disease patients who received Lumizyme (4000 L product) in the Taiwan 01 study and those who received Myozyme (160 L product) exclusively in AGLU01602/02403. Further, data from the ADVANCE study have shown that antibody responses before and after switching from Myozyme to Lumizyme are comparable or better. Therefore, she recommends approval of this efficacy supplement from an immunogenicity perspective. I concur with her assessment.

The Immunogenicity reviewer has not recommended PMRs or PMCs.

4. Nonclinical Pharmacology/Toxicology

The reader is referred to the Nonclinical review by Dr. F. Cai, dated July 8, 2014, for complete information.

The Applicant did not submit any new nonclinical study report or data with this efficacy supplement. However, the Nonclinical reviewers recommended that the Pregnancy Category be changed from "B" to "C" based on results of the pre- and postnatal developmental (Segment 3) study in mice, which was initially reviewed by Dr. N. Mehta (dated September 15, 2008). Dr. Cai evaluated Dr. Mehta's review and the original study report during this review cycle. The Nonclinical reviewers pointed out that the Segment 3 study showed a statistically significant increase in the number of pup deaths (F₁ generation) after treatment with alglucosidase alfa 40 mg/kg IV every other day, as compared to the vehicle + saline control group, during lactation days (DL) 15 to 21 (12.2% vs. 6.7% mortality; $P \leq 0.05$). Since all animals in the treatment groups received diphenhydramine (DPH) via intraperitoneal injection prior to administration of alglucosidase alfa to prevent hypersensitivity reactions, Dr. Cai pointed out that most appropriate control group should have been vehicle + DPH. Since the mortality rate was even lower (4.9%) in animals that received vehicle + DPH, the difference in mortality rate is even greater if the vehicle + DPH group is used as a control to compare against the animals that received alglucosidase alfa 40 mg/kg every other day. The Applicant and the Division held a teleconference on July 7, 2014 to discuss these findings, and the Applicant agreed to change the Pregnancy Category to "C".

In addition, the Nonclinical reviewers recommended labeling changes to Section 8.1 (Pregnancy) to conform to the format of the Proposed Pregnancy and Lactation Labeling Rule (PLLR). They provided labeling recommendations in collaboration with the Maternal Health Team (MHT) of the Pediatric Maternal Health Staff (PMHS), which have been incorporated

into final labeling. Minor revisions were also made in Section 13.1 (Carcinogenesis, Mutagenesis, Impairment of Fertility).

The Nonclinical reviewer has not recommended PMRs or PMCs.

5. Clinical Pharmacology

The reader is referred to the Clinical Pharmacology review by Dr. C. Hon, dated July 8, 2014, for complete information.

The Applicant did not submit any new Clinical Pharmacology data with this efficacy supplement to evaluate the PK comparability between Myozyme (160 L scale) and Lumizyme (4000 L scale). However, the Clinical Pharmacology review team considers this approach acceptable since the Applicant submitted adequate CMC data to support analytical comparability between two products.

(b) (4)

The reader is referred to the Clinical Pharmacology review by Dr. Tie-Mien Chen, dated August 26, 2008, for details. At the time of Lumizyme approval (4000 L scale), the 2000 L and 4000 L scale products were found to be analytically comparable and, therefore, PK comparability between these two products was not evaluated. Since then, the 4000 L scale product has undergone additional manufacturing changes (b) (4) that made the product closer to the 160 L scale product. Refer to additional details in Section 3.

The currently approved Lumizyme label contains PK data from late-onset Pompe disease patients who received the 2000 L product. Since this product was shown not to be comparable to Myozyme (160 L scale), Dr. Hon states that labeling should be updated to remove the PK data from the 2000 L product. Instead, only the PK information from the 160 L product should be included. This approach was discussed in team meetings with leadership from the Office of Biotechnology Products (OBP). In addition, since physicochemical comparability has been established between the 160 L product and the 4000 L product, OBP stated that a new PK study to compare these two products would not be necessary.

I concur with Dr. Hon's recommendation to remove the 2000 L PK data from the Lumizyme label and to only include the PK data obtained from the 160 L product, which has been shown to be comparable to the 4000 L product. In addition, the 2000 L product is not marketed in the U.S. or elsewhere, so its PK data are not relevant for the prescribers. I also agree that a new PK comparability study is not necessary given the physicochemical comparability between the 160 L and 4000 L products.

The Clinical Pharmacology reviewer has not recommended PMRs or PMCs.

6. Clinical Microbiology

Not relevant to this application.

7. Clinical/Statistical- Efficacy

The reader is referred to the Clinical review by Dr. J. Tomaino, dated July 8, 2014, and the Statistical review by Dr. F. Cooner, dated July 18, 2014, for complete information. Dr. Tomaino recommends approval of this supplemental BLA from a clinical perspective, and I agree with her recommendation. Below, I will summarize key findings from her review.

Currently, Lumizyme is restricted to treatment of patients 8 years and older with late (non-infantile) onset Pompe disease who do not have evidence of cardiac hypertrophy. The Applicant is proposing to expand the indication to all patients with Pompe disease and change the indication to:

“Lumizyme (alglucosidase alfa) is a lysosomal glycogen-specific enzyme indicated for patients with Pompe disease (GAA deficiency).”

In addition to CMC data that evaluated physicochemical comparability between 160 L and 4000 L products, the Applicant submitted data from an ongoing investigator-sponsored, single-center, uncontrolled clinical study in Taiwan (Taiwan01) to further support expansion of the Lumizyme indication to all Pompe disease patients. Based on prior experience where the 2000 L product failed to establish comparability with the 160 L product, it was unclear whether CMC data alone would leave residual concerns to establish comparability between the 160 L (Myozyme) and 4000 L product (Lumizyme). Since it was not possible to know prior to review that new chemistry information would establish comparability between these two products, the Division requested that Genzyme also submit information from this ongoing clinical study in Taiwan that evaluates infantile-onset Pompe disease patients who are treated with Lumizyme, in case clinical data were needed to provide additional support for the chemistry data. The Division recommended a comparison of clinical outcome (i.e., ventilator-free survival and overall survival) between infantile-onset patients in Taiwan01 treated with the 4000 L product, infantile-onset patients treated with the 160 L product (from AGLU01602 and its extension AGLU02403), and untreated patients (historical cohort from AGLU00400).

AGLU01602 was an open-label, multicenter, multinational study that evaluated the safety and efficacy of alglucosidase treatment (160 L scale product) in patients with infantile-onset Pompe disease. Enrollment was restricted to patients aged 7 months or less at first infusion with clinical signs of Pompe disease and cardiac hypertrophy, but without ventilatory support at study entry. AGLU02403 was a long-term extension study of patients with infantile-onset Pompe disease who were previously enrolled in AGLU01602. AGLU00400 was a multicenter, multinational, natural history study of 168 patients diagnosed with infantile-onset Pompe disease with symptom onset within the first year of life and received only palliative and supportive care. A subgroup of 62 patients within the AGLU00400 cohort with matching

screening criteria as AGLU01602 was selected as a historical control group. This subgroup was used as the control population for the infantile-onset patients treated with Myozyme in AGLU01602 and Taiwan01.

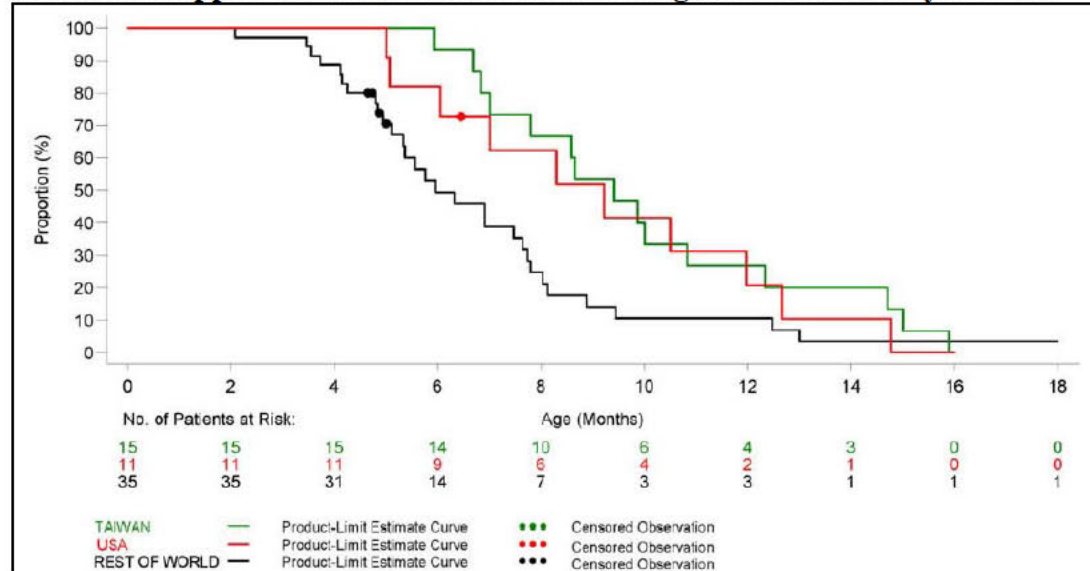
Since physicochemical comparability has been established between the 160 L and 4000 L products during this review cycle, clinical data were found not to be critical to approve Lumizyme for use in patients with infantile-onset disease. Nevertheless, submitted clinical data provide additional assurance that infantile-onset Pompe disease patients treated with Lumizyme will experience similar ventilator-free survival outcomes as those treated with Myozyme in the trial that supported Myozyme approval (AGLU01602 and its extension AGLU02403). Key findings from the Taiwan01 study are summarized below.

Taiwan01

General Description/Study Design

Taiwan01 is an ongoing, investigator-sponsored, open-label, single-center, observational study that began enrollment on March 8, 2006. This study was developed to assess the clinical outcome of Pompe disease patients who are identified through the National Taiwan University Hospital (NTUH) newborn screening program, and to compare their prognosis to those who are diagnosed based on clinical symptoms. The Taiwan01 study provided data on survival estimates in a population of infantile-onset treatment-naïve patients who were treated exclusively with Lumizyme (2000 L or 4000 L), and met the same key inclusion criteria as the patients enrolled in the clinical trial that supported marketing approval of Myozyme (AGLU01602 and its extension AGLU02403). The FDA field investigator noted that all patients received the 2000 L product until October 2009, and patients began receiving the 4000 L product starting approximately November 2009. Of the 18 patients included in the analysis, 2 patients received the 2000 L product only, 7 patients received the 4000 L product only, and the remaining 9 patients received both. Since the 4000 L product only became available in Taiwan in September 2009, many of the patients were previously exposed to the 2000 L product, a product that was never approved in the U.S. Based on prior evaluation of the physicochemical attributes of the 2000 L product, it is expected that inclusion of 2000 L product-treated patients in the analysis would negatively impact the overall efficacy of the 4000 L product if the difference in attributes of the 2000 L product had a meaningful effect on clinical outcome. Therefore, I agree with the Clinical reviewer that it is acceptable to include patients who received the 2000 L product in the primary analysis. The Statistical reviewer also considered it reasonable to pool these groups together for the efficacy analysis since patients who received the 4000 L product exclusively and those who received at least some 2000 L product showed very similar efficacy results.

Figure 1 depicts a comparison of survival estimates between infantile-onset patients in Taiwan and those in the U.S. based on natural history data. Since the two populations have similar natural history of disease progression (i.e., death by 18 months of age when untreated) and this clinical site in Taiwan follows the same recommended clinical care and assessments as U.S. sites participating in the Pompe Registry, I agree with the Clinical reviewer that it is reasonable to assume that data from the Taiwan01 study are applicable to the U.S. population.

Figure 1: Kaplan-Meier Estimates of Patients Who Were Alive and Free of Invasive Ventilator Support from Birth to 18 Months of age: Natural History Patients

Source: Applicant's response to FDA Information Request dated March 19, 2014, Module 1.2 Safety Information Amendment, Figure 1.

Patient population

A total of 18 infantile-onset Pompe disease patients enrolled in the Taiwan01 study met the same key inclusion criteria as the patients enrolled in the clinical trial that supported marketing approval of Myozyme (AGLU01602/02403). All patients were Asian; 9 were male and 9 were female. Patients had a confirmed diagnosis of Pompe disease as identified through the newborn screening program. All patients were treated with Lumizyme prior to 6 months of age (0.2 to 5.8 months at first infusion). All 18 patients in the Taiwan01 study were CRIM positive, whereas 14 patients were CRIM positive and 4 patients were CRIM negative in AGLU01602/02403.

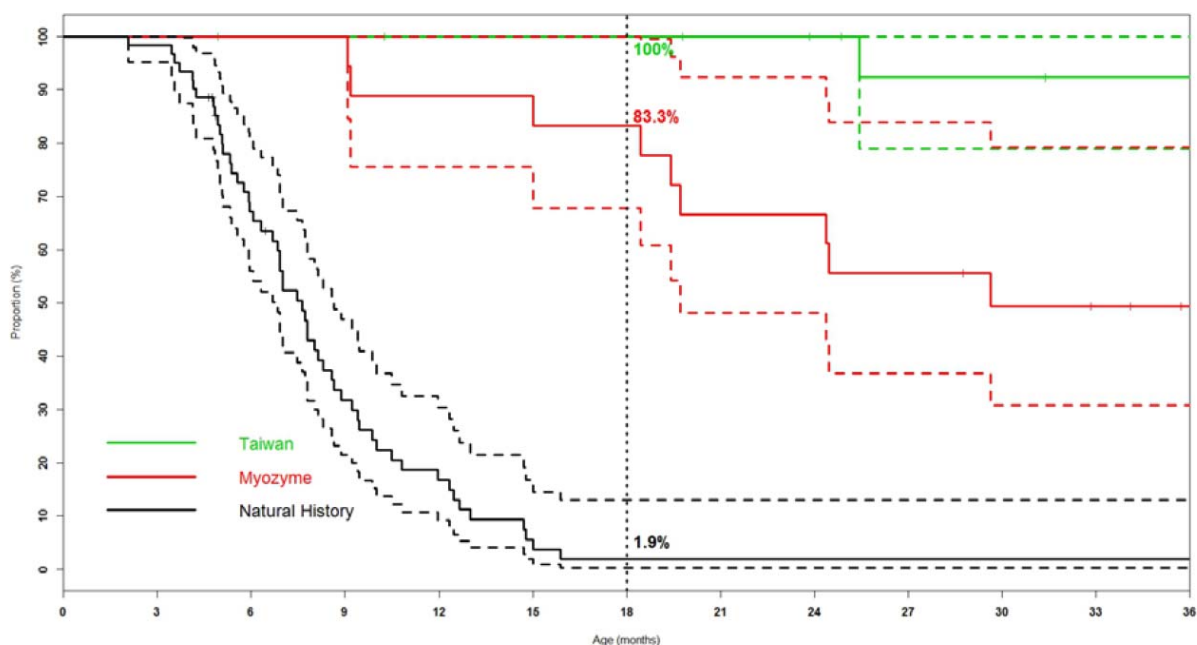
Primary efficacy analysis

The primary efficacy analysis was a comparison of ventilator-free survival of the infantile-onset patients enrolled in Taiwan01 to infantile-onset patients enrolled in AGLU01602/02403 and the natural history cohort (AGLU00400) at 18 months of age using the Kaplan-Meier method. This analysis was proposed post-hoc to support the analytical comparability between the 160 L and 4000 L products. (b) (4)

Of the 18 patients in the Taiwan01 study who were included in the analysis (with matching eligibility criteria as AGLU01602), 2 patients (on 4000 L product) had not reached 18 months of age when the primary endpoint assessment occurred. Of the remaining 16 at risk patients, 100% were alive and invasive ventilator-free at 18 months of age. It should be noted that there were three deaths in the Taiwan01 study, but all occurred after the primary efficacy assessment at 18 months of age. All patients died around 3 years of age from respiratory failure related to the underlying disease. In comparison, 15 (83%) of 18 patients in AGLU01602/2403 and 1

(2%) of 61 patients in the AGLU00400 historical cohort were alive and invasive ventilator-free at 18 months of age. Figure 2, replicated from the Statistical review by Dr. Cooner, illustrates the Kaplan-Meier estimates of patients who were alive and free of invasive ventilator support from birth to 18 months.

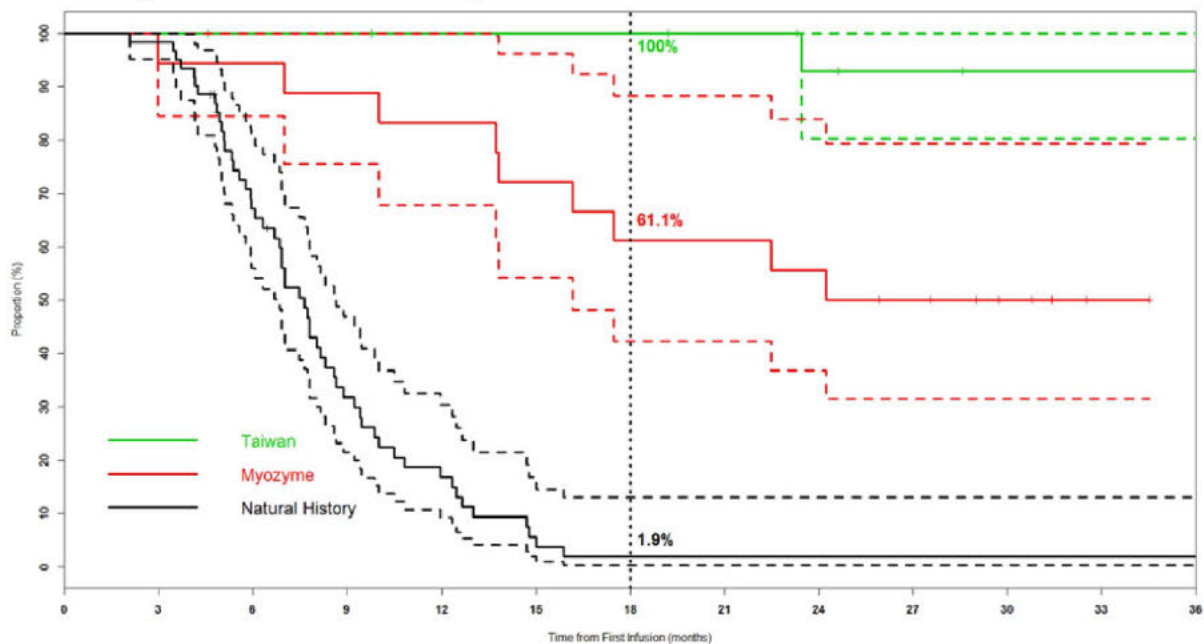
Figure 2: Kaplan-Meier Estimates of Ventilator-Free Survival From Birth to 36 Months of Age (Estimated Percentage at 18 Months with Confidence Interval Bands) in Infantile-Onset Pompe Disease Patients



Source: Statistical review by Dr. F. Cooner, dated July 18, 2014, Figure 1.

In order to avoid a selection bias that could result from some patients needing to survive long enough to be able to enroll into the studies, the Statistical reviewer repeated the primary analysis using time elapsed from the first infusion (Figure 3). Since the historical cohort was not treated with alglucosidase alfa, the time adjustment does not apply to this group. The Statistical reviewer noted that this analysis affected the results of AGLU01602/02403 but not Taiwan01. She stated that this observation is expected since patients from Taiwan01 received their first infusion earlier in their lives due to early diagnosis of Pompe disease through newborn screening, whereas patients from AGLU01602/02403 were diagnosed based on clinical signs of disease.

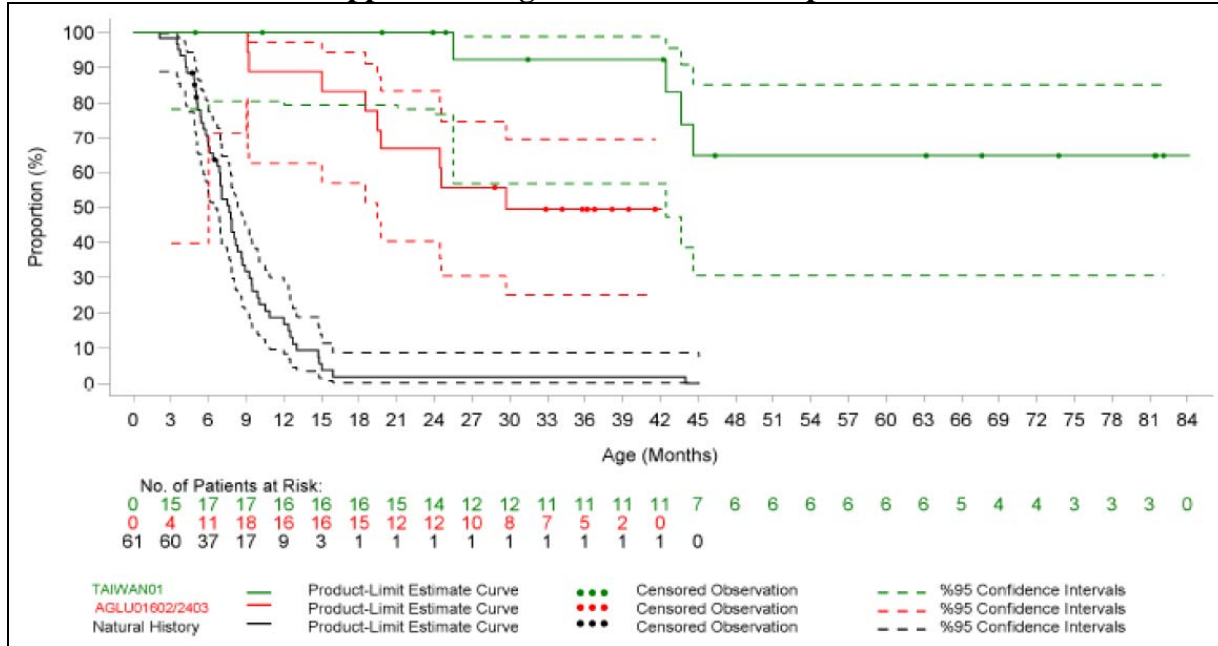
Figure 3: Kaplan-Meier Estimates of Ventilator-Free Survival From First Infusion to 36 Months of Age (Estimated Percentage at 18 Months with Confidence Interval Bands) in Infantile-Onset Pompe Disease Patients



Source: Statistical review by Dr. F. Cooner, dated July 18, 2014, Figure 2.

Dr. Cooner concluded that ventilator-free survival from these two studies can be considered comparable relative to the natural history cohort and that the Taiwan01 study showed higher survival rates through Month 36 for both analyses (i.e., from birth or first infusion). (b) (4)

The maximum follow-up time for AGLU01602/02402 was 42 months of age, and for Taiwan01 was 84 months of age (Figure 4). At 42 months of age, the Kaplan-Meier estimates of patients alive and ventilator-free was 92.3% (95% CI: 56.6%, 98.9%) in Taiwan01 and 49.4% (95% CI: 25.2%, 69.7%) in AGLU01602/02403. At 84 months of age, 64.6% (95% CI: 30.6%, 85.1%) of infantile-onset Pompe patients in Taiwan01 were alive and invasive ventilator-free. Only one patient in the AGLU0400 historical cohort was alive and invasive ventilator-free at 42 months of age and the survival estimate for this group was 1.9% (95% CI: 0.2%, 8.7%). It should be noted that the number of patients available for comparison beyond 39 months in AGLU01603/02403 was very limited (2 patients at 39 months and no patient at 42 months). Therefore, these data should be interpreted with caution. However, I agree with the Clinical reviewer that perceived differences in long-term outcomes between studies would not be expected to reflect differences in efficacy between the two products since they are deemed to be comparable.

Figure 4: Kaplan-Meier Estimates of Percentages of Patients Who Were Alive and Free of Invasive Ventilator Support Through the Last Follow-Up

Source: Applicant's sBLA submission 125291/136, dated January 30, 2013, Clinical Study Report, Section 10.1, Figure 10-2.

In both Taiwan01 and AGLU01602/2403, some patients received dosages other than the currently approved dosage of 20 mg/kg every other week. In Taiwan01, dose or dosage adjustments were permitted as per standard of care. In AGLU01602/2403, patients were randomized to receive either 20 mg/kg or 40 mg/kg every other week. As a result, the Clinical reviewer assessed the 18-month ventilator-free survival in patients who only received the approved dosage of 20 mg/kg every other week. Of the 10 patients who received 20 mg/kg every other week consistently throughout the study, 10 of (100%) 10 patients in the Taiwan01 study were alive and invasive-ventilator free at 18 months as compared to 8 (88.9%) of 9 patients in AGLU01602/02403 who were alive and invasive-ventilator free at 18 months of age. Therefore, the Clinical reviewer concluded that ventilator-free survival is similar between Myozyme- and Lumizyme-treated patients who were treated exclusively with the approved dosage of 20 mg/kg every other week.

As noted above, patients in the Taiwan01 study received the 2000 L product, 4000 L product, or both. Of the 18 patients, 7 patients received the 4000 L product only, 2 patients received the 2000 L product only, and the remaining 9 patients received both. At 18 months, 100% of the patients who received the 4000 L product exclusively were alive and ventilator-free.

Impact of CRIM Status on Efficacy

All of the patients enrolled in the Taiwan01 study were CRIM positive, whereas 14 of 18 patients in AGLU01602/2403 were CRIM positive and 4 were CRIM negative. In AGLU01602/02403, 2 of the 3 patients who did not meet the primary endpoint and required invasive ventilation by 18 months of age were CRIM negative. One patient required invasive ventilation at 9.2 months of age and died at 32 months of age. The second patient required

invasive ventilation at 9.1 months of age and died at 27.1 months of age. The additional 2 CRIM-negative patients required invasive ventilation at 18.5 months and 24.5 months of age and died at 34.3 months and 31.9 months of age, respectively. Therefore, all 4 of the CRIM negative patients treated with Myozyme died before 36 months of age. When the Statistical reviewer conducted the primary analysis excluding the 4 CRIM negative patients from AGLU1602/2403, the percentage of patients who were alive and invasive ventilator-free at 18 months of age increased from 83.3% (15 of 18) to 92.9% (13 of 14). This observation is not unexpected since the classic infantile-onset CRIM-negative patients are known to have the most severe form of Pompe disease. Poorer clinical outcome in CRIM-negative Pompe disease patients treated with enzyme replacement therapy has been attributed to development of high sustained anti-drug antibodies (ADA).^{4, 5} This impact of ADA on efficacy in CRIM-negative patients has prompted research for immune tolerance regimens that could mitigate immune responses to life-saving therapeutic proteins.

Since the Taiwan01 study did not include any CRIM-negative patients treated with the 4000 L product, the Clinical team sent an Information Request during the review cycle to request available clinical outcome data on CRIM-negative infantile-onset Pompe disease patients treated with the 4000 L product from the Pompe Registry and ongoing AGLU09411 (ADVANCE) switchover study. Of the 4 CRIM-negative patients in the Pompe Registry who were treated exclusively with the 4000 L product, 2 patients died, one at 0.7 year of age and another at 1 year of age. The third patient required invasive ventilation at 1.8 years of age, and the fourth patient has been treated for 2.4 years without reports of requiring invasive ventilation or death. It is difficult to draw clear conclusions based on limited data in a few patients. However, classic infantile-onset CRIM-negative patients are known to have the most severe form of Pompe disease and a poor clinical outcome is not unexpected in this patient population.

In addition, CRIM status was obtained in 42 patients enrolled in the ADVANCE study, and 34 of these patients had infantile-onset disease. Data obtained from the ADVANCE study most closely mimic what would happen upon expansion of the Lumizyme indication to all Pompe disease patients, since patients who have been treated with Myozyme will likely be switching to Lumizyme. Of the 34 infantile-onset patients, 10 were CRIM negative. Of the 10 CRIM-negative infantile-onset patients, 5 patients required invasive ventilation at the time of enrollment (prior to switching to Lumizyme). As of April 2, 2014, no additional CRIM-negative patients required invasive-ventilation and none of the CRIM-negative patients died after switching to Lumizyme. Based on available data, CRIM-negative infantile-onset patients seem to remain stable without evidence of clinical decline after switching to Lumizyme.

Impact of Immunogenicity on Efficacy

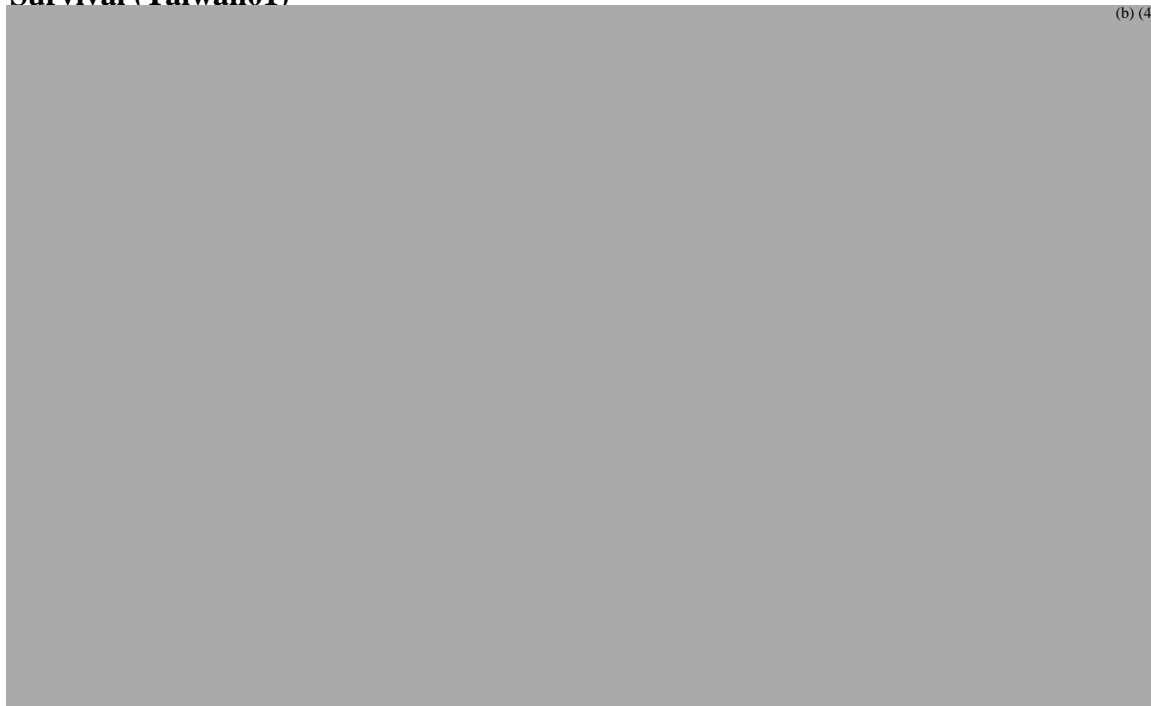
The reader is also referred to Section 3 of this document and the Immunogenicity review by Dr. C. Tami, dated July 17, 2014, for complete information.

⁴ Kishnani PR, et al. Cross-reactive immunologic material status affects treatment outcomes in Pompe disease infants. *Mol Genet Metab* 2010;99:26-33.

⁵ Abbott M, et al. Atypical immunologic response in a patient with CRIM-negative Pompe disease. *Mol Genet Metab* 2011;104:583-86.

Immunogenicity data were available in 17 of 18 infantile-onset disease patients in the Taiwan01 study. Of the 17 patients, 16 (94.1%) seroconverted. No patient had high sustained titer, defined by the Applicant as having a peak titer $\geq 25,600$ and the last titer equaling to the peak titer or 1 dilution level lower. As shown in Figure 5, there does not appear to be an obvious relationship between IgG titers and clinical outcome in infantile-onset Pompe disease patients treated with Lumizyme. For example, 2 of the 17 patients did not survive (marked as blue lines in Figure 5) despite low antibody titers. Their deaths occurred approximately 156 weeks after initiating Lumizyme treatment (beyond the primary efficacy endpoint assessment). However, the patient with the highest titer of 12,800 survived and did not require invasive ventilation.

Figure 5: Antibody Formation Over Time By Status of Invasive Ventilator Use and Survival (Taiwan01)



By contrast, two CRIM-positive patients who received Myozyme in AGLU01602/2403 developed high sustained antibody response and died, as shown in Figure 6.

Figure 6: Antibody Formation Over Time By Status of Invasive Ventilator Use and Survival for CRIM Positive Patients (AGLU01602/02403)



Although immunogenicity data from the Taiwan01 study do not support a clear relationship between IgG titers and clinical outcome, there is evidence to suggest that high sustained IgG titers are associated with poorer clinical outcome as shown in two infantile-onset Pompe disease patients treated with Myozyme in AGLU01602/02403 and in published literature (Banugarua S, et al. *Genet Med* 2011). This observation is communicated in the approved labeling for Myozyme. The Lumizyme labeling will be updated accordingly to also include this information since the two products have established physicochemical comparability.

The impact of genetic mutations and enzyme activity levels on clinical outcome could not be assessed adequately due to the small sample size. The reader is referred to the Clinical review by Dr. Tomaino, dated July 8, 2014, for details.

8. Safety

The reader is referred to the Clinical review by Dr. J. Tomaino, dated July 8, 2014, for complete information.

The safety review for this efficacy supplement focused on data collected from the infantile-onset Pompe disease patients who received the 4000 L product in the Taiwan01 study and AGLU09311 (ADVANCE) switchover study. Because Taiwan01 study is an investigator-sponsored study, there may have been underreporting of adverse reactions as they were voluntarily reported.

Overall, the adverse reactions reported during Taiwan01 and ADVANCE studies were similar to those reported during the clinical trial that supported approval of Myozyme, and no new safety signals were identified. The ADVANCE study was conducted in the U.S. and provides safety data that are applicable to patients in the U.S. with infantile-onset Pompe disease who will likely be switched from their current treatment of Myozyme (160 L) to Lumizyme (4000 L) upon approval of this efficacy supplement.

There were no patients in Taiwan01 or ADVANCE who experienced adverse reaction that resulted in permanent discontinuation of Lumizyme treatment.

There were three deaths in Taiwan01 study, but all occurred after the primary efficacy assessment at 18 months of age. Of the 12 of 18 patients with available follow-up data at 36 months, 1 patient had required invasive ventilation at 25.4 months, and 3 patients had died (mean age of death 3.6 years) due to respiratory failure related to underlying disease. Similarly, 3 infantile-onset patients died during the ADVANCE study or shortly after withdrawal from the study, all due to respiratory failure. One additional patient died after the data cut-off date for this submission. Death due to respiratory failure is expected in patients with Pompe disease, especially those with infantile-onset disease, regardless of treatment with enzyme replacement therapies. Of the patients enrolled in AGLU01602/AGLU02403, longer-term data were available in 14 patients through the Pompe Registry. It should be noted that data are entered into the Pompe Registry voluntarily by physicians; therefore, data collection may have been inconsistent. At 36 month follow-up, 4 of 14 patients were reported to have died (mean age of death 3.4 years). Of these 4 patients, 1 was CRIM positive and 3 were CRIM negative.

The most common adverse reactions that occurred in Taiwan01 study included signs and symptoms of hypersensitivity reactions and included anaphylaxis, rash, pyrexia, pruritus, and eyelid edema. Six (33.3%) of 18 patients in the Taiwan01 study experienced hypersensitivity reaction. Two of 18 patients in Taiwan01 study experienced anaphylaxis based on the Sampson criteria.⁶ Anaphylaxis is a known serious, adverse reaction associated with both Myozyme and Lumizyme. Most product labels for enzyme replacement therapies, including Myozyme and Lumizyme, contain a boxed warning on the risks of life-threatening anaphylaxis and severe hypersensitivity reactions associated with the use of these products. In addition, since patients with classic infantile-onset Pompe disease have impaired cardiorespiratory function, the boxed warning for Myozyme contains a statement on the risk of cardiorespiratory failure due to fluid overload in patients with compromised cardiac or respiratory function.

Most common adverse reactions that occurred in the ADVANCE study were pyrexia, diarrhea, respiratory tract infection, vomiting, cough, pneumonia, and rash. Three of 99 patients in the ADVANCE study experienced anaphylaxis. Again, no new or unexpected adverse reactions were identified during this study.

⁶ Sampson HA, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391-7.

Impact of immunogenicity on safety

The reader is referred to the Clinical review by Dr. J. Tomaino, dated July 8, 2014, and the Immunogenicity review by Dr. C. Tami, dated July 17, 2014, for complete information.

Enzyme replacement therapies are highly immunogenic; therefore, anti-drug antibody formation, including development of neutralizing antibodies, is the primary safety concern associated with this therapeutic class. In general, hypersensitivity reactions are more common in patients who develop anti-drug antibodies. In Taiwan01 study, 6 of 18 patients experienced signs and symptoms of hypersensitivity reactions, and all 6 tested positive for anti-rhGAA IgG. One patient in the Taiwan01 study did not seroconvert, and this patient did not experience a hypersensitivity reaction. These findings are consistent with what is known about the relationship of antibody formation and hypersensitivity reactions.⁷ This relationship is also described in the approved label for Myozyme.

In summary, Dr. Tomaino has concluded that adverse reactions reported from patients who were treated with Lumizyme (4000 L scale product) in Taiwan01 and ADVANCE studies were similar to those observed during the trial that supported approval of Myozyme (160 L scale product). No new or unexpected adverse reactions were identified from the data provided. Anaphylaxis and hypersensitivity reactions remain the most frequent and concerning adverse reactions associated with alglucosidase alfa treatment, which are adequately addressed in labeling through a boxed warning. I agree with Dr. Tomaino that no new safety concerns arose from the review of the submission that would preclude approval of this efficacy supplement.

The Clinical reviewer has not recommend PMRs or PMCs.

9. Advisory Committee Meeting

There was no Advisory Committee meeting for this application as there were no decisional issues that required input from the Advisory Committee during the review cycle.

10. Pediatrics

Recombinant human acid alpha-glucosidase was granted an orphan product designation on August 19, 1997. Therefore, the regulations that pertain to the Pediatric Equity in Research Act (PREA) do not apply to this product. The submission was not presented to the Pediatric Review Committee (PeRC).

The Division consulted the Pediatrics and Maternal Health Staff (PMHS) to aid in the review of the labeling. Their recommendations have been incorporated into final labeling.

⁷ Wang J, et al. Neutralizing antibodies to therapeutic enzymes: considerations for testing, prevention, and treatment. *Nat Biotechnol* 2008; 26: 901-908.

11. Other Relevant Regulatory Issues

Financial Disclosures

Upon review of the clinical investigator financial disclosure information, the Clinical reviewer noted that there were no investigators or sub-investigators who participated in the Taiwan01 study with disclosable financial interest as defined in 21 CFR 54.2. However, she noted that

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[REDACTED] (b) (4)
[REDACTED] of which (b) (6)
[REDACTED] I agree with the

Clinical reviewer that these arrangements do not raise concerns over the integrity of the data. In addition, establishment of physicochemical comparability between the 160 L (Myozyme) and 4000 L (Lumizyme) products during the review cycle resulted in clinical data no longer being critical for approval of Lumizyme for the treatment of patients with infantile-onset Pompe disease.

Office of Scientific Investigations

The Division requested an inspection of the clinical site that conducted the Taiwan01 study (PI: Wuh-Liang Hwu, MD, PhD), since the primary clinical data that were submitted to support the comparability between the 160 L and 4000 L products were collected from this one site. The FDA field investigator noted that all patients received the 2000 L product until October 2009, and that patients began receiving the 4000 L product starting approximately November 2009. The field investigator verified efficacy data and noted that there was no evidence of under-reporting of adverse events. Based on findings from the FDA field investigator, the medical reviewer concluded that the study appeared to have been conducted adequately and that the data generated by this site may be used in support of the respective indication. The reader is referred to the Clinical Inspection Summary by Dr. S. Leibenhaut, dated June 27, 2014, for details.

Elimination of the REMS with ETASU

Lumizyme was approved in 2010 with a Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU) to restrict its use to treatment of patients with non-infantile onset Pompe disease who are at least 8 years of age to mitigate the potential risk of rapid disease progression in the infantile-onset patients and to communicate the risks of anaphylaxis and severe allergic reactions to prescribers and patients. At the time of Lumizyme approval, there were insufficient analytical (i.e., results from chemical, biochemical, and *in vitro* biological testing) and clinical data to support the safety and efficacy of Lumizyme in the infantile-onset Pompe population; therefore, Lumizyme was approved for use only in late-onset Pompe disease patients who are at least 8 years of age. The REMS assured that patients with the infantile-onset form of Pompe disease were treated with another alglucosidase alfa product manufactured at a 160 L scale, Myozyme, which was approved in 2006. Based on the

information included in the efficacy supplement, the applicant is requesting to eliminate the REMS.

The two goals of the REMS are:

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

The Lumizyme Access, Control, and Education (ACE) Program includes all components of a REMS to ensure that the benefits of Lumizyme outweigh the risks. The ACE program includes goals, a communication plan, elements to assure safe use, an implementation system, and a system of assessments. A medication guide was not required because patients would be expected to receive treatment only at specialized infusion centers under the supervision of trained personnel.

I agree with the Clinical reviewer that existing REMS with ETASU should be released at the time of this efficacy supplement approval. Since this approval would expand the indication to all patients with Pompe disease, current age-specific restriction will no longer apply. In addition, the risk of anaphylaxis, severe allergic reactions, and immune-mediated reactions are adequately communicated in the Boxed warning and the Warnings and Precautions section of the Lumizyme label. The risks of anaphylaxis and severe allergic reactions are well-known risks that are associated with the use of enzyme replacement therapies.

Based on a review of the 4-year REMS assessment by Dr. I. Cerny from the Division of Risk Management (review dated July 2, 2014), the prescribers appear to have a reasonable understanding of Lumizyme risks and appear to be appropriately communicating these risks. Patients have demonstrated fair-to-good knowledge on the risk of severe allergic reactions with Lumizyme treatment, but they have demonstrated poor knowledge on the risk of cutaneous and systemic immune-mediated reactions. Dr. Cerny noted that patients, however, knew appropriate actions to take if these reactions were to occur. The DRISK reviewer stated in his review that the observed outcome in patients is acceptable since the survey questions may have been too complex in terms of what patients need to know to ensure safe use of the product. Dr. R. Pratt, also from DRISK, who has reviewed the Applicant's proposed REMS modification agreed with Dr. Cerny's assessment and stated in his review, dated July 20, 2014, that this isolated finding reported in the REMS assessment should not preclude elimination of the second goal of the REMS. Therefore, DRISK recommends the Applicant be released from the REMS requirement for Lumizyme upon approval of this efficacy supplement. In addition, they recommend an external communication strategy be developed to notify stakeholders of the release from the REMS requirement.

I agree with the DRISK reviewers' assessments since the existing REMS provides little information to patients regarding the underlying etiology of cutaneous and systemic immune-

mediated reactions and patients have demonstrated an understanding of what they should do if they develop such reactions, which is most important to ensuring safe use of the product. The Agency plans to communicate the new expanded indication of Lumizyme and the elimination of the REMS to prescribers and patients through a press release and notifications to relevant professional and patient organizations. The Applicant also indicated (on June 13, 2014, in response to FDA Information request) that, if successful in updating the indication for Lumizyme to include all Pompe disease patients, they intend to provide a communication to healthcare providers regarding the updated Lumizyme label and reiterate the importance of reviewing the adverse events associated with Lumizyme treatment and the importance of informing patients about these risks. The Applicant stated that the communication will also emphasize the importance of monitoring Lumizyme-treated patients for certain underlying risks, such as performing antibody testing every 3 months for IgG antibody formation.

On June 4, 2014, the Division presented to the REMS Oversight Committee (ROC) our recommendation to remove the REMS with ETASU. The Committee agreed with the Division's recommendation.

(b) (4)

12. Labeling

Proprietary Name

Since Lumizyme is an approved product, there were no new discussions regarding the appropriateness of the proprietary name.

(b) (4)

Labeling Supplement During the Review Cycle

A labeling supplement was approved on May 22, 2014 to add flu-like illness to the Post-marketing section of the labeling. The reader is referred to the Labeling Supplement review by Dr. J. Tomaino, dated April 29, 2014, for details.

Labeling Changes

Multiple labeling negotiations occurred between the Applicant and the review team during the review cycle. Key changes to the labeling are summarized below.

(b) (4)

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS)
immediately following this page

In addition to the review team and the PMHS consultants, the labeling was also reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and the Office of Prescription Drug Promotion (OPDP). Their comments and recommendations have been incorporated into final labeling. For final labeling agreements, the reader is referred to the approved label for Lumizyme.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

Approval of BLA 125291/Supplement 136 to expand the Lumizyme indication to include all Pompe disease patients

Risk Benefit Assessment

Pompe disease is a serious and life-threatening disease. Since the approval of Myozyme and Lumizyme, infantile-onset patients have been surviving well beyond the first years of life and late-onset patients have been experiencing slower disease progression with improved respiratory function and muscle strength. Although the 160 scale product (Myozyme) was approved for all Pompe disease patients, it is currently restricted to infantile-onset patients 12 months of age and younger due to the drug shortage. Approval of the 4000 L product (Lumizyme) for treatment of the full spectrum of the Pompe disease population (without a restrictive REMS) would allow infantile-onset patients and patients with late-onset disease who are 8 years and younger market access to treatment with the 4000 L product (without need to enroll in a study to access the product).

In this efficacy supplement, the Applicant submitted data that established analytical comparability (i.e., comparable results from chemical, biochemical, and *in vitro* biological testing) between the 160 L (Myozyme) and 4000 L (Lumizyme) products so that the

Lumizyme indication could be expanded to all Pompe disease patients. In addition, clinical data from the Taiwan01 study have demonstrated similar ventilator-free survival outcomes as those treated with Myozyme in the trial that supported Myozyme approval (AGLU01602 and its extension AGLU02403), providing additional clinical support for analytical comparability. No new safety concerns were raised in this study as well as the ongoing ADVANCE (AGLU09311) study that assessed patients 12 months of age and older who are switched from Myozyme to Lumizyme.

Most serious risks associated with the class of enzyme replacement therapies are anaphylaxis and hypersensitivity reactions. In addition, patients with compromised cardiorespiratory function may be at risk for acute cardiorespiratory failure during infusion due to fluid overload. These risks and mitigating strategies are well described in the boxed warning of the Lumizyme label. Furthermore, Lumizyme infusions are administered in an infusion center where patients can be closely monitored.

Based on a review of the submitted data and what is known about pharmacologically related products, the risks of Lumizyme in infantile-onset Pompe disease patients and patients younger than 8 years of age appear to be acceptable in view of the established benefits. Therefore, I agree with the reviewers that Lumizyme should be approved to expand the indication to all Pompe disease patients.

Recommendation for Postmarketing Risk Evaluation and Management Strategies

In 2010, Lumizyme was approved with a REMS to restrict its use to treatment of patients with non-infantile onset Pompe disease who are at least 8 years of age to mitigate the potential risk of rapid disease progression in the infantile-onset patients and to communicate the risks of anaphylaxis and severe allergic reactions to prescribers and patients. Based on a review of the information submitted in this efficacy supplement, both the Clinical reviewer and the Division of Risk Management (DRISK) reviewers have concluded that the REMS with ETASU is no longer needed. I agree with their assessment. The reader is referred to the 4-year REMS assessment review by Dr. I. Cerny, dated July 2, 2014, the REMS modification review by Dr. R. Pratt, dated July 20, 2014, as well as Section 11 of this document for additional details.

Recommendation for other Postmarketing Requirements and Commitments

The review team has not recommended any PMRs or PMCs.

Recommended Comments to Applicant

No additional comments to the Applicant are recommended at this time.

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/s/

JESSICA J LEE
07/22/2014

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
BLA 125291/136

MEDICAL REVIEW(S)

ADDENDUM TO CLINICAL REVIEW

Application Type	Efficacy supplement for Lumizyme to expand the indication to all Pompe patients
Application Number(s)	sBLA 125291/136
Priority or Standard	Priority
Submit Date(s)	January 30, 2014
Received Date(s)	January 30, 2014
PDUFA Goal Date	August 1, 2014
Division / Office	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Reviewer Name(s)	Juli Tomaino, MD, Medical Officer Jessica Lee, MD, Clinical Team Leader
Review Completion Date	July 8, 2014
Established Name	Alglucosidase alfa
(Proposed) Trade Name	Lumizyme
Therapeutic Class	Enzyme Replacement Therapy
Applicant	Genzyme
Formulation(s)	Intravenous
Dosing Regimen	20 mg/kg every other week
Indication(s)	Pompe Disease
Intended Population(s)	Infantile-onset Pompe patients

ADDENDUM TO CLINICAL REVIEW

After the clinical review was finalized, we received clarification from the Applicant on the 2 patients from the Taiwan01 trial who were censored in the Kaplan-Meier analysis. The original review states that of the 18 patients enrolled in the Taiwan01 trial who met the same inclusion criteria as patients enrolled in the AGLU01602/02403 trial, 2 were lost to follow up. However, the 2 patients were censored because they had not yet reached 18 months of age the time of the analysis. In addition, minor editorial revisions were made.

Pages 29, 33 and 51 of the clinical review, dated July 8, 2014, have been revised and are shown below. Refer to the clinical review, dated July 8, 2014, for the full document.

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Lumizyme (4000 L) and Myozyme (160 L). As previously agreed upon with the Division, the patients who were included in the Taiwan01 efficacy analysis were required to meet the same inclusion criteria as the patients enrolled in AGLU1602/AGLU02403 to allow for a comparison of survival outcomes between the Lumizyme (4000 L) treated patients and the Myozyme (160 L) patients. The primary efficacy endpoint for the survival comparison was invasive ventilator-free survival at 18 months of age. Invasive-ventilator free survival at 18 months was similar between the infantile-onset patients treated with Lumizyme (4000 L) and Myozyme (160 L). Of the 18 patients enrolled in the Taiwan01 trial who met the same inclusion criteria as patients enrolled in the AGLU01602/02403 trial, 2 patients had not reached 18 months of age at the time of the analysis. Of the remaining 16 patients, 100% percent of patients in the Taiwan01 trial were alive and invasive ventilator-free at 18 months of age. In comparison, 15/18 (83.3%) of patients in AGLU01602/2403 and 1/61 (1.9%) of patients in the AGLU00400 historical cohort were alive and invasive ventilator-free at 18 months of age.

In the Taiwan01 and AGLU01602/2403 trials, some patients received doses other than the currently approved dose of 20 mg/kg every other week. The 18-month ventilator-free survival was assessed in patients who received only the approved dose of 20 mg/kg every other week. Of the 10 patients who received the 20 mg/kg every other week dose, 100% patients in the Taiwan01 trial were alive and invasive-ventilator free at 18 months vs. 8/9 (88.9%) patients in the AGLU01602/02403 trial who were alive and invasive-ventilator free at 18 months of age. Therefore, ventilator-free survival was similar between Myozyme (160 L) and Lumizyme (4000 L) treated-patients who were treated exclusively with the approved dose of 20 mg/kg every other week.

Although there was no significant difference between the Taiwan01 and AGLU01602/2403 cohorts in the percentage of patients who were alive and free of invasive ventilator support at 18 months of age, the apparent differences between the curves based on visual inspection at 18 months is likely related to the inclusion of more severely affected CRIM negative patients in AGLU01602/02403. Refer to Figure 2 in Section 6.1.4 Analysis of Primary Endpoints (s). All of the patients enrolled in the Taiwan01 trial were CRIM positive and the majority of the patients (14/18) in AGLU01602/2403 were CRIM positive. Of the 3 patients in AGLU01602/02403 who required invasive ventilation by the 18 month time point and failed the primary endpoint at 18 months, 2 patients were CRIM negative. In contrast, no patients in the Taiwan01 trial were CRIM negative. To determine whether the inclusion of CRIM negative patients in the AGLU01602/02403 trial influenced the results, the Statistical reviewer reanalyzed the primary efficacy endpoint excluding the CRIM negative patients from the AGLU01602/02403 trial. The results from the Taiwan01 trial were unchanged since all patients were CRIM positive; 100% of patients were alive and invasive ventilator-free at 18 months of age. However, when the 4 CRIM negative patients were excluded from AGLU1602/2403, the percent of patients who were alive and invasive ventilator-free at 18 months of age increased to 13/14 (92.9%) from 15/18 (83.3%). This was expected since classic infantile-onset CRIM negative patients are known to have the most severe form of Pompe disease. Poor outcomes are likely related to the disease severity rather than to the scale of alglucosidase alfa. Ventilator-free survival remained similar between Myozyme (160 L) and Lumizyme (4000 L) treated-patients.

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relationship between genotype and the impact on clinical outcome at this time; therefore, an analysis based on genotypes will not be performed in this review.

6.1.3 Subject Disposition

Eighteen patients from the Taiwan01 trial met the same inclusion criteria as patients enrolled in AGLU01602/02403, and were treated exclusively with Lumizyme, the larger scale of alglucosidase alfa. There were 3 deaths, 2 patients had not reached 18 months of age at the time of the analysis, and no patients withdrew due to adverse events (AEs). Data were collected in this trial since 2006 through the data cut-off date of June 30, 2013.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint was the proportion of infantile-onset patents enrolled in Taiwan01 who were alive and invasive ventilator-free at 18 months compared to infantile-onset patients enrolled in AGLU01602/02403), and the natural history (AGLU00400) cohort.

Of the 18 patients enrolled in the Taiwan01 trial who met the same inclusion criteria as patients enrolled in AGLU01602/02403, 2 patients had not reached 18 months of age at the time of the analysis and were censored. Of the remaining 16 patients, 100% percent of patients in the Taiwan01 trial were alive and invasive ventilator-free at 18 months of age. In comparison, 15/18 (83.3%) of patients in AGLU01602/2403 and 1/61 (1.9%) of patients in the AGLU00400 historical cohort were alive and invasive ventilator-free at 18 months of age. Of note, 61 out of the 62 patients from the historical cohort were included in the efficacy analysis because the date of death was unknown for one patient. The Statistical reviewer for the original Myozyme (BLA 125141) review noted that including this patient would not have changed the interpretation of the trial (see Lisa Kammerman's Statistical review dated April 27, 2006 for details). Figure 2 below shows the Kaplan-Meier curves that compare the Taiwan01, AGLU01602/2403, and natural history cohorts.

Pyrexia	2 (11.1)
Tachypnea	2 (11.1)

*Pneumonia due to infectious causes versus aspiration pneumonia

(Source: reviewer's analysis using applicant's data, sBLA 125291, dated January 30, 2014, module 5.3.5.4 Taiwan01 analysis dataset)

Of the AEs occurring in $\geq 10\%$ of patients, respiratory failure, pneumonia infectious, atelectasis, and increased blood creatine phosphokinase probably represent clinical manifestations of Pompe disease. However, rash, pyrexia, and tachypnea could be associated with hypersensitivity reactions (infusion-associated reactions, as defined by the applicant), and will be discussed in the following sections of this review. The review team has requested that the applicant revise the Adverse Reactions section of the label to include only the signs and symptoms that are likely related to Lumizyme.

7.3.3 Dropouts/Discontinuations

There were no patients in the Taiwan01 who experienced an adverse reaction that lead to permanent treatment discontinuation. ~~Two patients in the Taiwan01 trial were lost to follow-up at 4.9 months and 10.3 months, respectively. These patients were considered to be censored observations in the primary efficacy analysis.~~

7.3.4 Significant Adverse Events

There were 14 severe adverse events that occurred in 3 patients during the Taiwan01 trial. Eight of the 14 severe events occurred in the same patient (patient 10378), who had a significant medical history of severely compromised cardiac and respiratory function. This patient eventually died at 3 years of age (see Table 6 above). The severe adverse events included atelectasis, bronchiolitis, device-related infection, gastric hemorrhage, left ventricular hypertrophy, pneumonia, respiratory failure, respiratory tract infection, and torsade de pointes. All of these events can be attributed to clinical manifestations of Pompe disease or to the complications related to Pompe disease.

7.3.5 Submission Specific Primary Safety Concerns

Of note, the Agency is moving away from using the term "infusion reaction" and is currently recommending that the term "infusion reaction" be replaced with "hypersensitivity reaction" or "anaphylaxis," as appropriate. Although the term "infusion reaction" implies a temporal relationship, infusion reactions are not well defined and may encompass a wide range of clinical events, including anaphylaxis. However, the approved Myozyme label uses the term "infusion reactions" or "infusion-associated reactions." In this review, to provide accurate reference to the language included in the approved Myozyme label, the term "infusion reaction" will be stated only when referring to the Myozyme label. (b) (4)

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/s/

JULI A TOMAINO
07/24/2014

JESSICA J LEE
07/24/2014

CLINICAL REVIEW

Application Type	Efficacy supplement for Lumizyme to expand the indication to all Pompe patients
Application Number(s)	sBLA 125291/136
Priority or Standard	Priority
Submit Date(s)	January 30, 2014
Received Date(s)	January 30, 2014
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Division / Office	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Reviewer Name(s)	Juli Tomaino, MD, Medical Officer Jessica Lee, MD, Clinical Team Leader
Review Completion Date	July 8, 2014
Established Name	Alglucosidase alfa
(Proposed) Trade Name	Lumizyme
Therapeutic Class	Enzyme Replacement Therapy
Applicant	Genzyme
Formulation(s)	Intravenous
Dosing Regimen	20 mg/kg every other week
Indication(s)	Pompe Disease
Intended Population(s)	Infantile-onset Pompe patients

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer considers BLA 125291/136 acceptable to recommend approval of Lumizyme (4000 L) for the treatment of Pompe disease patients. This reviewer agrees with the applicant's proposal to expand the Lumizyme indication to all Pompe disease patients. At the time of the Lumizyme approval, the clinical and analytical data were insufficient to support the safety and efficacy of Lumizyme in the infantile-onset Pompe population. This supplemental BLA included data that established the physicochemical comparability between Lumizyme (4000 L) and Myozyme (160 L), both manufactured by Genzyme, which was further supported by clinical efficacy and safety data from an open-label, single-center clinical trial that demonstrated similar survival outcomes between treatment-naïve infantile-onset Pompe patients, treated with Lumizyme (4000 L), and patients from the clinical trials that supported approval of Myozyme (160 L). The clinical data were requested a priori in the case that the comparability data left residual concerns about efficacy; however, the supportive clinical data were considered to be unnecessary due to the establishment of comparability. Therefore, this reviewer recommends approval of sBLA 125291/136 that will expand the Lumizyme indication to all Pompe patients.

1.2 Risk Benefit Assessment

Patients with infantile-onset Pompe disease or patients who are younger than 8 years of age with Pompe disease are intended to be treated with Myozyme (160 L) in the United States. In 2010, Lumizyme, made on a 4000 L bioreactor scale, was approved for treatment of juvenile/adult onset Pompe disease who are at least 8 years of age. At the time of the Lumizyme approval, chemical comparability was not established between Myozyme (160 L) and Lumizyme (4000 L). Therefore, the indication for Lumizyme could not be extended to infantile-onset Pompe patients and Lumizyme (4000 L) was approved with a REMS that restricted the use of Lumizyme to Pompe patients with late-onset disease who are ≥ 8 years of age. However, due to ongoing drug shortages of the 160 L product, and the restrictions of the Lumizyme REMS, patients who are ≥ 12 months of age, previously treated with the 160 L product, are currently being switched to Lumizyme (4000 L) as part of an ongoing phase 4, open-label, prospective trial. Refer to Section 2.5 below for a detailed regulatory history of these products.

The applicant now proposes to expand the Lumizyme (4000 L) indication to all Pompe patients in the United States based on the information in this submission, which included an analytical evaluation that established physicochemical comparability between Myozyme (160 L) and Lumizyme (4000 L), and supportive clinical efficacy data in treatment-naïve infantile-onset Pompe patients from the Taiwan01 trial. The Taiwan01 trial provided data on survival estimates in a population of infantile-onset treatment-naïve patients who received therapy exclusively with Lumizyme (4000 L), and met the same key inclusion criteria as the patients enrolled in the clinical trials that supported marketing approval of Myozyme. The overall and ventilator-free survival estimates were found to be similar between the patients in the Taiwan01 trial, who

received treatment with Lumizyme (4000 L), and patients from the clinical trials that supported approval of Myozyme (160 L).

In the infantile-onset patient population, the safety profile of Lumizyme (4000 L) was found to be similar to the known safety profile of Myozyme (160 L), which included signs and symptoms consistent with anaphylaxis, hypersensitivity reactions, immune-mediated reactions, and cardiorespiratory distress. The postmarketing safety data submitted for patients treated with Lumizyme (4000 L) also did not reveal new or unexpected safety signals.

The greatest risks associated with the class of enzyme replacement therapies are anaphylaxis and hypersensitivity reactions. In addition, patients with compromised cardiorespiratory function may be at risk for acute cardiorespiratory failure during the infusion. These risks and mitigating strategies described below are well described in the boxed warning in the Lumizyme label. Furthermore, Lumizyme infusions are administered in an infusion center where patients are closely monitored and trained medical staff have readily available therapeutic support, including epinephrine and cardiopulmonary resuscitation equipment, in the event that a patient experiences an adverse reaction. The infusion volumes and rates are outlined in detail in the Lumizyme label based on patient weight. In addition, the label indicates that vital signs should be administered at the end of each volume increase, and the infusion may be slowed or temporarily stopped if the patient experiences signs and symptoms of anaphylaxis, hypersensitivity infusion, or cardiorespiratory distress. Alglucosidase alfa is the only approved treatment indicated for Pompe disease, which is rapidly fatal in patients with the infantile-onset phenotype. For patients with the late-onset phenotype, the disease progression is attenuated; however, patients experience progressive muscle weakness and compromised respiratory function, resulting in death. Since the approval of alglucosidase alfa, infantile-onset patients are surviving well beyond the first years of life and late-onset Pompe patients have slower disease progression with improved respiratory function and muscle strength. There are no other available therapies for Pompe disease and the risks and mitigation strategies are clearly communicated in the label; therefore, Lumizyme offers substantial clinical benefits compared to the risks that are associated with the product.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

In 2010, Lumizyme was approved with a REMS to restrict Lumizyme from use in the treatment of infantile-onset patients and to communicate the risks of anaphylaxis and severe allergic reactions to prescribers and patients. At the time of approval, the clinical and analytical data were insufficient to support the safety and efficacy of Lumizyme in the infantile-onset Pompe population; Lumizyme was approved for the treatment of late-onset Pompe patients who are at least 8 years of age. Based on the information included in the efficacy supplement, the applicant is requesting to be released from the Lumizyme REMS.

The two goals of the REMS are:

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

The REMS Elements are:

- Communication Plan
- Elements to Assure Safe Use (Lumizyme Alglucosidase alfa Control and Education (ACE) Program)
- Implementation System

This reviewer recommends that the applicant be released from the first goal upon approval of this efficacy supplement since approval would expand the indication to all patients with Pompe disease and the age-specific restriction will no longer apply.

In addition, the applicant should be released from the second goal since the risk of anaphylaxis, severe allergic reactions, and immune-mediated reactions are adequately communicated in the Boxed Warning of the Lumizyme label. Furthermore, multiple enzyme replacement therapies have been approved with similar safety profiles to Lumizyme, including the risk of anaphylaxis and severe allergic reactions; none were approved with a REMS. The risk of anaphylaxis and severe allergic reactions are currently well-known risks that are associated with the class of enzyme replacement therapies. These risks are adequately communicated through the Warnings and Precautions section of the approved labels.

Additionally, the applicant proposes to incorporate the language from the Boxed Warning of the currently approved label for Myozyme into the Boxed Warning of the revised label for Lumizyme, which further addresses the risks that are specific to infantile-onset patients through labeling. (b) (4)

(b) (4)

Therefore, this reviewer recommends that the applicant be released from the Lumizyme REMS upon approval of this efficacy supplement. On June 4, 2014, the recommendation to release the Lumizyme REMS was presented to the REMS Oversight Committee (ROC); the Committee agreed with the Division to release the applicant from the REMS.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

Pompe disease is an autosomal recessive, progressive, and often fatal neuromuscular glycogen storage disease, due to absence or deficiency of the enzyme, acid α -glucosidase or alglucosidase alfa (GAA). GAA is responsible for catabolism of glycogen in the lysosomes. Deficiency of GAA enzyme results in accumulation of glycogen in heart and skeletal muscle, including respiratory muscles.

Pompe disease occurs in 1/40,000 live births worldwide. It is estimated that the current worldwide prevalence may be 5,000-10,000 people—of both genders and of varying ages and ethnicities.¹ Historically, infants with Pompe disease died by 1-2 years of age,² but since the advent of recombinant enzyme replacement therapy (ERT), survival is improving.

There are two main phenotypes: early-onset (infantile) where there is total or almost total absence of GAA, and late-onset (juvenile/adult) where there is deficiency of GAA (up to 30% of normal levels) but not absence of the enzyme. Disease progresses slowly in adults and depends on age at onset. Earlier age at onset is associated with disease that is more aggressive. Symptoms in infants include failure to thrive, hypotonia, hypertrophic cardiomyopathy, enlargement of tongue and liver, and hearing difficulties. Juvenile/adult onset Pompe disease symptoms are mainly related to skeletal and respiratory muscle weakness resulting in fatigue, muscle weakness and cramps, and difficulty with mobility and respiration.³

The amount of GAA enzyme, determined by visualization of GAA proteins by western blot analysis, determines cross reactive immunologic material (CRIM) status. Complete absence or <1% of normal levels of GAA (negative western blot) is considered CRIM negative, whereas presence of a GAA band on western blot is considered CRIM positive. The majority of patients develop anti-drug antibodies regardless of CRIM status. CRIM negative and CRIM positive patients who develop high sustained anti-drug antibody titers have poorer prognosis than CRIM positive patients with low antibody titers.⁴

There are currently two approved enzyme replacement therapies (ERT) indicated for Pompe disease: Myozyme and Lumizyme. Both are recombinant human GAA (rhGAA) but made on different bioreactor scales. Myozyme, made on a 160-L scale, was the first treatment approved in 2006 for Pompe disease. The clinical trial that supported marketing approval demonstrated

¹ <http://pompe.com/en/healthcare-professionals/genetics-epidemiology/incidence-prevalence.aspx>

² <http://www.ninds.nih.gov/disorders/pompe/pompe.htm>

³ Hirschhorn R, Arnold J, Reuser J. Glycogen Storage Disease Type II: Acid Alpha-Glucosidase (Acid Maltase) Deficiency. The Metabolic and Molecular Bases of Inherited Disease. 8th Edition. New York: McGraw-Hill; 2001; 3389-3420

⁴ Banugarua, S, et al. The impact of antibodies in clinical outcomes in diseases treated with therapeutic protein: Lessons learned from infantile Pompe disease. Genet Med 2011;13(8):729-736

markedly improved ventilator-free survival in infantile-onset Pompe patients treated with rhGAA enzyme compared to historical, untreated controls.⁵ The label states that Myozyme has not been adequately studied in other forms of Pompe disease. In 2010, Lumizyme, made on a 4000-L scale, was approved for treatment of juvenile/adult onset Pompe disease based on improvements in 6 minute walk test and forced vital capacity compared to placebo.⁶ Refer to Section 2.5 below for details on the regulatory history.

2.1 Product Information

Lumizyme is a human recombinant lysosomal glycogen-specific enzyme, acid α -glucosidase or alglucosidase alfa (rhGAA), and is produced by recombinant DNA technology in the Chinese hamster ovary cell line. GAA degrades glycogen by catalyzing the hydrolysis of α -1,4- and α -1,6- glycosidic linkages of lysosomal glycogen.⁶ Currently, Lumizyme is approved for the treatment of patients with late (non-infantile) onset Pompe disease who are 8 years and older and who do not have evidence of cardiac hypertrophy. In this efficacy supplement, the applicant proposes to expand the indication of Lumizyme to all patients with Pompe disease.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1: Current Therapies with Approved Indications for Treatment of Pompe Disease

	Myozyme	Lumizyme
Name	Human recombinant Alglucosidase alfa (rhGAA)	Human recombinant Alglucosidase alfa (rhGAA)
Indication	Pompe patients	Juvenile/adult onset Pompe patients > 8yo
Approval date	April 28, 2006	May 24, 2010
Primary Endpoints	Overall survival, Ventilator free survival (infantile-onset patients)	6 minute walk test, Forced Vital Capacity (late-onset patients)
Secondary endpoints	Left ventricular mass index, muscle strength, developmental milestones, pulmonary function tests	Muscle weakness measured by quantitative muscle testing, maximum inspiratory/expiratory pressure
Bioreactor scale	160 L	4000 L

⁵ Kishnani PS, et al. Recombinant human acid alfa-glucosidase: Major clinical benefits in infantile-onset Pompe disease. *Neurology* 2007; 68:99-109.

⁶ Approved Lumizyme label, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125291s0063lbl.pdf, last updated 7/9/2012, accessed 6/30/2014.

2.3 Availability of Proposed Active Ingredient in the United States

In 2006, Myozyme (160 L) was the first therapy approved for the treatment of Pompe patients. In 2010, Lumizyme, made on a 4000 L bioreactor scale, was approved for treatment of juvenile/adult onset Pompe disease based on improvements in 6 minute walk test and forced vital capacity compared to placebo.⁶ At the time of the Lumizyme approval, chemical comparability was not established between Myozyme (160 L) and the larger scales of alglucosidase alfa. Therefore, the indication for Lumizyme could not be extended to infantile-onset Pompe patients. Patients with infantile-onset Pompe disease or patients who are younger than 8 years of age with Pompe disease are treated with Myozyme (160 L) in the United States. However, due to ongoing drug shortages of the 160 L product, patients who are ≥ 12 months of age, previously treated with the 160 L product, are being switched to Lumizyme (4000 L), and are treated as part of an ongoing phase 4, open-label, prospective trial to evaluate the efficacy and safety of alglucosidase alfa produced at the 4000 L scale (AGLU09411, ADVANCE). Refer to Section 2.5 below for a detailed regulatory history of these products.

Of note, alglucosidase alfa that is manufactured at the 4000 L scale is approved for the treatment of Pompe disease, regardless of phenotype, in over 70 countries outside of the United States. Myozyme is the trade name for the 4000 L product outside of the United States.

2.4 Important Safety Issues with Consideration to Related Drugs

Enzyme replacement therapies are highly immunogenic; therefore, anti-drug antibody formation, including development of neutralizing antibodies, is the primary safety concern associated with this therapeutic class. Patients who develop antibodies may experience anaphylaxis and hypersensitivity reactions or decreases in efficacy, depending on the type of antibody (IgE vs. anti-GAA IgG). For example, the majority of patients in the clinical trial that supported marketing approval for Myozyme tested positive for IgG to GAA (up to 89%) and up to 14% experienced hypersensitivity reactions.⁷ Furthermore, 100% of the patients in the Late-onset Pompe Study (LOTS trial) that supported approval of Lumizyme developed IgG to GAA.

Immunogenicity is also related to prognosis in this patient population. Cross reactive immunologic material (CRIM) status is important in management and prognosis, as it influences development of antibodies and treatment outcomes. CRIM negative patients and CRIM positive patients who develop high sustained antibody titers have poorer prognosis than CRIM positive patients with low antibody titers.⁸ Of note, the majority of patients develop antibodies regardless of CRIM status.

The labels for enzyme replacement therapies, including Myozyme and Lumizyme, contain a boxed warning that states that life-threatening anaphylaxis and severe allergic and immune-

⁷ Approved Myozyme label, available at <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>. Myozyme labeling and approval documentation. Last approved 7/9/2012, last accessed 6/30/2014.

⁸ Banugarua, S, et al. The impact of antibodies in clinical outcomes in diseases treated with therapeutic protein: Lessons learned from infantile Pompe disease. Genet Med 2011;13(8):729-736.

mediated reactions are associated with these drugs. In addition, since patients with classic infantile-onset Pompe disease have impaired cardiorespiratory function, the boxed warning for Myozyme contains a statement on the risk of cardiorespiratory failure for patients with compromised cardiac or respiratory function.⁷

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

Regulatory timeline:

April 2006: Myozyme, manufactured on a 160 L bioreactor scale, was approved as the first available treatment for Pompe disease. Approval was based primarily on one clinical trial of eighteen infants with infantile-onset Pompe disease and demonstrated significantly improved overall survival and ventilator-free survival at 18 months of age when compared to an untreated historical cohort. Since approval, there have been continued problems with manufacturing ability to maintain the necessary supply of Myozyme, resulting in drug shortages.

May 2008: Genzyme submitted BLA 125291 for approval of Lumizyme, produced on a 2000 L bioreactor scale. The data to support marketing approval were obtained from one multicenter, double-blind, placebo-controlled trial of 90 late-onset Pompe patients (Late Onset Pompe Study, "LOTS"). The efficacy endpoints were 6-minute walk test (6MWT) and percent predicted forced vital capacity (FVC). (b) (4)

Therefore, chemical comparability was not established between the 160 L and 2000 L products. In parallel with the BLA submission, Genzyme was developing a linear scale-up to produce a 4000 L product.

October 21, 2008: An Endocrinology and Metabolic Drugs Advisory Committee (EMDAC) was convened and accelerated approval was recommended under 21 CFR 601 Subpart E, based on improvement in percent predicted FVC for treatment of patients with late (non-infantile) onset Pompe disease, ages 8 years and older, who do not have evidence of cardiac hypertrophy. In addition, the committee recommended a REMS and post-marketing safety studies to evaluate the risk of anaphylaxis, the impact of immunogenicity, and potential chronic immune-mediated reactions. However, accelerated approval was not granted and 2000 L product was never approved in the United States due to manufacturing problems that arose after the AC meeting.

February 27, 2009: A Complete Response (CR) action was taken and a Warning Letter was issued by FDA's Office of Compliance for CGMP deficiencies identified during a 2008 inspection of the Allston Landing, MA manufacturing facility. Genzyme responded to the CR letter on May 15, 2009; however, deficiencies were again noted during the inspection and another CR letter was issued on November 13, 2009 with the same recommendation to withhold approval. Multiple discussions between the FDA and Genzyme occurred, and FDA encouraged Genzyme to submit CMC information on the 4000 L product since the 4000 L product was

manufactured in the Geel, Belgium facility, not in Allston Landing, MA. A response to the second CR letter was submitted to the FDA on December 16, 2009.

May 24, 2010: Based on review of the physicochemical comparability data included in the second Complete Response submission, FDA determined that the 2000 L product used in the LOTS trial was comparable to the new 4000 L product. Furthermore, the new 4000 L product contained improvements in the critical chemical attributes over the 2000 L product. Therefore, additional clinical trials using the 4000 L product were considered unnecessary. Lumizyme, produced on a 4000 L bioreactor scale, was approved for patients with late onset Pompe disease 8 years and older. However, safety and efficacy had not been demonstrated for patients with infantile-onset Pompe or for patients younger than 8 years of age with late-onset Pompe.

November 17, 2010: A Type C meeting was held to discuss expanding the Lumizyme indication to patients younger than 8 years of age. The Agency did not agree that data from the Pompe Registry *alone* was sufficient to demonstrate efficacy in this population. Previously, survival data in Lumizyme (2000 L) treated infantile-onset patients from the Pompe Registry were accepted in the original approval of Lumizyme (BLA 125291) because the data were used to support the findings from the Late Onset Treatment Study (LOTS), and provide further evidence of the safety and efficacy of Lumizyme (2000 L) for the treatment of Pompe patients ≥ 8 years of age, without the need for an additional clinical trial. However, as described previously in this section, the 2000 L product was not approved due to concerns that the biochemical differences between Myozyme (160 L) and Lumizyme (2000 L) may lead to decreased efficacy. In May 2010, the 4000 L product, which contained improvements in the chemical attributes, was approved for patients ≥ 8 years of age with late-onset Pompe disease. Therefore, since clinical data on survival of infantile-onset patients treated with Lumizyme (4000 L) had not been collected outside of the Pompe Registry, the Agency recommended a randomized, double-blind, parallel dose study comparing Myozyme (160 L) and Lumizyme (4000 L) in treatment naïve infant-onset and late-onset patients less than 8 years of age to be conducted over a time period to evaluate meaningful differences in these populations. Genzyme has had significant challenges with enrollment for this clinical trial given that there is an approved therapy for Pompe patients who are younger than 8 years of age (Myozyme). At the time of this review, one patient had been enrolled.

March 2012: Ongoing drug shortages of the 160 L product led to restriction of 160 L to patients < 12 months of age. All Pompe patients who are ≥ 12 months of age previously treated with the 160 L product are switched to the 4000 L under study AGLU09411 (ADVANCE).

Feb. 19, 2013: Type C meeting was held to discuss a path forward to expand the indication of Lumizyme to all patients with Pompe, given the ongoing drug shortages of Myozyme (160 L). Genzyme and the Division discussed potential sources of data that could be included in an efficacy supplement to expand the indication of Lumizyme (4000 L) to all Pompe patients. The Division recommended that Genzyme submit an analytical comparability package to establish chemical comparability between the 160 L and 4000 L products that is supported by clinical data showing survival in infantile-onset patients who have received treatment with the Lumizyme

(4000 L). In addition, safety data could be obtained from postmarketing data and the ongoing ADVANCE trial. These discussions led to the request for a pre-sBLA meeting.

July 8, 2013: The Division provided written feedback, at the applicant's request, to pre-sBLA meeting request. The Division recommended that an efficacy supplement containing the following data might be adequate to support expansion of the Lumizyme indication.

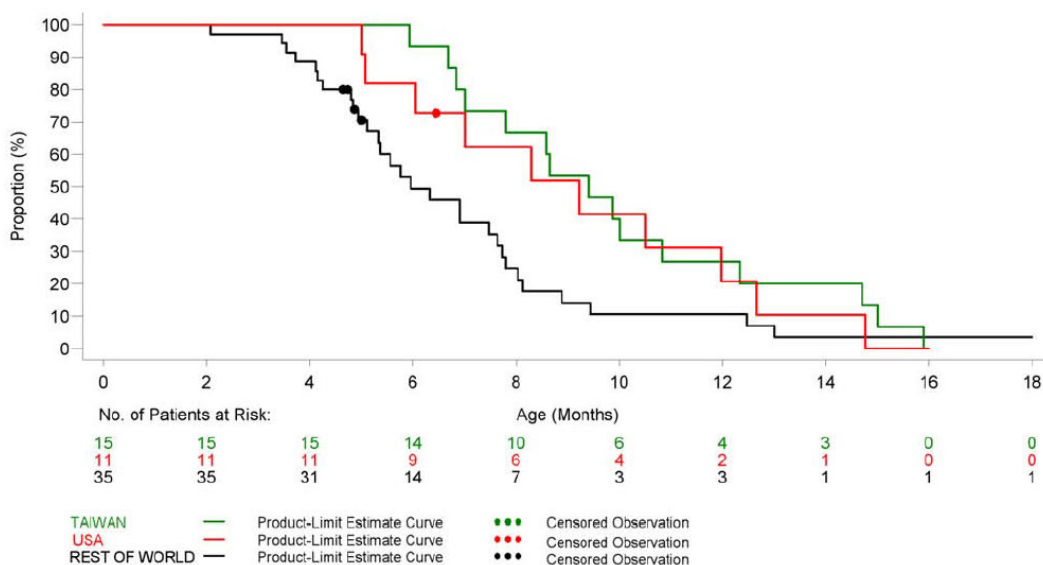
- Data to establish analytical comparability between 160 L and 4000 L products.
- Supportive clinical data (overall survival and ventilator-free survival) from an ongoing investigator-sponsored study from Taiwan in infantile-onset patients with comparison to the original cohort of infantile-onset patients (with matched inclusion criteria) from trials that supported marketing approval of Myozyme.
- Safety data from the ongoing switch-over trial (ADVANCE) and from available longer-term postmarketing data.

2.6 Other Relevant Background Information

Applicability of data from the Taiwan01 Trial to the U.S. Population

The applicant provided data to support the applicability of foreign data to the U.S. population. The natural history study (AGLU004) included 62 patients identified who met the inclusion criteria for ALGU01602 and was used to provide an untreated cohort for comparison to the AGLU01602 trial that supported the approval of Myozyme. Of the 62 patients, 15 patients were from Taiwan and 11 patients were from the United States. There was a 12th patient from the United States but the date of death was unknown; therefore, this patient was excluded from the analysis. The patients from Taiwan and the United States exhibited similar outcomes and all died prior to 18 months of age. Refer to Figure 1: Kaplan-Meier Estimates of Patients Who Were Alive and Free of Invasive Ventilator Support from Birth to 18 Months of Age - Natural history patients. This finding supports that the natural history of disease progression is similar for infantile-onset patients in Taiwan and the United States, regardless of geographic location and ethnicity.

Figure 1: Kaplan-Meier Estimates of Patients Who Were Alive and Free of Invasive Ventilator Support from Birth to 18 Months of Age - Natural history patients



(Source: applicant's response to March 19, 2014 IR, dated 4/2/2014, module 1.2 Safety Information Amendment, page 4/26)

Figure 1 above illustrates that the natural history of disease progression is similar between infantile-onset patients in Taiwan and the United States. Therefore, the supportive clinical data from the Taiwan01 trial are suitable for comparison to the data from trials that supported approval of Myozyme in the United States and are generalizable to the U.S. population of infantile-onset patients.

Additionally, clinical sites from Taiwan, including the clinical site where the Taiwan01 trial was conducted, are enrolled in the Pompe Registry and follow the recommended schedule of assessments for Pompe patients. The Pompe Registry involves a standard schedule of assessments, which is consistent globally, and in line with current treatment guidelines. The applicant also supports annual training courses, including the Asia-Pacific Conference of Lysosomal Storage Disease and Physician Training, which is consistent with the training held in the U.S. to support consistent global management of patients with Pompe disease.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Appropriately organized data sets were provided for efficacy and safety populations.

3.2 Compliance with Good Clinical Practices

The applicant stated that the studies were conducted in accordance with the Institutional Review Board (IRB) and/or Independent Ethics Committee (IEC), and in accordance with Good Clinical Practice (GCP) as defined by the International Conference on Harmonization (ICH) Guideline Topic E6 entitled “Guideline for Good Clinical Practice.” Taiwan01, an investigator-sponsored study conducted at a single center in Taiwan, received approval from the Institutional Review Board (IRB) of the National Taiwan University Hospital (NTUH). The investigator obtained informed consent from parents/guardians prior to enrollment.

Clinical Site Inspections:

A clinical site inspection for the clinical site in Taiwan (Taiwan01) was performed. Based on the findings from the FDA field investigator, the medical reviewer concluded that the trial appeared to have been conducted adequately and the data generated by this site may be used in support of the respective indication. Refer to Clinical Inspection Summary by Dr. Susan Leibenhaut, dated June 27, 2014, for details.

Protocol Deviations: Protocol deviations are not applicable to the Taiwan01 trial since patients in the Taiwan01 trial were followed under an investigator-sponsored trial at the National Taiwan University Hospital and the trial was not conducted under a pre-specified protocol under an IND. Protocol deviations for trial AGLU09411 are discussed in Section 7.4.5 Special Safety Studies/Clinical Trials.

3.3 Financial Disclosures

The applicant adequately disclosed financial arrangements with the clinical investigators from the Taiwan01 and AGLU09411 (ADVANCE) trials. The investigators who participated in study Taiwan01 stated that they did not enter into any financial agreement. (b) (4)

Of note, the newborn screening program was developed and initiated prior to FDA’s suggestion that these data from Taiwan could be used in this sBLA application. Three investigators from AGLU09411 disclosed financial arrangements. These arrangements do not raise concern over the integrity of the data. See Appendix for further details.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Chemistry reviewer has determined that the quality product critical attributes are comparable between Myozyme (160 L) and Lumizyme (4000 L), both manufactured by Genzyme. The historical and head-to-head release and characterization results were comparable for activity, purity, and 1°, 2°, 3° structure-indicating tests (i.e., no differences in receptor binding affinity, kinetic parameters and aggregation levels are comparable, and no differences in protein structure and product-related impurity tests). Process-related impurities were the same or lower for

Lumizyme 4000 L. There were minor, expected differences in

(b) (4)

Refer to CMC review by Christopher Downey for details.

4.2 Clinical Microbiology

The formulation and dosing of Lumizyme remained the same as previously approved. There are no additional concerns.

4.3 Preclinical Pharmacology/Toxicology

No new preclinical pharmacology/toxicology studies were submitted because Lumizyme is already approved and marketed. See pharmacology/toxicology review by Fang Cai, dated July 8, 2014, for details on labeling recommendations.

4.4 Clinical Pharmacology

No new clinical pharmacology information was submitted in this application.

4.4.1 Mechanism of Action

Lumizyme (alglucosidase alfa) is an enzyme replacement therapy, which consists of the human enzyme acid α -glucosidase (GAA). Lumizyme binds to mannose-6-phosphate receptors on the cell surface, after which it is internalized and transported into lysosomes, then undergoes proteolytic cleavage that results in increased enzymatic activity. It then exerts enzymatic activity in cleaving glycogen. Alglucosidase alfa degrades glycogen by catalyzing the hydrolysis of α -1,4- and α -1,6- glycosidic linkages of lysosomal glycogen.

4.4.2 Pharmacodynamics

New clinical pharmacodynamic studies have not been conducted for Lumizyme.

4.4.3 Pharmacokinetics

No new pharmacokinetic studies were conducted for Lumizyme. The reader is referred to the Clinical Pharmacology review by Christine Hon, dated July 8, 2014, for additional details.

5 Sources of Clinical Data

This efficacy supplement contains analytical comparability data and supportive clinical data from three sources listed below.

- Taiwan01: an investigator-sponsored clinical trial conducted at a single site in Taiwan to evaluate the safety and efficacy of alglucosidase alfa at the larger scales (2000 L and 4000 L) in the treatment of patients with infantile-onset Pompe disease in comparison to survival data from the trials that supported marketing approval of Myozyme (160 L), AGLU01602/AGLU02403, and the untreated natural history cohort (AGLU00400).
- AGLU09411 (ADVANCE): an ongoing, open-label, prospective clinical trial in the United States in infantile-onset patients and late-onset patients less than 8 years of age who previously received Myozyme (160 L) and switched to Lumizyme (4000 L) at ≥ 12 months of age. Since March 2012, Genzyme has offered patients to enroll into this clinical trial to allow continued treatment with Lumizyme (4000 L) during ongoing drug shortages of Myozyme (160 L); Myozyme (160 L) is currently restricted to patients less than 12 months of age in the United States.
- Safety data listings from available post-marketing data on all patients treated with larger scales of alglucosidase alfa.

Study AGLU01602 was an open-label, multicenter, multinational, dose-ranging study of the safety, efficacy, pharmacokinetics, and pharmacodynamics of recombinant human acid alpha-glucosidase (rhGAA) treatment in patients ≤ 6 months old with infantile-onset Pompe disease. Study AGLU02403 was a long-term extension study of patients with infantile-onset Pompe disease who were previously enrolled in study AGLU01602.

Study AGLU00400 was a multicenter, multinational, natural history study of 168 patients diagnosed with infantile-onset Pompe disease, who had symptom onset within their first year of life and received only palliative and supportive care. A historical control subgroup of 62 patients was selected from the entire cohort who participated in the AGLU00400 study based on matching inclusion and exclusion criteria of study AGLU01602. This cohort of 62 patients was used as the control population, and their survival was compared to the severe infantile-onset patients who were treated with Myozyme in Study AGLU01602.

5.1 Tables of Studies/Clinical Trials

Table 2: Summary of Studies/Clinical trials

Study#	Objective	Study Design	Dosage regimen	N patients	Diagnosis of Patients	Duration of Treatment	Type of Report
Trial for Efficacy and Safety Evaluation							
Taiwan 01	Safety and efficacy	Investigator Sponsored, Open-Label	Lumizyme 20 mg/kg IV Every other week*	25 (18 Infantile-Onset Patients)	Pompe disease	Ongoing	Ongoing Interim Report

Trial for Safety Evaluation							
AGLU 09411	Safety and efficacy	Phase 4, open-label, prospective switch-over	Same dose and dose regimen used prior to enrollment into the trial	99	Pompe disease	Ongoing	Ongoing Interim Report
Controlled Trials of alglucosidase alfa for comparison of efficacy and safety							
AGLU 01602	Long-term safety and efficacy	Phase 2/3, randomized, open label, historically controlled, dose ranging	Myozyme 20 mg/kg or 40 mg/kg IV Every other week	18	Infantile-onset Pompe disease	52 weeks	AGLU 01602 Legacy Data Sets
AGLU 02403	Long-term safety and efficacy	Phase 2/3, randomized, open label, historically controlled, dose ranging	Myozyme 20 mg/kg or 40 mg/kg IV Every other week	16	Infantile-onset Pompe disease	52 weeks repeated	AGLU 02403 Legacy Data Sets
AGLU 004-00	Natural History of Infantile-onset Pompe Disease	Epidemiological	NA	62	Infantile-onset Pompe disease	NA	AGLU 0400 Legacy Data Sets

(Source: reviewer's table adapted from applicant's submission, BLA 125291/136, dated 1/30/14, Module 5.2 Tabular Listing of All Clinical Studies)

*See Section 5.3.1 for a discussion of Study Treatments.

5.2 Review Strategy

In addition to the CMC analytical comparability package, supportive clinical data from two clinical trials (Taiwan01 and AGLU09411) and postmarketing safety reports were submitted in this efficacy supplement. The three sources of clinical data will be reviewed separately.

- 1) Taiwan01 provides the main source of supportive clinical efficacy data to support ventilator-free survival in infantile-onset Pompe patients treated exclusively with the larger scales of alglucosidase alfa, and compares the efficacy outcomes from the trials that supported marketing approval of Myozyme (160 L), AGLU1602/AGLU02403. As previously agreed upon with the Division, the patients who were included in the Taiwan01 efficacy analysis were required to meet the same inclusion criteria as the patients enrolled in AGLU1602/AGLU02403 to allow for comparison of survival. However, the applicant provided two analysis datasets: patient enrolled set and full analysis set (see section 5.3.1 below). The patient enrolled set contains an additional 7 patients who did not meet the inclusion criteria of AGLU01602. Since only the full analysis

dataset contains the patients who met the same inclusion criteria as patients in AGLU01602, this review will focus on the patients in the full analysis dataset from the Taiwan01 trial. A review of the efficacy analysis will be provided in Section 6 of this document. A review of the safety analysis will be provided in Section 7 of this document.

- 2) Only the safety and immunogenicity data will be reviewed for AGLU09411, a switch-over trial, since the absence of a concurrent control arm (placebo or active comparator) makes interpretation of a treatment effect extremely difficult. The rate of glycogen accumulation over time and its relationship to clinical outcome in Pompe patients who discontinue ERT or switch from one ERT to another have not been established. Furthermore, the duration of treatment required to observe clinical benefit is not known when patients switch from one ERT to another ERT. If this sBLA is approved, patients who are already receiving treatment with Myozyme would be switched to Lumizyme. Therefore, AGLU09411 provides useful, real-world, clinical safety and immunogenicity data. A brief description of the study design will be included in Section 5.3 and a review of the safety and immunogenicity data will be included in Section 7 of this document.
- 3) A summary of the available postmarketing safety data was provided for serious adverse events, hypersensitivity reactions, and deaths for all patients treated with the larger scales of alglucosidase alfa. The postmarketing safety data will be reviewed in Section 8 of this document.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Taiwan01

The goal of this trial is to compare ventilator-free survival outcomes of patients with infantile-onset Pompe disease who were treated exclusively with the larger scales of alglucosidase alfa to survival outcomes of infantile-onset patients who were treated with Myozyme (160 L).

Title: Interim Report of Ongoing Taiwan Investigator-Sponsored Study: A Long Term Follow-Up of Pompe Disease

Study Objectives

Primary Objective:

To estimate the proportion of patients with classical infantile-onset Pompe disease in Taiwan treated with alglucosidase alfa manufactured at the larger scales (2000 L/4000 L) who are alive and free of invasive ventilator support at 18 months of age as compared to patients in the trials that supported marketing approval of Myozyme (160 L) (AGLU01602/2403) and the natural historical study (AGLU00400).

Secondary Objective:

To evaluate the safety of the larger scale of alglucosidase alfa based on adverse events spontaneously reported to the Genzyme Pharmacovigilance and Epidemiology Department, laboratory assessments, and immunogenicity.

Study Design: An open-label, single-center, investigator-sponsored trial that was developed to monitor cases of Pompe disease identified through the National Taiwan University Hospital (NTUH) newborn screening program, and to compare their prognosis to the clinically identified cases in Taiwan. Infants with positive screening results for Pompe disease were referred to the NTUH for diagnostic confirmation. For those patients receiving alglucosidase alfa, similar assessments were completed as in the trials that supported marketing approval of Myozyme (160 L), AGLU01602/2403, and the Pompe Registry, focusing on ventilator and survival outcomes.

Study Population: As previously agreed upon with the Division, the inclusion criteria for patients from Taiwan01 must meet the protocol inclusion criteria for the AGLU01602 trial. Specifically, enrolled patients must have a diagnosis of classical infantile-onset disease with evidence of cardiac hypertrophy and should have initiated treatment with alglucosidase alfa at the larger scale prior to 6 months of age.

Study Treatments: The intent was to treat patients with dose and duration of alglucosidase alfa that reflect current standard of care (20 mg/kg IV infusion every other week). Patients were categorized as having received the standard 20 mg/kg every other week regimen if they continued to receive that dose throughout the trial. Otherwise, they were categorized as “Others.” Patients in the “Others” dose group also included patients who switched to other dosing regimens during the trial even if they received the 20 mg/kg every other week at the first infusion or any subsequent infusions.

Procedures/Safety Considerations/Monitoring:

Baseline visit:

- Demographics
- Baseline disease characteristics
- Pompe disease history
- Method of diagnosis
- Phenotype (Infantile-onset or Late-onset)
- Genotype and CRIM status
- GAA activity

During the first year (52 weeks), study visits occurred every 2 weeks. In the subsequent years of the study (2 to 18 years), study visits occurred every 6 months. When available, the following data were collected during every study visit:

- Myozyme infusions, including date of first infusion, the dose administered for each infusion, the frequency, and dose changes where applicable
- Patient status (Alive or Deceased)
- Ventilation status including type and number of hours on ventilatory support
- Laboratory assessments of AST, ALT, and CK

- Adverse event data that were reported spontaneously to Genzyme by the Investigator, similarly to other post-marketing data
- Anti-rhGAA antibodies as available to Genzyme through Genzyme's clinical immunology testing service (Genzyme Clinical Specialty Laboratory)
- Additional laboratory testing for complement activation, serum tryptase, anti-rhGAA immunoglobulin E (IgE), skin testing, and circulating immune complexes was recommended for IARs suggestive of hypersensitivity reactions.

In general, Taiwan01 trial followed the schedule of assessments from ALGU01602. Refer to section 9.4 Appendix Figure 6: Taiwan01 Study Schedule of Events: First Year of the trial and Figure 7: Taiwan01 Study Schedule of Events: Years 2-18 of the Trial.

Efficacy Endpoints:

Primary Efficacy Endpoints:

- The proportion of classical infantile onset Pompe patients treated with the larger scales of alglucosidase alfa in Taiwan who are alive and free of invasive ventilator support at 18 months of age with comparison to survival/ventilator-free survival of infantile-onset Pompe patients enrolled in AGLU01602/2403 and the natural history cohort from AGLU00400
- Survival of classic infantile-onset patients from the Taiwan cohort at 18 months

Secondary Efficacy Endpoints:

- Association of cross-reacting immunologic material (CRIM) status, antibody response, genotype, and enzyme activity level with invasive ventilator-free survival
- Muscle glycogen levels at baseline and 6 months post-treatment from muscle biopsies.

Planned Methods of Analysis: The sample size was not determined based on statistical power for this investigator-sponsored trial. For efficacy analysis, p-values less than 0.05 were considered statistically significant. No formal statistical analyses were performed for safety data.

Analysis datasets:

- Full Analysis (FA) Set: a subset of 18 patients out of the 25 patients enrolled in the Patient Enrolled (PE) dataset who satisfied the inclusion criteria for AGLU01602 (classic infantile-onset Pompe disease with evidence of cardiac hypertrophy, treatment initiated prior to 6 months of age, and received at least 1 infusion of alglucosidase alfa at the larger scales without previous exposure to the 160L scale of alglucosidase alfa).

The primary efficacy analysis estimated the proportion of patients treated with alglucosidase alfa who were alive and free of invasive ventilator support at 18 months of age using the Kaplan-Meier method for the 18 patients enrolled in the Taiwan01 trial who met the inclusion criteria for AGLU01602/02403, and the results were compared to patients enrolled in the AGLU01602/2403 trials and the untreated historical cohort in AGLU00400. The Kaplan-Meier estimation included

adjustment for left-truncated data by including patients based on the start date of alglucosidase alfa treatment. This adjustment is not applicable to the historical cohort because patients in AGLU00400 were not treated with alglucosidase alfa and the data were retrospectively collected. In addition, ventilator support data were not available for the historical cohort (AGLU00400), so the percentage of patients alive at specific time points in the historical cohort could reflect an overestimate of the primary efficacy endpoint (alive and free of invasive ventilation) since it also includes patients who are receiving invasive ventilator support. Patients who dropped out or had missing data were treated as censored observations.

For the clinical data analysis, the follow-up duration of a patient was defined as the number of months between the date of first infusion and the data cut-off date of March 15, 2013, if the patient was alive. For deceased patients, the duration in the trial was the number of months between the date of first infusion and the date of death. Since many of the patients included in the Taiwan01 trial were identified through newborn screening, it is important to note that these patients have likely been on alglucosidase alfa treatment since birth or shortly thereafter. However, immunogenicity data and adverse event (AE) data spontaneously reported to Genzyme were analyzed based on the cut-off date of June 30, 2013.

Sensitivity Analysis included the following:

- Repeating the Kaplan-Meier estimation and the proportional hazards regression using all available follow-up. For this analysis, there was no censoring of missing data at a specific time point.

Subgroup Analyses:

Subgroup analyses were planned since certain factors (e.g., dosing regimen, drug production scale, genotype, baseline GAA enzyme activity level, anti-drug antibody status) could influence invasive ventilator-free survival. To assess associations between these factors and invasive ventilator-free survival, Kaplan-Meier estimates of invasive ventilator-free survival were generated for the subgroups. For the purpose of the subgroup analysis, patients were classified as having received “4000 L Alone” versus “Others” (patients who received only 2000 L and died before 4000 L became available or who received 2000 L initially and later switched to 4000L when it became available). Patients whose first drug infusion date was after the first shipment (September 7, 2009) of 4000 L drug product to Taiwan were considered as having received the 4000 L drug product alone. Even though it was possible that some of the patients in this group could have received a small number of infusions with the 2000 L drug product, it was considered insignificant given that the patients had been receiving 4000 L drug product for approximately 3.5 years up to the data cut-off date of March 15, 2013.

Analyses were performed on the following subgroups:

- Dosing regimen: 20 mg/kg every other week (qow) versus Others (20 mg/kg weekly or 40 mg/kg every other week)
- Drug production scale: 4000 L alone versus Others (patients who received only 2000 L and died before 4000 L became available or who received 2000 L initially and later switched to 4000 L when it became available)

- Classification of Genotype: Missense/Missense, Missense/Frameshift, Missense/In-frame Deletion, Missense/Nonsense, and Missense/Splice site
- GAA Enzyme Activity Level at Baseline: Above versus Below Median (0.94 nmol/hr/mg protein)
- Status of Inhibitory/Neutralizing Antibody: Positive versus Negative

Analyses were also planned for patient CRIM status (positive or negative), but these analyses were not performed as all enrolled patients in Taiwan01 were CRIM-positive.

Safety Analysis:

Safety data were reported spontaneously to Genzyme by the Investigator in a manner similar to other post-marketing data. Adverse events were not collected at pre-specified time points as part of the Taiwan01 trial since patients were assessed for adverse events throughout the trial according to clinical practice (see section 9.4 Appendix Figure 6: Taiwan01 Study Schedule of Events: First Year of the trial and Figure 7: Taiwan01 Study Schedule of Events: Years 2-18 of the Trial). Spontaneous treatment-emergent AEs (TEAEs) were defined as events with start dates on or after the date of the first dose of alglucosidase alfa. Serious adverse events (SAEs) were reported to Genzyme Global Pharmacovigilance and Epidemiology Department within 24 hours of the Investigator's first knowledge of the event, regardless of whether the event appeared to be related to the study drug.

The safety analysis set was the same as the FA set.

Safety Events of Special Interest:

- Infusion-associated reactions (IARs)
 - Defined as AEs that occurred during the infusion or post-observation period (≤ 2 hours) following the infusion. AEs that occurred after the post-infusion observation period and were assessed as related to alglucosidase alfa were also considered IARs.
- Anaphylactic Reactions
 - Defined as severe, potentially fatal (life-threatening) systemic allergic reaction that occurred suddenly after contact with an allergy-causing substance (applicant cites Sampson, et al⁹). Reactions may include, but are not limited to, symptoms and signs of anaphylactic shock, circulatory collapse, severe hypotension, and IgE-mediated hypersensitivity reactions. Symptoms may include, but are not limited to, bronchospasm, generalized hives, angioedema, hypotension, and/or pruritus with skin rash.
- Immune-Mediated Reactions

⁹ Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report-- Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117(2):391-7

- Defined as local or systemic disease caused by the formation of circulating immune complexes and their deposition in tissues or vascular endothelium. Reactions are self-limited and usually develop within 7-10 days of antigen exposure, starting with constitutional flu-like symptoms of fever, myalgia, arthralgia, and rash.

Immunogenicity Assessments:

All immunological testing was performed by the Genzyme Clinical Specialty Laboratory and was performed at the request of the Investigator in the post-marketing setting. A positive test was based on ELISA and confirmed by radioimmunoprecipitation (RIP). Patient immunoglobulin G (IgG) antibody titer values were determined based on 3 sources of information:

- IgG antibody test result (positive or negative)
- the actual titer value
- the result of RIP (positive or negative).

If an actual titer value was not reported and the result of IgG antibody test or if RIP was negative, then the titer value was assigned as 0.

The following antibody assessments were performed:

- Anti-rhGAA IgG antibody seroconversion status
- Anti-rhGAA IgG antibody time to seroconversion
- Anti-rhGAA IgG antibody titer value
- Anti-rhGAA IgG antibody peak titer value
- Anti-rhGAA IgG antibody last titer value reported for a patient during the study
- IgG inhibitory (neutralizing) antibody to rhGAA
 - both inhibition to enzyme activities and enzyme uptake were tested

Additional immunogenicity assessments:

- Complement activation
- Serum tryptase
- anti-rhGAA immunoglobulin E (IgE)
- Skin testing
- Circulating immune complex testing was recommended for hypersensitivity reactions

5.3.2 AGLU09411(ADVANCE)

As explained above in Section 5.2, only the safety and immunogenicity data will be reviewed for AGLU09411, a switch-over trial, since the absence of a concurrent control arm (placebo or active comparator) makes interpretation of a treatment effect extremely difficult. Therefore, the AGLU09411 data reviewed in this document are intended to provide safety data, and not efficacy data.

AGLU09411 (ADVANCE) is an ongoing, phase 4, open-label, prospective 52-week trial in patients with Pompe disease to evaluate the efficacy and safety of alglucosidase alfa produced at the 4000 L scale (Lumizyme) in Pompe patients previously treated with 160 L alglucosidase alfa (Myozyme). Due to ongoing production constraints with Myozyme, AGLU09411 also allows for continuation of therapy with alglucosidase alfa. Patients in the United States who have a confirmed diagnosis of Pompe disease, are at least 1 year of age, and were previously treated with alglucosidase alfa at the 160 L scale are eligible for enrollment into the trial. Patients who are clinically unstable and not expected to survive for 52 weeks are excluded. Following the 52-week treatment period, patients have an opportunity to continue treatment with Lumizyme in an extension period until Lumizyme is approved by the FDA for treatment of all Pompe patients. Patients are to remain on a stable dose of alglucosidase alfa for the duration of the trial, if clinically feasible. Concomitant medications will be monitored throughout the trial. Patients will be allowed to continue on any medications, except Myozyme (160 L) since they will be switched to Lumizyme (4000 L) after enrollment into the trial.

Following participation in the AGLU09411 trial (including the extension treatment period), patients are transitioned to commercially available therapy with alglucosidase alfa and are also encouraged to participate in the Pompe Registry in order to assess long-term survival and other efficacy and safety parameters. An independent Data and Safety Monitoring Board (DSMB) is consulted as needed on an ad hoc basis as outlined in the DSMB Charter. An independent Allergic Reaction Review Board (ARRB) is consulted as needed on an ad hoc basis as outlined in the ARRB Charter.

Safety Assessments occurred at specified time points, as outlined in the Study Schedule of Events (section 9.4 Appendix Figure 8: AGLU09411: Study Schedule of Events):

- Physical exam
- Vital signs
- Clinical laboratory tests
 - Blood Chemistry: sodium, potassium, calcium, chloride, blood urea nitrogen, creatinine, uric acid, alanine aminotransferase, aspartate aminotransferase, total bilirubin, creatine kinase, creatine kinase with MB fraction, lactate dehydrogenase, alkaline phosphatase, total protein, albumin, glucose, phosphorus, gamma-glutamyl transpeptidase, brain natriuretic peptide
 - Hematology: complete blood count with differential and platelets, including hematocrit, hemoglobin, red blood cells, white blood cells, neutrophils, lymphocytes, monocytes, eosinophils, basophils
 - Urinalysis: urine color, appearance, specific gravity, pH, protein, glucose, ketones, bilirubin, hemoglobin, urine creatinine, and microscopy if indicated
- Electrocardiogram (12-lead ECG)

Immunogenicity Assessments:

- Anti-rhGAA antibody
- IgG inhibitory/neutralizing antibody
- Complement activation, serum tryptase, anti-rhGAA IgE

- Skin testing for patients who experience an infusion-associated reaction that is suggestive of IgE-mediated hypersensitivity reaction, with persistent symptoms of bronchospasm, hypotension, and/or urticaria requiring intervention OR any other signs or symptoms at the discretion of the Investigator. Skin testing may be another predictor of IgE-mediated reaction and may be suggested for confirmation of the IgE results.
- Circulating Immune Complex Detection for patients who exhibit evidence of symptoms suggestive of an immune complex disease (i.e., proteinuria).

Planned Methods of Analysis: For the purpose of this interim clinical report, only the safety results were provided. The safety analysis set consists of all patients who received at least 1 infusion of Lumizyme during the trial. Data were presented using summary tables, figures, and/or patient data listings. No formal hypothesis testing was planned.

6 Review of Efficacy

Efficacy Summary

Clinical data from the Taiwan01 trial were submitted as supportive evidence of clinical efficacy in addition to the CMC analytical data that established physicochemical comparability between Myozyme (160 L) and Lumizyme (4000 L). Given the ongoing drug shortages of Myozyme (160 L) and resulting restriction of Myozyme (160 L) to Pompe patients < 12 months of age, the Division agreed that demonstration of physicochemical comparability between the two products, further supported by convincing clinical data from the Taiwan01 trial, may be adequate to support the expansion of the Lumizyme indication to all Pompe patients. Lumizyme (4000 L) has been commercially available since 2010 outside of the United States for the treatment of all Pompe patients; therefore, ongoing clinical trials are scarce. Furthermore, the applicant has experienced significant difficulty recruiting for the requested phase 4 trial in the U.S., a head-to-head comparison of Myozyme (160 L) and Lumizyme (4000 L). The Taiwan01 trial was a single center, investigator-sponsored trial that was not designed to demonstrate efficacy of Lumizyme and intended to be an observational, prospective trial to describe the clinical outcomes of patients who were diagnosed by newborn screening compared to those who were diagnosed based on clinical symptom presentation. The investigator had collected data on clinical outcomes for infantile-onset patients who were treated exclusively with the larger scales of alglucosidase alfa. However, after review, the supportive clinical data were considered to be unnecessary due to the establishment of comparability; these data were requested a priori in the case that the comparability data left residual concerns about efficacy.

The intent of the clinical data from the investigator-sponsored clinical trial in Taiwan (Taiwan01) is to provide the efficacy data in infantile-onset Pompe patients treated exclusively with the larger scale of alglucosidase alfa that further supports chemical comparability between Myozyme (160 L) and Lumizyme (4000 L). The survival data from the Taiwan01 trial were compared to the survival data from the trials that supported the approval of Myozyme (160 L) (AGLU1602/AGLU02403) to determine whether efficacy and safety were similar between

Lumizyme (4000 L) and Myozyme (160 L). As previously agreed upon with the Division, the patients who were included in the Taiwan01 efficacy analysis were required to meet the same inclusion criteria as the patients enrolled in AGLU1602/AGLU02403 to allow for a comparison of survival outcomes between the Lumizyme (4000 L) treated patients and the Myozyme (160 L) patients. The primary efficacy endpoint for the survival comparison was invasive ventilator-free survival at 18 months of age. Invasive-ventilator free survival at 18 months was similar between the infantile-onset patients treated with Lumizyme (4000 L) and Myozyme (160 L). Of the 18 patients enrolled in the Taiwan01 trial who met the same inclusion criteria as patients enrolled in the AGLU01602/02403 trial, 2 were lost to follow up. Of the remaining 16 patients, 100% percent of patients in the Taiwan01 trial were alive and invasive ventilator-free at 18 months of age. In comparison, 15/18 (83.3%) of patients in AGLU01602/2403 and 1/61 (1.9%) of patients in the AGLU00400 historical cohort were alive and invasive ventilator-free at 18 months of age.

In the Taiwan01 and AGLU01602/2403 trials, some patients received doses other than the currently approved dose of 20 mg/kg every other week. The 18-month ventilator-free survival was assessed in patients who received only the approved dose of 20 mg/kg every other week. Of the 10 patients who received the 20 mg/kg every other week dose, 100% patients in the Taiwan01 trial were alive and invasive-ventilator free at 18 months vs. 8/9 (88.9%) patients in the AGLU01602/02403 trial who were alive and invasive-ventilator free at 18 months of age. Therefore, ventilator-free survival was similar between Myozyme (160 L) and Lumizyme (4000 L) treated-patients who were treated exclusively with the approved dose of 20 mg/kg every other week.

Although there was no significant difference between the Taiwan01 and AGLU01602/2403 cohorts in the percentage of patients who were alive and free of invasive ventilator support at 18 months of age, the apparent differences between the curves based on visual inspection at 18 months is likely related to the inclusion of more severely affected CRIM negative patients in AGLU01602/02403. Refer to Figure 2 in Section 6.1.4 Analysis of Primary Endpoints (s). All of the patients enrolled in the Taiwan01 trial were CRIM positive and the majority of the patients (14/18) in AGLU01602/2403 were CRIM positive. Of the 3 patients in AGLU01602/02403 who required invasive ventilation by the 18 month time point and failed the primary endpoint at 18 months, 2 patients were CRIM negative. In contrast, no patients in the Taiwan01 trial were CRIM negative. To determine whether the inclusion of CRIM negative patients in the AGLU01602/02403 trial influenced the results, the Statistical reviewer reanalyzed the primary efficacy endpoint excluding the CRIM negative patients from the AGLU01602/02403 trial. The results from the Taiwan01 trial were unchanged since all patients were CRIM positive; 100% of patients were alive and invasive ventilator-free at 18 months of age. However, when the 4 CRIM negative patients were excluded from AGLU1602/2403, the percent of patients who were alive and invasive ventilator-free at 18 months of age increased to 13/14 (92.9%) from 15/18 (83.3%). This was expected since classic infantile-onset CRIM negative patients are known to have the most severe form of Pompe disease. Poor outcomes are likely related to the disease severity rather than to the scale of alglucosidase alfa. Ventilator-free survival remained similar between Myozyme (160 L) and Lumizyme (4000 L) treated-patients.

Even though establishing efficacy was not the primary intent of the AGLU09411 (ADVANCE) trial, available efficacy data were requested from the applicant to further support the use of Lumizyme (4000 L) in infantile-onset patients, including clinical outcome data on CRIM negative patients and patients who are < 8 years of age who switched from Myozyme (160 L) to Lumizyme. AGLU09411 has a number of limitations with regard to its adequacy to support efficacy claims. For example, a switch-over trial design without a concurrent control arm (placebo or active comparator) makes it difficult to interpret the treatment effect of Lumizyme. The rate of glycogen accumulation over time and its relationship to clinical outcome in Pompe patients who discontinue ERT or switch from one ERT to another have not been established. Furthermore, the duration of treatment required to observe clinical benefit is not known when patients switch from one ERT to another ERT. However, upon approval of this supplemental BLA that will expand the indication of Lumizyme to all Pompe patients, patients in the United States who have been receiving treatment with Myozyme will likely be switched to Lumizyme. Therefore, AGLU09411 provides real-world, clinical data that are supplementary to the clinical efficacy data obtained in treatment-naïve Pompe patients. At the time of enrollment into the trial, there were 18/99 (18.2%) patients who were dependent on invasive ventilation. There were 34 infantile-onset patients with documented CRIM status: 10 patients were CRIM negative and 24 patients were CRIM positive. At entry into the trial, 5/10 (50.0%) CRIM-negative patients and 8/24 (33.3%) CRIM-positive patients were dependent on invasive-ventilation. After switching, no additional CRIM negative patients required invasive ventilation, and no CRIM negative patients had died at the time of this review. One CRIM-positive infantile-onset patient died at 1.3 years of age after switching. Five late-onset patients who were diagnosed and treated at < 8 years of age required invasive ventilation at enrollment. One additional late-onset patient required invasive ventilation after switching. There were 2 patients with unknown CRIM status who required invasive ventilation after switching. Therefore, 3/81 patients who were not dependent on invasive ventilation prior to switching, required invasive ventilation after switching and 4 patients died after switching. The age at death ranged from 15 months to 16 years of age and the exposure time to alglucosidase alfa ranged from 9 months to 8 years prior to enrolling in AGLU09411. Refer to Tables 11 and 13 in Section 7.4.5 Special Safety Studies/Clinical Trials for further details. Although efficacy was not the primary area of interest in the switch-over trial (AGLU09411), there does not appear to be a significant loss of efficacy after patients switch from Myozyme (160 L) to Lumizyme (4000 L).

Additionally, the rate of anti-drug antibody development was the same for patients treated with Lumizyme (4000 L) and those treated with Myozyme (160 L). Sixteen of the 17 patients (88.9%) in the Taiwan01 trial formed anti-rhGAA IgG, which is consistent with the percentage described in the Myozyme labeling (89%).⁷

The 18-month survival data were comparable between infantile-onset patients treated with Lumizyme (4000 L) and Myozyme (160 L) and the physicochemical comparability of the two product has been established. Therefore, these data support expanding the Lumizyme indication to all patients with Pompe disease.

6.1 Indication

The applicant is proposing to expand the indication to all patients with Pompe disease and change the indication to:

Lumizyme (alglucosidase alfa) is a lysosomal glycogen-specific enzyme indicated for patients with Pompe disease (GAA deficiency).

Currently, the indication statement specifies that Lumizyme is restricted to patients 8 years and older with late (non-infantile) onset Pompe disease who do not have evidence of cardiac hypertrophy.

6.1.1 Methods

See section 5.3 Discussion of Individual Studies/Trials for details. It should be noted that the intent of the clinical data from the investigator-sponsored clinical trial in Taiwan (Taiwan01) is to provide the efficacy data that further supports chemical comparability between Myozyme (160 L) and Lumizyme (4000 L).

6.1.2 Demographics

Comparisons of demographic information between the patients enrolled in Taiwan01, AGLU01602/02403, and the natural history cohort are shown below in Table 3. There were 18 patients from the Taiwan01 trial who met the same inclusion criteria as patients enrolled in AGLU01602/02403.

Overall, the disease characteristics were similar between the patients in the Taiwan01 trial and the patients enrolled in AGLU01602/02403. It should be noted that all 18 patients in the Taiwan01 trial were CRIM positive, whereas 14/18 patients in AGLU01602/02403 were CRIM positive and 4/18 were CRIM negative. Although CRIM negative patients generally have poorer outcomes, the majority of the patients in AGLU01602/02403 were CRIM positive, allowing for comparison to the Taiwan01 trial population. Patients enrolled in Taiwan01 initiated treatment at a younger age since patients in Taiwan are identified with Pompe disease through a newborn screening program, which was not available at the time AGLU01602/02403 was conducted. Patients enrolled in AGLU01602/02403 were diagnosed based on clinical presentation, later in infancy compared to the patients enrolled in Taiwan01. The natural history cohort is an untreated cohort; therefore, variables specific to treatment were not applicable.

Table 3: Comparison of Patient Demographics: Taiwan01, AGLU01602/02403, Natural History Cohort (AGLU0400)

	Taiwan01 (N=18)	AGLU01602/02403 (N=18)	AGLU0400 (Natural History Cohort) (N=62)
Male, n (%)	9 (50)	11 (61.1)	28 (45.2)
Race, n (%)			
Asian	18 (100)	3 (16.7)	18 (29.0)

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Black	0	4 (22.2)	4 (6.5)
Caucasian	0	7 (38.9)	31 (50.0)
Hispanic	0	2 (11.1)	1 (1.6)
Other	0	2 (11.1)	1 (1.6)
Unknown	0	0	7 (11.3)
Age at Symptom Onset (months)			
Mean \pm SD	1.2 \pm 1.3	1.6 \pm 1.8	1.9 \pm 1.8
Median	0.5	1.0	1.6
Min., Max.	0.1, 0.5	0.0, 5.4	0.0, 5.9
Age at Initial Diagnosis (months)			
Mean \pm SD	1.4 \pm 1.6	3.7 \pm 2.2	3.6 \pm 1.9
Median	0.6	4.4	4.1
Min., Max.	0.0, 5.8	0.2, 6.8	4.4, 6.6
Age at First Infusion (months)			
Mean	1.6	5.1	NA
Median	1.0	5.6	NA
Std. Dev.	1.60	1.96	NA
Min., Max.	0.2, 5.8	1.2, 7.3	NA
Age Group at First Infusion (months), n (%)			
>0 to \leq 2 months	12 (66.7)	2 (11.1)	NA
>2 to \leq 4 months	4 (22.2)	2 (11.1)	NA
>4 to \leq 6 months	2 (11.1)	7 (38.9)	NA
>6 to \leq 12 months	0	7 (38.9)	NA
>12 to \leq 24 months	0	0	NA
>24 to \leq 36 months	0	0	NA
>36 months	0	0	NA
CRIM status, n(%)			
Positive	13 (72.2)	14 (77.8)	NA
Negative	0	4 (22.2)	NA
Unknown*	5 (27.8)	0	NA
*Patient's CRIM status was reported as 'unknown' if Western Blot analysis was not performed. For study Taiwan01, all patients were CRIM-positive, as per the investigator.			

(Source: adapted from applicant's submission, sBLA 125291/136, dated January 30, 2014, module 5.3.5.4 Taiwan01 Clinical Study report, pages 25-28/158).

Note: Natural history cohort did not include treatment administration, and therefore, alfa alglucosidase infusion information is not available (NA).

Note: In AGLU01602, age was corrected for gestation when indicated; this correction was not applied to the Taiwan cohort data.

The most common genotype classification of patients enrolled in Taiwan01 was missense/missense (10/18, 55.6%). Other less common genotypes included missense/frameshift, missense/in-frame deletion, missense/nonsense, and missense/splice site. Similarly, the most common genotype classification for patients enrolled in AGLU01602/02403 was missense/missense (5/18, 27.8%); however, only 9 out of the 18 patients had a documented genotype classification. Since only 9/18 patients enrolled in AGLU01602/02403 had a documented genotype classification, it is not possible to draw a conclusion regarding the

relationship between genotype and the impact on clinical outcome at this time; therefore, an analysis based on genotypes will not be performed in this review.

6.1.3 Subject Disposition

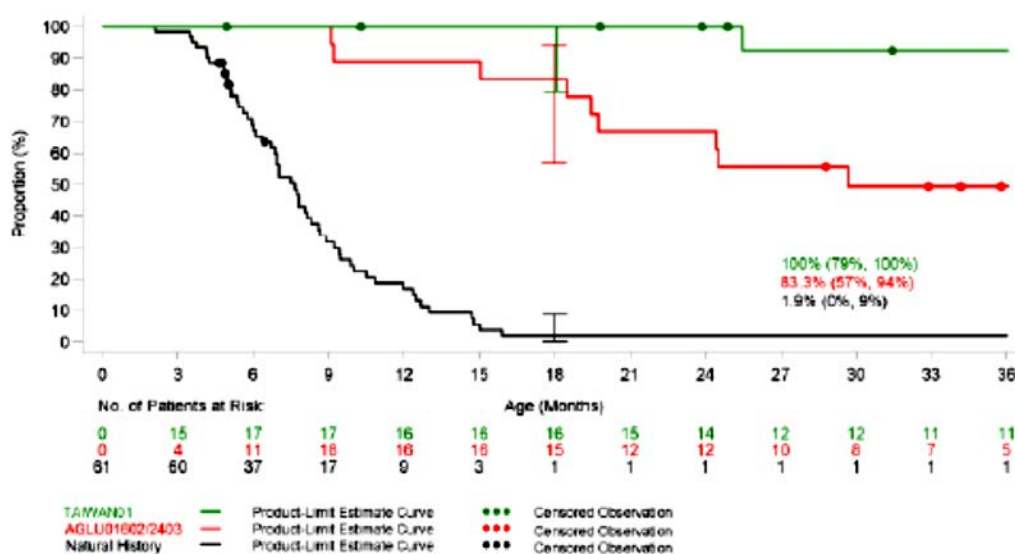
Eighteen patients from the Taiwan01 trial met the same inclusion criteria as patients enrolled in AGLU01602/02403, and were treated exclusively with Lumizyme, the larger scale of alglucosidase alfa. There were 3 deaths, 2 patients were lost to follow up, and no patients withdrew due to adverse events (AEs). Data were collected in this trial since 2006 through the data cut-off date of June 30, 2013.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint was the proportion of infantile-onset patents enrolled in Taiwan01 who were alive and invasive ventilator-free at 18 months compared to infantile-onset patients enrolled in AGLU01602/02403), and the natural history (AGLU00400) cohort.

Of the 18 patients enrolled in the Taiwan01 trial who met the same inclusion criteria as patients enrolled in AGLU01602/02403, 2 were lost to follow up. Of the remaining 16 patients, 100% percent of patients in the Taiwan01 trial were alive and invasive ventilator-free at 18 months of age. In comparison, 15/18 (83.3%) of patients in AGLU01602/2403 and 1/61 (1.9%) of patients in the AGLU00400 historical cohort were alive and invasive ventilator-free at 18 months of age. Of note, 61 out of the 62 patients from the historical cohort were included in the efficacy analysis because the date of death was unknown for one patient. The Statistical reviewer for the original Myozyme (BLA 125141) review noted that including this patient would not have changed the interpretation of the trial (see Lisa Kammerman's Statistical review dated April 27, 2006 for details). Figure 2 below shows the Kaplan-Meier curves that compare the Taiwan01, AGLU01601/2403, and natural history cohorts.

Figure 2: Kaplan-Meier Estimates of Patients Who Were Alive and Free of Invasive Ventilator Support From Birth to 36 Months of Age – Estimated Percentage With 95% Confidence Interval at 18 Months



(Source: applicant's submission, BLA 125291/136, dated 1/30/14, Clinical Study Report: Taiwan01, page 31/158)

Although there was no significant difference between the Taiwan01 and AGLU01602/2403 cohorts in the percentage of patients who were alive and free of invasive ventilator support at 18 months of age (p-value 0.0862), the apparent differences between the curves based on visual inspection at 18 months may be related to the inclusion of more severely affected CRIM negative patients in AGLU01602/02403. Two of the three patients in AGLU01602/02403 who required invasive ventilation by the 18 month time point and failed the primary endpoint at 18 months were CRIM negative. In contrast, no patients in the Taiwan01 trial were CRIM negative. However, since the majority of the patients enrolled in AGLU01602/02403 were CRIM positive (14/18), it is unlikely that the differences in CRIM status between the two trials impacted the overall results. See Section 6.1.7 Subpopulation for additional details on clinical outcomes in CRIM negative patients.

Longer-term survival data were provided for patients up to 36 months of age. For patients enrolled in AGLU01602/AGLU02403, data were available through the Pompe Registry for 14 patients who participated in the AGLU01602/02403 trial. At 36 months, 4 of the 14 patients had died (mean age of death of 3.4 years, median: 3.83 years, range: 1.6 - 4.4 years). Of these 4 patients, 1 was CRIM positive and 3 were CRIM negative. Similarly, 12/18 patients enrolled in the Taiwan01 trial had available follow-up at 36 months. Of those 12 patients, 1 patient required invasive ventilation at 25.4 months, and 3 patients died at ages 42.4, 43.6, and 44.5 months, respectively (mean age of death of 3.6 years). The 36-month survival data are supportive of the primary efficacy endpoint of survival at 18 months. However, perceived differences between trials in long-term outcomes wouldn't be expected to reflect differences in efficacy between the products since they are deemed to be comparable. Additionally, there are limitations to

interpreting registry data. As stated in an article by Byrne et al,¹⁰ many physicians become aware of the Pompe Registry when they initiate ERT and data entry is voluntary by physicians. Although physicians are requested to follow the minimum assessments outlined by the Pompe Registry, data collection may be inconsistent, clinical evaluations may occur at varying time points, and reports may be retrospective and subject to recall bias by patients or physicians.

Primary Analysis by Dose Regimen

Patients enrolled in the Taiwan01 trial were divided into two dose groups: (1) patients who received only the standard, approved dose of 20mg/kg every other week (n =10), and (2) “Others” (n = 8), comprised of patients who underwent any change to the dose or frequency of administration. The first infusion for all patients in the Taiwan01 trial was with the approved dose regimen of 20 mg/kg every other week. Dose adjustments were allowed as per standard of clinical care (see Section 5.3 for details of the trial design). The patients in the “Others” dose group received a variety of doses (mainly 20 mg/kg weekly or 40 mg/kg every other week) for variable amounts of time in addition to the approved dose. At 18 months of age, 100% of patients were alive in both dose groups.

Similarly, in AGLU01602/02403, efficacy was shown to be similar between dose groups (9 patients received 20 mg/kg every other week vs. 9 patients received 40 mg/kg every other week). Since two doses were evaluated in AGLU01602/02403 and dose adjustments were permitted as per standard of care during the Taiwan01 trial, ventilator-free survival at 18 months of age was assessed for patients who were treated exclusively with the approved dose of 20 mg/kg every other week. Of the 9 patients in AGLU01602/02403 who were treated with 20 mg/kg every other week, 1 patient died at age 19.4 months, and 3 patients required invasive-ventilation at ages 9.1 months, 19.7 months, and 22.4 months. Of the 10 patients in the Taiwan01 trial who received the 20 mg/kg every other week dose, 10/10 (100%) of the patients were alive and invasive-ventilator free at 18 months vs. 8/9 (88.9%) patients in the AGLU01602/02403 trial who were alive and invasive-ventilator free at 18 months of age. Survival and ventilator-free survival appear to be similar between Myozyme and Lumizyme for patients who were treated exclusively with the approved dose of 20 mg/kg every other week.

6.1.5 Analysis of Secondary Endpoints

Secondary endpoints included the association of CRIM status, antibody response, genotype, and enzyme activity level with invasive-free ventilation. In addition, muscle glycogen levels at baseline and 6 months post-treatment based on muscle biopsies were analyzed.

Since all patients enrolled in the Taiwan01 trial were CRIM positive and 100% were alive and free of invasive ventilation at 18 months, the secondary analysis evaluating the association between CRIM status and clinical outcome was not performed for the Taiwan01 trial. A

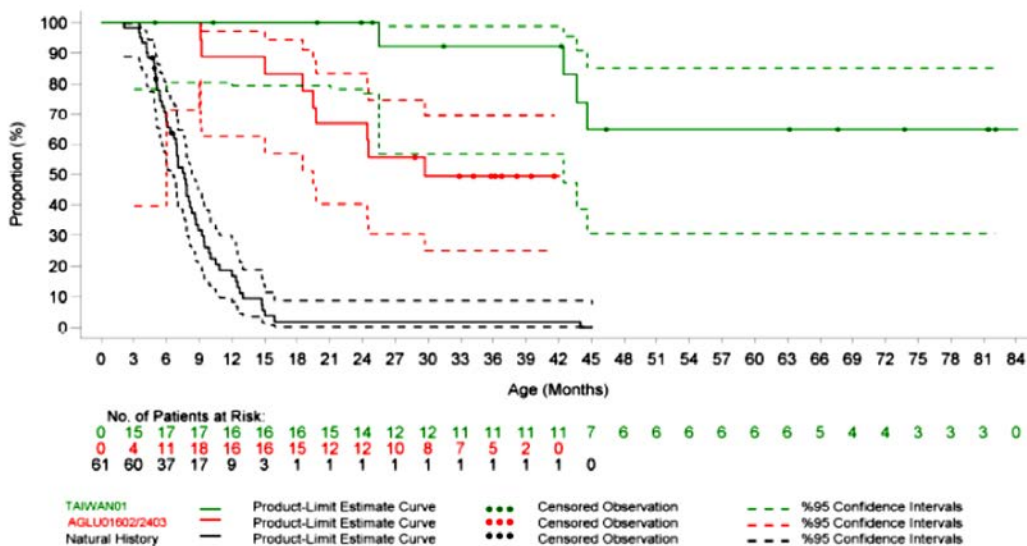
¹⁰ B.J. Byrne et al. Pompe disease: Design, methodology, and early findings from the Pompe Registry. *Molecular Genetics and Metabolism*. 2011;103:1–11

discussion of the survival data in CRIM negative patients is included below in Section 6.1.7 Subpopulations. Antibody response, genotype and enzyme activity levels were assessed as subgroup analyses. Refer to Section 6.1.7 Subpopulations of this document.

6.1.6 Other Endpoints

Survival data were analyzed at the last follow-up for both the AGLU01602/02403 and Taiwan01 trials. The maximum follow-up time for AGLU01602/02402 was 42 months and for Taiwan01 was 84 months. In the Taiwan01 trial, the Kaplan-Meier estimates of patients alive and ventilator-free at 42 months was 92.3% (95% CI: 56.6%, 98.9%) compared to 49.4% (95% CI: 25.2%, 69.7%) of patients in AGLU01602/02403. At 84 months, 64.6% (95% CI: 30.6%, 85.1%) of infantile-onset Pompe patients in the Taiwan01 trial were alive and invasive ventilator-free. As expected, only one patient in the AGLU0400 historical cohort was alive and invasive ventilator-free at 42 months of age (1.9% (95% CI: 0.2%, 8.7%)). The number of patients available for comparison beyond 39 months from AGLU01603/02403 was very small (2 patients at 39 months and 0 patients at 42 months) which makes it difficult to draw conclusions. The Kaplan-Meier curve that illustrates the longer-term follow up survival is shown below in Figure 3.

Figure 3: Kaplan-Meier Estimates of Patients Alive and Ventilator-Free at the Last Follow Up



(Source: applicant's submission, BLA 125291/136, dated 1/30/14, Clinical Study Report: Taiwan01, page 31/158)

6.1.7 Subpopulations

To assess associations between factors that could influence survival outcomes, Kaplan-Meier estimates of invasive ventilator-free survival were generated for subgroups in the Taiwan01 trial:

- Dosing regimen: 20 mg/kg every other week versus Others (20 mg/kg weekly or 40 mg/kg every other week)
- Drug production scale: 4000 L alone versus Others (patients who received only 2000 L and died before 4000 L became available or who received 2000 L initially and later switched to 4000 L when it became available)
- Classification of Genotype: Missense/Missense, Missense/Frameshift, Missense/In-frame Deletion, Missense/Nonsense, and Missense/Splice site GAA
- Enzyme Activity Level at Baseline: Above versus Below Median (0.94 nmol/hr/mg protein)
- Status of Inhibitory/Neutralizing Antibody: Positive versus Negative

Of note, three patients were tested for inhibition of enzyme uptake and inhibition of enzyme activity and all three were negative for both; therefore, a comparison of positive versus negative inhibitory/neutralizing antibody status was not performed.

CRIM Status

The percentage of patients alive and free of invasive ventilation at 18 months of age was not statistically significant for the primary efficacy analysis. However, the Taiwan01 trial did not enroll any CRIM negative patients and the AGLU01602/2403 trial enrolled 4 CRIM negative patients. To determine whether the inclusion of CRIM negative patients in the AGLU01602/02403 trial impacted the results, the Statistical reviewer performed the primary efficacy analysis excluding the CRIM negative patients from the AGLU01602/02403 trial. The results from the Taiwan01 trial were unchanged since all patients were CRIM positive; 100% of patients were alive and invasive ventilator-free at 18 months of age. However, the percent of patients alive and free of invasive ventilation at 18 months of age in AGLU01602/02403 increased from 15/18 (83.3%) to 13/14 (92.9%). Even though the percent of patients alive and ventilator-free increased when CRIM negative patients were excluded, ventilator-free survival remained similar between Myozyme (160 L) and Lumizyme (4000 L) treated-patients.

To examine the impact of CRIM status further, an Information Request was sent to the applicant requesting available data from the Pompe Registry on clinical outcomes (survival and ventilator-free survival) for infantile-onset patients who have received treatment exclusively with Lumizyme (4000 L). Of note, a manufacturing modification that (b) (4)

(b) (4) On May 23, 2014, the applicant provided available information from the Pompe Registry on the clinical outcome of classic infantile-onset CRIM negative patients who were treated exclusively with Lumizyme (4000 L). In addition, clinical outcomes were provided on classic infantile-onset CRIM negative patients who were treated exclusively with Lumizyme (4000 L) since the May 2011 manufacturing modification. There were 4 CRIM-negative patients treated exclusively with Lumizyme (4000 L). Of those 4 patients, 2 patients died at 0.7 and 1 years of age, respectively. The third patient required invasive ventilation at 1.8 years of age. The fourth patient was treated exclusively with Lumizyme (b) (4) for 2.4 years and has not been reported to have died. It is difficult to make generalizable conclusions based on limited data in a few patients. However, classic infantile-

onset CRIM negative patients are known to have the most severe form of Pompe disease and poor outcomes appear to be related to the disease rather than to the scale of alglucosidase alfa.

Furthermore, CRIM negative patients also had poor outcomes in the trials that supported the approval of Myozyme (160 L). There were 4 CRIM negative patients enrolled in AGLU1602 (the trial that supported the approval of Myozyme). Two of the three patients who required invasive ventilation by 18 months of age and failed the primary endpoint were CRIM negative. One patient required invasive ventilation at 9.2 months of age and died at 32 months of age. The second patient required invasive ventilation at 9.1 months of age and died at 27.1 months of age. The additional 2 CRIM negative patients required invasive ventilation at 18.5 months and 24.5 months of age and died at 34.3 months and 31.9 months of age, respectively. Therefore, all 4 of the CRIM negative patients treated with Myozyme died before 36 months of age. In comparison, two of the four Lumizyme (4000 L) patients died before 1 year of age, one required invasive ventilation at 1.8 years of age, and one is reported to have survived as of the time of this review. There do not appear to be significant differences between the outcomes of CRIM negative patients treated with Myozyme (160 L) compared to those treated with Lumizyme (4000 L).

To obtain additional information on a larger number of CRIM negative patients, clinical outcome data were reviewed from the switch-over trial (AGLU09411). CRIM status was not routinely collected as per the AGLU09411 protocol since the trial was designed to allow for continued therapy given the ongoing supply constraints of Myozyme; however, efficacy outcomes were provided in response to the Division's Information Request. The AGLU09411 trial has limitations with regard to its adequacy to support efficacy claims. For example, a switch-over trial design without a concurrent control arm (placebo or active comparator) makes it difficult to interpret the treatment effect of Lumizyme. However, upon approval of this supplemental BLA that will expand the indication of Lumizyme to all Pompe patients, patients in the United States who have been receiving treatment with Myozyme will likely be switched to Lumizyme. Therefore, AGLU09411 provides real-world, clinical data that are supplementary to the clinical efficacy data obtained in treatment-naïve Pompe patients. Genzyme contacted the study sites to acquire information on CRIM status, which was cross-checked with the Pompe Registry database. CRIM status was obtained for 42 patients enrolled in AGLU09411 and 34 of the patients had infantile-onset disease. Of these 34 infantile-onset patients, 10 were CRIM negative. Of the 10 CRIM negative infantile-onset patients, 5 patients required invasive ventilation at the time of enrollment (prior to switching). As of April 2, 2014, no additional CRIM negative patients required invasive-ventilation and none of the CRIM negative patients died after switching. Refer to Section 7.4.5 and Table 11 for further details.

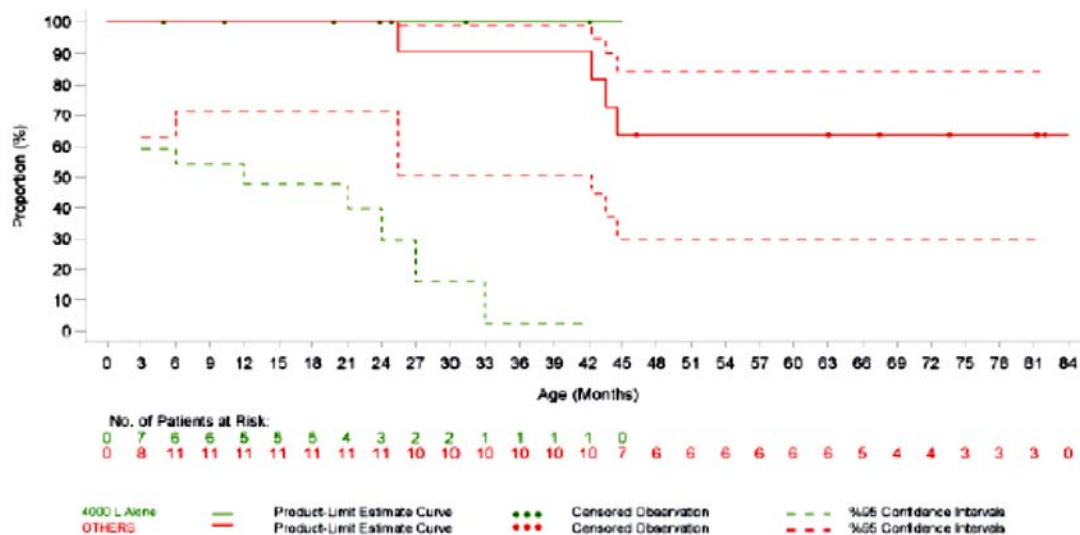
Drug Production Scale

Of the 18 patients in the Taiwan01 trial, 7 patients were treated exclusively with the 4000 L product ("4000 L alone") and 11 patients received treatment with either the 2000 L product or both the 2000 L and 4000 L products ("Others"). Patients whose first infusion date was after September 7, 2009, the date of the first shipment of 4000 L product to Taiwan, were considered as having received the 4000 L drug product alone. This reviewer does not expect the 2000 L product to be superior to the 4000 L product based on its physicochemical attributes. Therefore,

this reviewer believes that it is acceptable to include patients who were treated with the 2000 L product in the analysis would negatively impact the overall efficacy of 4000 L, if the difference in chemical attributes in the 2000 L had any meaningful impact on efficacy. Importantly, the approved Lumizyme (4000 L) product contained improvements in product quality as compared to the 2000 L product, which was never approved in the United States. The reader is referred to BLA 125291/098, CMC Review Memo, Resubmission of Lumizyme Manufactured at 4000 L Bioreactor Scale, by Juhong Liu, dated 4/29/2010. Due to more recent manufacturing changes, the current commercially available Lumizyme (4000 L) contains further improvements that may reflect improvements in efficacy. Refer to CMC review by Chris Downey, for details.

Furthermore, the patients enrolled in the clinical trial that supported the approval of Lumizyme (LOTS trial) were treated with the 2000 L product during the trial. However, the data were insufficient to support approval for patients younger than 8 years of age and patients with infantile-onset Pompe disease; therefore, the indication of Lumizyme was restricted to patients who are at least 8 years of age in the United States. (Refer to Section 2.5 Regulatory Timeline for additional details). Of note, Lumizyme (4000 L) is currently the commercially available product outside of the U.S. for the treatment of all Pompe patients. The 2000 L product was not approved in the United States and has not been available commercially outside of the United States since 2009. Figure 4 shows the Kaplan-Meier Estimate of percentages of patients who were alive and invasive ventilator-free through the last available follow-up assessment by production scale.

Figure 4: Kaplan-Meier Estimates of Patients Who Were Alive And Invasive Ventilator-Free Through the Last Follow-Up by Production Scale



(Source: applicant's submission, BLA 125291/136, dated 1/30/14, Clinical Study Report: Taiwan01, page 39/158)

At 18 months, 100% of the patients in both the 4000 L and "Others" group were alive and ventilator-free. The patients in the 4000 L group had shorter duration of follow-up than those in the "Others" group since the 4000 L scale product has only been available in Taiwan since 2009. There were very few patients with available data beyond 42 months and comparisons beyond 42

months cannot be made. However, the figure shows that there were no deaths in the 4000 L group during the time that the patients were followed.

Classification of Genotype

The most common genotype classification of patients enrolled in Taiwan01 was missense/missense (10/18, 55.6%). Other less common genotypes included missense/frameshift, missense/in-frame deletion, missense/nonsense, and missense/splice site. For the patients enrolled in the Taiwan01 trial, survival by genotype classification was analyzed comparing patients with missense/missense mutations (10/18) and missense/frameshift mutations (4/18). At 18 months of age, 100% of the patients in both genotype groups were alive. However, due to the small sample size, it is not possible to draw a conclusion regarding the relationship between genotype and the impact on clinical outcome at this time.

Enzyme Activity Level

In the Taiwan01 trial, GAA activity based on skin fibroblast assay was performed in 9 patients and GAA activity based on lymphocyte assay testing was performed in 18 patients. In general, GAA enzyme activities of < 1% are most commonly seen in patients with the infantile-onset form of the disease, which is the more severe, rapidly progressive phenotype.¹¹ However, infantile-onset Pompe disease is not diagnosed based on enzyme activity level but by a constellation of clinical symptoms that present in infancy. After identification of symptoms and laboratory findings consistent with Pompe disease, the diagnosis of Pompe is confirmed by GAA analysis. The values typically observed in patients with infantile-onset disease for lymphocyte GAA activity with acarbose is < 8 nmole/mg/protein and skin fibroblast GAA activity is < 1%.¹²

In the Taiwan01 trial, skin fibroblast GAA activity ranged from 0.1 - 0.2 nmol/hr/mg protein (n=9) and lymphocyte GAA activity ranged from 0.4 - 4.4 nmol/mg/ protein (n=18). The patients enrolled in the Taiwan01 trial were diagnosed by newborn screening, but based on the values of GAA activity typically observed in infantile-onset Pompe patients, the values of GAA activity for the patients enrolled in the Taiwan01 trial fall within the expected ranges. Of note, in the AGLU01602/02403 trial, only the skin fibroblast assay was used for GAA activity testing and ranged from 0.56 to 2.34 nmol/hr/mg protein. Even though the range is slightly larger for the patients in the AGLU01602/02403 trials, the patients were required to meet clinical diagnostic criteria of infantile-onset Pompe disease. Survival was analyzed for patients who were alive at 18 months of age with respect to GAA enzyme activity level at baseline; however, definite conclusions cannot be made due to the small sample size.

Anti-rhGAA Antibody Titers

¹¹ Kishnani, P., et al. Pompe disease diagnosis and management guideline. Genet Med. 2006; 8(5): 267-88.

¹² Jack, R., et al. The use of acarbose inhibition in the measurement of acid alpha-glucosidase activity in blood lymphocytes for the diagnosis of Pompe disease. Genet Med 2006;8(5):307-312.

Of the 18 patients in the Taiwan01 trial, 17 patients underwent antibody analysis. One patient was excluded because the sample was not submitted to Genzyme for analysis. Sixteen of the seventeen patients (88.9%) in the Taiwan01 trial formed anti-rhGAA IgG. The percentage of patients who seroconvert is consistent with the percentage described in the Myozyme label (89%).⁷ Therefore, rates of seroconversion appear to be similar between infantile-onset patients who were treated with Lumizyme (4000 L) and those who received treatment with Myozyme (160 L).

As noted in the approved Myozyme label, patients developing sustained titers $\geq 12,800$ of anti-rhGAA antibodies may have a poorer clinical response to treatment, or may lose motor function as antibody titers increase.⁷ In the Taiwan01 trial, no patients were reported to have developed high sustained antibody titers. The median peak titer was 1600 (range: 0 to 12,800). The median last titer was 400 (range: 0 to 12,800). Only one patient had a titer of 12,800 and the remaining patients had titers of 6400 or less. Table 4: Summary of Seroconversion Status and Maximum IgG Titers for Patients in the Taiwan01 Trial below describes the antibody status and peak titers recorded during the Taiwan01 trial.

Table 4: Summary of Seroconversion Status and Maximum IgG Titers for Patients in the Taiwan01 Trial

Patient ID	Week first seroconverted	IgG antibody titer at week first seroconverted	Maximum titer reported during study	Week of maximum titer	Titer value at last visit
10375 ¹	Week 72	800	800	72	800
10377	Week 205	400	1600	312	800
10378	Week 156	100	100	156	100
10381	Week 105	3200	12800	346	12800
10382	Week 221	400	1600	245	800
10460	Week 9	200	800	254	800
10528 ²	NA	NA	NA	NA	NA
10529	Week 12	6400	6400	12	400
10530	Week 12	400	400	12	NA
70001	Week 4	200	6400	25	200
70002	Week 4	800	800	4	800
70003 ¹	Week 4	100	6400	12	200
70004 ¹	Week 10	1600	1600	10	100
70006	Week 38	<100	<100	38	NA
70008	Week 8	800	3200	26	400
70011	NA	NA	NA	NA	NA
70012	Week 24	200	200	24	100
70013	Week 32	3200	3200	32	3200

Source: Listing 16.2.8.2

NA=not available

¹ In some patients, the maximum titer values occurred more than once; in this case, the first time of maximum titer is listed.

² No post-baseline assessments for IgG were available.

(Source: applicant's submission, sBLA 125291/136, dated January 30, 2013, section 5.3.5.4, Taiwan01 Clinical Study Report, page 53/158)

Antibody formation over time by status of invasive ventilator use and survival was analyzed for the Taiwan01 trial. There was no correlation between the clinical outcome and antibody titer level. Of note, the peak titers for the patients who died (patient 10529 and 10378) were 6400 and 100, respectively. The severe baseline disease and compromised cardiorespiratory function

probably contributed to the poor outcome of these patients. However, the patient with the highest titer (12800) did not require invasive ventilation and survived. Peak titers are also shown above in Table 4: Summary of Seroconversion Status and Maximum IgG Titers for Patients in the Taiwan01 Trial. In contrast, at the completion of the AGLU01602/02403 trial, 6 patients had high sustained antibody titers and all 6 patients had poor clinical outcomes. These results were likely confounded by 4 of these 6 patients being CRIM negative, who are known to develop high antibody titers and have poor clinical outcomes. Figure 5 below shows the antibody status by clinical outcome for the patients in the Taiwan01 trial.

Figure 5: Antibody Formation Over Time by Clinical Outcome (Invasive ventilation use or death): Taiwan01 Trial



6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Proposed dosing and administration: The recommended dosage of Lumizyme is 20 mg/kg body weight administered every 2 weeks as an intravenous infusion. The proposed dose is the same as the currently approved dose and frequency of administration of Myozyme and Lumizyme. There were no differences in survival outcomes with respect to dose during the Taiwan01 trial. Refer to Section 6.1.4 Primary Analysis of Endpoint (s): Primary Analysis by Dose Regimen for details.

Similarly, in AGLU01602/02403, efficacy was shown to be similar between dose groups (data not shown). Refer to Section 6.1.4 Analysis of Primary Endpoint, Dose Regimen, above for additional details.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence of efficacy and tolerance effects could be affected by immunogenicity to enzyme replacement products. In general, patients who develop anti-rhGAA IgG are at risk for decreased efficacy due to the formation of anti-drug antibodies.^{7, 13} Refer to Section 7.4.2 Laboratory Findings for details on anti-rhGAA IgG antibody formation.

6.1.10 Additional Efficacy Issues/Analysis

None.

7 Review of Safety

Brief Summary of Adverse Events

Overall, the safety profiles reported from the Taiwan01 and AGLU09411 trials (patients treated with Lumizyme (4000 L)) were similar to those observed during the trials that supported approval of Myozyme (160 L). The safety data from the Taiwan01 trial (infantile-onset patients treated exclusively with Lumizyme) were compared to the known safety data from the current approved Myozyme label to determine whether the safety profiles are similar for infantile-onset patients treated with Lumizyme and Myozyme. Taiwan01 trial was a single-center, investigator-sponsored trial and was not designed to demonstrate efficacy of Lumizyme. Therefore, there were limitations to the data collection including voluntary report of adverse events, which may have resulted in underreporting. However, the nature of the adverse reactions were similar to those reported from the trials that supported approval of Myozyme. No new safety concerns were identified. Additionally, the safety and immunogenicity data obtained from the AGLU09411 trial were compared to the known safety profile of Myozyme to determine whether the risks are similar for patients who are switched from Myozyme to Lumizyme. AGLU09411 was conducted in the United States and provides safety data that are applicable to patients in the U.S. with infantile-onset Pompe disease who will likely be switched from their current treatment with Myozyme (160 L) to Lumizyme (4000 L), if the Lumizyme indication is expanded to treat all phenotypes of Pompe patients.

The serious adverse events (SAEs) that were reported for infantile-onset patients treated with Lumizyme during the Taiwan01 trial were similar to the SAEs reported for infantile-onset patients treated with Myozyme. The most common nonfatal SAEs reported in $\geq 10\%$ of patients (≥ 2 patients) during the Taiwan01 trial were rash, respiratory failure, infectious pneumonia,

¹³ Wang, J., et al. Neutralizing antibodies to therapeutic enzymes: considerations for testing, prevention and treatment. *Nature Biotechnology* 2008; 26(8): 901-908.

atelectasis, increased blood creatine phosphokinase, anaphylaxis, pyrexia, and tachypnea. (See Table 10 below). Similarly, the most common serious treatment-emergent adverse events occurring in $\geq 10\%$ of patients during the clinical trials that supported approval of Myozyme (160 L) were pneumonia, respiratory failure, respiratory distress, catheter-related infection, respiratory syncytial virus infection, gastroenteritis and fever.⁷ Of note, catheter-related infection, respiratory syncytial virus infection, gastroenteritis were also reported during the Taiwan01 trial but at lower frequencies, which is likely due to underreporting because of the trial design (investigator-sponsored trial with voluntary reports of adverse events). Common adverse events such as respiratory failure, pneumonia, respiratory infections were likely related to the underlying disease rather than related to the treatment.

There were three deaths during the Taiwan01 trial; however, these patients each died around 3 years of age from respiratory failure related to the underlying disease. Antibody titers were not available for one patient and the other two patients did not have high sustained antibody titers. Death due to respiratory failure is expected with Pompe disease, especially in patients with infantile-onset Pompe disease.¹⁴ Of the 99 patients who were enrolled into AGLU09411, there were 10 CRIM negative and 24 CRIM positive infantile-onset patients. These patients were treated with Myozyme (160 L) prior to enrollment into AGLU09411. The CRIM negative infantile-onset patients ranged in age from 1 to 5.7 years and 6/10 (60%) required invasive ventilation at the time of enrollment into the trial. The CRIM positive infantile-onset patients ranged in age from 1 to 11.3 years and 8/24 (33.3%) required invasive ventilation at the time of enrollment into the trial. Refer to Table 11 for additional details. Although treatment with enzyme replacement therapy has been shown to extend survival and ventilator-free survival, longer-term follow up demonstrates that beyond 24 - 36 months, most patients with classic infantile-onset Pompe disease eventually experience some clinical decline.¹⁵ However, some patients are now surviving into the second decade of life. Therefore, the deaths reported in the Taiwan01 trial were not unexpected in this classic infantile-onset patient population. Similarly, 3 patients died during AGLU09411 or shortly after withdrawal from the trial. One additional patient died after the data cut-off date for this submission. All of the deaths occurred in patients with infantile-onset Pompe disease and were related to respiratory failure. The age at death ranged from 15 months to 16 years of age and the exposure time to alglucosidase alfa ranged from 9 months to 8 years prior to enrolling in AGLU09411. Details on the patient deaths are included below in Table 6 (Taiwan01) and Table 13 (AGLU09411).

The most common adverse reactions included primarily signs and symptoms of anaphylaxis and hypersensitivity reactions. Two patients (2/18, 11.1%) experienced anaphylaxis based on the Sampson criteria.⁹ Anaphylaxis is a known serious, adverse reaction associated with both Myozyme and Lumizyme. As described in the Myozyme label, based on clinical trial data and postmarketing safety experience, 1% of patients developed anaphylactic shock and/or cardiac

¹⁴ Byrne, B., et al. Pompe Disease: Design, methodology, and early findings from the Pompe Registry. *Molecular Genetics and Metabolism* 103 (2011) 1–11.

¹⁵ Kishnani, P., et al. Early Treatment with Alglucosidase alfa Prolongs Long-Term Survival of Infants with Pompe Disease. *Pediatr Res* 2009;66:329–335.

arrest during Myozyme infusions, and approximately 14% of patients developed reactions that involved at least 2 out of 3 body systems.

Six out of the eighteen (33.3%) patients in the Taiwan01 trial experienced at least 1 hypersensitivity reaction. The most common signs and symptoms that were suggestive of hypersensitivity reactions and reported in at least 2 patients were rash (4/18, 22%), pyrexia (2/18, 11.1%), pruritus (2/18, 11.1%), and eyelid edema (2/18, 11.1%). The remaining occurred in one patient each: bradycardia, chills, discomfort, facial edema, irritability, decreased oxygen saturation, rhinorrhea, tachypnea, urticaria, and wheezing. Importantly, decreased oxygen saturation, tachypnea, wheezing and urticaria occurred in the patients who were reported to have anaphylaxis. These signs and symptoms are similar in nature to the most common adverse reactions that required intervention (hypersensitivity reactions) during in clinical trials with Myozyme. As stated in the Myozyme label, hypersensitivity reactions were reported in 20/39 (51%) patients and included rash, flushing, urticaria, fever, cough, tachycardia, decreased oxygen saturations, vomiting, tachypnea, agitation, increased blood pressure, cyanosis, hypertension, irritability, pallor, pruritus, retching, rigors, tremor, hypotension, bronchospasm, erythema, face edema, feeling hot, headache, hyperhidrosis, increased lacrimation, livedo reticularis, nausea, periorbital edema, restlessness, and wheezing.⁷

Furthermore, hypersensitivity reactions are more common in patients who develop anti-drug antibodies (anti-rhGAA IgG).⁷ In the Taiwan01 trial, 6 patients were anti-rhGAA IgG positive and all experienced signs and symptoms of hypersensitivity reactions. One patient did not seroconvert and did not experience hypersensitivity reactions. These findings are consistent with what is known about the relationship of antibody formation and hypersensitivity reactions. Refer to Section 7.3.4 of this review for further details.

Additionally, there did not appear to be an impact on anti-drug antibody formation when patients switch from Myozyme (160 L) to Lumizyme (4000 L), based on the data from the AGLU09411 trial. Sixty-eight of the 99 (68.7%) patients enrolled in AGLU09411 were antibody positive at baseline. The patients enrolled in AGLU09411 were previously treated with Myozyme and the majority of patients are expected to develop anti-rhGAA antibodies during treatment with alglucosidase alfa. Thirty-one of the 99 (31.3%) patients enrolled into AGLU09411 were seronegative at baseline; of these, 21 (21.2%) remained seronegative throughout the trial. The rate of seroconversion and pattern of antibody development when patients switch between enzyme replacement therapies has not been established. Therefore, it is difficult to make conclusions on the pattern of antibody formation when patients switch from Myozyme to Lumizyme based on the data from AGLU09411. However, switching from Myozyme to Lumizyme did not appear to impact the development of anti-rhGAA antibodies since the majority of seronegative patients did not seroconvert. Refer to immunogenicity review by Cecilia Tami for further details.

In conclusion, the adverse reactions reported from the Taiwan01 and AGLU09411 trials in patients who were treated with Lumizyme (4000 L) were similar to those observed during the trials that supported approval of Myozyme (160 L). No new or unexpected adverse reactions

were identified from the data provided. Since anaphylaxis and hypersensitivity reactions are the most frequent and concerning adverse reactions associated with alglucosidase alfa, the boxed warning of the current Myozyme and Lumizyme labels adequately address the risk of anaphylaxis and hypersensitivity reactions. It is particularly important to monitor classic infantile-onset Pompe disease patients with compromised cardiorespiratory function during the infusion for signs and symptoms of anaphylaxis or hypersensitivity reactions. Therefore, the boxed warning that communicates the risk of anaphylaxis and hypersensitivity reactions will be retained in the proposed Lumizyme label.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety data submitted contained data from two trials, Taiwan01 and AGLU09411, and available postmarketing data. These data provide safety information for infantile-onset, treatment-naïve patients treated exclusively with the larger scale of alglucosidase alfa (Taiwan01), all Pompe patients who have been switched from Myozyme to Lumizyme (AGLU09411), and long-term postmarketing safety data on Lumizyme. Descriptions of the trial designs are located in Section 5.3 of this review.

Taiwan01: Adverse events reported during Taiwan01 for the 18 infantile-onset patients who met the same inclusion criteria for AGLU01602/02403 were reviewed and compared to the known safety profile of Myozyme (160 L) to determine whether the infantile-onset Pompe patients treated with the larger scales of alglucosidase alfa, Lumizyme, have a comparable safety profile to infantile-onset Pompe patients treated with Myozyme (160 L). Data have been collected since 2006 through the data cut-off of June 30, 2013.

AGLU09411 (ADVANCE): Adverse events reported for patients enrolled in this trial who switched therapy from Myozyme (160 L) to Lumizyme (4000L) were compared to the known safety profile of patients treated exclusively with Myozyme. Ninety-nine patients were enrolled and received at least 1 infusion of Lumizyme (4000 L) since March 22, 2012 through June 20, 2013. A review of the supportive safety data submitted from this trial is included under Section 7.4.5 Special Safety Studies/Clinical Trials.

Post-marketing safety data:

Safety data were reviewed from worldwide post-marketing use of Lumizyme (4000L), as available through spontaneous reports to the Genzyme Global Pharmacovigilance and Epidemiology (GPE) Database. The postmarketing reports from September 29, 2009 through June 30, 2013 (cut-off date for this submission) represent a total of 1,962 patients, of which 1,857 patients were treated in a commercial setting. Of note, the total exposure includes a very limited exposure to Myozyme (160 L) only in the United States since Lumizyme (4000 L) is restricted to non-infantile onset patients who are at least 8 years of age in the United States. Post-marketing safety data comprise all serious adverse events (SAEs) (including all serious infusion-

associated reactions (IARs) and deaths), anaphylaxis, significant allergic reactions, immune-mediated reactions (regardless of seriousness), and immunogenicity data. A review of the post-marketing safety data is provided in Section 8 of this review.

7.1.2 Categorization of Adverse Events

Adverse events were spontaneously reported by the investigator to the Genzyme Pharmacovigilance Department. All events were coded by MedDRA, version 16.0. It should be noted that the applicant did not perform a direct comparison of safety data between the Taiwan01 and AGLU01602/02403 because the adverse events reported during the Taiwan01 trial were based only on what was reported to Genzyme by the investigator. However, in this review, the safety data from the Taiwan01 trial is compared to the known safety data that are provided in the current approved Myozyme label to determine whether the safety profiles are similar.

This clinical reviewer compared verbatim terms with the applicant's coded/preferred term to ensure consistency in coding and revised as needed. Overall, this clinical reviewer's analysis was similar to the applicant's analysis, but the following adjustments were made by the clinical reviewer prior to re-analysis of the Taiwan01 safety data:

- Recoded one event from "Device related infection" to "Catheter related infection"
- Recoded one event of "Feeling cold" to "Chills"
- Recoded one event of "Hypersensitivity" to "Drug hypersensitivity"
- Recoded one event of "Femoral neck fracture" to "Femoral fracture"
- Recoded one event of "Supraventricular extrasystoles" to "Increased frequency of junctional premature contractions"
- Recoded three events of "Pneumonia" and one event of "Pneumonia mycoplasma" to "Pneumonia infection" to better differentiate between patients with aspiration pneumonia
- Recoded one event of "Pruritus generalized" to "Pruritus"
- Recoded one event each of "Papule", "Erythema", and "Generalized erythema" to "Rash"

7.1.3 Pooled Safety Data from Clinical Trials to Compare Incidence

The safety data were not pooled across studies since the patient populations differed between Taiwan01 and AGLU09411. Patients enrolled in the Taiwan01 trial were treatment-naïve and treated exclusively with the larger scale of alglucosidase alfa. In contrast, patients enrolled into AGLU09411 were switched from Myozyme (160 L) to Lumizyme (4000 L) at ≥ 12 months of age to ensure continued treatment given the production constraints of Myozyme. However, an Integrated Summary of Safety (ISS) was provided in which safety data from Taiwan01, AGLU09411, and post-marketing data were reviewed and found to be similar to the known safety profile for both Myozyme and Lumizyme.

7.2 Adequacy of Safety Assessments

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

Eighteen patients from Taiwan01, who were treated exclusively with the larger scales of alglucosidase alfa, met the inclusion criteria from AGLU01602/02403 to allow for comparison between the two infantile-onset populations. Ten patients enrolled in the Taiwan01 trial received only the standard, approved dose of 20mg/kg every other week. The patients in the “Others” dose group (N=8) received a variety of doses (mainly 20 mg/kg weekly or 40 mg/kg every other week) for variable amounts of time in addition to the approved dose. There were no differences observed in clinical outcome between the dose regimens. See Section 6.1.4 Analysis of Primary Endpoint(s), Primary Analysis by Dose Regimen for details. The numbers of patients exposed to the approved dose during AGLU01602/02403 (9 patients received 20 mg/kg every other week) were similar to the numbers of patients in the Taiwan01 trial who were exposed exclusively to the approved dose. The number of patients and duration of exposure to the approved dose is adequate to inform the safety database in combination with the additional safety data from the switch-over trial (AGLU09411). Table 5 below shows the exposure to alglucosidase alfa at the larger scales for the 18 patients in the Taiwan01 trial.

Table 5: Exposure to Larger Scales of Alglucosidase alfa: Taiwan01 safety analysis set

Number of Months on Treatment	
n	18
Mean	45.5
Median	40.5
Std. Dev.	24.70
Min., Max.	4.6, 81.1
Duration of Months on Treatment, n (%)	
< 3 Months	0
≥3 - < 6 Months	1 (5.6)
≥6 - < 9 Months	0
≥9 - < 12 Months	1 (5.6)
≥12 - < 24 Months	2 (11.1)
≥24 - < 36 Months	2 (11.1)
≥36 - < 48 Months	5 (27.8)
≥48 - < 60 Months	0
≥60 - < 72 Months	3 (16.7)
≥72 Months	4 (22.2)

(Source: applicant’s submission, BLA 125291/136, dated 1/30/14, Clinical Study Report: Taiwan01, page 41/158)

Twelve of the 18 patients in the Taiwan01 trial were treated > 36 months with alglucosidase alfa, which represents an adequate duration of therapy to assess safety in this population. Additional supportive long-term safety data will be reviewed in subsequent sections of this review, which includes safety data from patients in the United States who were switched from Myozyme (160 L) to Lumizyme (4000 L) during the AGLU09411 trial, and post-marketing data for patients treated exclusively with the larger scales of alglucosidase alfa worldwide.

7.2.2 Explorations for Dose Response

Patients were divided into two dose groups in the Taiwan01 trial: patients who received 20mg/kg every other week vs. patients who received other doses or frequency of administration (“Others”). All patients received the initial infusion with the approved dose of Lumizyme 20 mg/kg every other week. Dose adjustments were permitted as per standard of care. If patients underwent adjustments to the dose or frequency of administration, they were considered as the “Others” dose group. See Section 6.1.7 for additional details. There were no notable differences in adverse events between patients who were treated with 20 mg/kg every other week and patients who received other doses.

7.2.3 Special Animal and/or In Vitro Testing

None.

7.2.4 Routine Clinical Testing

Patients were evaluated with physical examination, vital signs, and laboratory testing before and during the trial as outlined in Section 9.4 Appendix (Figure 6: Taiwan01 Study Schedule of Events: First Year of the trial and Figure 7: Taiwan01 Study Schedule of Events: Years 2-18 of the Trial). The routine clinical testing and safety monitoring appear to be adequate to ensure the safety of the patients enrolled in the Taiwan01 trial.

7.2.5 Metabolic, Clearance, and Interaction Workup

Metabolic, clearance and interaction workup was not performed during the clinical trials.

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

No new or unexpected adverse reactions for the class of enzyme replacement therapies were identified from the data in this submission.

7.3 Major Safety Results

7.3.1 Deaths

Three deaths were reported for patients enrolled in Taiwan01 who met the inclusion criteria for AGLU01602/02403, all occurring after the 18 month primary analysis period. Patients deaths are described below in Table 6.

Table 6: Deaths during Taiwan01 Trial

Patient ID	Age at first infusion	Age at Death	Reason	Comments
10529	3 months	3 years 7 months	Respiratory failure	Malfunctioning endotracheal tube while sleeping at home. During the 6 months

				prior to death, the patient was frequently admitted to hospital for respiratory distress and infections.
10378	3 months	3 years 7 months	Respiratory failure	Died during an inpatient hospital stay for pneumonia and respiratory distress. Significant medical history of severely compromised cardiac and respiratory function.
10528	5 months	3 years 8 months	Respiratory failure/Cardiac arrest	Patient died outside of the hospital from cardiac arrest secondary to tracheal obstruction from food. Medical history of impaired swallowing related to Pompe.

(Source: reviewer's table, adapted from applicant's submission, sBLA 125291, dated January 30, 2014, Clinical Study Report: Taiwan01, pages 132-146/158)

Respiratory failure as the cause of death is expected with Pompe disease, especially in patients with infantile-onset Pompe disease.¹⁴ Although treatment with enzyme replacement therapy has been shown to extend survival and ventilator-free survival, longer-term follow up demonstrates that beyond 24-36 months, patients with infantile-onset Pompe disease eventually experience a clinical decline.¹⁵

7.3.2 Nonfatal Serious Adverse Events

Seven of the 18 (38.9%) patients experienced at least one serious adverse event (SAE). The most common nonfatal SAEs reported in $\geq 10\%$ of patients (≥ 2 patients) during the Taiwan01 trial were rash, respiratory failure, infectious pneumonia, atelectasis, increased blood creatine phosphokinase, anaphylaxis, pyrexia, and tachypnea. Similarly, the most common serious treatment-emergent adverse events occurring in $> 10\%$ of patients during the clinical trials that supported approval of Myozyme (160 L) were pneumonia, respiratory failure, respiratory distress, catheter-related infection, respiratory syncytial virus infection, gastroenteritis and fever.⁷ Of note, catheter-related infection, respiratory syncytial virus infection, gastroenteritis were also reported during the Taiwan01 trial but at lower frequencies, which is likely due to underreporting because of the trial design (investigator-sponsored trial). Therefore, the SAEs that were reported for infantile-onset patients treated with Lumizyme (larger scales of alglucosidase alfa during the Taiwan01 trial appear to be similar to the SAEs reported for infantile-onset patients treated with Myozyme (160L). Table 7 below shows the nonfatal serious adverse events reported in $\geq 10\%$ of patients from the Taiwan01 trial.

Table 7: Nonfatal Serious Adverse Events in $\geq 10\%$ of patients: Taiwan01

Event	Patients N = 18 n (%)
Rash	3 (16.7)
Respiratory failure	3 (16.7)
Pneumonia infectious*	3 (16.7)
Atelectasis	2 (11.1)
Blood creatine phosphokinase increased	2 (11.1)
Anaphylaxis	2 (11.1)

Pyrexia	2 (11.1)
Tachypnea	2 (11.1)

*Pneumonia due to infectious causes versus aspiration pneumonia

(Source: reviewer's analysis using applicant's data, sBLA 125291, dated January 30, 2014, module 5.3.5.4 Taiwan01 analysis dataset)

Of the AEs occurring in $\geq 10\%$ of patients, respiratory failure, pneumonia infectious, atelectasis, and increased blood creatine phosphokinase probably represent clinical manifestations of Pompe disease. However, rash, pyrexia, and tachypnea could be associated with hypersensitivity reactions (infusion-associated reactions, as defined by the applicant), and will be discussed in the following sections of this review. The review team has requested that the applicant revise the Adverse Reactions section of the label to include only the signs and symptoms that are likely related to Lumizyme.

7.3.3 Dropouts/Discontinuations

There were no patients in the Taiwan01 who experienced an adverse reaction that lead to permanent treatment discontinuation. Two patients in the Taiwan01 trial were lost to follow-up at 4.9 months and 10.3 months, respectively. These patients were considered to be censored observations in the primary efficacy analysis.

7.3.4 Significant Adverse Events

There were 14 severe adverse events that occurred in 3 patients during the Taiwan01 trial. Eight of the 14 severe events occurred in the same patient (patient 10378), who had a significant medical history of severely compromised cardiac and respiratory function. This patient eventually died at 3 years of age (see Table 6 above). The severe adverse events included atelectasis, bronchiolitis, device-related infection, gastric hemorrhage, left ventricular hypertrophy, pneumonia, respiratory failure, respiratory tract infection, and torsade de pointes. All of these events can be attributed to clinical manifestations of Pompe disease or to the complications related to Pompe disease.

7.3.5 Submission Specific Primary Safety Concerns

Of note, the Agency is moving away from using the term "infusion reaction" and is currently recommending that the term "infusion reaction" be replaced with "hypersensitivity reaction" or "anaphylaxis," as appropriate. Although the term "infusion reaction" implies a temporal relationship, infusion reactions are not well defined and may encompass a wide range of clinical events, including anaphylaxis. However, the approved Myozyme label uses the term "infusion reactions" or "infusion-associated reactions." In this review, to provide accurate reference to the language included in the approved Myozyme label, the term "infusion reaction" will be stated only when referring to the Myozyme label. (b) (4)

Anaphylaxis and Hypersensitivity Reactions

Anaphylaxis and hypersensitivity reactions are known adverse reactions associated with enzyme replacement therapies. The applicant reported anaphylaxis, severe allergic reactions, and infusion-associated reactions (IARs) separately. In this review, the term “infusion-associated reactions” will be replaced with “hypersensitivity reactions,” and the signs and symptoms associated with those reactions will be described.

Two patients (10529 and 70002) experienced anaphylaxis based on the Sampson criteria.⁹ The narratives were provided and this reviewer agrees that symptoms described were suggestive of anaphylaxis and related to alglucosidase alfa. Anaphylaxis is a known serious, adverse reaction associated with both Myozyme and Lumizyme. As described in the Myozyme label, based on clinical trial data and postmarketing safety experience, 1% of patients developed anaphylactic shock and/or cardiac arrest during Myozyme infusions. In clinical trials and expanded access programs with Myozyme, approximately 14% of patients developed hypersensitivity reactions that involved at least 2 out of 3 body systems. The risk of anaphylaxis is appropriately communicated through the approved labels for both medications in the Black Box Warning and Section 5 Warnings and Precautions.

Six out of the eighteen (33.3%) patients in the Taiwan01 trial experienced at least 1 hypersensitivity reaction. The most common ARs that were suggestive of hypersensitivity reactions and reported in at least 2 patients were rash (4/18, 22%), pyrexia (2/18, 11.1%), pruritus (2/18, 11.1%), and eyelid edema (2/18, 11.1%). The remaining occurred in one patient each: bradycardia, chills, discomfort, facial edema, irritability, decreased oxygen saturation, rhinorrhea, tachypnea, urticaria, and wheezing. Decreased oxygen saturation, tachypnea, wheezing and urticaria occurred in the patients who were reported to have anaphylaxis. Although bradycardia and urticaria may be suggestive of anaphylaxis, neither of the patients who experienced urticaria or bradycardia had other signs and symptoms that were suggestive of anaphylaxis; therefore, urticaria and bradycardia are listed as hypersensitivity reactions. Overall, the signs and symptoms reported from the Taiwan01 trial are similar in nature to the most common adverse reactions that required intervention (infusion reactions) during clinical trials with Myozyme. As stated in the Myozyme label, infusion reactions were reported in 20/39 (51%) patients and included rash, flushing, urticaria, fever, cough, tachycardia, decreased oxygen saturations, vomiting, tachypnea, agitation, increased blood pressure, cyanosis, hypertension, irritability, pallor, pruritus, retching, rigors, tremor, hypotension, bronchospasm, erythema, face edema, feeling hot, headache, hyperhidrosis, increased lacrimation, livedo reticularis, nausea, periorbital edema, restlessness, and wheezing.⁷

Immune-Mediated Reactions

A medical review of all AEs, with an emphasis on renal disorders, skin disorders, arthralgia and other arthropathies, was performed by Genzyme Global Pharmacovigilance and Epidemiology to determine whether the reactions were consistent with an immune-mediated reaction. Search

terms included glomerulonephritis, proteinuria, hematuria, vasculitis, skin lesion, skin necrosis, arthralgia, myalgia, arthropathy, lymphadenopathy, serum sickness, type III immune complex mediated reaction, and influenza like symptoms. Based upon this analysis, no patient experienced an AR that was suggestive of an immune-mediated reaction during the Taiwan01 trial. This reviewer agrees with the applicant's analysis that there do not appear to be events that are consistent with immune-mediated reactions.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Nine out of the 18 (50%) patients in the Taiwan01 trial reported at least 1 adverse event. Of note, all adverse events were reported as treatment-emergent adverse events (TEAEs); however, reports of non-serious, non-treatment emergent events are unlikely to reveal new or unexpected adverse events in this population. The most common TEAEs occurring in $\geq 10\%$ of patients during the Taiwan01 trial were rash, respiratory failure, pneumonia infectious, pyrexia, atelectasis, blood creatine phosphokinase increased, drug hypersensitivity, eyelid edema, pruritus, tachypnea, and urticaria. Of these TEAEs, rash, pyrexia, eyelid edema, pruritus, tachypnea and urticaria are signs and symptoms that are consistent with hypersensitivity reactions. The others are consistent with clinical manifestations of Pompe disease. The number of events and percentages differ slightly from the applicant's analysis due to the reviewer's recoding. Refer to Section 7.1.2 Categorization of Adverse Events for a description of recoded terms. TEAEs are shown below in Table 8.

Table 8: Treatment- Emergent Adverse Events Reported in $\geq 10\%$ of Patients- Taiwan01

Event	Patients N = 18 n (%)
Rash	4 (22.2)
Respiratory failure	3 (16.7)
Pneumonia infectious	3 (16.7)
Pyrexia	3 (16.7)
Atelectasis	2 (11.1)
Blood creatine phosphokinase increased	2 (11.1)
Drug hypersensitivity	2 (11.1)
Eyelid edema	2 (11.1)
Pruritus	2 (11.1)
Tachypnea	2 (11.1)
Urticaria	2 (11.1)

(Source: reviewer's analysis using applicant's data, sBLA 125291, dated January 30, 2014, module 5.3.5.4 Taiwan01 analysis dataset)

In comparison to the TEAEs reported in the current approved Myozyme label, the most common treatment-emergent adverse events occurring in $\geq 20\%$ of patients were fever, diarrhea, rash, vomiting, cough, pneumonia, otitis media, upper respiratory tract infection, gastroenteritis and decreased oxygen saturation.⁷ The number of events reported and percentages of patients who

experienced these events in the Taiwan01 trial were smaller than those described in the Myozyme label, most likely because the adverse events from Taiwan01 were spontaneously reported during this investigator-sponsored trial. Overall, the types of AEs reported during Taiwan01 are consistent with the AEs described in current approved label for Myozyme or are expected clinical manifestations of Pompe disease.

7.4.2 Laboratory Findings

Laboratory values were collected (ALT, AST, and CK) but due to the small sample size and variability in reporting time points, no formal analysis was performed. Furthermore, changes in these laboratory parameters may be related to the underlying Pompe disease, making it difficult to establish causality to alglucosidase alfa. However, changes from baseline at 18 months (78 weeks) were reviewed for the 18 patients enrolled in the Taiwan01 trial. Table 9 below shows the overall change from baseline for ALT, AST, and CPK lab values at 18 months.

Table 9: Change from Baseline Lab Value at 18 months (ALT, AST, CPK)

	ALT	AST	CPK
Baseline Value (U/L)			
N	17	16	17
Mean ± std	66.9 (34.9)	129.8 (46.9)	867.5 (465.2)
Median (Range)	54.0 (29.0, 138.0)	115.0 (78.0, 219.0)	752.0 (369.0, 2406.0)
18-month Value (U/L)			
N	15	15	15
Mean ± std	124.4 (61.3)	205.5 (122.3)	921.3 (544.1)
Median (Range)	106.0 (34.0, 240.0)	154.0 (77.0, 480.0)	769.0 (303.0, 1972.0)
Change from Baseline at 18 months (U/L)			
N	14	13	14
Mean ± std	52.8 ± 52.1	67.3 ± 112.9	36.7 ± 640.9
Median (Range)	43 (-38, 171)	38 (-59, 327)	-81 (-1124, 1132)

(Source: reviewer's table, adapted from applicant sBLA submission, Abbreviated-Synoptic Clinical Study Report: Taiwan01, dated 1/30/2014, Table 14.3.4.1, page 150-151/158)

The table above shows the change from baseline for the laboratory values collected during the Taiwan01 trial. The 18 month time point was selected since 18 months was the time point selected for the primary efficacy endpoint; however, the individual patients experienced fluctuations in these laboratory values throughout the trial. The large range for each value shows the high level of variability, making it difficult to establish a trend for this small patient population. Additionally, elevations in ALT, AST, and CPK are known to be a manifestation of Pompe disease, rather than related to the ERT treatment. There are a paucity of data on long-term survivors with infantile-onset Pompe disease; however, one study that reviewed medical records of CRIM-positive, infantile-onset Pompe patients between 1999 and 2011, noted that at baseline, the median range for ALT (53-256 U/L), AST (118-672 U/L), and CPK (481-1061 U/L) were markedly elevated and overall, remained elevated during the study duration. CPK did not change

significantly from baseline during the first 24 months of therapy. Although some decreases were noted between 4.5 and 10 months of ERT, after 2 years of therapy, CPK, ALT and AST trended upward. At the most recent follow-up (up to 70 months of ERT therapy), the median ranges for ALT (51-407 U/L), AST (71-742 U/L), and CPK (191-4096 U/L) remained elevated. Despite survival, patients continued to have residual motor delays, which suggests chronic muscle damage that may be reflected in the elevated laboratory values.¹⁶ Therefore, the trends observed in ALT, AST, and CPK during the Taiwan01 trial were expected and consistent with what has been reported for patients with infantile-onset Pompe disease.

Anti-rhGAA IgG

In general, patients who develop anti-rhGAA IgG are at risk for decreased efficacy due to the formation of anti-drug antibodies, as described in the approved Myozyme label.⁷ In the infantile-onset Pompe population, decreased efficacy may result in death or respiratory failure, requiring ventilation. As described in the approved Myozyme label, infusion reactions were more common in antibody-positive patients: 8 of 15 patients with high antibody titers experienced infusion reactions, whereas none of 3 antibody-negative patients experienced infusion reactions.⁷ As stated previously in Section 7.3.4 of this review, 6/18 patients in the Taiwan01 trial were reported to have hypersensitivity reactions (infusion reaction); all 6 patients were anti-rhGAA IgG positive. One patient did not seroconvert and did not experience infusion reactions. These findings are consistent with what is known about the relationship of antibody formation and hypersensitivity reactions. However, since the patients in the Taiwan01 trial did not develop high antibody titers, as was demonstrated in the clinical trials with Myozyme, appropriate comparisons cannot be made. Refer to Table 4 above for a summary of seroconversion status and peak titers for the patients enrolled in the Taiwan01 trial.

7.4.3 Vital Signs

Vital signs were assessed during the Taiwan01 trial according to the Section 9.4 Appendix Figure 6: Taiwan01 Study Schedule of Events: First Year of the trial and Figure 7: Taiwan01 Study Schedule of Events: Years 2-18 of the Trial. Since this investigator-sponsored trial was not designed to demonstrate efficacy of Lumizyme, there are limitations to the data collection. Vital signs were collected as per standard of care during infusion visits and routine clinical follow-up. Abnormal vital signs were included in the patient narratives of serious adverse reactions, including anaphylaxis and hypersensitivity reactions. However, no formal analyses were performed since the data on vital signs were not provided in the submission.

7.4.4 Electrocardiograms (ECGs)

ECGs were performed during the Taiwan01 trial. Hypertrophic cardiomyopathy was the most common finding, which is expected since the patients enrolled in the Taiwan01 trial were required to have a diagnosis of classic infantile-onset Pompe disease that is associated with

¹⁶ Prater, S., et al. The emerging phenotype of long-term survivors with infantile Pompe disease. *Genetics in Medicine* 2012; 17(9): 800-810.

cardiomyopathy. There did not appear to be major changes on the ECGs from the baseline findings. For patients with acute underlying respiratory illness or compromised cardiac and/or respiratory function, there is a known risk of cardiorespiratory failure, as described in Section 5.4 Risk of Acute Cardiorespiratory Failure of the Lumizyme label. The increased risk is possibly associated with fluid overload during the infusions of Lumizyme.⁶ The applicant proposes to include the text from the Boxed Warning in the currently approved Myozyme label into the revised Lumizyme label, which adequately addresses the risk of cardiorespiratory failure in infantile-onset Pompe patients.

7.4.5 Special Safety Studies/Clinical Trials

AGLU09411 (ADVANCE) Trial

Safety data from AGLU09411, a phase 4, open-label, ongoing prospective trial evaluating patients treated with 160L alglucosidase alfa (Myozyme) who were switched to treatment with 4000L alglucosidase alfa (Lumizyme) at ≥ 12 months of age will be reviewed in this section. An abbreviated clinical study report was submitted to present the interim safety findings from the beginning of the trial (March 2012) through the data cut-off date for this interim study report of June 30, 2013. Refer to Section 5.3 for details on the study design. Furthermore, AGLU09411 was conducted in the United States and provides safety data that are applicable to patients in the U.S. with infantile-onset Pompe disease who will likely be switched from their current treatment with Myozyme (160 L) to Lumizyme (4000 L) if the Lumizyme indication is expanded to treat all phenotypes of Pompe patients. This trial also provides safety information for patients who are less than 8 years of age but do not have classic infantile-onset Pompe disease.

Patient Disposition

Ninety-nine patients were screened and treated in AGLU09411. Of these, 81 (81.8%) patients completed the week 52 visit at the time of the data cut-off for this submission. There were 2 patients who did not meet all inclusion criteria but were included with the agreement of the applicant's medical officer: patient 10065043 was receiving investigational gene therapy at the time of screening, and patient 10635079 was consented prior to 1 year of age but did not receive treatment with Lumizyme until 12 months of age. This reviewer does not believe including these two patients impacted the results of the safety analysis. Table 10 below shows the patient disposition.

Table 10: Patient Disposition: AGLU09411

	Number of Patients N = 99 n (%)
Number of patients screened	
Number of patients who passed screening	97 ^a
Treated, n (%)	99 (100.0)
Completed Week 52, n (%)	81 (81.8) ^b
Withdrawn, n (%)	3 (3.0)
Reason withdrawn	
Death	2 (2.0) ^c
Refused further treatment	1 (1.0)

Source: Table 14.1.1

Percentages are based on total number of patients treated.

^a Patient 10065043 was included in the study even though he was receiving investigational gene therapy at the time of screening. And, Patient 10635079 was included in the study even though the patient's parents consented before the patient was 1 year of age.

^b All treated patients, including those patients who did not yet complete the Week 52 visit, are included in safety analyses.

^c Two additional patients died: 1 patient died after the cut-off date for this interim analysis, and 1 patient refused further treatment and subsequently died after study withdrawal at Week 30.

(Source: applicant's submission, sBLA 125291/136, dated January 30, 2014, module 5.3.5.2 AGLU09411 Clinical Study Report Body, page 17/851)

Exposure of Lumizyme (4000L)

All 99 patients were previously treated with Myozyme (160 L). The majority of patients (82/99, 82.8%) had at least 52 weeks of exposure to Lumizyme (4000 L), which appears adequate to assess the safety profile for patients who are switched from Myozyme to Lumizyme. The mean duration of treatment with Lumizyme was 389.8 days (median: 437 days, range: 13-466 days). The total exposure was comparable between male and female patients. Of note, after receiving treatment with Lumizyme (4000 L), 1 patient (10015011) temporarily received treatment with Myozyme (160 L) at the request of the investigator for 4 months, and then returned to treatment with Lumizyme. Additionally, four patients received immunomodulation therapy: patient 10015011 (prophylactic immune tolerance induction treatment during participation in trial AGLU03807), patient 10355062 (IVIG), patient 10455081 (rituximab and methotrexate), and patient 10665015 (rituximab and methotrexate). This reviewer does not believe that including these patients in the safety analysis impacted the results.

Dose Regimen

Sixty-six (66.7%) patients received the approved dose of 20 mg/kg every other week. Smaller percentages of patients received other dose regimens:

- 20 mg/kg every other week: 66 patients, 66.7% (approved dose)
- 20 mg/kg weekly: 11 (11.1%) patients
- 40 mg/kg every other week: 10 (10.1%) patients
- 40 mg/kg weekly, 2 (2.0%) patients
- Others (variable doses and frequencies): 10 (10.1%) patients

Demographics

All patients who were 12 months of age or older and receiving treatment with Myozyme (160L), regardless of phenotype, were given the opportunity to enroll into AGLU09411. The number of males (51 patients, 51.1%) and females (48 patients, 48.5%) were comparable. The majority of patients were white (69.7%), and 81.8% were less than 8 years of age at the time of first infusion with Lumizyme (4000 L). Of the 99 patients enrolled, 38 (38.4%) patients initiated treatment with Myozyme (160 L) prior to 6 months of age, and 25 (25.3%) patients initiated treatment between 6 months and 1 year of age. By definition, 63 (63.6%) patients had classic infantile-onset Pompe disease. Since the majority of patients had classic infantile-onset disease, the safety data reported from this trial provides additional supportive safety data to the Taiwan01 safety reports.

On April 2, 2014, Genzyme provided available information on the CRIM status of patients enrolled in the AGLU09411 in response to an Information Request, dated March 19, 2014. Of note, CRIM status was not routinely collected as per the AGLU09411 protocol since the trial was designed to allow for continued therapy given the ongoing supply constraints of Myozyme. Importantly, efficacy outcomes were provided in response to the Division's information request to supplement the efficacy (survival) data collected in the Taiwan01 trial in treatment-naïve, infantile-onset patients. In order to obtain the data requested, Genzyme contacted the sites to obtain information on CRIM status and cross-checked with the Pompe Registry database. CRIM status was obtained for 42 patients enrolled in AGLU09411; 34 of these patients had infantile-onset disease. Of these 34 patients, 10 were CRIM negative and 24 were CRIM positive. Table 11 below describes the demographics by CRIM status for AGLU09411. Refer to the Section 9.4 Appendix Table 16: AGLU09411 Demographics for further details.

Table 11: Demographics and Clinical Characteristics: AGLU09411

Clinical Review
Juli Tomaino, MD
Efficacy supplement for sBLA 125291/136
Lumizyme (alglucosidase alfa)

		Infantile-onset, CRIM-negative patients	Infantile-onset, CRIM-positive patients	CRIM Unknown	Late-onset patients, treated at < 8 years of age
Number of patients	n(%)	10 (100.0)	24 (100.0)	35 (100.0)	23 (100.0)
Male gender	n(%)	4 (40.0)	11 (45.8)	18 (51.4)	13 (56.5)
Age at diagnosis (years)	Mean ±SD	0.2 ± 0.18	0.5 ± 0.22	0.4 ± 0.23	2.0 ± 1.25
	Median (min,max)	0.1 (0.0, 0.5)	0.5 (0.1, 0.9)	0.4 (0.0, 0.8)	1.6 (0.9, 5.2)
Age at start of 160L product (years)	Mean ±SD	0.4 ± 0.44	1.0 ± 1.43	0.7 ± 1.71	2.4 ± 1.29
	Median (min,max)	0.3 (0.0, 1.5)	0.6 (0.1, 6.8)	0.4 (0.0, 10.4)	1.9 (1.1, 5.3)
Age at switch-over to 4000L product (months)	Mean ±SD	3.1 ± 1.82	4.5 ± 2.89	4.4 ± 3.40	5.6 ± 2.83
	Median (min,max)	3.0 (1.0, 5.7)	3.5 (1.0, 11.3)	3.7 (1.0, 15.4)	6.2 (1.1, 12.6)
Length of time treated with 4000L product months	Mean ±SD	11.7 ± 4.62	13.2 ± 3.82	12.3 ± 3.62	13.1 ± 3.28
	Median (min,max)	14.1 (3.0, 14.7)	14.4 (0.6, 14.9)	14.2 (0.4, 15.3)	14.3 (3.6, 14.8)
Length of time treated with 160L product (months) at switch over to 4000L product	Mean ±SD	32.8 ± 18.66	42.4 ± 35.71	43.8 ± 32.51	39.2 ± 32.43
	Median (min,max)	35.1 (9.7, 58.6)	31.7 (1.9, 130.1)	38.0 (5.5, 108.3)	39.6 (0.4, 108.8)
Number of patients who required invasive ventilation prior to switch	n(%)	6 (60.0)	8 (33.3)	10 (28.6)	5 (21.7)
Number of patients who were on invasive ventilation at time of switch-over	n(%)	5 (50.0)	8 (33.3)	8 (22.9)	5 (21.7)
Number of patients who required invasive ventilation after switch- over	n(%)	0	0	2 (5.7)	1 (4.3)
Number of deaths after switch-over ¹	n(%)	0	1 (4.2)	0	0
Age at time of death (years)	Mean ±SD	0	1.3 ± 0	0	0
	Median (min,max)	0	1.3 (1.3, 1.3)	0	0

Source: AGLU09411 Table 14.1.2

¹ One patient death is provided in the table. However, there were 3 additional patient deaths as noted below.

There were 4 patients deaths. Refer to Table 13 for a description of all patients deaths during AGLU09411.

(Source: applicant's submission, Safety Information Amendment- Response to IR dated March 19, 2014, module 1.11.2, dated April 2, 2014, pages 12-13/26).

*Note that the row titled "Age at switch-over to 4000L product" should state "(years)" as the unit and not months. The inclusion criteria states that patients who are at least 12 months of age will be enrolled in the trial.

There were 34 infantile-onset patients with documented CRIM status; 10 patients were CRIM negative and 24 patients were CRIM positive. At the time of switching from previous therapy with Myozyme to Lumizyme, there were 26/99 (26.3%) patients who dependent on invasive ventilation. Of these patients, 5/10 (50.0%) CRIM-negative, infantile-onset patients and 8/24 (33.3%) CRIM-positive, infantile-onset patients were dependent on invasive-ventilation at entry into the trial. After switching, no additional CRIM-negative patients required invasive ventilation, and no CRIM-negative patients had died at the time of this review. Five late-onset patients who were diagnosed and treated at < 8 years of age required invasive ventilation at

enrollment. One additional late-onset patient required invasive ventilation after switching. There were 2 patients with unknown CRIM status who required invasive ventilation after switching. Of the 99 patients enrolled in the trial, there were 4 deaths. The table above shows one CRIM-positive, infantile-onset patient who died at 1.3 years of age after switching. Refer to Table 13 for descriptions of the other three patient deaths. The age at death ranged from 15 months to 16 years of age and the exposure time to alglucosidase alfa ranged from 9 months to 8 years prior to enrolling in AGLU09411. All patients died from respiratory distress, related to complications of Pompe disease. Although efficacy was not the primary area of interest in this trial, there does not appear to be a significant loss of efficacy after patients switch from Myozyme to Lumizyme.

Adverse Events

Overall, the applicant's and the clinical reviewer's analyses were similar, but adjustments were made by the clinical reviewer prior to re-analysis of the AGLU09411 safety data. Refer to Section 9.4 Appendix Table 17: AGLU09411 Recoded Preferred Terms for a detailed list of the recoded preferred terms. Ninety-seven percent of patients experienced at least one adverse event (AE) and 45.5% of patients experienced a serious adverse event (SAE). No patients discontinued due to an AE and 2 patients died of causes considered to be related to disease progression. Table 12 below summarizes the adverse events that were reported for AGLU09411 (switch-over trial) with comparison to AGLU01602/2403 (trials that supported approval of Myozyme).

Table 12: Summary of Adverse Events: AGLU09411 Compared to AGLU01602/2403

Parameter	AGLU01602/AGLU02403	AGLU09411
Number of patients	18	99
Exposure Median (range)	121.4 weeks [range: 59.7-150 weeks]	62 weeks [range: 2-67 weeks]
Patients experiencing AEs	18 (100%)	97 (97%)
Deaths	6 ¹	4 ²
Discontinuation	1 ³	1 patient refused treatment and subsequently died
Patients with Serious AEs	18 (100%)	45 (45.5%)
Patients with Severe AEs	15 (83%)	26 (26%)
Patients with IARs	11 (61%)	20 (20%)

¹ 3 of the 6 patients died following study completion or withdrawal

² 2 patients died during the reporting period; 1 following withdrawal/refusal to treatment and 1 after the data cut-off

³ 1 patient withdrew at the family wishes and subsequently died 5 months later

(Source: applicant's submission, sBLA 125291/136, dated January 30, 2014, module 2.7.4 Summary of Clinical Safety, page 21/124)

Note that the study designs, patient population, and overall objectives of the two trials shown above are different; therefore, some differences are expected especially for the percentages of patients who experienced SAEs and hypersensitivity/infusion reactions.

Deaths

Three patients (10065050, 10755060, 10735032) died during AGLU09411 or shortly after withdrawal from the trial. One additional patient (10455081) died after the data cut-off date for this submission. All of the deaths were considered to be unrelated to Lumizyme. The age at death ranged from 15 months to 16 years of age and the exposure time to alglucosidase alfa ranged from 9 months to 8 years prior to enrolling in AGLU09411. Details on the patient deaths are included in the Table 13 below.

Table 13: Deaths during AGLU09411

Patient ID	Age at diagnosis	Age at Death	Previous duration of treatment with Myozyme before switch	Reason for Death (study week)	Comments
10065050	< 1 year	16 years	9/14/2004 to 4/3/2012	Cardiac arrest and pneumonia (b) (6)	Diagnosed with infantile-onset Pompe on an unknown date in 1996. Significant medical history of bronchiectasis, left pneumothorax, ventilator-dependent, recurrent pneumonia, muscle weakness, gastrostomy tube dependent. Anti-rhGAA positive (1600).
10755060	< 1 year	15 months	4/1/2011 to 4/17/2012	Respiratory failure (b) (6)	Diagnosed with infantile-onset Pompe disease April 23, 2011. Medical history significant for aspiration, congestive heart failure, obstructive sleep apnea, chronic hypoxia, failure to thrive, bacteremia, respiratory failure. Anti-rhGAA positive (< 100).
10455081	< 1 year	21 months	9/5/2011 to 6/18/2012	Respiratory failure (b) (6)	Diagnosed with infantile-onset Pompe on August 26, 2011. Medical history significant for atelectasis, recurrent respiratory infections, left main-stem bronchus compression, hypertrophic cardiomyopathy, chronic respiratory failure. Anti-rhGAA peak titer (6400), titer was 3200 before death.
10735032	< 1 year	4 years	7/4/2008 to 4/10/2012	Respiratory failure (b) (6)	Diagnosed with infantile-onset Pompe on June 18, 2008. Medical history significant for respiratory distress and influenza B. Patient withdrew from the trial at week 29; patient was not clinically improving. Family declined interventions, including intubation, and discontinued therapy with rhGAA on week 30, prior to death. Anti-rhGAA negative.

(Source: reviewer's table, adapted from applicant's submission, sBLA 125291/136, dated January 30, 2014, Clinical Study Report Body: AGLU09411, pages 42-43/851)

Treatment-Emergent Adverse Events (TEAEs)

Ninety-six out of 99 (97%) patients reported 1,441 adverse events during AGLU09411. Of these, 365 were TEAEs. The number and percentages may differ slightly from the applicant's since this reviewer recoded the preferred terms for the purposes of this safety review. Overall, the results were similar to the applicant's analysis.

The most common TEAEs occurring in $\geq 20\%$ of patients were pyrexia (44.4%), diarrhea (38.4%), respiratory tract infection (40.4%), vomiting (28.3%), cough (27.3%), pneumonia (21.2%), and rash (21.2%). Similar TEAEs were reported in $\geq 20\%$ of patients in clinical trials that supported the approval of Myozyme and included fever, diarrhea, rash, vomiting, cough, pneumonia, otitis media, upper respiratory tract infection, gastroenteritis and decreased oxygen saturation.⁷ No new or unexpected TEAEs were identified during AGLU09411.

Serious Adverse Events

Forty-six of ninety-nine (46.5%) patients experienced 154 serious adverse events (SAE). SAEs that occurred in $\geq 5\%$ of patients during AGLU09411 were pyrexia, pneumonia, respiratory tract infection, dyspnea, and respiratory distress. Table 14 below shows the SAEs that occurred during AGLU09411 in $\geq 5\%$ of patients.

Table 14: Serious Adverse Events occurring in $\geq 5\%$ of patients during AGLU09411

System Organ Class	Patients (N =99) n (%)
Event	
General disorders and administration site conditions	
Pyrexia	8 (8.1)
Infections and infestations	
Pneumonia	19 (19.2)
Pneumonia, viral	5 (5.1)
Respiratory tract infection	5 (5.1)
Respiratory, thoracic and mediastinal disorders	
Dyspnea	5 (5.1)
Respiratory distress	7 (7.1)

(Source: reviewer's table, created using applicant's data, sBLA 125291/136, dated January 30, 2014, module 5.3.5.2 AGLU09411)

The SAEs that occurred during AGLU09411 were similar to the serious treatment-emergent adverse reactions that occurred in $\geq 10\%$ of patients during the clinical trials that supported the approval of Myozyme: pneumonia, respiratory failure, respiratory distress, catheter-related infection, respiratory syncytial virus infection, gastroenteritis and fever.⁷ Of note, respiratory failure, catheter-related infection, respiratory syncytial virus, gastroenteritis also occurred during AGLU09411 but in a smaller percentage of patients. One explanation for fewer patients experiencing certain SAEs, such as respiratory failure, could be related to the differences between the patient populations of the AGLU09411 trial and the trials that supported the approval of Myozyme. For example, patients in the Myozyme trials were treatment-naïve, newly

diagnosed infants < 6 months of age, whereas the patients in AGLU09411 were previously-treated and were at least 12 months of age. Therefore, the AGLU09411 trial tends to select for patients who have survived to at least 12 months of age and are tolerating treatment prior to enrollment in AGLU09411.

Hypersensitivity Reactions

The majority of the hypersensitivity reactions occurred during the infusion or up to 24 hours post-infusion. The applicant defined potential infusion reactions as “all AEs occurring during an infusion or within 2 hours after the completion of an infusion.” All reactions that occurred during this time period, regardless of causality, were reported as potential infusion reactions. However, this reviewer considered hypersensitivity reactions as signs and symptoms that are suggestive of hypersensitivity reactions and occurred during the infusion or up to 24 hours post-infusion.

Based on this reviewer’s analysis, 20 patients experienced 78 adverse reactions that were suggestive of hypersensitivity reactions during the infusion or up to 24 hours post-infusion. The types of adverse reactions are similar to the applicant’s analysis; however, the percentages may differ slightly since the applicant characterized separately infusion-associated reactions, anaphylaxis, and allergic reactions/hypersensitivity reactions. Table 15 below shows the hypersensitivity reactions that occurred in at least 2 patients during AGLU09411.

Table 15: Hypersensitivity Reactions Occurring in ≥ 2 Patients During AGLU09411

Event	Number patients (N =99) n (%)
Pyrexia	6 (6.1)
Urticaria	4 (4.0)
Vomiting	4 (4.0)
Abdominal pain	3 (3.0)
Nausea	3 (3.0)
Rash	3 (3.0)
Chills	2 (2.0)
Cough	2 (2.0)
Diarrhea	2 (2.0)
Edema	2 (2.0)
Flushing	2 (2.0)
Headache	2 (2.0)
Rhonchi	2 (2.0)
Throat irritation	2 (2.0)

(Source: reviewer’s table, created using applicant’s data, sBLA 125291/136, dated January 30, 2014, module 5.3.5.2 AGLU09411)

The signs and symptoms suggestive of hypersensitivity reactions reported during AGLU09411, regardless of time of onset, are consistent with those described in the current approved label for Lumizyme and Myozyme.

Anaphylaxis

Three patients experienced events that were suggestive of anaphylaxis. This reviewer agrees that the narratives provided for the 3 patients are consistent with anaphylactic reactions. Anaphylaxis is a known associated risk of enzyme replacement therapies. The risks of Anaphylaxis and Allergic Reactions are adequately described in Section 5 Warnings and Precautions and in the Boxed Warning of the approved Lumizyme and Myozyme labels.

Immunogenicity Findings Related to Safety

Immune-mediated reactions are known to be associated with Myozyme and Lumizyme, and are described in the current approved labels of both products (Section 5.2 Immune Mediated Reactions). Clinical signs and symptoms of type III immune complex mediated reactions include lymphadenopathy, serum sickness, glomerulonephritis, hematuria, proteinuria, papular rash, purpura-like eruptions, arthritis, serositis, and vasculitis. Eight of the 99 patients were identified with ARs that were suggestive of immune complex disease; 4 patients reported arthralgia and 1 patient each reported arthropathy, myalgia, proteinuria, and skin lesions. All patients were reported to have recovered except for the patient who experienced proteinuria (outcome was pending at the time of this review). Importantly, no patients tested positive for circulating immune complexes. No new or unexpected immune-mediated reactions were identified from the AGLU09411 trial.

Immunogenicity Related to Anti-rhGAA IgG antibodies

Sixty-eight of the 99 (68.7%) patients enrolled in AGLU09411 were antibody positive at baseline. The patients enrolled in AGLU09411 were previously treated with Myozyme and the majority of patients are expected to develop anti-rhGAA antibodies during treatment with alglucosidase alfa. Thirty-one of the 99 (31.3%) patients enrolled into AGLU09411 were seronegative at baseline; 21 (21.2%) remained seronegative throughout the trial. Most of the patients who seroconverted developed antibodies within the first 4 months, which is consistent with what has been observed in other trials with alglucosidase alfa. The rate of seroconversion and pattern of antibody development when patients switch between enzyme replacement therapies has not been previously established. The AGLU09411 trial is the first trial to describe antibody response in patients who are switched. However, switching from Myozyme to Lumizyme did not appear to impact the development of anti-rhGAA antibodies since the majority of seronegative patients did not seroconvert. Refer to immunogenicity review by Cecilia Tami for further details.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There were no dose dependent adverse events seen in the clinical trials.

7.5.2 Time Dependency for Adverse Events

Taiwan01:

Time to adverse event varied from adverse events occurring on day 1 through day 1800;

however, it is difficult to make conclusions based on the data provided since adverse events were spontaneously reported for this investigator-sponsored trial.

AGLU09411:

During the first 6 months of therapy after switching to Lumizyme, 91/99 (91.9%) patients reported adverse events compared to 86/90 (95.6%) patients who reported adverse events after 6 months of therapy with Lumizyme. No trends were observed between duration of therapy and time to onset of adverse reactions or types of adverse events.

7.5.3 Drug-Demographic Interactions

Drug-demographic interactions were not performed for the Taiwan01 trial since all of the patients were similar with respect to age and ethnicity; all were infants with little variation in age, all were Asian, and all treated at the same clinical site in Taiwan.

7.5.4 Drug-Disease Interactions

Drug- disease interactions were not assessed in this submission.

7.5.5 Drug-Drug Interactions

Drug-drug interactions were not assessed in this submission.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Not assessed in this pediatric efficacy supplement.

7.6.2 Human Reproduction and Pregnancy Data

Not assessed in this pediatric efficacy supplement.

7.6.3 Pediatrics and Assessment of Effects on Growth

Assessment of the effects on growth was not performed.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There are no overdose, drug abuse potential, or withdrawal and rebound concerns with Lumizyme and were not assessed in this submission.

7.7 Additional Submissions/Safety Issues

120-Day Safety Update Report

As agreed upon with the sponsor in the written response to the pre-sBLA meeting request, dated July 8, 2013, the sponsor provided the 120-day safety update report on June 2, 2014. The safety update included safety data from the AGLU09411 trial and post-marketing experience since the database cut-off of June 30, 2013 for original sBLA submission. The sponsor also provided additional safety reports from the Taiwan01 trial. Overall, the safety reports were similar to the data reviewed in the sBLA submission, dated January 30, 2014, and were consistent with the known safety profile of alglucosidase alfa. The sponsor did not propose revisions to the draft labeling based on the 120-day safety update report.

ALGU09411 Safety Update

During the update reporting period, the number of patients enrolled in AGLU09411 increased from 99 patients to 105 patients; 102 patients were actively participating in the trial during the reporting period. The majority of patients received the approved dose of alglucosidase alfa 20 mg/kg every other week. Other dose regimens included 20 mg/kg weekly, 40 mg/kg every other week, and 40 mg/kg weekly. A small number of patients received a variety of other doses and frequencies. The median age at first Myozyme (160 L) infusion was 0.6 years (range 0 to 11.4 years) and median age at first infusion with Lumizyme (4000 L) was 4.2 years. The majority of patients (82.9%) were less than 8 years of age at the time of the first infusion with Lumizyme (4000 L). Of the 105 patients, 41 patients were treated with Myozyme (160 L) prior to 6 months of age, and 26 patients were treated between 6 months and 1 year of age.

For trial AGLU09411, two additional deaths were reported during the safety update reporting period. One patient was a 10 year old male with infantile-onset Pompe disease, diagnosed on October 23, 2003. Significant medical history includes prolonged QT interval, low bone density, reactive airway disease, gastrointestinal tube dependent, wheelchair bound, and BiPAP dependency. He was previously treated with alglucosidase alfa (160 L) from 2003 to 2012 prior to entry into AGLU09411. The peak antibody titer was 1600 and decreased to 700 in January 2014. On (b) (6), he was found unresponsive at home and died of respiratory failure. The family declined an autopsy and no further information was available. The second patient was an 11 year old male with infantile-onset Pompe disease diagnosed in March 2001. His medical history was significant for chronic respiratory failure, acute on chronic respiratory failure, ventilator-dependent, and recurrent pneumonia. The peak antibody titer was 200 and had not changed as of the last value obtained on October 20, 2013. In (b) (6) he had repeated episodes of respiratory failure and pneumonia requiring hospitalization in the intensive care unit. He died in (b) (6) from cardiorespiratory arrest and hypoxic brain injury.

During the reporting period, 81/102 (79.4%) experienced 542 adverse events. The most frequent adverse events were pyrexia, vomiting, diarrhea, cough, upper respiratory tract infection, pneumonia, and rash. Severe adverse events reported in $\geq 5\%$ of patients were pneumonia and respiratory distress. No new common adverse events and reactions were identified.

Twenty-seven patients experienced 111 adverse reactions that occurred during the infusion or up to 24 hours post-infusion. The most frequent adverse reactions in ≥ 2 patients included pyrexia, cough, urticaria, vomiting, diarrhea, flushing, nausea, chills, hypertension, abdominal pain, tachycardia, headache, rhonchi, wheezing, and throat irritation. Other reactions that occurred less frequently included arthralgia/arthropathy, myopathy, eyelid ptosis, and peripheral edema. These reactions are likely signs and symptoms of hypersensitivity or immune-mediated reactions and are consistent with the current approved labeling for alglucosidase alfa. Adverse events reported up to 24 hours post-infusion that are likely clinical manifestations of Pompe disease, rather than hypersensitivity reactions, include ECG abnormalities, heart valve incompetence and right ventricular hypertrophy. No new or unexpected hypersensitivity reactions were identified during the 120-day safety update reporting period.

During the safety update period, two additional patients experienced events that were suggestive of anaphylaxis. One patient had previously reported mild to moderate dyspnea, wheezing, urticaria, and flushing; however, the patient experienced new, more significant urticaria and respiratory distress at week 47. The peak anti-rhGAA IgG titer was 12,800 and was positive for complement activation. The anti-rhGAA titer decreased to 3,200 by week 92 and the patient had recovered from all reactions. Another patient experienced tachypnea, wheezing, decreased blood pressure, tachycardia, and pyrexia. The patient recovered from all reactions. The patient was negative for IgE but peak anti-rhGAA IgG titer was 25,600.

No new information on antibody development was identified during the safety update period. The 120-day safety update report stated that there were 32 seronegative patients at baseline enrollment into the trial. Of these, 22 remained seronegative and 10 seroconverted. Of those 10 patients who seroconverted, 2 experienced adverse reactions during the infusion; however, the peak titers were low at 400 and 800.

Post-Marketing Safety Reports During 120-Day Update Reporting Period

There were no new or unexpected adverse reactions identified from the postmarketing data that were provided in the safety update report. There were 24 deaths that occurred in 12 infantile-onset patients, 9 late-onset patients, and 4 patients with unknown phenotype. Most of the deaths were related to respiratory failure, pneumonia, or hypertrophic cardiomyopathy. Six patients met the criteria for anaphylaxis, 3 patients with infantile-onset, 2 patients with late-onset, and 1 with unspecified phenotype but was suspected to have late-onset Pompe disease. The signs and symptoms reported that were consistent with anaphylaxis, hypersensitivity, or immune-mediated reactions were similar to those reported in the sBLA submission and similar to the currently labeled adverse reactions for Lumizyme.

Taiwan01 Trial

Additionally, the sponsor submitted an update of serious adverse events and reactions that were reported during the safety update period for the Taiwan01 trial. These adverse reactions were similar to those reported in the sBLA submission and consistent with the currently labeled safety profile for alglucosidase alfa.

8 Post-market Experience

Since March 3, 2009, Lumizyme, manufactured at the 4000 L scale, has been available to patients outside of the United States for commercial use. The majority of events reported in the postmarketing safety data are from patients who received treatment with Lumizyme since most of the countries had switched to use of 4000 L product by the start date of the safety update reporting period (September 29, 2009).

Safety data from worldwide post-marketing use of larger scale alglucosidase alfa as available through spontaneous reports to the Genzyme Global Pharmacovigilance and Epidemiology (GPE) Database from September 29, 2009 through June 30, 2013 (cut-off date for this submission) represents a total exposure of 1,962 patients. Of those, 1,857 patients were treated in a commercial setting. Additional information provided during the reporting period of July 1, 2013 through September 28, 2013 did not reveal new safety findings. Limitations of the postmarketing safety data include: 1) treatment duration is not collected by Genzyme GPE in the post-marketing setting, 2) reports are voluntary and spontaneous, 3) relationship to treatment is not always included in the reports, and 4) if events recurred within the same case report for one patient, all instances of the event were counted for frequency reports, which may lead to over reporting. Despite the limitations of the postmarketing safety data, the data provide useful information on the longer-term, global experience of patients with Pompe disease who are treated with Lumizyme.

During the reporting period, there were 1,184 total serious adverse events. Of these, 493 occurred in patients with infantile-onset, 291 in patients with late-onset, and 400 in patients with unknown phenotype. There were more reports of SAEs in patients with infantile-onset Pompe disease, but this is reflective of the increased severity of disease compared to patients with late-onset Pompe.

The most frequent serious adverse events were respiratory failure, death, pneumonia, dyspnea, pyrexia, urticaria, and anaphylaxis. The applicant listed disease progression as a SAE, however, most of the SAEs were consistent with the clinical manifestations of Pompe disease, which include respiratory failure and pneumonia. However, urticaria and anaphylaxis are known adverse reactions that are associated with Lumizyme. No new serious adverse reactions were identified from a review of the postmarketing safety data when compared to the adverse reactions that are described in the currently approved label for Lumizyme.

Hypersensitivity reactions were also consistent with the known safety profile of Lumizyme: rash, pyrexia, hypotension, urticaria, erythema, dyspnea, nausea, decreased oxygen saturation, pruritus, flushing, chest discomfort, vomiting, and anaphylaxis. Most of the reported reactions occurred within minutes to 2 hours from initiation of the infusion. For the majority of reactions, the infusions were temporary interrupted and resumed at a slower rate once the event(s) resolved. Reactions were generally managed with the administration of antihistamines, corticosteroids, intravenous fluids, oxygen, and/or epinephrine when clinically indicated. No new or unexpected serious hypersensitivity reactions were identified from the postmarketing safety data reviewed in

this submission. The interventions in response to the hypersensitivity reactions were also consistent with what is already described in the current approved label for Lumizyme (Boxed Warning and Section 5.1 Anaphylaxis and Allergic Reactions).

Additionally, the immune-mediated and delayed-onset reactions that were reported in the postmarketing data are described in Section 5.3 Immune Mediated Reactions and Section 6.3 Postmarketing Experience of the Lumizyme label; arthralgia, arthropathy, membranous glomerulonephritis, influenza-like illness, lymphadenopathy, myalgia, nephrotic syndrome, proteinuria, and skin lesions. No new immune-mediated or delayed-onset reactions were identified from the postmarketing reports.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

This reviewer agrees with the applicant’s proposal to revise the Lumizyme label to incorporate information from current approved Myozyme label into the following sections: Boxed Warning, Highlights, Sections 5, 6, 8.4, 12, and 14. Since comparability has been established and the indication will be expanded to include all Pompe patients, it is appropriate to include relevant information from the clinical trials that supported approval of Myozyme for the treatment of infantile-onset Pompe patients. Furthermore, the applicant proposes to include additional safety information in Section 6.1 for patients who switched from Myozyme to Lumizyme during AGLU09411. Since no new safety signals were identified during AGLU09411, a general statement to inform prescribers that no new safety events were identified should be included in the label. During the labeling negotiations, the review team has requested information from the AGLU09411 trial on patients who experienced an initial hypersensitivity reaction or anaphylaxis after switching to determine whether the risk increased after switching products. If there appear to be increased risk of hypersensitivity or anaphylaxis after switching from Myozyme (160 L) to Lumizyme (4000 L), a statement describing this risk should be added into the label. However, the AGLU09411 trial did not collect previous adverse reaction experience. Based on the

Information Request, the applicant attempted to collect information from the Genzyme safety database on patients who were enrolled in AGLU09411 and may have had a documented hypersensitivity reaction, including anaphylaxis, during a previous clinical trial or in the post-marketing setting. Of the 27 patients in the AGLU09411 trial who experienced a hypersensitivity reaction, including anaphylaxis, 11/27 (40.7%) had previously experienced a hypersensitivity reaction in a clinical trial other than AGLU09411 (3 patients) or in the post-marketing setting (8 patients). Genzyme does not have information necessary to confirm whether the remaining 16 patients experienced a previous hypersensitivity reaction prior to enrollment in AGLU09411. Since the data in the post-marketing setting are voluntarily reported and often incomplete, it does not appear reasonable to assume that all reactions experienced during the AGLU09411 trial were the initial hypersensitivity reactions. Since available data are inadequate to support a definitive conclusion, this reviewer does not recommend that a statement be added to the labeling to include the number of patients who experienced initial hypersensitivity reactions after switching from Myozyme (160 L) to Lumizyme (4000 L) at this time. Additionally, the applicant proposes to delete information related to the Lumizyme REMS since the REMS will likely be released upon approval of this efficacy supplement.

In general, this reviewer agrees with the applicant's proposed revisions to include the information from the Myozyme label since the review of the analytical data have established comparability between Myozyme (160 L) and Lumizyme (4000 L). (b) (4)



9.3 Advisory Committee Meeting-

None

9.4 Supplementary Tables

Figure 6: Taiwan01 Study Schedule of Events: First Year of the trial

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Figure 7: Taiwan01 Study Schedule of Events: Years 2-18 of the Trial

year	2	2	3	3	4	4	5	5	6~12	6~12	13~18	13~18
week	26	52	26	52	26	52	26	52	26	52	26	52
weight and height	x	x	x	x	x	x	x	x	x	x	x	x
vital signs: BT	x	x	x	x	x	x	x	x	x	x	x	x
vital signs: HR, RR, BP	x	x	x	x	x	x	x	x	x	x	x	x
Physical examination and neurologic examination	x	x	x	x	x	x	x	x	x	x	x	x
CXR/ whole spine AP-Lat	x	x		x		x		x		x		x
echocardiogram	x	x		x		x		x		x		x
EKG	x	x		x		x		x		x		x
24hr holter	x	x		x		x		x		x		x
CBC/DC	x	x	x	x	x	x	x	x	x	x	x	x
biochemistry*: AST, ALT, ALK-P, BUN, Cre, CK	x	x	x	x	x	x	x	x	x	x	x	x
blood gas	x	x	x	x	x	x	x	x	x	x	x	x
antibody (IgG): red-tipped empty tube 2ml whole blood, submitted at room temperature to Dr. Wuh-Liang Hwu Lab	x	x	x	x	x	x	x	x	x	x	x	x
save plasma: green-tipped empty tube 2ml whole blood, submitted at room temperature to Dr. Wuh-Liang Hwu Lab	x	x	x	x	x	x	x	x	x	x	x	x
Urine routine	x	x	x	x	x	x	x	x	x	x	x	x
Urine oligosaccharides (Glc4): Urine 10ml, submitted at room temperature to Dr. Wuh-Liang Hwu Lab	x	x	x	x	x	x	x	x	x	x	x	x
MRI/MRS/DTI /MRA of brain				x				x		a ^{at 3 year}		a ^{at 3 year}
MRI/MRS/DTI of heart				x				x		a ^{at 3 year}		a ^{at 3 year}
MRI/MRS/DTI of thigh (to lower spine)				x				x		a ^{at 3 year}		a ^{at 3 year}
Lung function Test (for both standing and supine positions)				a				x	x	x	x	x
sleep study		x		x		x		x		x		a ^{at 3 year}
Oph checkup	a	a	a	x	a	x	a	x	a	x		
ENT checkup (Include hearing test)	a	x	x	x	x	x	x	x		x		
Rehabilitation checkup	x	x		x		x		x				
Speech therapy checkup		x		x		x		x		a		
IQ test					x					x ^{at 6 year}		
Nutrition checkup	a			a		a		a		a		a
walk test (6MWT and 4 step Test)	x	x		x		x		x		x		x
Questionnaire		x		x		x		x		x		x
AIMS	x	x										
PDMS-2	x	x		x		x		x		x		x
PEDI and Pompe PEDI	x	x		x		x		x		x		x
GMFM66	x	x		x		x		x		x		x
Modified BSID-II	x	x		x								
CDTI-II	x	x		x		x		x				
Crunches										x		x

Lumizyme (alglucosidase alfa)

[illegible]

(Source: applicant's submission, sBLA 125291/136, dated January 30, 2013, section 5.3.5.4, Taiwan01 Clinical Study Report 16.1.1 Protocol, pages 13-14/89)

Figure 8: AGLU09411: Study Schedule of Events

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	Screening	52-Week Treatment Period							
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
	(-3 months)	Day 1	Week 2 (±7 days)	Week 4 (±7 days)	Week 6 (±7 days)	Week 8 (±7 days)	Week 10 (±7 days)	Week 12 (±7 days)	Week 14 (±7 days)
Obtain Informed Consent	X								
Confirm Study Eligibility	X	X							
Demographics and Baseline Characteristics	X								
Urine Pregnancy Test ^a	X			X		X		X	
GAA Mutation Analysis ^b	X								
Physical Examination	X	X							
ECHO ^{c,d} /ECG ^d	X	ECHO							
Pulmonary Function Tests ^{c,d}	X	X							
Hematology/Chemistry/ Urinalysis	X								
IgG Antibodies ^{c,e}	X	X		X		X		X	
IgG Inhibitory Antibodies ^{c,f}	X	X		X		X		X	
Plasma PK (optional) ^g	X	X							
Pompe MFH/GMFCs	X								
GMFM-88 ^{c,d}	X	X							
Weight ^h	Continuous Monitoring								→
Height	X	X							
Vitals ^h	Continuous Monitoring								→
Ventilator Use Status ^h	X	X	X	X	X	X	X	X	X
Infusion of Alglucosidase Alfa (e.g., qw or qow) ⁱ	Continuous Monitoring								→
Adverse Event Assessment	Continuous Monitoring								→
Concomitant Medications/ Therapies ^j	Continuous Monitoring								→

	52-Week Treatment Period								
	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16	Visit 17	Visit 18
	Week 16 (±7 days)	Week 18 (±7 days)	Week 20 (±7 days)	Week 22 (±7 days)	Week 24 (±7 days)	Week 26 (±7 days)	Week 28 (±7 days)	Week 30 (±7 days)	Week 32 (±7 days)
Urine Pregnancy Test ^a	X		X		X		X		X
Physical Examination						X			
ECHO ^d /ECG ^d						X			
Pulmonary Function Tests ^d						X			
Hematology/Chemistry/ Urinalysis						X			
IgG Antibodies ^e	X		X		X		X		X
IgG Inhibitory antibodies ^f	X		X		X		X		X
Plasma PK (optional) ^g						X			
GMFM-88 ^d						X			
Weight ^h	Continuous Monitoring								
Height						X			
Vitals ^h	Continuous Monitoring								
Ventilator Use Status ^h	X	X	X	X	X	X	X	X	X
Infusion of Alglucosidase Alfa (e.g., qw or qow) ⁱ	Continuous Monitoring								
Adverse Event Assessment	Continuous Monitoring								
Concomitant Medications/ Therapies ^j	Continuous Monitoring								

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	52-Week Treatment Period								
	Visit 19	Visit 20	Visit 21	Visit 22	Visit 23	Visit 24	Visit 25	Visit 26	Visit 27
	Week 34 (±7 days)	Week 36 (±7 days)	Week 38 (±7 days)	Week 40 (±7 days)	Week 42 (±7 days)	Week 44 (±7 days)	Week 46 (±7 days)	Week 48 (±7 days)	Week 50 (±7 days)
Urine Pregnancy Test ^a		X		X		X		X	
Physical Examination									
ECHO ^d /ECG ^d									
Pulmonary Function Tests ^d									
Hematology/Chemistry/ Urinalysis			X						
IgG Antibodies ^e		X		X		X		X	
IgG Inhibitory Antibodies ^f		X		X		X		X	
GMFM-88 ^d									
Weight ^b	Continuous Monitoring →								
Height									
Vitals ^b	Continuous Monitoring →								
Ventilator Use Status ^b	X	X	X	X	X	X	X	X	X
Infusion of Alglucosidase Alfa (e.g., qw or qow) ⁱ	Continuous Monitoring →								
Adverse Event Assessment	Continuous Monitoring →								
Concomitant Medications/ Therapies ^j	Continuous Monitoring →								

	52-Week Treatment Period	Extension Treatment Period	Follow-Up Visit
	Visit 28 ^k		
	Week 52 (±7 days)	Repeating 6-Month Modules (±21 days)	Last Infusion + 30 days (±7 days)
Urine Pregnancy Test ^a	X	X	
Physical Examination	X	X	
ECHO ^d /ECG ^d	X	X	
Pulmonary Function Tests ^d	X	X	
Hematology/Chemistry/ Urinalysis	X	X	
IgG Antibodies ^e	X	X ^l	
IgG Inhibitory Antibodies ^f	X	X ^l	
GMFM-88 ^d	X	X	
Weight ^b	Continuous Monitoring →		
Height	X	X	
Vitals ^b	Continuous Monitoring →		
Ventilator Use Status ^b	X	X	
Infusion of Alglucosidase Alfa (e.g., qw or qow) ⁱ	Continuous Monitoring →		
Adverse Event Assessment	Continuous Monitoring →		X
Concomitant Medications/Therapies ^j	Continuous Monitoring →		X

ECG=electrocardiogram; ECHO=echocardiogram; GAA=acid α-glucosidase; GMFCS=Gross Motor Function Classification System;

GMFM-88=Gross Motor Function Measure-88 Scale; IgG=immunoglobulin G; MFH=Motor Function History; PK=pharmacokinetics; qow=every other week; qw=every week

^a Testing is for female patients of childbearing potential only.

^b Gene mutation analysis is required for all patients. If gene mutation analysis was conducted prior to signing the informed consent, these results may be used provided that the analysis was conducted by a certified laboratory, written results are provided to the site, and participants (patients and/or parents/legal guardians) give consent to use the results.

^c If assessment was conducted within 1 month prior to Day 1, these assessment results may be used and the assessment does not need to be repeated at Day 1.

^d Decline in cardiac status, motor function, and pulmonary function must be confirmed by retest within 4 weeks.

^e Serum IgG samples are collected pre-infusion at each timepoint.

^f Inhibitory antibody test results will be obtained for those patients who test positive for IgG.

^g Samples will be obtained from time 0 to 24 hours, which captures the vast majority of plasma exposure (area under the concentration-time curve), including the critical period where alglucosidase alfa distributes to the target tissues, which are the sites of activity.

^h Assessment completed for every infusion.

ⁱ Treatments will be administered at the same dose and dose regimen used for the patient's routine treatment prior to the study if clinically feasible.

^j All concomitant medications and therapies, including those given as prophylaxis or prior to an infusion, will be recorded on the eCRF.

^k Patients who are prematurely withdrawn from the study will be asked to complete all Week 52 assessments as discontinuation assessments prior to withdrawal, if possible.

^l Assessment completed every 3 months during the extension treatment period.

(Source: applicant's submission, sBLA 125291/136, dated January 30, 2014, section 5.3.5.2 Protocol or Amendment, AGLU09411 Clinical Study Report 16.1.1 protocol, section 15.1 Appendix A, pages 68-71/76)

Table 16: AGLU09411 Demographics

	Number of Patients Treated with 4000L alglucosidase alfa N = 99
Male, n (%)	51 (51.5)
Ethnicity, n (%)	
Hispanic or Latino	16 (16.2)
Not Hispanic or Latino	79 (79.8)
Not Reported	1 (1.0)
Unknown	2 (2.0)
Race, n (%)	
Asian	8 (8.1)
Black	24 (24.2)
White	69 (69.7)
Not Reported	2 (2.0)
Age at first <i>Myozyme</i> infusion (years)	
n	98*
Mean	1.7
Median	0.6
Std. Dev.	2.62
Min., Max.	0.0, 11.4
Age group at first <i>Myozyme</i> infusion, n (%)	
< 0.5	38 (38.4)
0.5 - < 1	25 (25.3)
1 - < 5	26 (26.3)
5 - < 8	4 (4.0)
8 - < 12	6 (6.1)
Age at first <i>Lumizyme</i> (4000L) infusion (years)	
n	99
Mean	5.2
Median	4.2
Std. Dev.	3.77
Min., Max.	1.0, 18.7
Age group at first <i>Lumizyme</i> (4000L) infusion, (years)	
< 2	22 (22.2)
2 - < 5	35 (35.4)
5 - < 8	24 (24.2)
8 - < 12	11 (11.1)
≥ 12	7 (7.1)

*Age at first infusion of *Myozyme* was not calculated for patient 10675056 who received first infusion during year 1999 but the specific date was unknown.

(Source: reviewer's table, adapted from applicant submission sBLA 125291/136, dated January 30, 2014, module 5.3.5.2 AGLU09411 Clinical Study Report Body, page 22-23/851)

Table 17: AGLU09411 Recoded Preferred Terms

Applicant's term (number of events recoded)	Reviewer's term
Abdominal discomfort (6) Abdominal pain upper (10)	Abdominal pain
Abnormal faeces (1)	Abnormal fecal odor
Abscess limb (1)	Abscess
Axillary mass (1)	Axillary soft tissue mass
Blood pressure systolic increased (1)	Blood pressure increased
Bloody discharge (1)	Bloody discharge from tracheostomy
Bronchial hyperreactivity (1)	Bronchospasm
Bronchial secretion retention (6) Increased bronchial secretion (3)	Bronchiectasis
Burning sensation (1)	Paresthesia
Cardiac failure congestive (1)	Cardiac failure
Catheter site discharge (1) Catheter site erythema (1) Catheter site inflammation (2) Catheter site oedema (1)	Gastrostomy site inflammation
Catheter site erythema (1) Catheter site oedma (2) Catheter site swelling (1)	Catheter site inflammation
Chest discomfort (2)	Chest pain
Conjunctivitis infective (1)	Conjunctivitis
Convulsion (2)	Seizure
Deafness unilateral (1)	Deafness
Device component issue (1)	Device access issue
Erythema (6)	Rash
Eye pruritus (1)	Eye irritation
Eye swelling (1)	Eyelid edema
Faeces discoloured (2)	Dark stools
Frequent bowel movements (3)	Diarrhea
Gastroenteritis viral (3) Viral test positive (1) Gastrointestinal infection (2)	Gastroenteritis
Gastrostomy tube removal (1)	Device dislocation
Heart rate increased (2)	Tachycardia
Ligament sprain (1)	Limb injury
Lobar pneumonia (2)	Pneumonia
Macule (1) Papule (3) Rash erythematous (1) Rash macular (1) Rash pruritic (1) Viral rash (1) Rash pustular (1)	Rash
Medical Device Malfunction (4)	Device malfunction
Motor developmental delay (1)	Motor dysfunction
Muscle contractions involuntary (1)	Muscle contracture
Myalgia (1)	Musculoskeletal pain
Nasal discharge discolouration (1)	Nasal congestion

Clinical Review
Juli Tomaino, MD
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Lumizyme (alglucosidase alfa)

Oedema (3) Oedema pheripheral (6)	Edema
Otitis media acute (6) Otitis media chronic (1)	Otitis media
Oropharyngeal pain (5)	Pharyngitis
Pneumonia parainfluenzae viral (1) Pneumonia respiratory syncytial viral (2)	Pneumonia viral
Respiratory tract haemorrhage (3)	Hemoptysis
Skin disorder (1)	Skin exfoliation
Increased viscosity of bronchial secretion (1) Increased sputum production (1) Secretion discharge (4)	Increased upper airway secretion
Staphylococcus test positive (1)	Staphylococcal infection
Ulcer (1)	Skin ulcer
Upper respiratory tract congestion (4) Upper Respiratory tract infection (40) Viral upper respiratory tract infection (4) Upper-airway cough syndrome (2) Bronchiolitis (2) Bronchitis (6) Viral test positive (1)	Respiratory tract infection
Use of accessory respiratory muscles (1)	Respiratory distress
Urinary tract infection staphylococcal (1)	Urinary tract infection
Vulvovaginal erythema (1)	Vulvovaginal disorder

(Source: reviewer's table)

Clinical Investigator Financial Disclosure – Taiwan01 Trial

Clinical Investigator Financial Disclosure
Review Template

Application Number: BLA 125291/136

Submission Date(s): January 30, 2014

Applicant: Genzyme

Product: Lumizyme

Reviewer: Juli Tomaino

Date of Review: May 29, 2014

Covered Clinical Study (Name and/or Number): Taiwan01

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
--	---	---

Total number of investigators identified: <u>2</u>		
Number of investigators who are applicant employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in applicant of covered study: _____</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*. Also discuss whether these interests/arrangements, investigators who are applicant employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are applicant employees, or lack of disclosure despite due diligence affect the approvability of the application.

Clinical Review
Juli Tomaino, MD
Efficacy supplement for sBLA 125291/136
Lumizyme (alglucosidase alfa)

There were no investigators or sub-investigators with disclosable financial interest as defined in 21 CFR 54.2 for the Taiwan ISS. However,

(b) (4)

(b) (6)

Clinical Investigator Financial Disclosure –AGLU09411 (ADVANCE) Trial

Clinical Investigator Financial Disclosure
Review Template

Application Number: BLA 125291/136

Submission Date(s): January 30, 2014

Applicant: Genzyme

Product: Lumizyme

Reviewer: Juli Tomaino

Date of Review: May 29, 2014

Covered Clinical Study (Name and/or Number): AGLU09411 (ADVANCE)

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>3 with disclosable financial interests</u>		
Number of investigators who are applicant employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>3</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>3</u> Proprietary interest in the product tested held by investigator: <u>0</u>		

Significant equity interest held by investigator in applicant of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*. Also discuss whether these interests/arrangements, investigators who are applicant employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are applicant employees, or lack of disclosure despite due diligence affect the approvability of the application.

The following disclosed financial interests/arrangements do not affect the approvability of the application or raise questions about the data integrity since the majority of the funding was for education, fellowship programs, and research.

(b) (6)

(b) (6)

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immediately following this page

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/s/

JULI A TOMAINO
07/08/2014

JESSICA J LEE
07/08/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number:
BLA 125291/136

Applicant: Genzyme

Stamp Date: 1/30/2014

Drug Name: Lumizyme
(αglucosidase alfa 4000 L)

NDA/BLA Type: efficacy
supplement

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	One clinical trial will be the source of efficacy data and is included in module 5. No additional ISE is required.
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	Dose-ranging study is not needed as this efficacy supplement intends to support chemical comparability of the two scales of Lumizyme.
EFFICACY					

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			PEDIATRIC AND MATERNAL HEALTH STAFF REQUEST FOR CONSULTATION	
TO: CDER Pediatric and Maternal Health Staff <i>(please check)</i> Pediatrics <input type="checkbox"/> Maternal Health <input type="checkbox"/> Both <input checked="" type="checkbox"/>			FROM <i>(Name, Office/Division, and Phone Number of Requestor)</i> : Elizabeth Ford/ODEIII/DGIEP/6-0193	
DATE 2/25/2014	IND NO.	NDA/BLA NO. 125291	TYPE OF DOCUMENT supplemental BLA	DATE OF DOCUMENT 1/30/2014
NAME OF DRUG Lumizyme		NAME OF FIRM Genzyme	CLASSIFICATION OF DRUG	PDUFA Goal Date 7/30/2014
Requested Consult Completion Date: 7/30/2014		<input type="checkbox"/> Urgent* (< 14 days)	<input type="checkbox"/> Priority (14-29 days)	<input checked="" type="checkbox"/> Routine ≥ 30 days
*Note: Any consult requests with a desired completion date of < 14 days from receipt must receive prior approval from PMHS team leaders. Also, please check one of the three boxes above and also put in a due date.				
REASON FOR REQUEST				
Pediatrics: <input checked="" type="checkbox"/> Labeling Review <input type="checkbox"/> Written Request/PPSR <input type="checkbox"/> PREA PMR/General Regulatory Question <input type="checkbox"/> SPA <input type="checkbox"/> Action Letter Review <input type="checkbox"/> 30-day IND Review <input type="checkbox"/> Other Protocol Review <input type="checkbox"/> Meeting Attendance <input type="checkbox"/> PeRC Preparation Assistance <input type="checkbox"/> Other (please explain):			Maternal Health Team: <input checked="" type="checkbox"/> Labeling Review <input type="checkbox"/> Pregnancy Exposure Registry (protocol or report) <input type="checkbox"/> Clinical Lactation Study (protocol or report) <input type="checkbox"/> Pregnancy PK (protocol or report) <input type="checkbox"/> 30-day IND Review <input type="checkbox"/> Risk Management – Pregnancy Prevention and Planning <input type="checkbox"/> Evaluation of possible safety signal <input type="checkbox"/> Guidance development <input type="checkbox"/> Other (please explain):	
Link to electronic submission (if available): This is an eCTD submission. Select the link to access the .enx file: < http://cberedrweb.fda.gov:8080/esp/cberedr.jsp?folderObjId=0bbcaea6813bf95a > APPLICATION INFORMATION: Application Number: 125291\136 eCTD Sequence Number: 0294 CBER Receipt Date: 30-Jan-2014			Materials to be reviewed: Draft labeling	
1. Please briefly describe the submission including drug's indication(s): Application: 125291/136 Goal Date: July 30, 2014 Drug Name: Lumizyme Sponsor: Genzyme Proposed Indication: From: LUMIZYME (alglucosidase alfa) is a lysosomal glycogen-specific enzyme indicated for patients 8 years and older with late (non-infantile) onset Pompe disease (acid α -glucosidase (GAA) deficiency) who do not have evidence of cardiac hypertrophy. The safety and efficacy of LUMIZYME have not been evaluated in controlled clinical trials in infantile-onset patients, or in late (non-infantile) onset patients less than 8 years of age To: LUMIZYME (alglucosidase alfa) is a lysosomal glycogen-specific enzyme indicated for patients with Pompe disease (acid α -glucosidase (GAA) deficiency).				

Division: DGIEP
Medical Team Leader: Jessica Lee
RPM: Elizabeth Ford

Background Summary. There are two main phenotypes of Pompe disease, infantile-onset and juvenile/adult onset. They differ in that the infantile-onset is more severe and with cardiac involvement, such as cardiac hypertrophy. Because of this difference, efficacy cannot be extrapolated from adult trials. There are two approved therapies for Pompe disease in the United States: Myozyme (produced on a 160L bioreactor scale) and Lumizyme (produced on a 4000L scale). Both are recombinant Alglucosidase alfa (rhGAA) but chemical comparability has not yet been established between the 160L and 4000L products based on glycosylation differences. There have been drug shortages of the 160L product (Myozyme) which was approved in 2006 in the United States for infantile-onset patients with Pompe disease. Myozyme was shown to be safe and effective in 18 patients with infantile-onset Pompe disease and demonstrated markedly improved survival and ventilator-free survival compared to an untreated historical cohort. Myozyme (160L) is currently restricted to Pompe patients under 12 months of age. A second treatment for Pompe disease, Lumizyme (4000L), was approved in 2010 for juvenile/adult onset Pompe patients and approved for treatment in patients over the age of eight years old. Of note, Myozyme is the approved name outside of the US for the 4000L product and all ages of Pompe patients are treated with the 4000L outside of the US.

Current Submission. The sponsor proposes to expand the indication for Lumizyme (4000 L) for the treatment of all Pompe patients. The current efficacy supplement contains data from the following sources:

- 1) Analytical comparability package
- 2) Supporting clinical (survival) data from infantile-onset patients treated exclusively with Lumizyme (4000 L) through a single study site in Taiwan, and comparison of survival data to the original cohort of infantile-onset patients from trials that supported Myozyme (160 L) approval, using same inclusion criteria.
- 3) Safety data from an ongoing, open-label switch-over trial where infantile-onset patients who received treatment previously with the 160 L product were switched to the 4000L product at 12 months of age.
- 4) Long-term post-marketing safety data

Consult for PMHS. DGIEP requests PMHS to attend team meetings for this product, and provide verbal input as appropriate. No formal written consult write-up is necessary.

3. Meeting dates:

Filing meeting on March 6, 2014 at 4PM. We will notify you of future meetings when they are scheduled.

4. DARRTS Reference ID # for Prior Peds or Maternal Health consults for this product (within the last 3 years):

Review team:

Project Manager: Elizabeth Ford

Clinical reviewer & Team Leader: Juli Tomaino & Jessica Lee

Pharmacology/Toxicology reviewer & Team Leader: Fang Cai & David Joseph

Clinical Pharmacology reviewer & Team Leader: Christine Hon & Yow-Ming Wang

Other:

PRINTED NAME or SIGNATURE OF REQUESTOR:

METHOD OF DELIVERY (Please check)

☐ DARRTS ☐ EMAIL ☐ HAND
☐ OTHER

Version: DARRTS 06/01/2011

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/s/

ELIZABETH A FORD

03/11/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: Open-label, single-center Investigator-sponsored study of patients with infantile-onset Pompe disease treated with alglucosidase alfa Indication: patients with infantile-onset Pompe disease. Pivotal Study #2 Indication:			X	Studies submitted were agreed upon during the pre-sBLA meeting. Clinical information is supportive of establishing chemical comparability.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			Previously agreed upon by the Division
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		Source of foreign data (Taiwan) was discussed at preBLA meeting and agreed upon. We plan to send an IR to the sponsor to request that they submit their rationale for applicability of foreign data to the US population.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		Source of foreign data (Taiwan) was discussed at preBLA meeting and agreed upon. We plan to send an IR to the sponsor to request that they submit their rationale.
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms	X			

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	in a legible format (deaths, serious adverse events, and adverse dropouts)?				
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes__

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Juli Tomaino, MD	3/6/14
Reviewing Medical Officer	Date
 Jessica Lee, MD	 3/6/14
Clinical Team Leader	Date

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/s/

JULI A TOMAINO
03/10/2014

JESSICA J LEE
03/10/2014

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

BLA 125291/136

CHEMISTRY REVIEW(S)



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Division of Therapeutic Proteins
Bethesda, MD 20892
Tel. 301-827-1790

Memorandum of Review (Addendum)

STN: 125291/136

Subject: CMC perspective on labelling discussions for the Efficacy Supplement to expand indication to include all Pompe patients

Applicant: Genzyme
Product: Lumizyme
Indication: For use in patients with Pompe disease (GAA deficiency)

Received Date: January 30, 2014
Review Date: July 30, 2014
Action Due Date: August 1, 2014

Primary Reviewer: Christopher Downey, PhD
Secondary Reviewer: Juhong Liu, PhD
Tertiary Reviewer: Susan Kirshner, PhD

Primary Review Team:
Medical Officer: Juli Tomaino, MD
Pharm/Tox: Fang Cai, PhD
Immunogenicity: Cecilia Tami, PhD
Clinical Pharmacology: Christine Hon, PhD
Statistics: Freda Cooner, PhD
DRISK (REMS): Robert Pratt, PharmD
PMHS: Alyson Karesh, MD
OSI: Susan Leibenhaut, MD
RPM: Kevin Bugin

Addendum to Include Labelling Discussions About Process Scale Information:

Herein I summarize and comment from a CMC/DTP perspective on the internal Agency discussions about 1) whether to include descriptions of manufacturing scale information and 2) whether to include PK data obtained using 160 L and 2000 L process scale materials in the Lumizyme label.

The currently approved Lumizyme label included pharmacokinetics (PK) data from a study performed on adult-onset Pompe patients using material produced by the now-defunct 2000 L scale manufacturing process; the current label does not include PK data from infantile-onset

patients.

(b) (4)

The Clin-Pharm reviewers determined in their labeling review that “it is not acceptable to have the Myozyme 160L PK information for infantile-onset disease patients in the same labeling that contains...2000L PK information for late-onset adult disease patients...because the PK of ...2000L product was shown to be not comparable to the Myozyme 160L product.” They therefore recommended including only the Myozyme160 L PK information for the infantile-onset disease patients in the Lumizyme labeling and removing the 2000L PK information for the late-onset disease adult patients.

(b) (4)

(b) (4)

DTP acknowledged Clin-Pharm’s concerns regarding the previously reviewed PK study that failed to demonstrate comparability with respect to PK for the 160L and 2000L materials. DTP agreed that inclusion of the 2000L data together with the 160 L data on the labeling might imply PK comparability between these scales that is inconsistent with the Clinical Pharmacology review conclusions regarding that study. The Clin-Pharm reviewers pointed out that Myozyme was approved with only the infant PK data in the label even though Myozyme was not specifically limited to infants. The Clinical reviewers determined that without a compelling and clinically relevant reason to include the 2000L PK data, they could not discount the results of the PK comparison of the 160L and 2000L products and include the 2000L PK data in the label.

(b) (4)



Reviewer comments:

- 1) *In separate studies, the 4000 L Lumizyme product has been shown to be analytically comparable, as defined by ICH 5QE, to the 160 L product and to the discontinued 2000 L product. Therefore, from a product quality perspective it would be acceptable to include clinical and PK data from both the 160 L and 2000 L scales in the Lumizyme labeling. However, analytical comparability has not been established between 160 L and 2000 L scales, and the Clin-Pharm team determined that the PK results were not comparable between these scales. We acknowledge that including PK data from 160 L and 2000 L materials in the label could create the false impression that these materials were deemed comparable with respect to PK. The Clin-Pharm reviewers also noted in the internal meetings that the 2000 L PK study in adults was limited by the sequential study design and small sample size and therefore was an inferior study to the 160 L studies in infants. Because the 2000 L process was discontinued and the infant-onset patients are the most sensitive of the patient populations, we concur with the Clin-Pharm recommendation to include only the infant onset/160 L PK data rather than only the adult onset/2000 L PK data in the label.*
- 2) *The decision to remove the 2000 L PK data from the label was made to avoid the unintended implication that 2000 L and 160 L are comparable with respect to PK. This decision does not mean that the DTP review of the current efficacy supplement determined that the 2000 L and 4000 L materials are no longer analytically comparable. It is still acceptable to include in the label clinical efficacy data obtained using 2000 L lots based on the established analytical comparability between the 2000 L and 4000 L scales.*

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/s/

CHRISTOPHER D DOWNEY
07/31/2014

JUHONG LIU
07/31/2014

SUSAN L KIRSHNER
08/01/2014



**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research**

Office of Biotechnology Products
Division of Therapeutic Proteins
Rockville, MD 20852
Tel. 301-827-2408

DATE: 7-3-14
SUBJECT: BLA 125291

FROM: Maria Cecilia Tami, PhD
THROUGH: Susan Kirshner, Ph.D
Review Chief, DTP, OBP

PRODUCT: Lumizyme, alglucosidase alfa, lyophilized powder
INDICATION: Treatment of patients 8 years and older with late (non-infantile) onset Pompe disease (acid α -glucosidase (GAA) deficiency) who do not have evidence of cardiac hypertrophy.

SPONSOR: Genzyme (a Sanofi Company)
ROUTE OF
ADMINISTRATION: Intravenous infusion
DOSAGE: 20 mg/kg body weight administered every 2 weeks
STRENGTH 5mg/ml

PURPOSE: 125291/136. Review of the immunogenicity section. This efficacy supplement proposes to update the patient population for Lumizyme to include all Pompe disease patients based on available Lumizyme safety and efficacy data for the treatment of patients under the age of 8 years with infantile and late-onset Pompe disease.

Date of Submission: January 30, 2014

Deadlines:

Filing Action-	March 31, 2014
Review completion-	July 8, 2014
Action due date -	August 1, 2014

RPM: Elizabeth Ford

RECOMMENDATION:

I recommend approval of this supplement from an immunogenicity perspective.

Justification

In this submission the Sponsor proposes to update the patient population for Lumizyme to include all Pompe disease patients, including patients under the age of 8 years with infantile and late-onset Pompe disease.

Recombinant alglucosidase alfa is currently manufactured at two production scales: 160 L and 4000L. Alglucosidase alfa manufactured at 160L scale was approved in 2006 (BLA 125141) for the treatment of Pompe disease in all patient populations and marketed under the name of Myozyme. Alglucosidase alfa manufactured at the 4000 L scale was approved in 2010 for the treatment of patients 8 years of age and older with late (non-infantile) onset Pompe disease and marketed under the name of Lumizyme. In 2012, due to drug shortages and manufacturing challenges, Myozyme was restricted to the treatment of infantile-onset Pompe disease patients less than 12 months of age, and patients older than 12 months were enrolled in a phase 4 study to continue treatment with Lumizyme. In this submission, the Sponsor provides product quality data and supportive safety and efficacy data that demonstrate that the 160L (myozyme) and the 4000L (Lumizyme) products are comparable (see the CMC and clinical reviews in DARRTS). Based on the established comparability, Lumizyme indication can be expanded to all patient population.

The Sponsor provides safety and efficacy data from two studies: 1) an Investigator-sponsored study in Taiwan of 18 treatment naive infantile-onset Pompe disease patients treated with Lumizyme; and 2) a Genzyme sponsored ongoing phase 4 study in infantile or late-onset patients 12 months of age and older who switched from treatment with alglucosidase alfa manufactured using a 160 L process (Myozyme) to aglucosidase alfa manufactured using a 4000 L product (ADVANCE study).

Infantile onset patients in the Taiwan study were all cross reactive immunologic material (CRIM) positive. CRIM positive patients express some mutated alglucosidase alfa. Therefore, recombinant human alglucosidase alfa may not appear to be foreign to their immune systems, reducing the likelihood that anti-drug antibodies (ADA) will develop. CRIM positive patients generally have a more favorable clinical prognosis and develop lower levels of anti rhGAA antibodies than the CRIM negative patients. Therefore, a favorable immunogenicity profile, with reduced ADA incidence and titer, in patients from the Taiwan study is expected. However, CRIM positive early onset patients exclusively receiving Lumizyme (Taiwan study) showed a better immunogenicity profile when compared to

CRIM positive early onset patients who exclusively received Myozyme, (study AGLU01602/2403) in that no patients developed high sustained antibody titers, peak IgG titers were lower, and time to seroconversion was longer. Moreover, unlike the studies to support Myozyme, no correlation was observed between IgG titers and incidence of serious adverse events or clinical outcome, including invasive ventilator and survival in the Taiwan study.

Data from the ADVANCE study show that antibody responses before and after switching from Myozyme to Lumizyme are comparable or better. Twenty-one out of 99 patients remained seronegative until the data cut off and patients who sero converted developed low antibody titers. As with the Taiwan population, no correlation between antibody titers and clinical outcome was observed.

Overall, the data provided support comparable immunogenicity profiles in infantile onset patients who received the 4000 L product (Taiwan 01 study) and patients who received 160L product exclusively (AGLU 1602/2403). Further, data from the switch over study support similar impact of antibody response on safety before and after switching. Consequently, from an immunogenicity perspective, the patient population for Lumizyme can be updated to include all patients with Pompe disease.

BACKGROUND INFORMATION

Alglucosidase alfa is a recombinant human acid alpha-glucosidase (rhGAA) produced in CHO cells that is identical to a commonly occurring form of human GAA in amino acid. Alglucosidase alfa is a hydrolase that degrades lysosomal glycogen to glucose. During trafficking to the lysosome, GAA is proteolytically processed, resulting in the formation of an enzymatically active multi-subunit complex. Genzyme developed alglucosidase alfa as an enzyme replacement therapy (ERT) for the treatment of Pompe disease.

Pompe disease is a rare inherited autosomal recessive genetic disease caused by the deficiency of lysosomal acid α -glucosidase (GAA). Pompe disease is characterized by organelle bound (lysosomal) and extra-lysosomal accumulation of glycogen in body tissues, especially cardiac and skeletal muscles, that disrupts the architecture and function of affected cells and leads to a variety of symptoms, clinical decline, and ultimately death.

Manufacturing History and clinical development

Genzyme manufactured alglucosidase alfa drug substance at three manufacturing scales: 160L (Myozyme), 2000L (no longer manufactured) and 4000 L (Lumizyme).

Myozyme (BLA 125141) was approved in April 2006 for use in all patients with Pompe disease based on pivotal clinical studies AGLU01602/2403 in infantile-onset Pompe patients treated with 160 L scale alglucosidase alfa.

Genzyme developed a larger manufacturing scale (2000L) for alglucosidase alpha that was submitted together with the 160L product data to BLA 125141 (Myozyme). The Agency concluded that alglucosidase alfa manufactured using the larger scale (2000L) should be classified as a different product based on (b) (4)

Therefore, the 2000L manufacturing process was withdrawn from the Myozyme application. Genzyme submitted a new BLA (125291) with clinical data from study AGLU02704 in patients with late-onset Pompe disease, patients 8 years of age and older, to support the licensure of the 2000L alglucosidase alpha product. In parallel with the submission of BLA 125291, Genzyme developed a linear scale up of the 2000L manufacturing scale to a 4000L bioreactor to meet increasing patient needs. Based on the clinical data from AGLU02704 study (2000L) and analytical comparability of the 2000L and 4000L material, the Lumizyme (BLA 125291) was approved on May 24, 2010 for patients 8 years and older with late onset Pompe disease who do not have evidence of cardiac hypertrophy as supported by the population studied in AGLU02704. During the review of the 4000 L scale application FDA noted that the (b) (4) the 4000 L scale appeared to be comparable to material produced at the 2000 L scale. However, a direct comparison between 4000 L material and 160 L material was not provided, so this assessment could not be confirmed. Lumizyme is manufactured only using the 4000 L scale process. Alglucosidase alfa manufactured at the 4000 L scale is the only scale available outside of the US and is approved for all Pompe patients in all countries except the US.

Since approval of Lumizyme, the supply and manufacturing capacity constraints for the alglucosidase alfa 160 L pilot scale was extensively discussed with Genzyme. In November 2011, Genzyme notified FDA that an acute Myozyme (160 L alglucosidase alfa) supply shortage was projected for 2012. The Sponsor restricted the use of Myozyme to treatment of patients 12 months and younger. Because the clinical trial to support Lumizyme was performed in patients 8 years and older, the Sponsor developed the ADVANCE protocol (AGLU09411), *A Phase 4, Open-Label, Prospective Study in Patients with Pompe Disease to evaluate the Efficacy and Safety of Alglucosidase Alfa Produced at the 4000 L Scale* in patients older than 12 months with Lumizyme as recommended by the FDA. This study was designed to monitor safety and efficacy of Lumizyme in patients older than 12 months who switched from Myozyme to Lumizyme.

Currently, Myozyme is restricted to Pompe patients under 12 months of age. Genzyme does not ship Myozyme 160 L to patients over 12 months of age and offers enrollment to these patients into the ADVANCE study to receive treatment with Lumizyme (4000 L). The transfer of these patients was necessary to prevent a stock-out of 160 L supply. Therefore, the majority (>90%) of infantile-onset Pompe disease patients are already receiving treatment with Lumizyme.

During a Type C meeting held in February 2013, the FDA suggested that approval of Lumizyme for treatment of patients with infantile-onset Pompe disease and patients under 8 years of age with late onset Pompe disease could be obtained by establishing comparability between the 160 L and 4000 L scales. To this end the sponsor was asked to provide analytical comparability data and supportive clinical data collected from Lumizyme treated infantile-onset Pompe disease in Taiwan enrolled in an Investigator-Sponsored Study (ISS) with classical infantile-onset phenotype using ventilator-free survival as an endpoint. The infants from Taiwan had to meet the AGLU01602 inclusion criteria of diagnosis of classical infantile-onset disease with evidence of cardiac hypertrophy <6 months of age and treated with alglucosidase alfa at the 4000L scale before the age of 6 months.

Clinical data to support Lumizyme label update (as agreed on 7-3-2013, WRO).

- Taiwan Study report: A clinical study report evaluating the safety and efficacy of alglucosidase alfa treatment (4000 L) in patients with infantile-onset Pompe disease treated in a single-center Investigator-sponsored study in Taiwan in comparison to infantile-onset patient results from the original 160 L cohorts from studies AGLU01602/AGLU02403 and the natural history cohort from study AGLU00400. Safety data were reported spontaneously to Genzyme by the Investigator. Data is provided for 25 patients of whom 18 have confirmed infantile onset disease.
- ADVANCE (AGLU09411): An abbreviated clinical study report of the safety data from the ongoing AGLU09411 study in infantile or late-onset patients 12 months of age and older who previously received 160 L alglucosidase alfa and switched to 4000 L product. The cut-off for the report was June 30, 2013 and includes safety data for 99 Pompe disease patients.
- Summary of safety data from clinical studies in which larger scale alglucosidase alfa is used in infantile-onset patients that are completed or ongoing since the clinical data cut-off of September 29, 2009 as well as post-marketing data through a cut-off of 30 June 2013.

SUBMISSION REVIEW

I. Immunogenicity assays

All assays used to assess for the presence of binding anti rhGAA IgG antibodies, and anti rhGAA antibodies able to inhibit enzyme uptake or activity were validated and previously reviewed.

Screening assays

ELISA

(b) (4)



Radioimmunoprecipitation (RIP) assay

(b) (4)



ELISA assay for detection of anti rhGAA IgE antibodies

(b) (4)



Neutralizing assay

Inhibitory Antibody Assay (Inhibition of Enzyme Activity)

(b) (4)



Inhibitory Antibody Assay (Inhibition of Enzyme Uptake)

(b) (4)



II. Clinical data

To allow for the evaluation of the immunogenicity profile of Lumizyme (4000L manufacturing scale) in patients under the age of 8 years with infantile and late-onset Pompe disease, the Sponsor agreed to provide the following information:

1. Taiwan Study:

- a. Assessment of the association between clinical outcome and CRIM status, antibody response (binding and neutralizing), genetic mutations and enzyme activity level in patients who received 4000L product.
- b. Assessment of the impact of ADA titers on the safety and efficacy of the 4000L product and comparison of the results to those patients who received 160L product exclusively (clinical studies AGLU01602/2403).

2. ADVANCE (AGLU09411)

- a. A comparison of the impact of antibody responses (ADA titers inhibitory and neutralizing antibody status) on safety before and after switching from 160L to 4000L product.

III. Immunogenicity assessment

Definitions:

High sustained antibody titer are defined as peak titers $\geq 25,600$ and a last titer equal to the peak titer or 1 dilution level lower.

Decreasing titers are those where the last titer is at least 2-fold dilution lower than the peak titer.

Tolerization is defined as samples with 2 or more consecutive negative values in the RIP assay.

1. Taiwan Study report

The Taiwan01 study is an open label ISS that started on March 8, 2006 and is ongoing. The primary objective of the study is to estimate the proportion of patients with infantile-onset form of Pompe disease in Taiwan treated with rhGAA manufactured at large scale (4000L) who are alive and free of invasive ventilation support at 18 months of age as compared to patients in the AGLU01602/2403 study (160L) and the natural historical study (AGLU00400, 62 patients). Treatment with rhGAA at the larger scale must have been initiated prior to 6 months of age and infantile-onset Pompe disease patients in the study should meet the inclusion criteria for AGLU01602. The secondary objective was to evaluate the safety profile of large scale rhGAA based on adverse events reported spontaneously to the Genzyme Pharmacovigilance and Epidemiology Department and other laboratory measurements including immunogenicity. Adverse events were not collected as part of the ISS.

This study was originally developed to monitor cases of Pompe disease identified through the newborn screening program at the National Taiwan University Hospital (NTUH). At the data cut-off date of March 15, 2013, 25 patients were enrolled in the study from which 18 met the criteria for infantile-onset form of Pompe disease. The cut-off date for adverse events (AE) and immunogenicity data is June 30, 2013.

The disposition of all treated patients is summarized in table 9-1 below.

Table 9-1
Patient Disposition

Parameter	n (%)
Patients Enrolled Set	25 (100.0)
Completed follow-up through cut-off date of 30 June 2013	19 (76.0)
Deaths through cut-off date of 30 June 2013	4 (24.0)
Full Analysis Set	18 (100.0)
Completed follow-up through cut-off date of 30 June 2013	15 (83.3)
Deaths through cut-off date of 30 June 2013	3 (16.7)

Source: Table 14.2.2.1

Reviewer's comment: *The demographics of the populations in Taiwan01, AGLU01602/2403, and the natural history study group have comparable male/female ratios. All patients in the Taiwan study were Asian, while the other studies included other races (16.7% and 29.0% Asian in the AGLU01602/2403 and natural history studies, respectively). However, the natural history study demonstrated similar disease progression regardless of geographic location/ethnicity as discussed during the midcycle meeting (please refer to Juli Tomaino's review) and therefore, data from the Taiwan study is applicable to US patients. In addition, while the mean age of infusion for the Taiwan and the AGLU01602/2403 study was less than 6 months, the mean age for first infusion in the Taiwan FA population was younger (1.6 months in Taiwan01 and 5.3 months in the AGLU01602/2403) since patients were identified through newborn screening.*

Patients in the study were identified using enzyme activity and DNA analysis. Genotype analysis was performed post-marketing with a small number of patients. Most patients in the Taiwan study had a missense/missense genotype classification. All patients in the study were confirmed as CRIM positive. Enzyme activity was measured in fibroblasts and lymphocytes.

Reviewer's comment: *Due to the small sample size, it was not possible to establish a correlation between genotype and clinical outcome.*

Immunogenicity assessment scheme and Sampling schedule

All immunological testing was performed by the Genzyme Clinical Specialty Laboratory.

Serum samples for anti-rhGAA immunoglobulin G (IgG) antibody testing are obtained at the screening visit (week 0) and then at week 4, 8, 12, 16, 20, 26, 38 and 52. For the following years, testing for antibodies is scheduled for weeks 26 and 52 every year. All patients were tested for the presence of IgG antibodies by ELISA and confirmed using a RIP assay. If a sample was confirmed positive, titer values were calculated.

Not all patients who tested positive for IgG antibodies were evaluated in the neutralization assays. The presence of IgG inhibitory antibodies was tested only if requested by Genzyme Global Pharmacovigilance and Epidemiology Department as the result of an adverse event. If the result was positive, an endpoint titer was calculated.

***Reviewer's comment:** While all seropositive patients in the ADVANCE study were tested for neutralization of enzyme uptake/activity (see below), in the Taiwan study, testing was performed based on adverse event occurrence in a selected patient population.*

For immune associate reactions (IAR) suggestive of hypersensitivity reactions additional testing was recommended including: complement activation, serum tryptase, anti-rhGAA immunoglobulin E (IgE), skin testing, and circulating immune complexes.

IAR are defined as AE that occurred during the infusion or the observation ≤ 2 hours following the infusion, and were considered related to alglucosidase alfa.

The definition of anaphylaxis is based on Sampson *et al* as a severe, potentially fatal systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance.

Immunogenicity results

Anti rhGAA IgG antibody titers

From the 18 patients (FA population), one patient (Patient 10528) was not evaluated for immunogenicity. From the remaining 17 patients, 16 seroconverted (patient 70011 remained seronegative). Titers ranged from 0 to 12,800 throughout the study. According to the investigator, no patients in the study received immune tolerance induction treatment.

Table 11-6 below summarizes the IgG antibody titers for patients in the study based on seroconversion, time to conversion, peak titer, and last titer. Individual IgG results over time for all individual patients in the study can be found in listing 16.2.8.2 of the eCTD submission.

Table 11-6
Summary of Seroconversion and Maximum IgG Titers for Individual Patients in the Taiwan Full Analysis Set

Patient ID	Week first seroconverted	IgG antibody titer at week first seroconverted	Maximum titer reported during study	Week of maximum titer	Titer value at last visit
10375 ¹	Week 72	800	800	72	800
10377	Week 205	400	1600	312	800
10378	Week 156	100	100	156	100
10381	Week 105	3200	12800	346	12800
10382	Week 221	400	1600	245	800
10460	Week 9	200	800	254	800
10528 ²	NA	NA	NA	NA	NA
10529	Week 12	6400	6400	12	400
10530	Week 12	400	400	12	NA
70001	Week 4	200	6400	25	200
70002	Week 4	800	800	4	800
70003 ¹	Week 4	100	6400	12	200
70004 ¹	Week 10	1600	1600	10	100
70006	Week 38	<100	<100	38	NA
70008	Week 8	800	3200	26	400
70011	NA	NA	NA	NA	NA
70012	Week 24	200	200	24	100
70013	Week 32	3200	3200	32	3200

Source: [Listing 16.2.8.2](#)

NA=not available

¹ In some patients, the maximum titer values occurred more than once; in this case, the first time of maximum titer is listed.

² No post-baseline assessments for IgG were available.

TABLE 14.3.4.2
IgG Antibody to Alglucosidase Alfa: Seroconversion, Time to Seroconversion, Peak Titer and Last Titer:
Full Analysis Set

Parameter	Statistic	Taiwan (N=18)
Seroconversion, N (%)	Yes	16 (88.9)
	No	1 (5.6)
Time to Seroconversion (Days)	n	11
	Mean	441.3
	Median	84
	SD	602.09
	Min, Max	27, 1547
Peak Titer	n	17
	Mean	2917.6
	Median	1600
	SD	3389.55
	Min, Max	0, 12800
Last Titer	n	17
	Mean	964.7
	Median	200
	SD	1633.99
	Min, Max	0, 6400

Reviewer's comment: antibody titers in the Taiwan study were relatively low with the highest titer being 12800, reached in only one patient (patient 10381 in red). Most of the patients show a trend toward decreasing titers over time as median peak IgG titers were 1600 and median last titers were 200. No patients in the Taiwan 01 study have high sustained antibody titers. This is expected since CRIM + patients generally tolerize, i.e. lose their ADA response, or show decreasing IgG titers over time, although some CRIM+ patients also mount high sustained antibody titers as was observed in 2 CRIM+ infantile onset patients treated with Myozyme (clinical studies AGLU01602/2403). Highlighted in yellow is the one patient who remained seronegative.

Neutralizing antibodies of enzyme activity or uptake

Three patients in the FA set of the study (10381, 10529 and 10530) were tested for inhibitory antibodies to rhGAA. The three patients tested negative for both inhibition of enzyme uptake and activity.

Reviewer's comment: as per protocol, IgG inhibitory antibodies to rhGAA were tested only if requested by the Genzyme Global Pharmacovigilance and Epidemiology Department as a result of an adverse event. In an information request dated March 19th, 2014, the Sponsor was asked to explain what triggered testing of inhibitory antibodies in the three patients from the Taiwan 01 study.

On April 2, 2014, the Sponsor explained that Genzyme's GPE approves requests from Investigators and treating physicians' for expedited testing for inhibitory antibodies for patients who experience adverse events suggestive of decreased response to treatment that could be due to inhibition of enzyme activity/uptake.

Patients 10381, 10529 and 10530 experienced adverse events suggestive of clinical decline or lack of response to treatment. Patient 10381 experienced creatinine phosphokinase decrease, Patient 10529 experienced aspiration pneumonia and respiratory failure and Patient 10530 experienced pneumonia and respiratory failure. For these patients, the GPE approved testing of inhibitory antibodies to rhGAA as per investigators request. All patients tested negative for inhibition of enzyme uptake and activity.

The response to our information request includes a full summary of the adverse events experienced by these patients that triggered testing for inhibitory antibodies. The information is not included in this review but can be found in the eCTD submission STN 125291/136.1, sequence 297.

Additional testing for infusion associated reactions suggestive of hypersensitivity

Two patients (10529 and 70002) experienced an AE suggestive of anaphylaxis or a hypersensitivity reaction to rhGAA.

Patient 10529 experienced urticaria and wheezing during infusion on several dates. Patients tested positive for IgE and Genzyme provided the physician with a customized desensitization protocol, which involved using a gradual dose escalation while changing the overall dosage from 20 mg/kg every 2 weeks to 10 mg/kg every week (qw).

Patient 70002 experienced hypersensitivity, generalized rash, and pruritus during infusion. The patient was treated with dexamethasone and recovered. This patient was not tested for IgE antibody titers.

Two patients (10529, 10433) were subjected to additional testing:

- None of the patients was positive for complement activation
- Both patients had serum tryptase results of <1.0 µg/L
- Patient 10529 was positive for IgE antibodies.

Adverse events by immunogenicity parameters

Adverse events for the Taiwan 01 study were reported to the Genzyme Pharmacovigilance Department spontaneously by the investigator. Table 14.3.1.2.2 summarizes the spontaneous adverse events and IgG anti-rhGAA antibody titers.

***Reviewer's comment:** Analysis of the data was performed by dividing patients based on peak antibody below or above 1600 rather than in quartile. The Sponsor was asked to provide a rationale for this approach as well as to present the spontaneous adverse event data stratified by quartiles of peak IgG antibody responses.*

The Sponsor explained that the median peak titer calculated from the 17 patients in the Taiwan ISS study was 1,600 with a range of 0 to 12,800. The median last titer was 400

and the range was 0 to 12,800. Because 1,600 represented the middle titer value (median), the Sponsor used this value to summarize adverse events and IgG antibody titers. The Sponsor emphasized that there is a downward trend in IgG antibody titers over time and that no patients in the Taiwan ISS study showed high sustained antibody titers.

As requested, the Sponsor provided the adverse event, serious adverse events and Infusion-Associated Reactions data stratified by quartiles of peak IgG antibody response. In addition, a summary of seroconversion status and quartiles of peak IgG for patients with adverse events, serious adverse events and infusion associated reactions is provided in Table 2 below.

Table 2: Summary of Safety by Seroconversion Status, Quartiles of Peak IgG Antibody (Taiwan01)

	Negative (N=1)		Positive (N=16)							
			Quartile 1 (100 – 400) n=4		Quartile 2 (800 – 800) (n=3)		Quartile 3 (1600 – 3200) (n=5)		Quartile 4 (6400 – 12800) (n=4)	
	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)
Patients with adverse events	0	0 (0.00)	24	3 (75.0)	4	2 (66.7)	7	2 (40.0)	30	2 (50.0)
Patients with serious adverse events	0	0 (0.00)	16	2 (50.0)	3	1 (33.3)	7	2 (40.0)	23	2 (50.0)
Patients with infusion-associated reactions	0	0 (0.00)	7	2 (50.0)	4	2 (66.7)	0	0 (0.00)	20	2 (50.0)

Source: Table 14.3.1.2.3, Table 14.3.1.2.4, Table 14.3.1.2.5

Note: Patient 10528 did not report IgG antibody data.

Note: If a patient had more than 1 event for a particular SOC, he/she is counted only once for that SOC.

Note: If a patient had more than 1 event for a particular PT, he/she is counted only once for that PT.

Note: Percentages are based on the total number of patients treated in the corresponding groups.

Note: MedDRA Dictionary Version 16.0 was used for coding.

Reviewer's comment: According to the Sponsor, there is no consistent relationship observed between the incidence of events and peak IgG antibody titers. I agree with this observation with regards to IgG titers in quartiles 1-3 where patients in quartile 1 show a higher incidence of adverse events than patients in quartiles 2 and 3. However, the highest incidence of adverse events, serious adverse events and infusion is observed in patients with the highest peak antibody titers (quartile 4). Nonetheless, safety data in the Taiwan study is consistent with that observed in the Myozyme studies and no new adverse events were reported. Safety data for the Taiwan study were recorded based on spontaneous reports to the Sponsor. Consequently, adverse event data were not collected systematically and may be incomplete. Therefore, this assessment may not be accurate.

Antibody formation over time by status of invasive ventilator and survival.

Individual patient data on IgG antibody titers for patients with infantile-onset Pompe disease in the Taiwan01 study is provided in listing 16.2.8.2 and Figure 14.3.1 below.



Upon request, the Sponsor provided the graphical representation of IgG titers over time by status of invasive ventilator and death for the CRIM positive patients in study AGLU01602/2403.

Reviewer's comment: Comparison of IgG titers over time by clinical outcome for CRIM positive infantile onset patients receiving exclusively the 4000L materials (Taiwan01 study) and those receiving exclusively the 160L material (from study AGLU01602/2403) shows a better profile for patients in the Taiwan study: no patients developed high sustained antibody titers and patients showed lower antibody titers. In contrast, two CRIM positive patients who received the 160L material developed a high sustained antibody response and died.

Patient ID	Seroconversion		Peak		Sample Date	Time Since First Infusion (Weeks)	Age at Test (Months)	PIR	RIP	Titer
	Days from First Infusion	Value	Days from First Infusion	Value						
10375			505	800	24JAN2008	72	20	POSITIVE	POSITIVE	800
					31JUL2008	99	26	POSITIVE	POSITIVE	200
					04FEB2009	126	32	POSITIVE	POSITIVE	200
					17JUL2009	149	37	POSITIVE	POSITIVE	<100
					21JUN2010	198	48	POSITIVE	POSITIVE	<100
					20JUL2010	202	49	POSITIVE	POSITIVE	<100
					18JUL2011	254	61	POSITIVE	POSITIVE	<100
					07AUG2012	309	74	POSITIVE	N/A	800
10377	1435	400	2184	1600	21NOV2007	72	18	NEGATIVE	NEGATIVE	N/A
					18JUN2008	102	24	NEGATIVE	NEGATIVE	N/A
					24SEP2008	116	28	NEGATIVE	N/A	N/A
					14JAN2009	132	31	NEGATIVE	NEGATIVE	N/A
					17JUN2009	154	36	NEGATIVE	N/A	N/A
					16DEC2009	180	42	NEGATIVE	N/A	N/A
					09JUN2010	205	48	POSITIVE	POSITIVE	400
					15SEP2010	219	51	POSITIVE	N/A	800
					09MAR2011	244	57	POSITIVE	N/A	400
					15JUN2011	258	60	POSITIVE	POSITIVE	800
					14DEC2011	284	66	POSITIVE	POSITIVE	800
					09FEB2012	292	68	POSITIVE	N/A	800
					02MAY2012	304	71	POSITIVE	N/A	800
					27JUN2012	312	73	POSITIVE	N/A	1600
					26DEC2012	338	79	POSITIVE	N/A	800
10378	1092	100	1092	100	14NOV2007	88	25	NEGATIVE	NEGATIVE	N/A
					05MAR2008	104	28	NEGATIVE	NEGATIVE	N/A
					20AUG2008	128	34	NEGATIVE	NEGATIVE	N/A
					03FEB2009	152	39	NEGATIVE	NEGATIVE	N/A
					04MAR2009	156	40	POSITIVE	POSITIVE	100
10381			2420	12800	19JUN2008	105	25	POSITIVE	N/A	3200
					13NOV2008	126	30	POSITIVE	N/A	3200
					28MAY2009	154	36	POSITIVE	N/A	1600
					10MAR2010	195	46	POSITIVE	N/A	800
					28SEP2010	224	52	POSITIVE	POSITIVE	3200
					16MAY2011	257	60	POSITIVE	N/A	800
					03FEB2012	294	69	POSITIVE	N/A	1600
					28JAN2013	346	80	POSITIVE	N/A	12800
10382	1547	400	1714	1600	14NOV2007	39	10	NEGATIVE	NEGATIVE	N/A
					13FEB2008	52	13	NEGATIVE	N/A	N/A
					23JUL2008	75	18	NEGATIVE	N/A	N/A
					26NOV2008	93	22	NEGATIVE	N/A	N/A
					18FEB2009	105	25	NEGATIVE	N/A	N/A
					05AUG2009	129	30	NEGATIVE	N/A	N/A
					11NOV2009	143	34	NEGATIVE	N/A	N/A
					28APR2010	167	39	NEGATIVE	NEGATIVE	N/A
					09FEB2011	208	48	NEGATIVE	NEGATIVE	N/A
					11MAY2011	221	51	POSITIVE	POSITIVE	400
					25OCT2011	245	57	POSITIVE	POSITIVE	1600
(contd)										
10382	1547	400	1714	1600	01FEB2012	259	60	POSITIVE	N/A	800
					11APR2012	269	62	POSITIVE	N/A	800
					30JAN2013	311	72	POSITIVE	N/A	800

Reviewer's comment: Figure 14.3.1 shows that there is no obvious relationship between IgG titers and clinical outcome. Antibody titers for Patient 10381 remained high after seroconversion and increased over time. Similarly, the antibody titers for Patients 10375, 10377, and 10382 increased over time after seroconversion. The Sponsor states that none of the patients from the Taiwan01 study had high sustained IgG antibody titers to

alglucosidase alfa. Based on the Sponsor's definition of high sustained antibody titers (patients who have a peak titer >25600 and a last titer that is equal to the peak titer or one dilution lower), the statement is true. However, it has been reported that antibody titers sustained at >6400 may result in sub optimal therapeutic responses. In fact, Banugaria et al 2013 set a cut off titer of >6400 in their proposed algorithm to manage CRIM negative infantile Pompe disease patients. Taking this into consideration, the Sponsor was asked to provide an explanation for not classifying antibody responses in these patients as high sustained. Antibody titers over time for these patients (excerpted from listing 16.2.8.2) are included in the review.

The Sponsor explained that patients with high sustained antibody titers are defined as those who have a peak titer $\geq 25,600$ and a last titer which is equal to the peak titer or is one dilution level lower than the peak titer. None of the patients in the Taiwan cohort meet the criteria for high sustained antibody titers, including patients 10381, 10375, 10377 and 10382 which peak antibody titers range from 800 to 12,800. A summary of the data on these patients was provided by the Sponsor and shown below.

Table 3: Summary of Seroconversion and Maximum IgG Titers for Individual Patients in the Taiwan Full Analysis Set

Patient ID	Week first seroconverted	IgG antibody titer at week first seroconverted	Maximum titer reported during study	Week of maximum titer	Titer value at last visit
103751	Week 72	800	800	72	800
10377	Week 205	400	1600	312	800
10381	Week 105	3200	12800	346	12800
10382	Week 221	400	1600	245	800

¹ In some patients, the maximum titer values occurred more than once; in this case, the first time of maximum titer is listed.

Reviewer's comment: *Although none of the patients in the Taiwan study meet the Sponsor's criteria for high sustained antibody titers, some patients (e.g 10381, 10382) seem to show increasing antibody titers. These patients, however, showed lower median and peak titer values than patients from the Myozyme studies AGLU01602/2403 (see figure 14.3.4.7.1 above). A summary slide comparing the immunogenicity summary data for the Taiwan 01 study and the CRIM positive patients in study AGLU01602/2403 as presented during the mid cycle meeting is included in Appendix 1 to this review.*

2. ADVANCE (AGLU09411)

Clinical study AGLU09411 is ongoing and includes 99 patients with early or late onset Pompe disease, 12 months or older who were treated with Myozyme (160L) prior to enrollment into this study. The majority of patients (81.8%) were under the age of 8 years at the time of first infusion with 4000L alglucosidase alfa. The disposition of all treated patients is summarized in table 2 below. All eligible patients receive intravenous (IV)

infusion of Lumizyme (4000L scale) for 52 weeks at the same dose and dose regimen used for their routine treatment prior to this study. Most of the patients in the study (81.8%) received 52 weeks of treatment. The number of patients per dose regimen is summarized in Table 4. Following the 52-week treatment period, patients can continue treatment with Lumizyme in an extension period until Lumizyme is approved for treatment of all Pompe patients.

Table 2 – Patient Disposition (Full Analysis Population)

Parameter	Alglucosidase alfa 4000L N (%)
Number of patients screened	99
Number of patients who passed screening	97 ^a
Treated, n (%)	99 (100.0)
Completed Week 52, n (%)	81 (81.8) ^b
Withdrawn, n (%)	3 (3.0)
Reason withdrawn	
Death	2 (2.0) ^c
Refused further treatment	1 (1.0)

Source: Table 14.1.1

Percentages are based on total number of patients treated.

^a Patient 10065043 was included in the study even though he was receiving investigational gene therapy at the time of screening. And, Patient 10635079 was included in the study even though the patient's parents consented before the patient was 1 year of age.

^b All treated patients, including those patients who did not yet complete the Week 52 visit, are included in safety analyses.

^c Two additional patients died: 1 patient died after the cut-off date for this interim analysis, and 1 patient refused further treatment and subsequently died after study withdrawal at Week 30.

Table 4 – Number of patients per dose regimen (Safety Population)

		Alglucosidase alfa 4000L (N=99)							
20 mg/kg QOW		40 mg/kg QOW		20 mg/kg Weekly		40 mg/kg Weekly		Others	
n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
66	(66.7)	10	(10.1)	11	(11.1)	2	(2.0)	10	(10.1)

Source: Table 14.3.1.6.3

Patients noted as “other” received different dose and frequency combinations. The number (percentage) of male and female patients was comparable at 51 (51.5%) and 48 (48.5%), respectively.

Four patients received immunomodulation treatment: 10015011 (prophylactic Immune Tolerance Induction (ITI) treatment during participation in Study AGLU03807), 10355062 (intravenous immunoglobulin, IVIG), 10455081 (rituximab and methotrexate), and 10665015 (rituximab and methotrexate).

Immunogenicity assessment scheme and Sampling schedule

Serum samples for anti-rhGAA immunoglobulin G (IgG) antibody testing are obtained at the screening visit (baseline, 3 months before therapy initiation) and then pre-infusion at day 1, and every 4 weeks until week 52.

All patients are tested for the presence of anti rhGAA antibodies using the ELISA assay. All IgG positive patients are tested for the presence of IgG inhibitory/neutralizing antibodies to alglucosidase alfa. Testing is conducted for research purposes only to evaluate responses to alglucosidase alfa, and not for the active clinical management of patients.

When a patient experiences a moderate, severe, or recurrent IAR suggestive of hypersensitivity reactions, additional blood samples are collected and tested for:

- Complement activation (plasma collected within 1 to 3 hours of the event)
- Serum Tryptase Activity Testing (serum collected within 1 to 3 hours of the event)
- Serum Anti-rhGAA IgE Antibody Testing (serum sample collected no sooner than 3 days after the event or prior to the following infusion)
- Skin testing may also be performed, if clinically indicated.

Assessment of circulating immune complexes will be performed in patients with evidence of symptoms suggestive of Immune Complex Disease (e.g., proteinuria).

Gene mutation analysis was performed for all patients and parents (if consented) unless mutation analysis was conducted prior to signing the informed consent by a certified laboratory, written results are provided to the site, and participants give consent to utilize the results.

***Reviewer's comment:** Note that in this study all anti rhGAA positive patients were tested for the presence of uptake/activity inhibitor antibodies.*

Immunogenicity results

Anti rhGAA IgG antibody titers

From the 99 patients in study AGLU09411, 31 were seronegative at baseline and 68 tested seropositive at least once. Twenty one patients remained seronegative throughout the entire study period. Ten patients seroconverted after study entry. For patients who were seronegative at baseline and seroconverted, the median time for IgG conversion from date of first infusion was 61 days (range: 21 to 224 days) and the median titer value at seroconversion was 100 (range: 100 to 1,600).

The information provided below related to IgG peak titers was excerpted from Table 22 from the ADVANCE study report.

Table 22 – IgG Peak Titer and Time to Peak Titer by Baseline Seroconversion Status (Safety Population)

Characteristic/Statistic	Seroconversion Status at Baseline		
	Negative (N=31)	Positive (N=68)	Overall (N=99)
Number of Patients Always IgG Negative	21 (67.7)	0	21 (21.2)
Number of Patients Ever IgG Positive	10 (32.3)	68 (100.0)	78 (78.8)
IgG Peak Titer of Ever IgG Positive Patients			
n	10	67	77
Geometric Mean	348.2	2159.8	1704.1
Standard Deviation	442.34	21611.31	20304.89
Median	400.0	3200.0	1600.0
Min, Max	100.0, 1600.0	100.0, 102400.0	100.0, 102400.0
Number of Patients Ever IgG Positive with IgG Peak Titer			
0	0	0	0
100	1 (3.2)	1 (1.5)	2 (2.0)
200	3 (9.7)	4 (5.9)	7 (7.1)
400	4 (12.9)	7 (10.3)	11 (11.1)
800	1 (3.2)	8 (11.8)	9 (9.1)
1600	1 (3.2)	13 (19.1)	14 (14.1)
3200	0	20 (29.4)	20 (20.2)
6400	0	6 (8.8)	6 (6.1)
12800	0	4 (5.9)	4 (4.0)
25600	0	0	0
51200	0	1 (1.5)	1 (1.0)
102400	0	3 (4.4)	3 (3.0)
204800	0	0	0
409600	0	0	0
819200	0	0	0

Source: Table 14.3.4.2.2

Note: Patient 10235099 tested negative at baseline without additional follow-up data during the study. Patient 10235098 tested positive at baseline also without additional follow-up data during the study.

Reviewer's comment: As shown in Table 22 antibody peak titers in patients who seroconverted during the AGLU09411 study (10) were lower (100 to 1,600) than those reached by patients seropositive at baseline (100 to 124,000). However, for most of the patients seropositive at baseline, titers did not increase markedly over the study course. The data is not included in this review but can be found in Table 23 and listing 16.2.8.7 in the Abbreviated-Synoptic Clinical Study Report for AGLU09411.

Data from patients who developed high sustained antibody titers, decreased titers or tolerization are summarized in Table 24 below.

- Only 2 patients in the study met the study criteria for high sustained antibody titers. Both patients were positive at baseline:
 - Patient 10375051 (peak titer 102,400, last titer 51,200 at Week 52)
 - Patient 10555058 (peak titer 102,400, last titer 51,200 at Week 52)
- Most of the patients with diminishing antibody titers were positive at baseline.

- Tolerization was only achieved by 1 patient who was seronegative at baseline and 2 who were baseline positive.

Table 24 – Summary of Patients with Sustained High IgG Antibody, Decreasing Titer, or Tolerization by Baseline Seroconversion Status (Safety Population)

	Seroconversion Status at Baseline		
	Negative (N=31)	Positive (N=68)	Overall (N=99)
Number of Patients Always IgG Negative (a)	21 (67.7)	0	21 (21.2)
Number of Patients Ever IgG Positive (b)	10 (32.3)	68 (100.0)	78 (78.8)
Number of Patients with Sustained and Elevated IgG Antibodies (c)	0	2 (2.9)	2 (2.0)
Number of Patients with Diminishing IgG Antibodies (d)	1 (3.2)	15 (22.1)	16 (16.2)
Number of Patients Developed Tolerization (e)	1 (3.2)	2 (2.9)	3 (3.0)

Source: Table 14.3.4.2.5

Note: (a) IgG negative for all visits.
 (b) IgG positive for at least one visit.
 (c) Peak titer \geq 25,600 and last titer=peak titer or 1 dilution level lower.
 (d) Last titer at least 2-fold dilution levels lower than peak titer.
 (e) At least 2 negative results at the end of the sequence of testing

Reviewer's comment: Although all patients in study AGLU09411 had received Myozyme prior to enrollment, 31 patients were seronegative at baseline. Ten of the 31 patients seroconverted after treatment with Lumzyme. From these data it is unclear:

- 1) Why the per cent of patients who remained seronegative in the ADVANCE study (21%, 21 out of 99) is higher than in the Taiwan study (5%, 1 out of 18) or the Myozyme (AGLU1602/2403) study (11%, 2 out of 18). The Sponsor was asked to provide an explanation for this observation.
 - 2) Why patients seroconverted after receiving Lumzyme despite their previous exposure to Myozyme. To address this concern, the Sponsor was asked to provide phenotype (i.e., infantile-onset or late-onset), CRIM status and genotype and mutational analysis of patients enrolled in the ADVANCE study.
- 1) The Sponsor does not have any explanation for this observation but speculates that this outcome is influenced by the fact that patients in the ADVANCE study had previously received treatment of 160L alglucosidase alfa while those enrolled in the AGLU01602 and the Taiwan01 studies were naïve to treatment. Previous concomitant medications administered prior to enrollment into the ADVANCE study could have prevented antibody formation in these seronegative patients. These medications may include prophylactic immune tolerance induction treatments as this information is not collected as per the ADVANCE study protocol.

Reviewer's comment: The Sponsor does not provide an explanation for our observation but the fact that most of the patients in the ADVANCE study who were seronegative at baseline remained seronegative through the data cut-off provides supportive evidence that switching from 160L alglucosidase alfa to 4000L alglucosidase alfa is safe from an immunogenicity perspective.

- 2) The following information was provided on April 2, 2014 regarding the Phenotype (i.e., infantile-onset or late-onset), CRIM status and genotype and mutational analysis of patients enrolled in the ADVANCE study.

CRIM status and phenotype were not collected for the ADVANCE patients as per the protocol.

The Sponsor determined the patients phenotype based on the medical history collected in the study. Patients diagnosed prior to 12 months of age and with cardiac involvement were considered to be infantile-onset. Patients not meeting these criteria were labeled as late onset for the purposes of the analysis. Based on this criterion, of the 99 patients, 69 (69.7%) patients were considered infantile-onset and 23 (23.2%) were considered late-onset patients treated at less than 8 years of age. The remaining 7 of the 99 patients did not fall into either of these two categories.

The Sponsor defined the CRIM status in 34 out of the 69 infantile-onset patients: 10 were CRIM negative, 24 were CRIM positive and 35 remained unknown.

The Sponsor updated the Adverse Event Dataset to include the genotype data that was collected in the study as well as the available CRIM status data and the calculated phenotype data and completed the Table provided in the information request (see below) with data from infantile-onset and late-onset patients less 8 than years of age who participated in Study AGLU09411.

Table 1: ADVANCE Study Demographics and Clinical Characteristics

		Infantile-onset, CRIM-negative patients	Infantile-onset, CRIM-positive patients	CRIM Unknown	Late-onset patients, treated at < 8 years of age
Number of patients	n(%)	10 (100.0)	24 (100.0)	35 (100.0)	23 (100.0)
Male gender	n(%)	4 (40.0)	11 (45.8)	18 (51.4)	13 (56.5)
Age at diagnosis (years)	Mean \pm SD	0.2 \pm 0.18	0.5 \pm 0.22	0.4 \pm 0.23	2.0 \pm 1.25
	Median (min,max)	0.1 (0.0, 0.5)	0.5 (0.1, 0.9)	0.4 (0.0, 0.8)	1.6 (0.9, 5.2)
Age at start of 160L product (years)	Mean \pm SD	0.4 \pm 0.44	1.0 \pm 1.43	0.7 \pm 1.71	2.4 \pm 1.29
	Median (min,max)	0.3 (0.0, 1.5)	0.6 (0.1, 6.8)	0.4 (0.0, 10.4)	1.9 (1.1, 5.3)
Age at switch-over to 4000L product (months)	Mean \pm SD	3.1 \pm 1.82	4.5 \pm 2.89	4.4 \pm 3.40	5.6 \pm 2.83
	Median (min,max)	3.0 (1.0, 5.7)	3.5 (1.0, 11.3)	3.7 (1.0, 15.4)	6.2 (1.1, 12.6)
Length of time treated with 4000L product months	Mean \pm SD	11.7 \pm 4.62	13.2 \pm 3.82	12.3 \pm 3.62	13.1 \pm 3.28
	Median (min,max)	14.1 (3.0, 14.7)	14.4 (0.6, 14.9)	14.2 (0.4, 15.3)	14.3 (3.6, 14.8)
Length of time treated with 160L product (months) at switch over to 4000L product	Mean \pm SD	32.8 \pm 18.66	42.4 \pm 35.71	43.8 \pm 32.51	39.2 \pm 32.43
	Median (min,max)	35.1 (9.7, 58.6)	31.7 (1.9, 130.1)	38.0 (5.5, 108.3)	39.6 (0.4, 108.8)
Number of patients who required invasive ventilation prior to switch	n(%)	6 (60.0)	8 (33.3)	10 (28.6)	5 (21.7)
Number of patients who were on invasive ventilation at time of	n(%)	5 (50.0)	8 (33.3)	8 (22.9)	5 (21.7)

		Infantile-onset, CRIM-negative patients	Infantile-onset, CRIM-positive patients	CRIM Unknown	Late-onset patients, treated at < 8 years of age
switch-over					
Number of patients who required invasive ventilation after switch- over	n(%)	0	0	2 (5.7)	1 (4.3)
Number of deaths after switch-over ¹	n(%)	0	1 (4.2)	0	0
Age at time of death (years)	Mean \pm SD	0	1.3 \pm 0	0	0
	Median (min,max)	0	1.3 (1.3, 1.3)	0	0

Source: AGLU09411 Table 14.1.2

¹ One patient death is provided in the table. However, there were 3 additional patient deaths as noted below.

The Sponsor reports three additional deaths in the ADVANCE study that were not included in the table: Two death occurred after the data cut off (patients 10455081 and 10735032 with infantile onset disease) and one death corresponds to a patient of unknown phenotype because age of diagnose was missing (patient 10065050). Therefore, a phenotype was not assigned and the patients was not include in this analysis.

Reviewer's comment: *As expected, the group of infantile onset CRIM negative patients showed the higher percentage of patients on invasive ventilation prior to or at time of switch over to Lumizyme (50-60%). However, no additional patients required invasive ventilation after switch over to 4000L material. Infantile onset CRIM positive patients showed a similar profile but the percentage of patients on invasive ventilation at the time of switch over was lower than their CRIM negative counterpart. Two infantile onset Pompe disease patents of unknown CRIM status required invasive ventilation after receiving 4000L in the study as of June 30, 3013 (the data cutoff for the interim CSR). The increase in the number of patients on invasive ventilation in this group is difficult to interpret due to lack of CRIM status information. Lastly, 1 patient in the late onset group treated before 8 years of age required invasive ventilation after the switchover. Overall, the data suggest that switching to the 4000L alglucosidase alfa material does not impact clinical outcome measured by invasive ventilation status.*

In an information request sent on May 8th, 2014, the Sponsor was asked to further analyze the available data correlating antibody titers with CRIM status and length of treatment prior to switch over particularly for patients that were seronegative at baseline and remained negative, those that seroconverted and those patients that were positive at baseline and developed high sustained antibody titers.

The requested information was provided on May 23rd, 2014.

(b) (4)


Reviewer's comment: *Patients showing the highest antibody titers over time were not classified for their CRIM status complicating the evaluation of the data. Based on the available data on CRIM status (red and blue), there is no observable relationship between CRIM status and antibody titers over time. Patients identified as CRIM negative seem to have comparable IgG titers over time to those identified as CRIM positive.*

(b) (4)



Reviewer's comment: *A correlation between antibody titers over time and phenotype or dose is not apparent.*

Table 14.3.4.2.7
IgG Titers at Baseline and Seroconversion Over Time by CRIM and Phenotype Status.
Safety Population

Statistic	Infantile Onset			Late Onset			Unknown Phenotype**	Overall (N=99)
	CRIM Negative (N=10)	CRIM Positive (N=24)	CRIM Unknown (N=35)	CRIM Negative (N=0)	CRIM Positive (N=7)	CRIM Unknown (N=22)	CRIM Positive (N=1)	
Baseline Titer								
n (%)	10 (100.00)	22 (91.67)	33 (94.29)	0	7 (100.00)	21 (95.45)	1 (100.00)	94 (94.95)
Mean	1130.0	718.2	1857.6		871.4	2185.7	800.0	1502.1
Standard Deviation	1510.00	1463.73	4842.91		727.36	5593.77		3985.43
Median	50.0	200.0	400.0		800.0	400.0	800.0	400.0
Min, Max	0.0, 3200.0	0.0, 6400.0	0.0, 25600.0		0.0, 1600.0	0.0, 25600.0	800.0, 800.0	0.0, 25600.0
IgG Peak Titer of Ever IgG Positive patients								
n (%)	6 (60.00)	20 (83.33)	26 (74.29)	0	7 (100.00)	17 (77.27)	1 (100.00)	77 (77.78)
Mean	3833.3	1400.0	12269.2		4628.6	8447.1	1600.0	7111.7
Standard Deviation	3005.11	1582.47	28370.97		3999.05	24379.86		20304.89
Median	4800.0	800.0	1600.0		3200.0	1600.0	1600.0	1600.0
Min, Max	200.0, 6400.0	100.0, 6400.0	200.0, 102400.0		400.0, 12800.0	400.0, 102400.0	1600.0, 1600.0	100.0, 102400.0
Patients Who Were Always IgG Positive Since Baseline, n (%)								
	5 (50.0)	16 (66.7)	26 (74.3)	0	6 (85.7)	14 (63.6)	1 (100.0)	68 (68.7)
Titer Value at Seroconversion for Seronegative Pts at Baseline								
n (%)	1 (10.00)	5 (20.83)	0	0	1 (14.29)	3 (13.64)	0	10 (10.10)
Mean	100.0	240.0			100.0	633.3		330.0
Standard Deviation		313.05				838.65		496.77
Median	100.0	100.0			100.0	200.0		100.0
Min, Max	100.0, 100.0	100.0, 800.0			100.0, 100.0	100.0, 1600.0		100.0, 1600.0
Time to IgG Seroconversion from Date of First Infusion (days) for Seronegative Pts at Baseline								
n (%)	1 (10.00)	5 (20.83)	0	0	1 (14.29)	3 (13.64)	0	10 (10.10)
Mean	168.0	113.4			86.0	28.0		90.5
Standard Deviation		84.46				0.00		73.79
Median	168.0	140.0			86.0	28.0		61.0
Min, Max	168.0, 168.0	21.0, 224.0			86.0, 86.0	28.0, 28.0		21.0, 224.0

Note: ** Patient 10065050 has undetermined phenotype, since he/she has missing diagnosis age, and was first treated at 7.9 years of age. This patient died at age 16.7 years.

Note: Patient 10235098 tested positive at baseline but without additional follow-up data during the study.

Note: Titer is imputed as 0 for IgG negative for calculating summary statistics.

Names of input datasets: ADAM.ADSL, ADAM.ADIM

Program name: Global-Biostats\rhGAA\Pompe\AGLU09411\FDA-LZ-May-2014\Programs\Output\tiggphencrim.sas

Output: tiggphencrim.rtf

Creation date: 22MAY2014 16:52

Reviewer's comment: The data summarized in Table 14.3.4.2.7 show that from the 31 patients who were seronegative at baseline, 10 seroconverted after switching to the 4000L product. Titers after seroconversion were low. Interestingly, patients identified as CRIM negative (column 1) show low titers at baseline and throughout the study. Moreover, 5 were negative at baseline and 4 remained seronegative until the data cut off date. These results are unexpected since CRIM negative patients generally develop anti rhGAA antibodies that result in a poor outcome to ERT. Al Khallaf et al. 2012, reported two CRIM negative siblings on ERT who developed unusually low antibody titers and showed a good clinical outcome. However, I was not able to find reports of CRIM negative patients on ERT with undetected anti rhGAA titers. One possible explanation for these results could be the use of concomitant medications prior to enrollment into the ADVANCE study which may include immune tolerance induction (ITT) regimens that were effective in abolishing antibody responses (as proposed by the Sponsor). Alternatively, these patients could be misdiagnosed CRIM positive patients.

Despite this observation, overall, the data indicate that antibody responses before and after switching from the 160L product to the 4000L product are comparable or even better.

Neutralizing antibodies of enzyme activity or uptake

All seropositive patients in the study were tested for the presence of inhibitory antibodies.

- One patient (10595046) tested positive for inhibitory enzyme uptake at Day 1 (baseline) and Weeks 4 and 52.
- No patients ever tested positive as of the data cut-off for inhibitory enzyme activity.

Reviewer's comment: *The patient who developed antibodies inhibitory of enzyme uptake though they did not meet the criteria for high sustained antibody titers, showed relatively high titers throughout the study. This patient was positive at baseline with a titer of 25,600, a peak titer of 102,400 at week 30 and a last titer of 25,600 at week 52.*

Additional testing for infusion associated reactions suggestive of hypersensitivity

Seven patients were subjected to additional testing (patients 10345030, 10375051, 10555058, 10595092, 10715017, 10015022 and 10015011):

- All patients were negative for anti-rhGAA IgE antibodies.
- Two (2) patients were positive for complement activation (patients 10015022 and 10015011).
- All patients had results for serum tryptase within the normal range (≤ 12.5 µg/L).
- No patients were tested for circulating immune complexes

Patients 10015011, 10555058 and 10735048 experienced reactions that met the criteria for anaphylaxis but only patient 10015011 was determined to experience an allergic reaction to the study drug. The other two patients experienced SAEs that were assessed by the investigator as not related to treatment.

Adverse events by immunogenicity parameters

Patients with high sustained antibody titers:

Fifteen SAEs were reported for the 2 patients with high sustained antibody responses. For patient 10375051, most of the SAEs (6/8) were considered IARs and were related to the study drug. The patients recovered from all events. For patient 10555058 none of the 7 SAE were considered related to the study drug and were not IAR

Patients positive for inhibitory antibodies for enzyme uptake

Patient 10595046 reported 3 SAEs (2 events of pneumonia and pneumonia parainfluenzae viral) that were considered not related to study treatment. The patient recovered from the events.

A summary of the safety data based on immunogenicity parameters is summarized in Tables 13, 14 and 15 below.

Table 13 – Summary of safety by seroconversion status, quartiles of peak IgG antibody (Safety Population)

	Negative (N=21)		Positive (N=77)							
			Quartile 1 (100 – 400) n=20		Quartile 2 (800 – 1600) n=23		Quartile 3 (3200 – 3200) n=20		Quartile 4 (6400 – 102400) n=14	
	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)
Patients with adverse events	278	19 (90.5)	308	20 (100.0)	301	23 (100.0)	215	20 (100.0)	298	14 (100.0)
Patients with serious adverse events	33	10 (47.6)	30	10 (50.0)	35	9 (39.1)	27	7 (35.0)	40	9 (64.3)
Patients with infusion-associated reactions	8	4 (19.0)	13	3 (15.0)	4	2 (8.7)	36	8 (40.0)	25	3 (21.4)

Source: Table 14.3.1.6.4, Table 14.3.2.1.9, Table 14.3.2.2.14

Note: All patients in Quartile 3 had a titer of 3200.

Note: If a patient had more than 1 event for a particular System Organ Class, he/she is counted only once for that System Organ Class.

Note: If a patient had more than 1 event for a particular Preferred Term, he/she is counted only once for that Preferred Term.

Note: Percentages are based on the total number of patients treated in the corresponding groups.

Note: Serious adverse events includes serious infusion-associated reactions.

Reviewer's comment: A correlation between the incidence of AEs, SAEs or IARs and IgG antibody titers is not evident. AEs were reported for all seropositive patients and most patients negative for anti rhGAA antibodies (19/21). However, the patients in IgG quartile 4 showed similar number of AEs than the other groups despite that fewer patients fell in this Quartile (298 AE in 14 patients), suggesting more AEs occurred in patients with the highest antibody titers. A similar pattern is observed for the incidence of SAEs. This trend is not observed for IARs.

Table 14 – Summary of safety by status of sustained and elevated IgG titers (Safety Population)

System Organ Class Preferred Term	With Sustained & Elevated Titers (N=2)		Without Sustained & Elevated Titers (N=76)	
	Events n	Patients n (%)	Events n	Patients n (%)
Patients with adverse events	58	2 (100.0)	1064	75 (100.0)
Patients with serious adverse events	15	2 (100.0)	117	33 (44.0)
Patients with infusion-associated reactions	8	1 (50.0)	70	15 (20.0)

Source: Table 14.3.1.6.5, Table 14.3.2.1.10, Table 14.3.2.2.15

Note: If a patient had more than 1 event for a particular System Organ Class, he/she is counted only once for that System Organ Class.

Note: If a patient had more than 1 event for a particular Preferred Term, he/she is counted only once for that Preferred Term.

Note: Percentages are based on the total number of patients treated in the corresponding groups.

Note: Serious adverse events includes serious infusion-associated reactions.

Table 15 – Summary of safety by status of inhibitory antibody (Safety Population)

Body System Organ Class Preferred Term	Inhibitory AB for Enzyme Uptake (N=77)				Inhibitory AB for Enzyme Activity (N=77)			
	Negative (N=76)		Positive (N=1)		Negative (N=77)		Positive (N=0)	
	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)
Patients with adverse events	1105	76 (98.7)	13	1 (100.0)	1118	76 (98.7)	0	0 (0.0)
Patients with serious adverse events	126	33 (43.4)	3	1 (100.0)	129	34 (44.2)	0	0 (0.0)
Patients with infusion-associated reactions	78	16 (21.1)	0	0 (0.0)	78	16 (20.8)	0	0 (0.0)

Source: Table 14.3.1.6.6, Table 14.3.2.1.11, Table 14.3.2.2.16

Note: If a patient had more than 1 event for a particular System Organ Class, he/she is counted only once for that System Organ Class.

Note: If a patient had more than 1 event for a particular Preferred Term, he/she is counted only once for that Preferred Term.

Note: Percentages are based on the total number of patients treated in the corresponding groups.

Note: Serious adverse events includes serious infusion-associated reactions.

Reviewer's comment: *the number of patients who developed high sustained antibody titers (2) or tested positive for antibodies that inhibit enzyme uptake (1) was too small to determine whether there is a correlation between these parameters and the incidence of AEs, SAEs or IARs.*

Four patients received immunomodulation treatment: 10015011 (prophylactic ITI treatment during participation in Study AGLU03807), 10355062 (IVIG), 10455081 (rituximab and methotrexate), and 10665015 (rituximab and methotrexate).

Reviewer's note: *Except for patient 10015011 who developed relatively high antibody titers, patients who received immune tolerance treatment were seronegative throughout the ADVANCE study (patients 10665015) or developed very low (patient 10355062, peak titer of 100) or relatively low IgG titers (patient 10455081, peak titers 6400) antibody titers.*

In order to allow a comparison of the immunogenicity profile between patients receiving the 4000L product and those who exclusively received 160L product, we requested that the Sponsor provide for patients who participated in Study AGLU09411 (when they switched over to the 4000L product) and for patients who received exclusively the 160L product (AGLU1602/2403 studies) graphical representation of antibody titers over time by clinical outcome. These data were provided in the response to our information request dated March 19, 2014 shown below.

AGLU09411 (ADVANCE): antibody formation over time by clinical outcome



Reviewer's comment: Data from the 95 patients in the ADVANCE study are plotted in the same figure and without patient identification precluding data analysis. The data suggest a lack of correlation between clinical outcome (invasive ventilator status and survival) and antibody titers: none of the patients who died were among those with the highest antibody titers. One of the patients who required invasive ventilation (shown in red in Figure 14.3.1.2.3) showed high sustained antibody titers but the other two patients had either low or medium antibody titers.

AGLU01602/2403: antibody formation over time by clinical outcome

CRIM positive patients

(b) (4)



CRIM negative patients

Reviewer's comment: Eighteen patients were initially enrolled in study AGLU01602 and 16 continued into study AGLU2403. All 16 patients in study AGLU2403 were IgG positive. Ten out of 16 patients had relatively low titers at all time points or had titers that peaked and then decreased with titers ranging between 200 – 1600 in the last assessment. All these patients were CRIM positive patients. Two CRIM positive patients developed a high sustained antibody response and died. The antibody response of high sustained titers in CRIM positive patients resembles that observed in CRIM negative patients (Figure 14.3.4.7.2) but probably reaches lower peak titers. All CRIM negative patients in study AGLU01602/2403 had sustained high antibody titers, with titers at the last visit ranging from 51,200 to 1,638,400. Two of these patients died and two were invasively ventilated. These data show a correlation between high sustained antibody titers and poor clinical outcome and death in CRIM positive and negative patients.

Taking together, the data provided support comparable immunogenicity profiles in infantile onset patients who exclusively received the 4000 L product (Taiwan 01 study) or 160L product (AGLU 1602/2403). Further, data from the switch over study support comparable impact of ADAs on safety before and after switching. These data mimic what would happen upon approval. Therefore, from an immunogenicity perspective, the patient population for the 4000L material can be updated to include all Pompe disease patients including patients under the age of 8 years with infantile and late-onset Pompe disease.

APPENDIX 1

	Taiwan Study (N = 18)	Myozyme study* (N = 18)
CRIM Positive, n (%)	18 (100)	14 (77.8)
Sero conversion IgG n (%)	16 (94.1) (17 evaluated)	12/14 (85.7)
Time to sero conversion (Median/range in days)	84 27-1,547	28 0-448
Peak titer (Median/range)	1,600 0-12,800	2400 0-409,600
Last titer (Median/range)	200 0-6400	200 0- 409,600
Inhibition of enzyme uptake/activity	0/3**	0-14

*Measured at a median of 180 (32 - 369) weeks in Taiwan01 and at a median of 116 (52 – 142) weeks in AGLU01601/02403.

** In Taiwan01, testing for inhibitory antibodies was performed only on patients whose adverse event was suggestive of antibody-mediated inhibition.

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/s/

Maria Cecilia TAMI
07/17/2014

SUSAN L KIRSHNER
07/17/2014



Memorandum of Review

STN: 125291/136

Subject: Efficacy Supplement – Expansion of indication to include all Pompe patients

Applicant: Genzyme
Product: Lumizyme
Indication: For use in patients with Pompe disease (GAA deficiency)

Received Date: January 30, 2014
Review Date: July 2, 2014
Filing Action Date: March 31, 2014
Action Due Date: August 1, 2014

Primary Reviewer: Christopher Downey, PhD
Secondary Reviewer: Juhong Liu, PhD
Tertiary Reviewer: Susan Kirshner, PhD

Primary Review Team:
Medical Officer: Juli Tomaino
Pharm/Tox: Fang Cai
Immunogenicity: Cecilia Tami
Clinical Pharmacology: Christine Hon
Statistics: Freda Cooner
DRISK (REMS): Kendra Worthy
PMHS: Alyson Karesh
RPM: Kevin Bugin

I. SUMMARY BASIS OF RECOMMENDATION:

- a. **Recommendation:** I recommend approval of this supplement.
- b. **Justification:** Genzyme produces two USA-licensed recombinant human alglucosidase alfa (rhGAA) enzyme replacement therapies for Pompe disease. Myozyme was approved for the treatment of all Pompe patients, and Lumizyme was subsequently approved for treatment of patients 8 years of age and older. These products are identical formulations of the same enzyme expressed and purified from the same cell line. The difference between the products is that Myozyme is manufactured with a fermentation scale of 160 L, whereas

Lumizyme is manufactured from a 4000 L process. Genzyme originally requested to scale-up Myozyme to a 2000 L process, but the Agency was concerned that the drug substance from the different manufacturing scales differed in critical quality attributes. There was insufficient clinical data to demonstrate comparability of the products in light of these differences. These concerns ultimately lead, after another scale-up to 4000 L, to approval of Lumizyme (4000 L) under a separate license than Myozyme (160 L). See the Background section of this review for additional details.

In this supplement, Genzyme requests to expand the commercial indication for Lumizyme to all patients. The basis for this request is that the 4000 L and 160 L products are comparable based on analytical (*i.e.* biochemical and physical) comparability data and supporting clinical data from an investigator-sponsored, uncontrolled study of infantile-onset patients treated with Lumizyme. Although the 160 L and 4000 L products are currently marketed in the USA under different licenses, the FDA considers this submission a comparability exercise as described in *ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process* since the same manufacturer has total control of the manufacturing processes, cell lines, and analytical testing for both production scales and complete knowledge of the product development history.

The analytical comparability portion of the submission is reviewed here. I note that Genzyme never previously provided a comprehensive analytical study comparing material produced by the 160 L process and the current 4000 L process; our previous concerns about differing product quality attributes were based on comparing 160 L product to product from the now defunct 2000 L process that preceded the 4000 L process.

The analytical comparability data consist of 3 components. The first is a comparison of 3 lots each of 160 L- and 4000 L-process drug substance tested side-by-side in a variety of assays. This study yielded highly comparable results for the two scales for critical quality attributes, including specific activity (*i.e.* potency), enzymatic kinetic parameters, primary, secondary, and tertiary structure, and levels of product-related impurities. The content of (b) (4)

(b) (4) were also comparable. Several test results suggest that the 4000 L lots have (b) (4) than the 160 L lots. (b) (4)

a desirable trait for this drug. (b) (4)

(b) (4) Since the data indicate a potentially clinically beneficial improvement for this trait, the expected small differences in test results sensitive to (b) (4) content are acceptable.

The second component of the analytical data is a comparison of release and extended characterization data for all previous drug substance and drug product lots produced from the two process scales. These data include release test results from more than 100 lots each of drug substance from both scales. The results show the materials from the two scales to be highly comparable for most attributes. The data are all consistent with the side-by-side studies, including higher values for the 4000 L drug substance lots than for the 160 L lots for tests sensitive to (b) (4) content. The 4000 L process has less lot-to-lot variability than the 160 L process for most attributes. The 4000 L process also consistently yields lower levels of host cell-derived impurities for the drug substance and of protein aggregate impurities for the drug product than the 160 L process. The (b) (4) levels for the 4000 L drug substance lots and 160 L lots since 2008 are comparable, with the levels for both slightly lower than levels for pre-2008 160 L lots. (b) (4)

The (b) (4) test results for 4000 L drug substance are also at the high end of the range of values for 160 L product. However, this result is acceptable since the results for this test were identical in side-by-side testing, and (b) (4) is a non-critical attribute that is not stability-indicting for rhGAA and is not known to correlate to any clinical impact.

The third component of the analytical data is a comparison of historical stability data for the two process scales. Genzyme provided stability data for all relevant drug substance and drug product lots stored under long-term storage conditions (5 °C) and for drug product stored under accelerated conditions (25 °C). The data for the long-term conditions show little change over time in most tests for materials manufactured at both 160 L and 4000 L scales. Aggregation measurably increases over time for a majority of the long-term lots. The rates of increase do not differ significantly between lots from the two manufacturing scales. The data from accelerated stability are also comparable for most attributes, including specific activity, protein concentration, and purity. The tests with significant trending over time are aggregation and the headspace oxygen content. There is not a significant difference between the rates of increase for aggregation for the two scales, and the rates of increase for headspace oxygen for the 4000 L results are, if anything, lower than for the 160 L product. (b) (4)

Together, the head-to-head comparability study and the historical release and stability data support that the products of the 160 L and 4000 L manufacturing processes are comparable for activity and structure. The only significant differences between the products are that the 4000 L product 1) has slightly higher levels of (b) (4), and 2) has less lot-to-lot variability and lower levels of manufacturing process-related impurities. Existing knowledge suggests that these differences are, if anything,

beneficial, and that there is very little risk of adverse impact to the safety or efficacy for patients switching from the 160 L product to the 4000 L product. Per ICH Q5E, products may be considered comparable when slight analytical differences are observed if they do not adversely impact safety and efficacy. I therefore recommend approval of this supplement.

II. COMMENTS TO SPONSOR:

No CMC-specific comments.

III. REVIEW

Background

Genzyme produces two recombinant alglucosidase alfa (rhGAA) enzyme replacement therapies that are approved in the United States to treat Pompe disease: Myozyme and Lumizyme. These two products are manufactured from the same cell line at different production scales. Myozyme drug substance (DS) is manufactured at a fermentation scale of 160 L and was approved for treatment of all Pompe patients in April 2006. This approval was supported by pivotal clinical data from infantile-onset Pompe patients (study AGLU01602/2403). Genzyme subsequently requested approval of scale-up to a 2000 L rhGAA manufacturing process under the Myozyme BLA. There were significant differences in critical glycosylation attributes for drug substance produced at the different scales. Since the sponsor did not provide sufficient clinical data to demonstrate comparability for all patient populations given these analytical differences, the Agency did not approve the change to 2000 L production scale for Myozyme.

After another process change increasing the scale from 2000 to 4000 L, the 4000 L-scale product was approved in 2010 as Lumizyme under a separate BLA. The 2000 L manufacturing process was discontinued. Lumizyme was approved only for Pompe patients 8 years old and over based on clinical trial data from late-onset Pompe patients (LOTS, AGLU02704) treated with 2000 L process scale material and analytical comparability between 2000 L and 4000 L process scale materials. Although the data available to the Agency suggested that the 4000 L process material may be more similar to the 160 L material than was the 2000 L material, Genzyme did not until now submit a comprehensive comparability study to establish comparability between the 160 L and 4000 L process-scale drug substance.

In response to PMC 14 for the Lumizyme BLA,

(b) (4)

(b) (4)

Due to supply issues for Myozyme, as of March 30, 2012 Genzyme restricted Myozyme to patients less than 1 year of age and enrolled patients between 1 and 8 years of age in the ADVANCE clinical trial to be treated by Lumizyme. In the current supplement, Genzyme requests to extend the commercial indication of Lumizyme to all Pompe patients based on *i*) comprehensive analytical comparability data between 4000 L-scale Lumizyme (b) (4) and 160 L-scale Myozyme and *ii*) supporting clinical data from a Taiwan-based investigator-sponsored study of infantile-onset patients treated with Lumizyme and safety data from the ADVANCE study. The Taiwan study includes data obtained from 2000 L- and 4000 L-scale (b) (4) rhGAA.

Here, I review the analytical comparability components of the supplement. Based in part on the discussion between the Agency and Genzyme in a July 3, 2013 meeting, Genzyme provided the following data to support analytical comparability between 160 L process scale Myozyme and 4000 L scale [REDACTED] (b) (4) time Lumizyme:

- 1) Head-to-head comparison of 3 lots each of drug substance produced at [REDACTED] (b) (4) 4000 L and 160 L process scales. The lots were analyzed by a selected subset of the DS release and characterization assays.
- 2) Comparisons of historical release and real time/real temperature stability data for [REDACTED] (b) (4) 4000 L and 160 L scale materials.
- 3) A comparison of available accelerated stability data for the [REDACTED] (b) (4) 4000 L and 160 L scale materials.

(b) (4)

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CMC labeling review

The proposed label has few changes to CMC-related information. The CMC-related changes are summarized below, organized by label sections. Throughout the proposed label, the sponsor refers to the product as “alglucosidase alfa” rather than “Lumizyme” as in the current label. I have no objection to this change.

Section 2 - Dosage and Administration. There are no changes to recommended dose (Section 2.1). Section 2.2, Table 1 is updated to include infusion volumes and rates for infant patients of 1.25 – 10 kg and 10.1 – 20 kg. This change is consistent with the expanded indication. There are no changes to the reconstitution and dilution instructions in section 2.3.

Section 3 - Dosage Forms and Strengths. There are no changes to this section.

Section 11- Description. The sponsor deleted the sentence: “th (b) (4)
The draft label changes the specific activity of alglucosidase alfa from (b) (4) to “3.6 to 5.4 Units/mg.”

Reviewer comments:

- 1) *Because approval of the expanded indication for infants for Lumizyme is based in part on physicochemical comparability of Lumizyme and Myozyme , there is no longer a need to emphasize a potential difference between the two products. Deleting the sentence describing the difference in manufacturing is therefore acceptable.*
- 2) *The proposed change to the specific activity reflects the current drug product release specification for Lumizyme approved on July 28, 2011 (BLA 125291/45) and is therefore acceptable.*

Section 16 – How Supplied/Storage and Handling. The only change to this section is the introduction of a 10-vial carton. Genzyme notes it plans to introduce these cartons in Q1 2014 and that the change will be reported in the annual report due by July 23, 2014.

Reviewer comments:

- 1) *I concur that this is a low-risk, annual reportable change. The introduction of a 10-pack carton is acceptable.*

IV. REVIEWER CONCLUSIONS:

Head-to-head comparability and historical release and stability data support that the 160 L and 4000 L manufacturing processes product that is comparable for activity, structure, and product-related impurities. The data indicate the 4000 L product is (b) (4) that the 160 L product. (b) (4). Per ICH Q5E, the existing knowledge is sufficiently predictive to ensure that these differences in quality attributes will have no adverse impact upon safety or efficacy of the drug product. The products produced at 160 L and 4000 L process scales are therefore comparable and approval is recommended.

V. FUTURE INSPECTION ITEMS:

(b) (4)
(b) (4)

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/s/

CHRISTOPHER D DOWNEY
07/14/2014

JUHONG LIU
07/14/2014

SUSAN L KIRSHNER
07/14/2014

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR BLA/NDA Supplements (OBP & DMPQ)

BLA/NDA Number: 125291/136 **Applicant:** Genzyme **Stamp Date:** 01/30/14
Established/Proper Name: Lumizyme® (alflucosidase alfa) **BLA/NDA Type:** Efficacy supplement

Brief description of the change:	Updating the Lumizyme indication to include all Pompe patients
Reviewer:	Christopher Downey
Office/Division:	OBP/DTP

On **initial** overview of the BLA/NDA **supplement** for filing:

The following was submitted in support of the change (check all that apply):

<input checked="" type="checkbox"/>	A detailed description of the proposed change
<input checked="" type="checkbox"/>	Identification of the product(s) involved
<input checked="" type="checkbox"/>	A description of the manufacturing site(s) or area(s) affected
<input checked="" type="checkbox"/>	A description of the methods used and studies performed to evaluate the effect of the change on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product
<input checked="" type="checkbox"/>	The data derived from such studies
<input type="checkbox"/>	Relevant validation protocols and data
<input type="checkbox"/>	A reference list of relevant standard operating procedures (SOP's)

The following deficiencies were identified (identify those that are potential filing issues):

IS THE PRODUCT QUALITY SECTION OF THE SUPPLEMENT FILEABLE? **Yes**

If the supplement is not fileable from the product quality perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Product Quality Reviewer Date

Branch Chief/Team Leader/Supervisor Date

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/s/

CHRISTOPHER D DOWNEY
03/31/2014

JUHONG LIU
03/31/2014

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR IMMUNOGENICITY (OBP)

BLA/NDA Number:

125291/136

Applicant:

Genzyme

Stamp Date:

January 30 2014

Established/Proper Name: BLA/NDA Type:

Lumizyme

sBLA

On initial overview of the application for filing:

	Content Parameter	Yes	No	Comment
1	Is the screening assay validation report(s) provided, indexed and paginated in a manner allowing substantive review to begin (module 5.3)?		X	Validation of Immunogenicity assays was previously submitted and reviewed.
2	Is the confirmatory assay validation report(s) provided, indexed and paginated in a manner allowing substantive review to begin (module 5.3)?		X	Validation of Immunogenicity assays was previously submitted and reviewed.
3	Is the titering assay validation report(s) provided, indexed and paginated in a manner allowing substantive review to begin (module 5.3)?		X	Validation of Immunogenicity assays was previously submitted and reviewed.
4	Is the neutralizing assay validation report(s) provided, indexed and paginated in a manner allowing substantive review to begin (module 5.3)?		X	Validation of Immunogenicity assays was previously submitted and reviewed.
5	Are assay SOPs provided (probably module 1)?		X	Validation of Immunogenicity assays was previously submitted and reviewed.
6	Are the immunogenicity data summarized in the summary of clinical safety (module 2.7) in a manner allowing substantive review to begin?	X		

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR IMMUNOGENICITY (OBP)**

	Content Parameter	Yes	No	Comment
7	Was the location of supporting clinical data provided in a manner allowing substantive review to begin?	X		
8	Are all required and requested IND studies completed and submitted in a manner allowing substantive review to begin?	X		

IS THE APPLICATION FILEABLE FROM AN IMMUNOGENICITY PERSPECTIVE? ___YES___

If the NDA/BLA or supplement is not fileable from an immunogenicity perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

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/s/

Maria Cecilia TAMI
03/26/2014

SUSAN L KIRSHNER
03/26/2014

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
BLA 125291/136

ENVIRONMENTAL ASSESSMENT



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Division of Therapeutic Proteins
Bethesda, MD 20892
Tel. 301-827-1790

Memorandum of Review (Addendum)

STN: 125291/136

Subject: Environmental Assessment for an Efficacy Supplement to expand indication to include all Pompe patients

Applicant: Genzyme
Product: Lumizyme
Indication: For use in patients with Pompe disease (GAA deficiency)

Received Date: January 30, 2014
Review Date: July 25, 2014
Action Due Date: August 1, 2014

Primary Reviewer: Christopher Downey, PhD
Secondary Reviewer: Juhong Liu, PhD
Tertiary Reviewer: Susan Kirshner, PhD

Addendum to Include Environmental Assessment:

Herein I review the Environmental Assessment provided by Genzyme in the Lumizyme Efficacy Supplement submitted on January 30, 2014 (BLA 125291/136). This document is an addendum to the product quality review filed on July 14, 2014.

Review:

Genzyme submitted a statement of exemption from preparing an environmental assessment under 21CFR section 25.31(c). This section provides for a categorical exclusion regarding an action on a BLA “when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment.” Alglucosidase alfa is a recombinant version of the naturally occurring human protein acid alpha-glucosidase and has the same metabolizes and degradation products the natural protein. Based on its expected production for all patients of 45 kg per year for direct human use and a dilution of 1.214×10^{11} liters per day of material entering the sewage treatment system, Genzyme calculates an expected introduction concentration (EIC) of 0.002079 ppb into the aquatic environment per year. Thus, the EIC at the point of entry into the aquatic environment will be far below 1 part per billion (ppb).

Reviewer comment: This drug is analogue of a naturally occurring protein, acid alpha-glucosidase. Genzyme’s EIC calculation supports that the expansion of the indication of

Lumizyme to all Pompe patients will not significantly impact the concentration or distribution in the environment of acid alpha-glucosidase, its metabolites, or its degradation products. The environmental assessment information provided is therefore acceptable to demonstrate that this product meets the criteria for categorical exclusion under 21 CFR Section 25.31(c).

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/s/

CHRISTOPHER D DOWNEY
07/25/2014

JUHONG LIU
07/25/2014

SUSAN L KIRSHNER
07/25/2014

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

BLA 125291/136

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number: 125,291/136
Supporting document/s: n/a
Applicant's letter date: January 30, 2014
CDER stamp date: January 30, 2014
Product: LUMIZYME® (alglucosidase alfa; recombinant human acid α -glucosidase; GAA)
Indication: Pompe disease (GAA deficiency)
Applicant: Genzyme Corporation
Framingham, MA
Review Division: Division of Gastroenterology and Inborn Errors Products
Reviewer: Fang Cai, Ph.D.
Supervisor/Team Leader: David Joseph, Ph.D.
Division Director: Donna Griebel, M.D.
Project Manager: Kevin Bugin, M.S, RAC

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of sBLA 125,291/136 are owned by Genzyme Corporation or are data for which Genzyme Corporation has obtained a written right of reference. Any information or data necessary for approval of sBLA 125,291/136 that Genzyme Corporation does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of sBLA 125,291/136.

1. Executive Summary

1.1 Introduction

LUMIZYME® (alglucosidase alfa, 4000L scale product) is a hydrolytic lysosomal glycogen-specific enzyme, and was approved in 2010 for patients 8 years and older with late (non-infantile) onset Pompe disease. The current submission is an efficacy supplement to the BLA in support of changing the indication to include all Pompe disease patients. The recommended dosage of LUMIZYME is 20 mg/kg body weight administered every two weeks as an intravenous infusion.

1.2 Brief Discussion of Nonclinical Findings

Nonclinical studies were not submitted in this supplement. This review is focused on the revision of the pregnancy subsection of the label, to comply with the PLLR format.

1.3 Recommendations

1.3.1 Approvability


Lumizyme (alglucosidase alfa) is recommended for approval for treatment of all Pompe disease patients.

1.3.2 Additional Nonclinical Recommendations

The labeling should be revised as described below.

1.3.3 Labeling

Established Pharmacologic Class (HIGHLIGHTS and section 11)

 (b) (4)
the EPC text phrase for alglucosidase alfa shown in the PRPLL is: “hydrolytic lysosomal glycogen-specific enzyme”. Therefore, “hydrolytic lysosomal glycogen-specific enzyme” should be used as the EPC text phrase for Lumizyme.

Sponsor’s Version:

8.1 Pregnancy

 (b) (4)

(b) (4)

Evaluation:

The proposed Pregnancy subsection is identical to the currently approved version. However, (b) (4)

(b) (4)

The pre-/postnatal developmental (segment 3) study in mice was submitted under BLA 125,141 (Myozyme®) and was reviewed by Dr. Niraj Mehta (Pharmacology/Toxicology review dated September 15, 2008). In this segment 3 study, CD1 mice were treated with Myozyme (alglucosidase alfa) at doses of 10, 20 or 40 mg/kg by intravenous injection every other day from gestation day (DG) 6 through lactation days (DL) 20-21. All animals in the treatment groups received diphenhydramine (DPH) via intraperitoneal injection prior to administration of alglucosidase alfa to prevent hypersensitivity reactions. The two control groups were treated with vehicle (IV) + saline (IP) or vehicle (IV) + DPH (IP). Although Dr. Mehta did not clearly state the relationship of the adverse

effects to the test article, he provided the following statement: **“The number of pups dying on DLs 15 to 21 was significantly increased ($p \leq 0.05$) in Group V (12.2%) compared to the Group I (6.7%) value.”** The “Group I” cited by Dr. Mehta is actually the vehicle + saline control group. It is noteworthy that mortality was 4.9% in the vehicle + DPH control group, thus showing a greater difference than the vehicle + saline control when compared to the 40 mg/kg group. This mortality data is shown on page 71 of the Pharmacology/Toxicology review of BLA 125,291 (Lumizyme®) dated January 30, 2009, by Dr. Niraj Mehta.

(b) (4)

The segment 3 study showed that alglucosidase alfa produced a statistically significant increase in the number of pups (F1 generation) that died during DL 15 to 21 at 40 mg/kg IV every other day (12.2% mortality; $p \leq 0.05$), compared to the vehicle + saline control group (6.7% mortality). The mortalities during the DL 15 – 21 in the vehicle + DPH control, 10, and 20 mg/kg groups were 4.9%, 2.1% and 0%, respectively. The lactation index (i.e. percent survival of pups during DL 4-21) was 83.4%, 93%, 90.3%, 96.7%, and 75.3% in the vehicle + saline control, vehicle + DPH control, 10, 20, and 40 mg/kg groups, respectively. The incidence of litters with pups dying during DL 15-21 in the vehicle + saline group, vehicle + DPH group, and 40 mg/kg IV group was 4/23 litters (including one entire litter loss), 2/22 litters (including one entire litter loss), and 5/23 litters (including two entire litter losses), respectively.

The most appropriate control group in the segment 3 study for assessment of test article-related effects is the group treated with vehicle + DPH, rather than the vehicle + saline group as used by the sponsor. It is emphasized that the comparison of pup mortality (i.e. deaths during DL 15 to 21 and lactation index) in the 40 mg/kg group to the mortality in the vehicle + DPH control group shows a larger difference than the comparison to the vehicle + saline control group. Although no statistical analysis was conducted between the treatment groups and the vehicle + DPH control group, the increased mortality during DL 15 to 21 and the decreased lactation index in the 40 mg/kg IV group appear to be drug-related based on the totality of the data. It should also be noted that no maternal toxicity was observed.

The pregnancy subsection should be revised to comply with the PLLR format. The recommended version below was developed in collaboration with the Maternal Health team (Tamara Johnson and Jeanine Best).

Recommended Version:

8.1 Pregnancy

Pregnancy Category C

Women of childbearing potential are encouraged to enroll in the Pompe Registry [see *Patient Counseling Information (17)*].

Risk Summary

There were no adequate and well-controlled studies with Lumizyme in pregnant women. However, animal reproduction studies have been conducted for alglucosidase alfa. In these studies, no effects on embryo-fetal development were observed in mice or rabbits given daily administration of alglucosidase alfa up to 0.4 or 0.5 times, respectively, the human steady-state AUC (area under the plasma concentration-time curve) at the recommended human bi-weekly dose during the period of organogenesis. An increase in pup mortality was observed when alglucosidase alfa was administered every other day in mice during the period of organogenesis through lactation at a dose 0.4 times the human steady-state AUC at the recommended human bi-weekly dose. Lumizyme should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

All reproductive studies included pre-treatment with diphenhydramine to prevent or minimize hypersensitivity reactions. The effects of alglucosidase alfa were evaluated based on comparison to a control group treated with diphenhydramine alone. Daily intravenous (IV) administration of alglucosidase alfa up to 40 mg/kg in mice and rabbits (0.4 and 0.5 times, respectively, the human steady-state exposure at the recommended bi-weekly dose) during the period of organogenesis had no effects on embryo-fetal development. Administration of 40 mg/kg IV every other day in mice (0.4 times the human steady-state exposure at the recommended bi-weekly dose) during the period of organogenesis through lactation produced an increase in mortality of offspring during the lactation period.

Sponsor's Version:

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4)



Recommended Version:

Long-term studies in animals to evaluate carcinogenic potential or studies to evaluate mutagenic potential have not been performed with alglucosidase alfa.

Intravenous administration of alglucosidase alfa every other day in mice at doses up to 40 mg/kg (0.4 times the human AUC at the recommended bi-weekly dose) had no effect on fertility and reproductive performance.

2 Drug Information**2.1 Drug**

LUMIZYME (alglucosidase alfa)

Code Name: N/A

Structure or Biochemical Description/ Molecular Weight:

LUMIZYME (alglucosidase alfa) consists of the human enzyme acid α -glucosidase (GAA), encoded by the most predominant of nine observed haplotypes of this gene. LUMIZYME is produced by recombinant DNA technology in a Chinese hamster ovary cell line. Alglucosidase alfa degrades glycogen by catalyzing the hydrolysis of α -1,4- and α -1,6-glycosidic linkages of lysosomal glycogen.

Alglucosidase alfa is a glycoprotein with a calculated mass of 99,377 daltons for the polypeptide chain, and a total mass of approximately 109,000 daltons, including carbohydrates.

Pharmacologic Class: hydrolytic lysosomal glycogen-specific enzyme

2.2 Relevant INDs, NDAs, BLAs, and DMFs: BLA 125,141 (Myozyme®)

2.3 Drug Formulation

Lumizyme is supplied as a sterile, nonpyrogenic, white to off-white, lyophilized cake or powder for reconstitution with 10.3 mL Sterile Water for Injection, USP. Each 50 mg vial contains 52.5 mg alglucosidase alfa, 210 mg mannitol, 0.5 mg polysorbate 80, 9.9 mg sodium phosphate dibasic heptahydrate, 31.2 mg sodium phosphate monobasic monohydrate. Following reconstitution as directed, each vial contains 10.5 mL reconstituted solution and a total extractable volume of 10 mL at 5 mg/mL alglucosidase alfa.

2.4 Comments on Novel Excipients: N/A**2.5 Comments on Impurities/Degradants of Concern: N/A****2.6 Proposed Clinical Population and Dosing Regimen**

This sBLA supports expanded use of Lumizyme (4000L scale product) in patients of all ages with Pompe disease (GAA deficiency). The recommended dose regimen is the same as the currently approved dose regimen, which is 20 mg/kg body weight administered every 2 weeks as an intravenous infusion.

Regulatory Background

There are two approved enzyme replacement therapies for Pompe disease in the United States. Myozyme (alglucosidase alfa, 160L scale product) and Lumizyme (alglucosidase alfa, 4000L scale product) both contain recombinant human acid α -glucosidase (GAA) expressed by Chinese Hamster Ovary (CHO) cells. Myozyme was approved in 2006 for all patients with Pompe disease, and Lumizyme was approved in 2010 for patients 8 years and older with late (non-infantile) onset Pompe disease. Alglucosidase alfa is taken up by cells via the mannose-6-phosphate receptor followed by transfer and localization to lysosomes. This enzyme degrades glycogen by catalyzing the hydrolysis of α -1,4- and α -1,6-glycosidic linkages of lysosomal glycogen.

In the Pharmacology/Toxicology Team Leader memorandum for BLA 125,291 dated February 12, 2009, Dr. David Joseph stated the following:

“Both Lumizyme and Myozyme® contain recombinant human acid α -glucosidase (alglucosidase alfa) as the active ingredient. However, Lumizyme is manufactured using a 2000L bioreactor, whereas Myozyme® is produced using a 160L bioreactor. Lumizyme exhibits biochemical differences in comparison to Myozyme® that could have a negative impact on efficacy. Furthermore, there is a lack of clinical studies to allow for a meaningful comparison of these products. Therefore, the FDA deemed that Lumizyme should be marketed under its own BLA, rather than BLA 125,141 (Myozyme®). The proposed indication for Lumizyme is for use in patients 8 years and older with late-onset (non-infantile) Pompe disease (GAA deficiency), whereas Myozyme® is indicated for patients of all ages with Pompe disease. Nonclinical studies of Lumizyme were not requested by the Agency to support the approval of Lumizyme, since the observed differences between Lumizyme and Myozyme® are not expected to result in a different toxicity profile.”

In a meeting with FDA on February 19, 2013, the Sponsor agreed on a regulatory pathway to expand the Lumizyme indication to include all Pompe patients and to ensure continued supply of alglucosidase alfa at the 4000 L scale for the Pompe patient

community in its entirety, including patients with infantile-onset Pompe disease and late-onset Pompe disease patients under 8 years of age.

The current submission is an efficacy supplement to the BLA in support of expanding the Lumizyme indication to include all Pompe patients. No nonclinical studies were required to approve the intended indication. However, the current pregnancy subsection of the label (8.1) should be revised in accordance with the FDA draft guidance for industry: Pregnancy, Lactation, and Females and Males of Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Implementing the New Content and Format Requirements. This review is focused on the revision of the pregnancy subsection of the label, to comply with the PLLR format. The Sponsor should be asked to revise the labeling as recommended.

cc:

sBLA 125,291/136

DGIEP

DGIEP/PM

DGIEP/D. Joseph

DGIEP/F. Cai

DGIEP/J. Lee

R/D Init.: D. Joseph 7/2/14

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/s/

FANG CAI
07/08/2014

DAVID B JOSEPH
07/08/2014
I concur.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

BLA Number: 125,291

Applicant: Genzyme Corporation

Stamp Date: 1/30/2014

Drug Name: Lumizyme
(alglucosidase alfa)

BLA Type: Supplement

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	√		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	√		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	√		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	√		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	√		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	√		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	√		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	√		

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	√		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			N/A
11	Has the applicant addressed any abuse potential issues in the submission?			N/A
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION
FILEABLE? _Yes_____**

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Fang Cai

3/5/2014

Reviewing Pharmacologist

Date

David Joseph

3/6/2014

Team Leader/Supervisor

Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

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/s/

FANG CAI
03/07/2014

DAVID B JOSEPH
03/07/2014

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
BLA 125291/136

STATISTICAL REVIEW(S)

Medical Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Biometrics Division:	Division of Biometrics III (DB III)
BLA/Serial #:	125-291 / 136
Stamp Date:	January 30, 2014
Review Priority:	Priority
Drug Name:	Lumizyme® alglucosidase alfa
Indication:	Extend to include patients with infantile-onset Pompe disease and late-onset Pompe disease patients under eight years of age
Sponsor:	Genzyme Corporation
Documents Reviewed:	Study Taiwan01 Report
Statistical Reviewer:	Freda W. Cooner, Ph.D., DB III
Statistical Team Leader:	Freda W. Cooner, Ph.D., DB III
DB III Division Director:	Stephen E. Wilson, Dr. PH., DB III
Medical Reviewer:	Juli Tomaino, M.D., DGIEP
Medical Team Leader:	Jessica Lee, M.D., DGIEP
Project Manager:	Elizabeth Ford / Kevin Bugin, DGIEP

Genzyme is submitting this efficacy supplemental BLA in support of updating the Lumizyme® indication to include all Pompe patients; more specifically, to include infantile-onset Pompe disease patients and late-onset Pompe disease patients under eight years of age.

Pompe disease is a rare, autosomal recessive genetic disease caused by the deficiency of lysosomal acid α -glucosidase (GAA), an enzyme that degrades glycogen. The resulting accumulation of glycogen in body tissues, especially cardiac and skeletal muscles, disrupts the architecture and function of affected cells, leading to a variety of symptoms, clinical decline, and ultimately death. Alglucosidase alfa, with active ingredient of recombinant human GAA (rhGAA), in a form of lyophilized powder for injection, has been developed as an enzyme replacement therapy (ERT) for the treatment of Pompe disease. The recommended dosage regimen is 20 mg/kg body weight administered every other week (qow) as an intravenous (IV) infusion.

Alglucosidase alfa, under the trade name Myozyme®, was originally submitted under BLA 125141 and manufactured at the 160 L and 2000 L scales. Per the feedback from the FDA, the 2000 L scale manufacturing process was withdrawn from the application. Based on the evaluation of ventilator-free survival results, the 160 L-scale product was approved for the treatment of Pompe disease on April 28, 2006, with the following indication: “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.”

(b) (4)

Genzyme

submitted BLA 125291 on May 30, 2008, which included data and results of a post marketing commitment safety, efficacy, and pharmacokinetics (PK) study (AGLU02704), also referred to as “LOTS”, which used the 2000 L product under the trade name Lumizyme®. Lumizyme® was approved on May 24, 2010, based on the evaluation of 6-minute walk test (6MWT) results, with an indication for Pompe patients eight years and older with late (non-infantile) onset Pompe disease who do not have evidence of cardiac hypertrophy, consistent with the population studied in LOTS.

In parallel with the Lumizyme® BLA submission, Genzyme had been developing a linear scale-up of the 2000 L scale manufacturing process to a 4000 L bioreactor working volume scale to meet increasing patient demand. Following the review of the amendment to the BLA, the FDA determined the 2000 L- and 4000 L-scale products were chemically comparable resulting in the clinical data from LOTS being used to support approval of the 4000 L-scale product. The 4000 L-scale product has been used in a phase 4, open-label, prospective efficacy and safety study (AGLU09411), also referred to as “ADVANCE”, where more than 90% of the subjects had previously received 160 L Myozyme®. Alglucosidase alfa manufactured at the 4000 L scale is the only product available outside of the US and is approved for all Pompe patients in all countries except the US.

During the February 19, 2013 Type C meeting, the FDA suggested that approval of Lumizyme® for use in patients with infantile-onset Pompe disease and patients under eight years of age with late-onset Pompe disease could be achieved by determining chemically analytical comparability between the two scales (160 L and 4000 L) and providing clinical data collected on infantile-onset Pompe disease patients in Taiwan enrolled in an Investigator-Sponsored Study, referred to as the Taiwan study thereafter. This submission includes the study report of the Taiwan study and updated safety information from the ADVANCE interim safety data, along with data to support chemically analytical comparability between the two scales. Genzyme proposed to revise the Lumizyme® package insert to include the following:

- Taiwan study data;
- ADVANCE interim safety data;
- Myozyme® package insert clinical safety (inclusive of the safety table) and efficacy data of infantile-onset clinical trial experience in AGLU01602/2403 and AGLU01702 studies;
- Any additional clinical data and post-marketing data from the Myozyme® package insert that was not already reflected in the Lumizyme® package insert (i.e., update to the black box warning).

The tabulation data in the CDISC-SDTM format and the analysis datasets in ADaM format for the Taiwan study, as well as the study reports for this submission have been

submitted in electronic Common Technical Document (eCTD) format to the EDR at:
[\\cdsesub1\bla\eCTD_Submissions\STN125291\0294.](#)

The Taiwan study was developed in order to monitor cases of Pompe disease identified through the National Taiwan University Hospital (NTUH) newborn screening program, and to compare their prognosis to the clinically identified cases in Taiwan. It was conducted in an open-label manner. The first subject was enrolled on March 8, 2006, and the study is still ongoing. Clinical data analyses were based on the interim data cut-off of March 15, 2013; but for immunogenicity data and adverse event (AE) data spontaneously reported to Genzyme, analyses were based on the cut-off of June 30, 2013. The study report submitted includes the interim data from 25 Taiwanese patients enrolled and treated in the study; 18 of which were determined to meet the criteria for infantile-onset Pompe disease.

In this new BLA efficacy supplement submission, Genzyme compared data from the Taiwan study to the results of Study AGLU01602, Study AGLU02403, and Study AGLU00400. Study AGLU01602 was an open-label, multicenter, multinational, dose-ranging study of safety, efficacy, PK, and pharmacodynamics (PD) for rhGAA treatment in patients no less than six months old with infantile-onset Pompe disease. Study AGLU02403 was a long-term extension study of patients with infantile-onset Pompe disease who were previously enrolled in Study AGLU01602. Study AGLU00400 was a multicenter, multinational, natural history study of 168 patients diagnosed with infantile-onset Pompe disease, who had symptom onset within their first year of life and received only palliative and supportive care. A historical control subgroup of 62 patients from within the AGLU00400 cohort was selected based on screening criteria adapted from the inclusion and exclusion criteria of Study AGLU01602, and this subgroup was used as the control population for the severe infantile-onset patients treated with Myozyme[®] in Study AGLU01602. Data from these earlier studies were reviewed during the original Myozyme[®] BLA 125141 review and are included in this new submission with the Taiwan study data.

The 18 patients from the Taiwan study that are included in the primary analysis were all Asian; 9 were male and 9 were female. The majority (12/18; 66.7%) of these patients had first infusion prior to 2 months of age and the latest patient received first infusion at 5.8 months of age. These 18 Taiwan study patients are mostly comparable to the patients from Study AGLU01602/2403 and the natural history cohort except that the mean age of first infusion was younger in the Taiwan study (median 1.0 month) than in Study AGLU01602/2403 (median 5.6 months). Out of the 18 patients, 7 were determined to have received 4000 L product alone using the cut-off date of the first 4000 L product shipment (September 7, 2009) and the first infusion date. Although some of these seven patients could have received 2000 L drug product for a short period, the sponsor considered it insignificant. The other 11 patients all had received 2000 L product and switched to 4000 L product if they remained in the study when 4000 L product became available. These two subgroups of patients presented very similar efficacy results and it is reasonable to pool these two subgroups together for the efficacy analyses.

The primary efficacy analysis was a comparison of ventilator-free survival of the infantile-onset patients from the Taiwan cohort to infantile-onset patients in Myozyme[®] pivotal Study AGLU01602 with its extension Study AGLU02403 and the natural history (AGLU00400) cohort at 18 months of age using Kaplan-Meier method. It should be noted that this analysis was proposed after the decision made in the aforementioned Type C meeting to use the Taiwan study efficacy data in support of chemically analytical comparability between the two scales (160 L and 4000 L). Due to the post-hoc nature of this efficacy analysis and the fact that the Taiwan study was conducted for research purposes, the results from this analysis are not suitable to support any efficacy labeling claims, and the inferential statistics of the Taiwan study should not be presented in the labeling.

For the Kaplan-Meier survival estimates, the sponsor claimed that the estimation included adjustment for left-truncated data by including patients in the risk set at the start of alglucosidase alfa treatment. However, it seems that in the survival plots provided by the sponsor, the age was used as the basis for time. To avoid selection bias because some patients had to survive long enough to enroll into the studies, the time elapsed from the first infusion should be used instead. The two figures below present the survival curves (with the confidence interval bands) and the Kaplan-Meier estimates using age and time from first infusion, respectively. The time adjustment is not applicable to the historical cohort because those patients were not treated with alglucosidase alfa and the data were retrospectively collected.

Two (2) patients from the Taiwan study were censored prior to age of 18 months or Month 18 from the first infusion, the rest 16 patients survived without invasive ventilator support. From the figures below, it can be observed that the time adjustment notably affected the results from Study AGLU01602/2403 but not the Taiwan study. This is expected because, as discussed before, the patients from the Taiwan study received their first infusion much earlier in their lives. The results from these two studies can be considered comparable relative to the natural history cohort, based on ventilator-free survival with both analyses; and the Taiwan study shows higher survival rates throughout Month 36 (from birth or first infusion). Although these results are not suitable for any efficacy labeling claims, they are supportive of chemically analytical comparability between the 160 L and 4000 L alglucosidase alfa products.

Figure 1. Ventilator-free Survival in months from birth

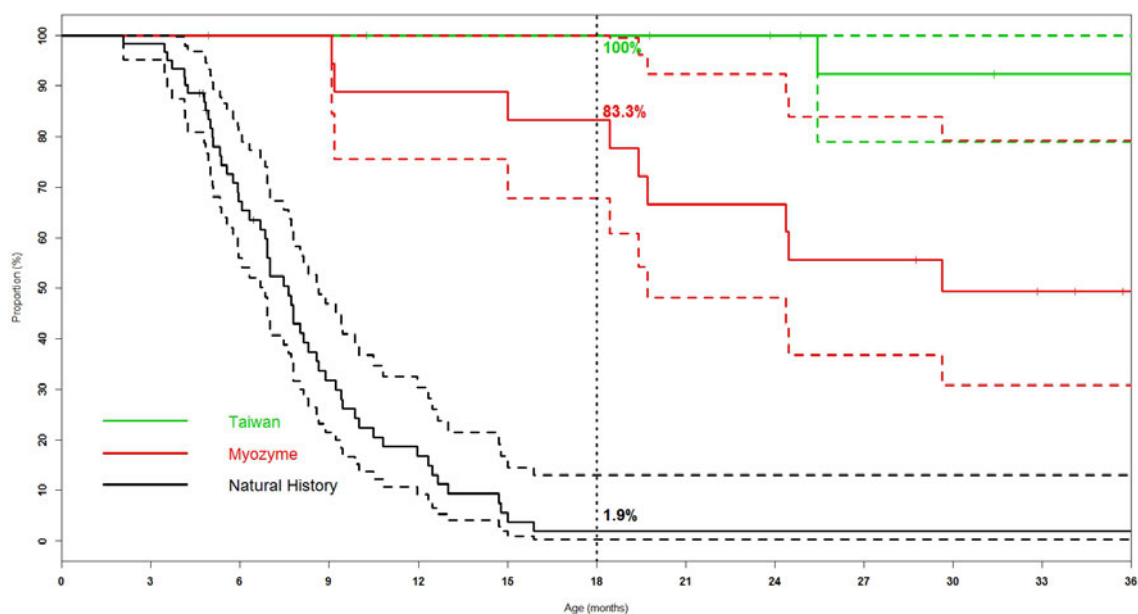
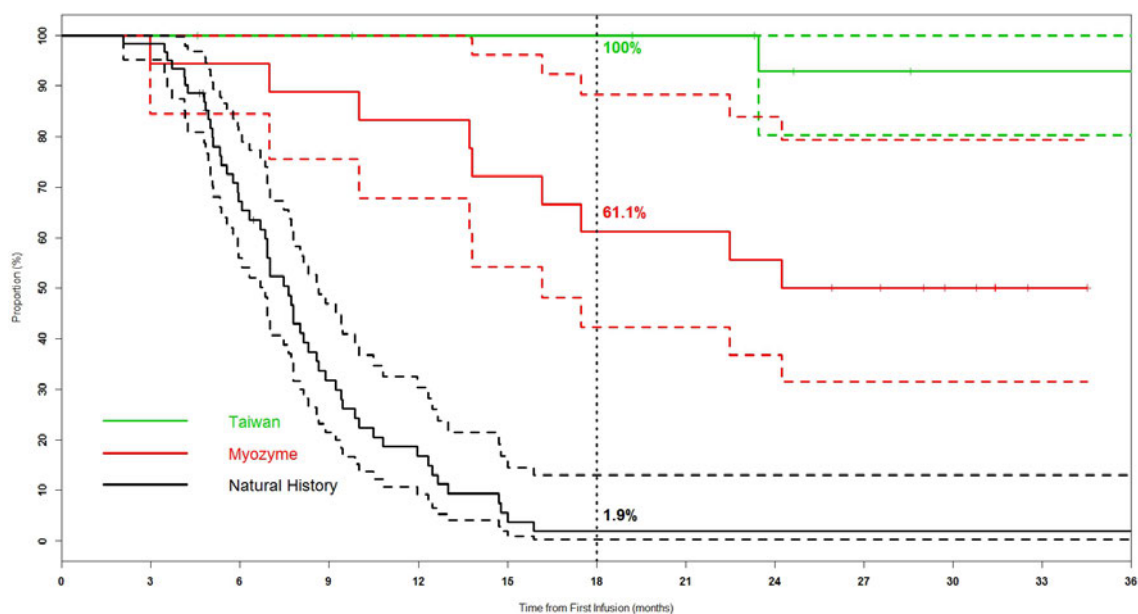


Figure 2. Ventilator-free Survival in months from first infusion



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/s/

FREDA COONER
07/18/2014

STATISTICS FILING REVIEW

BLA Number: 125291/136
eCTD Sequence #: 0294

Applicant: Genzyme Corporation

Stamp Date: Jan 30, 2014

Drug Name: Lumizyme®
alglucosidase alfa

BLA Type: 351(a) BLA
Efficacy Supplement
(Priority)

Indication: Include patients with
infantile-onset Pompe disease and
late-onset Pompe disease patients
under eight years of age

On **initial** overview of the Supplemental BLA application for RTF:

	Content Parameter for RTF	Yes	No	NA	Comments
1	Electronic Submission: Indexing and reference links within the electronic submission are sufficient to permit navigation through the submission, including access to reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			Efficacy data are from one study and so ISE is unnecessary; updated ISS and the complete study reports are submitted
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.			X	A total of 18 subjects (50% male; 100% Asian; median age at initial diagnosis was 0.6 month) comprise the primary efficacy analyses population
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

THE STATISTICAL SECTION OF THE APPLICATION IS **FILEABLE**

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.			X	The new study was not conducted under IND and so it will be a review issue
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	Not present
Appropriate references for novel statistical methodology (if present) are included.			X	Not present
Safety data organized to permit analyses across clinical trials in the BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

STATISTICS FILING REVIEW

Background

Genzyme is submitting this efficacy supplemental BLA in support of updating the Lumizyme[®] indication to include all Pompe patients; more specifically, to include patients with infantile-onset Pompe disease and late-onset Pompe disease patients under eight years of age.

Pompe disease is a rare, autosomal recessive genetic disease caused by the deficiency of lysosomal acid α -glucosidase (GAA), an enzyme that degrades glycogen. The resulting accumulation of glycogen in body tissues, especially cardiac and skeletal muscles, disrupts the architecture and function of affected cells, leading to a variety of symptoms, clinical decline, and ultimately death. Alglucosidase alfa, with active ingredient of recombinant human GAA (rhGAA), in a form of lyophilized powder for injection, has been developed as an enzyme replacement therapy (ERT) for the treatment of Pompe disease. The recommended dosage regimen is 20 mg/kg body weight administered every other week (qow) as an intravenous (IV) infusion.

Alglucosidase alfa, under the trade name Myozyme[®], was originally submitted under BLA 125141 and manufactured at the 160 L and 2000 L scales. Per the feedback from the FDA, the 2000 L scale manufacturing process was withdrawn from the application. Based on the evaluation of ventilator-free survival results, the 160 L-scale product was approved for the treatment of Pompe disease on April 28, 2006, with the following indication: “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.”

(b) (4)

Consequently, Genzyme submitted BLA 125291 on

May 30, 2008, which included data and results of a post marketing commitment safety, efficacy, and pharmacokinetics (PK) study (AGLU02704), also referred to as “LOTS”, which used the 2000 L product under the trade name Lumizyme[®]. Lumizyme[®] was approved on May 24, 2010, based on the evaluation of 6-minute walk test (6MWT) results, with an indication for Pompe patients eight years and older with late (non-infantile) onset Pompe disease who do not have evidence of cardiac hypertrophy, consistent with the population studied in LOTS.

In parallel with the Lumizyme[®] BLA submission, Genzyme had been developing a linear scale-up of the 2000 L scale manufacturing process to a 4000 L bioreactor working volume scale to meet increasing patient demand. Following the review of the amendment to the BLA, the FDA determined the 2000 L- and 4000 L-scale products were comparable resulting in the clinical data from LOTS being used to support approval of the 4000 L-scale product. The 4000 L-scale product has been used in a phase 4, open-label, prospective efficacy and safety study (AGLU09411), also referred to as “ADVANCE”, where more than 90% of the subjects had previously received 160 L Myozyme[®]. Alglucosidase alfa manufactured at the 4000 L scale is the only scale available outside of the US and is approved for all Pompe patients in all countries except the US.

During the February 19, 2013 Type C meeting, the FDA suggested that approval of Lumizyme[®] for use in patients with infantile-onset Pompe disease and patients under eight years of age with late-onset Pompe disease could be achieved by determining chemically analytical comparability between the two scales (160 L and 4000 L) and providing clinical data collected on infantile-

STATISTICS FILING REVIEW

onset Pompe disease patients in Taiwan enrolled in an Investigator-Sponsored Study, referred to as the Taiwan study thereafter. This submission includes the study report of the Taiwan study and updated safety information from the ADVANCE interim safety data, along with data to support analytical comparability between the two scales. Genzyme proposed to revise the Lumizyme[®] package insert to include the following:

- Taiwan study data;
- ADVANCE interim safety data;
- Myozyme[®] package insert clinical safety (inclusive of the safety table) and efficacy data of infantile-onset clinical trial experience in AGLU01602/2403 and AGLU01702 studies;
- Any additional clinical data and post-marketing data from the Myozyme[®] package insert that was not already reflected in the Lumizyme[®] package insert (i.e., update to the black box warning).

The tabulation data in the CDISC-SDTM format and the analysis datasets in ADaM format for the Taiwan study, as well as the study reports for this submission have been submitted in electronic Common Technical Document (eCTD) format to the EDR at:

[\\cdsesub1\bla\eCTD_Submissions\STN125291\0294.](#)

Overview of studies

The Taiwan study was developed in order to monitor cases of Pompe disease identified through the National Taiwan University Hospital (NTUH) newborn screening program, and to compare their prognosis to the clinically identified cases in Taiwan. It was conducted in an open-label manner. The first subject was enrolled on March 8, 2006, and the study is still ongoing. Clinical data analyses were based on the interim data cut-off of March 15, 2013; but for immunogenicity data and adverse event (AE) data spontaneously reported to Genzyme, analyses were based on the cut-off of June 30, 2013. The study report submitted includes the interim data from 25 Taiwanese patients enrolled and treated in the study; however, 18 of which were determined to meet the criteria for infantile-onset Pompe disease.

In this new BLA efficacy supplement submission, Genzyme compared data from the Taiwan study to the results of Study AGLU01602, Study AGLU02403, and Study AGLU00400. Study AGLU01602 was an open-label, multicenter, multinational, dose-ranging study of safety, efficacy, PK, and pharmacodynamics (PD) for rhGAA treatment in patients no less than six months old with infantile-onset Pompe disease. Study AGLU02403 was a long-term extension study of patients with infantile-onset Pompe disease who were previously enrolled in Study AGLU01602. Study AGLU00400 was a multicenter, multinational, natural history study of 168 patients diagnosed with infantile-onset Pompe disease, who had symptom onset within their first year of life and received only palliative and supportive care. A historical control subgroup of 62 patients from within the AGLU00400 cohort was selected based on screening criteria adapted from the inclusion and exclusion criteria of Study AGLU01602, and this subgroup was used as the control population for the severe infantile-onset patients treated with Myozyme[®] in Study AGLU01602. Data from these earlier studies were reviewed during the original Myozyme[®] BLA 125141 review and are included in this new submission with the Taiwan study data.

The primary objective of Genzyme's analysis was to estimate the proportion of patients with classical infantile-onset Pompe disease in Taiwan treated with alglucosidase alfa manufactured at the larger scales (2000L/4000L) who are alive and free of invasive ventilator support at 18 months of age and compare these results to the patient data in the pivotal study (AGLU01602/2403) for Myozyme[®] and the natural historical study (AGLU00400).

STATISTICS FILING REVIEW

All the clinical studies mentioned above are summarized in the table below:

Type of Study	Study Identifier	Objective(s) of Study	Study Design and Type of Control	Test products(s) Dosage regimen; route of administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Controlled Studies of alglucosidase alfa							
Safety and Efficacy	AGLU01602	Long-term safety and efficacy	Phase 2/3, randomized, open-label, historically controlled, dose ranging	Myozyme [®] ; 20 mg/kg/qow or 40 mg/kg/qow; IV	18	Infantile-onset Pompe disease	52 weeks
Safety and Efficacy	AGLU02403	Long-term safety and efficacy	Phase 2/3, randomized, open-label, historically controlled, dose ranging	Myozyme [®] ; 20 mg/kg/qow or 40 mg/kg/qow; IV	16	Infantile-onset Pompe disease	52 weeks repeated by 52 week modules
Other Study Reports							
Epidemiological	AGLU00400	Natural History of Infantile-onset Pompe Disease	NA	NA	62	Infantile-onset Pompe disease	NA
Safety and Efficacy	AGLU09411 (ADVANCE)	Safety and efficacy	A Phase 4, open-label, prospective Study	same dose and dose regimen used for their routine treatment prior to this study	99	Pompe disease	Ongoing
Safety and Efficacy	Investigator Sponsored Study in Infantile-onset patients in Taiwan (Taiwan01)	Safety and efficacy	Investigator Sponsored, Open-Label Study	Alglucosidase alfa; 20 mg/kg/qow IV	25 (18 Infantile-Onset Patients)	Pompe disease	Ongoing

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/s/

FREDA COONER
03/10/2014

MICHAEL E WELCH
03/10/2014

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

BLA 125291/136

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

CLINICAL PHARMACOLOGY REVIEW

BLA	125291\136 (eCTD sequence 0294)
Drug Name	Alglucosidase Alfa (Lumizyme)
Formulation	Lyophilized powder for intravenous infusion; 5 mg/mL vial
Dosing Regimen	20 mg/kg every 2 weeks
Description of Submission	Efficacy supplement for pediatric patients
Letter Date	1/30/2014
PDUFA Due Date	8/1/2014
Primary Reviewer	Christine Yuen-Yi Hon, Pharm.D.
Team Leader	Yow-Ming Wang, Ph.D.
OCP Division	DCP3
OND Division	DGIEP
Applicant	Genzyme
Proposed Indication	Treatment of patients with infantile-onset Pompe disease and patients under 8 years of age with late onset Pompe disease

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1. EXECUTIVE SUMMARY

1.1 Background

Pompe disease is a rare, autosomal recessive genetic disease caused by the deficiency of lysosomal acid α -glucosidase (GAA), an enzyme that degrades glycogen. The resulting accumulation of glycogen in body tissues, especially cardiac and skeletal muscles, disrupts the architecture and function of affected cells, leading to a variety of symptoms, clinical decline, and ultimately death.

Two α -glucosidase alfa products, Myozyme and Lumizyme, are currently approved in the U.S. Myozyme is manufactured at the 160 L scale and indicated for use in patients with Pompe disease and has been shown to improve ventilator-free survival in patients with infantile-onset Pompe disease. Lumizyme is manufactured at the 4000 L scale and indicated for patients 8 years and older with late-onset Pompe disease and do not have evidence of cardiac hypertrophy. The approval of Lumizyme 4000 L was based on clinical data from the “LOTS” study (AGLU02704) using the 2000 L scale products and the analytical comparability of the critical product quality between the 2000 L and 4000 L scale materials. Comparability was not demonstrated between lots manufactured using the 160 L and 2000 L processes in the original BLA submission for Lumizyme.

1.2 Regulatory History

Following the approval of Lumizyme, the Applicant and the Agency had several meetings to discuss the ongoing supply and manufacturing capacity constraints for Myozyme and the clinical data required to support a label update of Lumizyme to include all Pompe patients.

A Type C meeting was held between the Applicant and the Agency on February 19, 2013. The Agency suggested that approval of Lumizyme for use in patients with infantile-onset Pompe disease and patients under 8 years of age with late onset Pompe disease could be achieved by:

- Determining analytical comparability between the two scales (160 L and 4000 L). FDA recommended three lots from each scale to be used in the comparability study.
- Providing clinical data collected on infantile-onset Pompe disease in Taiwan enrolled in an Investigator-Sponsored Study. The infants from Taiwan should meet the AGLU01602 inclusion criteria of diagnosis of classical infantile-onset disease with evidence of cardiac hypertrophy <6 months of age and be treated with α -glucosidase alfa at the larger scale at less than 6 months of age.

In the current sBLA submission, the Applicant submitted the following chemistry, manufacturing, and controls (CMC) data and clinical study reports (Table 1):

- Analytical comparability evaluation of α -glucosidase alfa manufactured at the 160 L process scale (Myozyme) and α -glucosidase alfa manufactured at the 4000 L process scale (Lumizyme).

- TAIWAN-ISS (TAIWAN01) study report: This is an investigator sponsored study (ISS) in Taiwan with infantile onset Pompe patients to establish that Lumizyme is associated with ventilator-free survival.
- ADVANCE (AGLU09411) interim study report: The ADVACNE study provided safety data from the ongoing AGLU09411 study in Pompe disease patients 12 months of age and older who previously received Myozyme and switched to Lumizyme.

1.3 Recommendation

The immunogenicity information provided in this submission is considered acceptable and is supportive to the approval of Lumizyme for treatment of pediatric patients < 8 years of age from a clinical pharmacology perspective.

1.4 Phase 4 Commitment Study

No post-marketing commitment study is recommended in this review.

1.5 Summary of Clinical Pharmacology Findings

No pharmacokinetic (PK) data were available to evaluate the PK comparability of Myozyme (160 L scale) and Lumizyme (4000 L scale). However, the two products are found to be analytically comparable per the CMC review team.

In the TAIWAN01 study, 94.1% of patients (all cross-reactive immunologic material [CRIM]-positive) seroconverted after Lumizyme therapy. Compared with the CRIM-positive patients from the AGLU01602/2403 study who received Myozyme, these Taiwan patients had a longer median time to seroconversion, a lower median maximum antidrug antibody (ADA) titer value, and similar titer values at the time of the first seroconversion and at the last study visit. The immunogenicity impact on efficacy did not appear to be different between subjects receiving Lumizyme and Myozyme based on cross-study comparison between the TAIWAN01 study and AGLU01602/2403 trial.

In the switchover ADVANCE trial, 10 of 31 subjects who were seronegative at study entry seroconverted after receiving Lumizyme. These patients had relatively low ADA titers at peak and Week 52. For the subjects who were seropositive at study entry (65 of 99 patients), ADA titers slightly increased after the switchover to Lumizyme but generally trended downward at the end of the study period. Late-onset disease subjects appeared to have higher median titer values than infantile-onset disease subjects, and CRIM-negative subjects appeared to have higher median titer values than CRIM-positive subjects. There appeared to be no notable differences in immunogenicity impact on efficacy before and after the switchover from Myozyme to Lumizyme.

2. QUESTION BASED REVIEW

2.1 List the clinical studies with clinical pharmacology information submitted in the sBLA.

A summary of the clinical studies with clinical pharmacology information submitted in this sBLA is presented in Table 1.

The TAIWAN01 study is an open-label study which was developed in order to monitor cases of Pompe disease identified through the National Taiwan University Hospital (NTUH) newborn screening program, and to compare their prognosis to the clinically identified cases in Taiwan. Infants with positive screening results for Pompe disease were referred to the NTUH for diagnostic confirmation and were followed according to standard of care. For these Taiwan patients receiving alglucosidase alfa manufactured at the larger scales (2000 L/4000 L), similar assessments were completed as in the pivotal study AGLU01602 and its extension study AGLU02403 from the original BLA and the Pompe Registry, focusing on patients' outcomes and ventilator and survival status.

The primary objective of the analyses contained in the TAIWAN01 study report was to compare the proportion of infantile-onset disease patients in Taiwan treated with alglucosidase alfa who were alive and were ventilator free at 18 months of age with patients in the pivotal study (AGLU01602/2403) and the natural historical study (AGLU00400).

The ADVANCE (AGLU09411) trial is an ongoing, open-label, prospective study of patients in the United States aged 1 year or older who have a confirmed diagnosis of Pompe disease and were previously treated with 160 L alglucosidase alfa. Patients were to receive alglucosidase alfa produced at the 4000 L scale for 52 weeks at the same dose and dose regimen used for their routine treatment prior to this study.

Table 1. Clinical trials that support the sBLA submission.

Study identifier	Study Design	Study Population (N)	Regimen and Duration of Treatment	Product Scale	Clinical Pharmacology Data
TAIWAN01 (TAIWAN-ISS study)	Investigator sponsored, open-label, and prospective Phase 4 study	Infants with confirmed diagnosis of Pompe disease (18 infantile-onset, 5 late-onset)	20 mg/kg every other week (QOW), others	Lumizyme (4000 L), others	Immuno-genicity and PD
AGLU09411 (ADVANCE, ongoing, interim analysis as of June 30, 2013)	Open-label, prospective switchover study to evaluate the efficacy and safety of alglucosidase alfa manufactured at the 4000 L scale	Patients 12 months of age and older (63 infantile-onset, 36 late-onset)	Same dose and dose regimen as the previous 160 L scale product for 52 weeks	Lumizyme (4000 L)	Immuno-genicity

2.2 Has PK comparability between Myozyme and Lumizyme been assessed and demonstrated?

No, PK data are not available in this efficacy supplement to evaluate the PK comparability between Myozyme (160 L scale) and Lumizyme (4000 L scale). The Applicant submitted CMC data to support the analytical comparability between the two products.

(b) (4)

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The 2000 and 4000 L scale products were found to be analytically comparable, but PK comparability was not evaluated.

2.3  (b) (4)

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2.4 What are the differences in the patient population and follow-up period between the TAIWAN01 study and the Study AGLU01602/2403 of the original BLA?

The TAIWAN01 study and the AGLU01602/2403 trial each enrolled a total of 18 infantile-onset Pompe disease patients. While all subjects in the TAIWAN study were Asians, Study AGLU01602/2403 had subjects of different racial backgrounds, including nine Whites, four Blacks, three Asians, and two others. All patients in the TAIWAN01 study were CRIM-positive; 12 of 18 (66.7%) had a less severe genotype (10 missense/missense and 2 missense/in-frame

deletion) (see Table 5). On the other hand, 14 subjects were CRIM-positive and 4 subjects were CRIM-negative in the AGLU01602/2403 study. Genotype results were not available in Study AGLU01602/2403. The maximum follow-up was 84 months in the TAIWAN01 study and was 42 months in the AGLU01602/2403 trial.

2.5 What is the incidence of immunogenicity in the TAIWAN01 and the AGLU01602/2403 studies? How does immunogenicity compare between Lumizyme in the TAIWAN01 study and Myozyme in the Study AGLU01602/02403 of the original BLA?

Immunogenicity data were available in 17 of 18 infantile-onset disease patients in the TAIWAN01 study. Sixteen of the 17 patients (94.1%) seroconverted. The median (range) peak ADA titer for all 16 patients was 1600 (<100 – 12800). The median ADA titer at the last visit was 400 (0 – 12800), which occurred at a median of 186 weeks, with a range of 4 to 346 weeks. Only one Taiwan subject reached an ADA titer of 12800. For study AGLU01602/2403, 16 (12 CRIM-positive and 4 CRIM-negative) of 18 subjects seroconverted (88.9%). The median peak ADA titer for all 16 subjects was 4800 (400 – 409600). Their median ADA titer at the last visit was 200 (0 – 409600), which occurred at a median of 120 (51.4 – 146) weeks.

The antibody response of Lumizyme did not appear to be different from that of Myozyme in CRIM-positive infantile-onset Pompe disease patients.

The reviewer performed a comparison of ADA titers between patients received Lumizyme in the TAIWAN01 study and patients received Myozyme in the AGLU01602/02403 trial of the original BLA. The comparison was based on data from CRIM-positive subjects because the Taiwan study has CRIM-positive subjects only. As presented in Table 2, the median time to seroconversion was longer and the median maximum titer was lower for Lumizyme than for Myozyme. The median titer at 1st seroconversion and the titer at last visit were similar between Lumizyme and Myozyme. Of note, AGLU01602/2403 had higher ADA upper range values due to the presence of two patients with sustained high ADA titers (see Figure 1). In addition, the week at last visit was longer in the TAIWAN01 study than in the AGLU01602/2403 trial.

Table 2. The immunogenicity of the Lumizyme in the TAIWAN01 study and Myozyme in AGLU01602/2403 trial

	Median (Range)	
	Lumizyme (TAIWAN01)	Myozyme (AGLU01602/2403)
Number of CRIM-positive subjects	17	14
Race, W/B/A/O	0/0/13/0	7/2/3/2
Number of subjects seroconverted	16	12*
Week at 1 st seroconversion	18 (4, 221)	6.1 (3.7, 62.7)
Week at maximum titer	29 (4, 346)	31 (8, 130)
Week at last visit	186 (4, 346)	122 (51.4, 146)
Titer at 1 st seroconversion	400 (<100, 6400)	300 (<100, 3200)
Maximum titer	1600 (<100, 12800)	4800 (400, 409600)
Titer at last visit	400 (0, 12800)	200 (0, 409600)

*Two subjects had sustained high ADA titers
W, White; B, Black; A, Asian; O, others

2.6 In CRIM-positive subjects, does the immunogenicity impact on efficacy differ between Lumizyme in the TAIWAN01 study and Myozyme in Study AGLU01602/2403 of the original BLA?

No, in CRIM-positive infantile-onset disease patients, there appeared to be no notable difference in the immunogenicity impact on efficacy between Lumizyme in the TAIWAN01 study and Myozyme in the AGLU01602/2403 trial.

In study AGLU01602/2403, CRIM-negative subjects (data not shown) and CRIM-positive subjects who developed ADA and had sustained high ADA titers ≥ 12800 were found to have poor clinical response. As demonstrated in Figure 1, two of three CRIM-positive subjects who received Myozyme and had high sustained ADA titers ≥ 12800 died at around 90 and 142 weeks after the initiation of Myozyme therapy. Contrarily, the remaining 11 subjects who treated with Myozyme and developed low titers survived.

In the TAIWAN01 study, 16 of 17 infantile-onset disease patients who received Lumizyme had ADA titers < 12800 ; one subject reached an ADA titer of 12800. Two of the 17 subjects did not survive despite the low titers (Figure 2); the time of death for these two subjects was at approximately 156 weeks after the initiation of Lumizyme. This finding suggests that in addition to ADA titers, there may be other prognostic factors which could affect the clinical outcome of the patients.

Figure 1. Antibody formation over time by status of invasive ventilator use and survival for CRIM-positive in studies AGLU01602/02403

(Source: Figure 145.3.4-7.1 of AGLU01602 Clinical Study Report Body)



Figure 2. Antibody formation over time by status of invasive ventilator use and survival
(Source: Figure 14.3.1 of TAIWAN01 Study Report Body)



2.7 What is the immunogenicity before and after the switchover from Myozyme to Lumizyme in the ADVANCE trial?

There appears to be no noticeable difference in ADA titers before and after the switchover from Myozyme to Lumizyme in the ADVANCE trial.

The Applicant submitted an interim report for 99 subjects in the ADVANCE trial. Among these 99 subjects, 31 were seronegative and 65 were seropositive at study entry. Baseline ADA titers were not known for 3 subjects (2 infantile-onset and 1 late-onset disease patients) and onset of disease was not known for 1 other subject. Hence, these 4 patients were excluded from data analysis as described below. Ten of the 31 patients who were ADA-negative at entry seroconverted after receiving Lumizyme. Three patients (2 infantile-onset disease patients and 1 late-onset disease patient) had high ADA titers at baseline (before the switch) and sustained throughout the study period.

The reviewer performed two separate immunogenicity assessments on ADA titers before and after the switchover from Myozyme to Lumizyme with respect to patient population (infantile-onset vs. late onset) and CRIM status (CRIM-negative vs. CRIM-positive). Overall results showed that immune response after Lumizyme therapy did not appear to be worse than that after Myozyme therapy. Of note, the dataset used for these analyses was obtained from the information request (IR) response dated April 2, 2014 from the Applicant. This dataset (from Section 1.11.2 Safety Information Amendment on April 2, 2014) contains 69 infantile-onset disease patients as opposed to 63 infantile-onset disease patients described in the clinical study report for study ADVANCE trial (see aglu09411-1-15-body.pdf).

Table 3 summarizes the ADA titers before and after the switchover from Myozyme to Lumizyme between infantile-onset and late-onset disease patients. There were 2 and 1 infantile-onset and

late-onset disease subjects, respectively, with high baseline titer ≥ 12800 that sustained over 52 weeks.

Comparison of ADA titers between the patient populations shows that late-onset disease subjects appeared to have higher median titer values than infantile-onset disease subjects. In the 10 subjects who seroconverted after Lumizyme therapy, median titers at peak (200 and 400) and Week 52 (200 and 300) were relatively low in both the infantile-onset and late-onset disease patients. For those patients who were ADA-positive on Myozyme treatment, ADA titers slightly increased after the switchover to Lumizyme but generally trended downward at the end of the study period.

Table 3. ADA titers before and after the switchover from Myozyme to Lumizyme between infantile-onset and late-onset Pompe disease patients in ADVANCE trial

	Median [n] (Range)			
	Infantile-onset (N = 67) (16 not seroconverted)		Late-onset (N = 28) (5 not seroconverted)	
Baseline ADA status	Negative [#]	Positive ^{*, §}	Negative	Positive [*]
Number of ADA-positive patients after switch	6	45	4	19
Baseline titer before switch	-	800 [42] (100, 51200)	-	1600 [18] (100, 25600)
Maximum titer	200 [5] (200, 800)	1600 [44] (200, 102400)	400 [4] (400, 1600)	3200 [19] (400, 102400)
Week 52 titer	200 [5] (100, 800)	1600 [39] (100, 51200)	300 [4] (100, 1600)	1600 [19] (100, 25600)

*There were 2 infantile-onset and 1 late-onset disease subjects with high ADA baseline titer ≥ 12800 that sustained over 52 weeks

[#]One patient who seroconverted after Lumizyme received IVIG therapy

[§]Two patients who were ADA-positive at baseline received immune tolerance induction therapy

Table 4 depicts the ADA titers before and after the switchover from Myozyme to Lumizyme between CRIM-negative and CRIM-positive subjects. Forty-one of 95 subjects had known CRIM status and were included in the analysis. Four CRIM-negative and 3 CRIM-positive subjects did not seroconvert. Among these 7 subjects, 1 CRIM-negative subject received immune tolerance induction therapy.

Comparison of ADA titers between subjects with different CRIM status shows that CRIM-negative subjects appeared to have higher median titer values than CRIM-positive subjects. In the 7 subjects who seroconverted after Lumizyme therapy, median titers at peak (400 and 200) and Week 52 (200) were relatively low in both the CRIM-negative (N = 1) and CRIM-positive (N = 6) subjects. For those patients who were ADA-positive on Myozyme treatment, ADA titers slightly increased after the switchover to Lumizyme but generally trended downward at the end of the study period.

Table 4. ADA titers before and after the switchover from Myozyme to Lumizyme between CRIM-negative and CRIM-positive Pompe disease patients in ADVANCE trial

	Median [n] (Range)			
	CRIM-negative (N = 10) (4 not seroconverted*)		CRIM-positive (n = 31) (3 not seroconverted)	
Baseline ADA status	Negative	Positive	Negative	Positive
Number of ADA-positive patients after switch	1	5	6	22
Baseline titer after switch	-	3200 [4] (1600, 3200)	-	600 [22] (100, 6400)
Maximum titer	400	6400 [5] (200, 6400)	200 [5] (200, 800)	1600 [21] (100, 12800)
Week 52 titer	200	3200 [4] (3200, 3200)	200 [5] (100, 800)	1600 [19] (200, 6400)

* Among the 7 subjects who did not seroconvert, 1 CRIM-negative subject received immune tolerance induction therapy

2.8 Is there any difference in the immunogenicity impact on efficacy after switchover from Myozyme to Lumizyme in the ADVANCE trial?

The appeared to be no difference in immunogenicity impact on efficacy after the switchover from Myozyme to Lumizyme in the ADVANCE trial.

In response to FDA's IR on March 19, 2014, the Applicant provided a graphical presentation of antibody formation over time by clinical outcome for the ADVANCE study (Figure 3). There appeared to be no correlation observed between the clinical outcome (invasive ventilator status and survival) and antibody level for the study patients.

Figure 3. Antibody formation over time by status of invasive ventilator use and survival
(Source: Figure 14.3.1.2.3 of AGLU09411 Clinical Study Report Body)



The Applicant also provided additional clinical outcome data for both infantile-onset and late-onset disease patients < 8 years of age as per Agency's request (Table 5). Three additional subjects required invasive ventilation after the switchover (2 CRIM unknown and 1 late-onset subjects) and 1 subject died at an age of 1.3 years old.

Table 5. Clinical outcomes of subjects in the ADVANCE trial (AGLU09411)

(Source: Table 1 of 1.11.2. Safety Information Amendment)

	Number (%) of Patients			
	Infantile-onset, CRIM-negative	Infantile-onset, CRIM-positive	CRIM unknown	Late-onset patients treated at < 8 years of age
Required invasive ventilation				
Prior to the switchover	6 (60.0)	8 (33.3)	10 (28.6)	5 (21.7)
At time of switchover	5 (50.0)	8 (33.3)	8 (22.9)	5 (21.7)
After the switchover	0	0	2 (5.7)	0
Death after switchover	0	1 (4.2)*	0	0

*Age at the time of death was 1.3 years

2.9 What is the genotype classification of the patients and does genotype classification impact efficacy in the TAIWAN01 trial?

Table 6 presents the genotype classification of the 18 infantile-onset Pompe disease patients in the TAIWAN01 study. No genotype data were available for infantile-onset disease patients from the pivotal trial AGLU01602 in original BLA submission for comparison.

Table 6. Genotype classification of infantile-onset Pompe disease patients in TAIWAN01 trial

Genotype Classification	Number of patients (%)
Missense/Missense	10 (55.6)
Missense/Frameshift	4 (22.2)
Missense/In-Frame Deletion	2 (11.1)
Missense/Nonsense	1 (5.6)
Missense/Splice Site	1 (5.6)

The Applicant performed an exploratory subgroup analysis on the survival of the 18 patients in the Taiwan study. The 4 patients with a genotype classification of missense/frameshift had a long-term survival rate of 100% [95% CI: 29.24%, 100%] at 78 months, as compared to the 10 patients with a genotype classification of missense/missense that had a long-term survival rate of 50% [95% CI: 11.09%, 80.37%] at 72 months. The Applicant claimed that the interpretability of these numbers is questionable given the very small patient numbers as evidenced by the very wide confidence intervals.

The Applicant's analysis as described above was based on data from the two largest genotype subgroups i.e., missense/missense and missense/frameshift. Generally, genotypes containing frameshift, nonsense, and splice site mutations are more likely to result in severe phenotype and likely associated with poor prognosis. The reason for the observed better survival outcome in the

missense/frameshift group compared with the missense/missense group in this study is not clear. It is also not known what the outcome was for the two subjects with missense/nonsense and missense/splice site genotypes. Nonetheless, this result from the subgroup analysis of genotype is considered exploratory and should be interpreted as such.

3. LABELING

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/s/

CHRISTINE Y HON
07/08/2014

YOW-MING C WANG
07/08/2014

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR sBLA 125291/136

1. Filing and review form

CLINICAL PHARMACOLOGY				
Filing and Review Form for BLA 125,291/136				
	Information		Information	
BLA Number (efficacy supplement)	125,291/136	Brand Name	LUMIZYME	
OCP Division (I, II, III, IV, V)	DCP III	Generic Name	Alglucosidase alfa	
Medical Division	DGIEP	Drug Class	Lysosomal glycogen-specific enzyme	
OCP Reviewer	Christine Yuen-Yi Hon, Pharm.D.	Indication(s)	Patients with Pompe disease	
OCP Team Leader (Acting)	Jie Wang, Ph.D.	Dosage Form	Lyophilized powder for solution for intravenous infusion	
Pharmacometrics Reviewers	Lian Ma, Ph.D. and Justin Earp, Ph.D.	Dosing Regimen	20 mg/kg administered every 2 weeks	
Date of Submission	1/30/2014	Route of Administration	Intravenous infusion	
Estimated Due Date of OCP Review	07/08/2014	Sponsor	Genzyme	
Medical Division Due Date	07/18/2014	Priority Classification	Priority	
PDUFA Due Date	8/1/2014	Dosing Strength	5 mg/mL	
<i>Clin. Pharm. and Biopharm. Information</i>				
	“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.	×			
Tabular Listing of All Human Studies	×			
HPK Summary				
Labeling	×			
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:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

FILING FORM/CHECKLIST FOR sBLA 125291/136

Patients-				
single dose:				
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:				
Age:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
Immunogenicity:				
PD -	×	1		
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
Immunogenicity	×	2		
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
PK and PD comparability:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		2		

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR sBLA 125291/136

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted PK and PD comparability data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?		×		See section 3.4.
2	Has the applicant provided metabolism and drug-drug interaction information?			×	N/A for this enzyme product
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?		×		Dosed by IV infusion
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?		×		No new assays in the sBLA
5	Has a rationale for dose selection been submitted?			×	See section 3.1.
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?			×	See section 3.3.
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?			×	See section 3.3.
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	×			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			×	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			×	
11	Is the appropriate pharmacokinetic information submitted?			×	
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			×	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			×	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			×	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			×	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			×	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	×			
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	×			See sections 3.3. and 3.4.
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			×	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR sBLA 125291/136

Clinical Pharmacology Filing Memorandum

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2. Comments to the sponsor

There are no comments to be conveyed to the sponsor at this time.

3. Main clinical pharmacology findings on initial review of the submission

Pompe disease is a rare, autosomal recessive genetic disease caused by the deficiency of lysosomal acid α -glucosidase (GAA), an enzyme that degrades glycogen. The resulting accumulation of glycogen in body tissues, especially cardiac and skeletal muscles, disrupts the architecture and function of affected cells, leading to a variety of symptoms, clinical decline, and ultimately death.

MYOZYME and LUMIZYME are two approved alglucosidase alfa products being manufactured and distributed by the same sponsor. MYOZYME is indicated for use in patients with Pompe disease to improve ventilator-free survival in patients with infantile-onset Pompe disease, whereas its use in patients with other forms of Pompe disease has not been adequately studied. LUMIZYME is indicated for patients 8 years and older with late-onset Pompe disease who do not have evidence of cardiac hypertrophy. The safety and efficacy of LUMIZYME have not been evaluated in controlled clinical trials in infantile-onset patients or in late-onset patients less than 8 year of age.

3.1. Purpose of the sBLA submission

In the current sBLA, the applicant proposed to extend the LUMIZYME indication to include all Pompe patients including infantile-onset Pompe disease and late-onset Pompe disease for patients under 8 years. One of the reasons to extend the LUMIZYME indication is due to the drug shortage of MYOZYME.

3.2. Overview of the CMC comparability data and clinical trials

In addition to the safety data summary, the applicant submitted the following CMC and Clinical study reports (Table 1) to support the sBLA application:

- Analytical comparability evaluation of alglucosidase alfa manufactured at the 160 L process scale (MYOZYME) and alglucosidase alfa manufactured at the 4000 L process scale (LUMIZYME).
- TAIWAN-ISS study report: This is an investigator sponsored study (ISS) in Taiwan with infantile-onset Pompe patients to establish that LUMIZYME is associated with ventilator-free survival.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR sBLA 125291/136

- ADVANCE (AGLU09411) interim study report: The ADVACNE study provided safety data from the ongoing AGLU09411 study in Pompe disease patients 12 months of age and older who previously received MYOZYME and switched to LUMIZYME.

3.3. Overview of clinical pharmacology program contained in the sBLA

While there are no specific Clinical Pharmacology studies conducted or submitted to support the sBLA application, the following pharmacodynamic and immunogenicity data were contained in the clinical study reports referenced in Table 1.

3.3.1. Pharmacodynamics

In the TAIWAN-ISS study, glycogen levels in muscle biopsies at baseline and at 6 month post-treatment in 7 subjects were evaluated and reported.

3.3.2. Immunogenicity

In the TAIWAN-ISS trial, the formation of anti-drug antibodies (ADA), the ADA titers, and neutralizing ADA status were reported for each individual patients. The impact of immunogenicity on efficacy and safety were evaluated and provided in the clinical study report. The sBLA did not provide reports regarding immunogenicity assays used in the TAIWAN-ISS trial; however, the clinical study report stated that all immunological testing was performed by Genzyme.

In the ADANCE trial, because the majority of the patients were expected to be positive for ADA to MYOZYME prior to the switchover, the ADA titers, ADA seroconversion and time to seroconversion, and the neutralizing ADA status during treatment with LUMIZYME were evaluated and reported.

3.4. Reviewer's initial assessment of the comparability between MYOZYME and LUMIZYME from clinical pharmacology perspectives

While no specific clinical pharmacology studies were conducted to assess the comparability between LUMIZYME and MYOZYME, the comparability will be evaluated by the analytical comparability between the 160 L (MYOZYME) and 4000 L (LUMIZYME) scales of alglucosidase alfa and the clinical results from the current clinical trials (see section 3.2). If analytical comparability is established and the clinical efficacy/safety data are found to be comparable, there is no evidence to indicate that MYOZYME and LUMIZYME contain "different" active ingredient alglucosidase alfa from a clinical pharmacology perspective. The analytical comparability and clinical efficacy/safety comparability remain to be determined by the CMC and Clinical review teams, respectively.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

FILING FORM/CHECKLIST FOR sBLA 125291/136

Table 1: Clinical trials that support the sBLA submission.

Study identifier	Study Design	Study Population (N, number of subjects)	Regimen and Duration of Treatment	Product Scale	Clinical Pharmacology Data Submitted
TAIWAN-ISS	Investigator sponsored, open-label, and prospective Phase 4 study	Infants with confirmed diagnosis of Pompe disease (18 infantile-onset, 5 late-onset)	20 mg/kg every other week (QOW), others	LUMIZYME (4000 L), others	Immunogenicity and PD
AGLU09411 (ADVANCE, ongoing, interim analysis as of June 30, 2013)	Open-label, prospective switchover study to evaluate the efficacy and safety of alglucosidase alfa manufactured at the 4000 L scale	Patients 12 months of age and older (63 infantile-onset, 36 late-onset)	Same dose and dose regimen as the previous 160 L scale product for 52 weeks	LUMIZYME (4000 L)	Immunogenicity

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/s/

CHRISTINE Y HON
03/11/2014

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03/11/2014

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03/12/2014

HAE YOUNG AHN
03/12/2014

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
BLA 125291/136

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

REMS MODIFICATION REVIEW ADDENDUM

Date:	July 29, 2014
Reviewer:	Bob Pratt, Pharm.D. Risk Management Analyst Division of Risk Management
Acting Team Leader:	Jamie Wilkins-Parker, Pharm.D. Division of Risk Management
Acting Division Director:	Cynthia LaCivita, Pharm.D. Division of Risk Management
Drug Name(s):	Lumizyme [®] (alglucosidase alfa)
Therapeutic class:	Lysosomal glycogen-specific enzyme
Dosage forms:	Intravenous infusion 20 mg/kg administered every 2 weeks
OND Review Division:	Division of Gastroenterology and Inborn Errors Products
Application Type/Number:	BLA 125291
Supplement # and Date Received:	Suppl. 136; January 30, 2014
PDUFA/Action Date:	August 1, 2014
Applicant/sponsor:	Genzyme Corporation
OSE RCM #:	Master Record 2014-863

This memorandum serves to amend the Lumizyme® (alglucosidase alfa) REMS Modification Review dated July 20, 2014, (b) (4)

BLA 125291/S-136 (Seq. 309).

(b) (4)

the Lumizyme benefit-risk profile does indeed change based on information submitted in the efficacy supplement. The benefit-risk profile actually improves such that a REMS is no longer necessary to ensure the benefits outweigh the risks, as the product will now be approved for the treatment of all Pompe disease patients.

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/s/

ROBERT G PRATT
07/29/2014

CYNTHIA L LACIVITA
07/29/2014
Concur

Risk Evaluation and Mitigation Strategy (REMS) Memorandum
REMS Elimination OR REMS Element Removal

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Drug Evaluation III
Division of Gastroenterology and Inborn Errors Products

BLA: 125291
Products: Lumizyme (alglucosidase alfa)
APPLICANT: Genzyme Corporation
FROM: Donna Griebel, M.D.
DATE: 8/1/2014

A REMS for Lumizyme (alglucosidase alfa) was approved on May 24, 2010, and the most recent REMS modification was approved on July 16, 2012, to ensure the benefits of the drug outweighed the risk of rapid disease progression in infantile-onset Pompe disease patients and patients with late (non-infantile) onset disease less than 8 years of age, the risks of anaphylaxis and severe allergic reactions, and potential risks of severe cutaneous and systemic immune mediated reactions as listed in the labeling. The REMS consists of a communication plan, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

The Goals of the REMS are:

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


The currently approved REMS restricts distribution and consists of elements to assure safe use (ETASU) that include prescriber certification; healthcare facility certification; and documentation of safe use conditions to ensure patients are enrolled in the program.

On January 30, 2014, Genzyme Corporation submitted a proposed REMS modification to release the requirement for the REMS. The REMS modification included a REMS assessment dated June 13, 2014.

In 2006, prior to Lumizyme approval, another alglucosidase alfa product, Myozyme, was approved and indicated for use in all patients with Pompe disease. Myozyme and Lumizyme, both manufactured by Genzyme Corporation, are produced from the same cell line at different production scales. Myozyme is manufactured at the 160 L scale while Lumizyme is manufactured at the 4000 L scale. At the time of Lumizyme's original approval, the Agency

determined that Myozyme and Lumizyme were not analytically (i.e., biochemical, physical and in vitro biological) comparable and there were insufficient analytical and clinical data to support the safety and efficacy of Lumizyme in the infantile-onset Pompe population. Therefore, Lumizyme was approved for use only in late-onset Pompe disease patients who are at least 8 years of age. The REMS assured that Lumizyme was used only for patients with late (non-infantile) onset Pompe disease who are 8 years and older.

The current BLA supplement, submitted on January 30, 2014, provides for an expansion of the indication to include patients of all ages for the treatment of Pompe Disease. During this cycle, we have reviewed newly available information and have determined that Lumizyme and Myozyme are analytically comparable. Consequently, the safety and effectiveness of Myozyme and Lumizyme can be expected to be the same. In addition, a single-center clinical study of 18 infantile-onset Pompe disease patients, aged 0.2 to 5.8 months at the time of first infusion, further supports that infantile-onset patients treated with Lumizyme will have a similar ventilator-free survival outcome as those treated with Myozyme.

 (b) (4)
an FDA-review of the current information has determined that while safety risks for Lumizyme still exist, the benefit for those patients under the age of 8 years has been established; thus, the benefit-risk profile has shifted and is now favorable for those patients. Therefore, the elements of the REMS designed to achieve the goal of limiting treatment with Lumizyme to use in patients with non-infantile onset Pompe disease who are greater than or equal to 8 years of age are no longer necessary.

In addition, one of the ETASU, healthcare facility certification (which includes home infusion agencies), required that healthcare facilities attest that they have measures in place for appropriate patient monitoring and that they are prepared to treat patients who experience severe allergic reactions including anaphylaxis. These measures are standard operating procedure for hospitals and ambulatory infusion centers, and home infusion agencies also have accreditation standards requiring policies and procedures that address these measures. Therefore, it is not necessary to continue this certification measure to ensure the benefits of the treatment outweigh the risks.

The communication plan was also assessed and was determined to be complete. The prescriber survey respondents received and reported reading the Prescriber Introductory Letter. No other communication plan activities were required under the REMS and the prescriber assessment data were sufficient to ensure the communication plan met its goal. Additionally, the potential safety risks with use of the drug are adequately communicated in labeling through the Warnings and Precautions, and a Boxed Warning.

After consultations between the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE), we have determined that the REMS for Lumizyme is no longer necessary to ensure the benefits of the drug outweigh the risks described above.

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/s/

DONNA J GRIEBEL
08/01/2014

**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

REMS MODIFICATION REVIEW

Date:	July 18, 2014
Reviewer:	Bob Pratt, Pharm.D. Risk Management Analyst Division of Risk Management
Acting Team Leader:	Jamie Wilkins-Parker, Pharm.D. Division of Risk Management
Acting Deputy Division Director:	Reema Mehta, Pharm.D., M.P.H. Division of Risk Management
Drug Name(s):	Lumizyme [®] (alglucosidase alfa)
Therapeutic class:	Lysosomal glycogen-specific enzyme
Dosage forms:	Intravenous infusion 20 mg/kg administered every 2 weeks
OND Review Division:	Division of Gastroenterology and Inborn Errors Products
Application Type/Number:	BLA 125291
Supplement # and Date Received:	Suppl. 136; January 30, 2014
PDUFA/Action Date:	August 1, 2014
Applicant/sponsor:	Genzyme Corporation
OSE RCM #:	Master Record 2014-863

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EXECUTIVE SUMMARY

This is a review of Genzyme's proposed risk evaluation and mitigation strategy (REMS) modification for Lumizyme (alglucosidase alfa), BLA 125291/S-136, received from Genzyme Corporation on January 30, 2014. The Applicant's proposed modification requests the elimination of the Lumizyme REMS under Supplement 136 based on efficacy data in support of extending the Lumizyme indication to include treatment of Pompe disease patients of all ages.

Upon approval of S-136, the use of Lumizyme will extend to the treatment of all Pompe disease patients, thereby causing the REMS requirement and ETASU that restrict distribution to patients 8 years of age and older to no longer be required for safe use of the product. Furthermore, although the second goal of the REMS has been met only in part because of relatively poor understanding of severe immune mediated reactions on the part of patients and caregivers, DRISK believes the risk message and survey questions related to these reactions may have been too complex for patients, compared to what patients and prescribers need to know to ensure safe use of the product. Therefore, this isolated finding reported in the REMS assessments does not preclude elimination of the second goal of the REMS.

Therefore, DRISK recommends the Genzyme be released from the REMS requirement for Lumizyme and the Applicant sent a Release REMS Requirement letter upon approval of BLA 125291/S-136. DRISK also recommends an external communication strategy to stakeholders be developed to notify stakeholders of the release from the REMS requirement to ensure there are no unnecessary delays in patient access to Lumizyme as a result of the change in the distribution model for Lumizyme.

1. INTRODUCTION

The purpose of this review is to provide the Division of Risk Management's (DRISK) evaluation of the proposed risk evaluation and mitigation strategy (REMS) modification for Lumizyme (alglucosidase alfa), BLA 125291/S-136, submitted by Genzyme Corporation, received on January 30, 2014. The Applicant's proposed modification requests the elimination of the Lumizyme REMS under Supplement 136 based on efficacy data in support of extending the Lumizyme indication to include treatment of Pompe disease patients of all ages.

The currently approved REMS for Lumizyme restricts distribution and treatment to Pompe disease patients with late-onset disease who are eight years of age or older. The REMS consists of a communication plan (CP); elements to assure safe use (ETASU) that include prescriber special certification, healthcare facility special certification, and documentation of safe use conditions to ensure that patients are enrolled in the program; an implementation system; and a timetable for submission of assessments.

1.1 DISEASE BACKGROUND

Pompe disease is a rare, heterogeneous, autosomal recessive disorder caused by mutations in the gene for lysosomal alpha-1,4-glucosidase. Deficiency of the enzyme leads to accumulation of glycogen in the lysosomes and cytoplasm in cardiac and skeletal muscle cells (including respiratory muscle), which results in tissue destruction. The infantile-onset form of Pompe disease involves a total or near total deficiency of the enzyme and is clinically characterized by cardiomyopathy and severe generalized hypotonia. Without treatment, most infants die within

the first year or two of life. Late-onset Pompe disease results from a partial deficiency of the enzyme and is characterized by skeletal myopathy and a protracted course leading to respiratory failure. Late-onset disease may present at any age. There are currently two approved products, both sponsored by Genzyme, Myozyme and Lumizyme. Myozyme is approved for the treatment of all patients with Pompe disease. Lumizyme is intended for the treatment of patients 8 years and older with late (non-infantile) onset Pompe disease who do not have evidence of cardiac hypertrophy.

1.2 PRODUCT BACKGROUND

Alglucosidase alfa (recombinant human α -glucosidase) is an enzyme replacement therapy for the treatment of Pompe disease. Alglucosidase alfa was first approved on a 160 L bioreactor scale under the name Myozyme (BLA 125141) on April 28, 2006. In 2008, Genzyme submitted a BLA requesting approval of a 2000 L production scale that was used in a clinical study of late-onset Pompe disease. The Agency determined the 2000 L scale product was not chemically comparable to the 160 L scale product, and may have had comparatively decreased potency and efficacy; the 2000 L product never received approval because of subsequent manufacturing problems. Genzyme went on to develop a 4000 L scale product (Lumizyme), which was approved May 24, 2010, for the treatment of patients eight years of age and older with late-onset Pompe disease who do not have cardiac hypertrophy. However, chemical comparability of the 160 L and 4000 L scales had not been established at that time, and safety and efficacy of the 4000 L product had not been demonstrated in infantile-onset patients or in late-onset patients less than eight years of age. Therefore, Lumizyme's approved indication did not include treatment of patients younger than eight years of age – those patients were to be treated with Myozyme.

At the time of Lumizyme's approval, a REMS was required to ensure the benefits of the drug outweighed the risks. It restricted distribution and treatment to Pompe disease patients with late-onset disease who are eight years of age or older. This was done so that patients *younger* than eight years of age would not be treated with Lumizyme, which was potentially less efficacious than Myozyme, and therefore carried a risk of potential rapid disease progression from a theoretical lack of efficacy. The REMS also addressed additional risks related to allergic and immune-mediated reactions.

The goals of the REMS (also known as the Lumizyme ACE (Alglucosidase Alfa Control and Education) Program[®]) are to mitigate the potential risk of rapid disease progression in infantile-onset Pompe disease patients and patients with late (non-infantile) onset disease less than 8 years of age (because efficacy had not been established in those patients), and to ensure that the known risks of anaphylaxis and severe allergic reactions, and potential risks of severe cutaneous and systemic immune mediated reactions are communicated to prescribers and patients.

The currently approved REMS consists of a CP; ETASU that include prescriber special certification, healthcare facility special certification, and documentation of safe use conditions to ensure that patients are enrolled in the program; an implementation system; and a timetable for submission of assessments. (See Table 1 below for an abbreviated summary of the REMS.)

Table 1. Abbreviated Summary of Lumizyme REMS

REMS Goals	To mitigate the potential risk of rapid disease progression in infantile-onset Pompe disease patients and patients with late (non-infantile) onset disease less than 8 years of age for whom the safety and effectiveness of Lumizyme have not been evaluated.
	To ensure that the known risks of anaphylaxis and severe allergic reactions associated with the use of Lumizyme are communicated to patients and prescribers, and to ensure that the potential risks of severe cutaneous and systemic immune mediated reactions to Lumizyme are communicated to patients and prescribers.
REMS Elements	CP consisting of a Prescriber Introductory Letter and a Healthcare Professional Introductory Letter distributed at product launch.
	ETASU A – Special certification of HCPs who prescribe Lumizyme: Completion of prescriber training and enrollment.
	ETASU B – Special certification of healthcare facilities that dispense Lumizyme: Completion of healthcare facility training and enrollment; confirmation of infusion administration.
	ETASU D – Safe-use condition: Enrollment of patients and patient/caregiver acknowledgement of having received information and counseling from the prescriber.
Implementation System	Monitor compliance with enrollment, product distribution, and use of enrollment forms and other forms.
Timetable for submission of assessments	REMS assessments were to be submitted to FDA at 6 months and 1 year from the date of approval (May 24, 2010), then annually thereafter.

1.3 REGULATORY HISTORY

A brief summary of the key regulatory history relevant to the Lumizyme REMS is listed below in chronological order.

April 28, 2006: Alglucosidase alfa is approved on a 160 L bioreactor scale under the name Myozyme (BLA 125141).

May 30, 2008: Alglucosidase alfa 2000 L bioreactor scale application (BLA 125291) is submitted for approval.

February 27, 2009: BLA 125291 receives a Complete Response (CR) for facility, chemistry, manufacturing, control, and other deficiencies. (Genzyme provides a CR resubmission on May 15, 2009, but receives a second Complete Response on November 13, 2009, for unresolved deficiencies.)

December 16, 2009: Genzyme provides a second CR resubmission for approval of BLA 125291 on a 4000 L bioreactor scale.

May 24, 2010: BLA 125291 (Lumizyme) receives approval for the treatment of patients 8 years and older with late (non-infantile) onset Pompe disease who do not have evidence of cardiac hypertrophy. The application is approved with a REMS to restrict the use of Lumizyme to the indicated patient population and to ensure the risks of severe allergic reactions and immune mediated reactions are communicated to prescribers and patients.

March 11, 2011: Genzyme submits a proposed REMS modification, BLA 125291/S-043, (b) (4)

September 12, 2011: Modified Lumizyme REMS is approved, BLA 125291/S-043

(b) (4)

December 22, 2011: Genzyme submits a proposed REMS modification, BLA 125291/S-079, with revisions to the program training and certification program, enrollment forms, infusion confirmation form, and other REMS materials with the intent of improving customer use and understanding.

December 29, 2011: In the face of ongoing drug shortages of Myozyme, Genzyme submits to IND 10780 the protocol for study AGLU09411, a Phase 4, open-label, prospective study in patients with Pompe disease to evaluate the efficacy and safety of Lumizyme. Eligibility criteria include that the patient must be at least one year of age and have received previous treatment with the 160 L product. Patient enrollment begins in March 2012.

March 2012: Ongoing drug shortages of Myozyme led to a strategy to restrict its use to patients less than 12 months of age. Patients older than 12 months of age were switched from Myozyme to Lumizyme under a Phase 4 open-label clinical study. This allowed patients between the ages of 12 months and 8 years to continue to receive treatment with alglucosidase alfa without contravening the REMS.

July 16, 2012: Modified Lumizyme REMS is approved, BLA 125291/S-079 that made revisions and improvements to the Lumizyme ACE Program on-line training and certification program, the Patient Enrollment and Acknowledgement form, the REMS document (editorial revisions and the addition of language related to substitution of vials from one enrolled patient to a second enrolled patient), the addition of new safety information to the REMS materials regarding nephrotic syndrome, and REMS forms and other program information to improve customer use and understanding.

January 30, 2014: Genzyme submits supplemental efficacy application BLA 125291/S-136 in support of the treatment of all Pompe disease patients with the 4000 L scale bioreactor product. The supplement included data that established the chemical comparability between Myozyme (160 L) and Lumizyme (4000 L) and provided efficacy data from a foreign clinical trial that further supported the chemical comparability of the two enzymes.

2. MATERIALS REVIEWED

- October 21, 2009: Division of Risk Management REMS Final Review, Yasmin Choudrhy, M.D.
- May 24, 2010: Approved REMS, BLA 125291
- February 2, 2011: Division of Risk Management Review of 6-Month REMS Assessment Report, Therese Cvetkovich, M.D.
- April 14, 2011: Division of Risk Management REMS Modification Review, Yasmin Choudrhy, M.D.
- July 28, 2011: Division of Risk Management Review of 12-Month REMS Assessment Report, Therese Cvetkovich, M.D.
- September 12, 2011: Supplement Approval Letter, BLA 125291/S-043, (b) (4)
- June 19, 2012: Division of Risk Management REMS Modification Review, Yasmin Choudrhy, M.D.

- July 16, 2012: Supplement Approval Letter, BLA 125291/S-079, REMS modification
- July 19, 2012: Division of Risk Management Review of 2-Year REMS Assessment Report, Igor Cerny, Pharm.D.
- September 30, 2013: Division of Risk Management Review of 3-Year REMS Assessment Report, Igor Cerny, Pharm.D.
- January 30, 2014, BLA 125291/S-136 submission (Seq. 294). Sections reviewed include:
 - Section 1.16, Risk Management Plan
 - Section 2.7.4, Summary of Clinical Safety
- June 4, 2014: REMS Oversight Committee Meeting (Internal)
 - Slides, Draft Meeting Minutes
- June 13, 2014: REMS assessment for a supplemental efficacy application, BLA 125291/S-136 (Seq. 309)
- July 2, 2014: Division of Risk Management Review of 4-Year REMS Assessment Report, Igor Cerny, Pharm.D.
- July 8, 2014: Division of Gastroenterology and Inborn Errors Products (DGIEP) Clinical Review, BLA 125291/S-136, Juli Tomaino, M.D.

3. APPLICANT'S PROPOSED REMS MODIFICATION: ELIMINATION OF THE REMS

Genzyme proposed elimination of the REMS upon approval of the supplemental efficacy application that extends the indication to all Pompe disease patients (S-136).

4. RATIONALE FOR PROPOSED REMS ELIMINATION

The goals of the REMS are as follows:

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

Approval of the supplemental application to extend Lumizyme's indication to the treatment of all Pompe disease patients would allow elimination of the first goal of the REMS, which is to restrict distribution of Lumizyme to late-onset patients older than 8 years of age.

The second goal of the REMS is to communicate the risk of severe allergic reactions and potential risk of severe immune-mediated reactions to prescribers and patients. The Applicant asserts these risks are clearly stated in the Prescribing Information and Important Safety Information and concludes the REMS assessment reports have shown prescribers have effectively informed patients about these risks. Elimination of the second goal requires a determination that communication efforts under a REMS are no longer necessary to ensure the benefits of the drug outweigh the risks. The determination is based on completion of the CP, the results of the REMS assessments, available safety information, and the future approach to risk management. The rationale to support the REMS elimination is discussed in Sections 5 and 6.

5. DISCUSSION

A. Assessment of whether the CP is still necessary

The purpose of the CP for the Lumizyme REMS is to provide for the dissemination of risk information about rapid disease in infantile-onset Pompe disease patients and patients with late (non-infantile) onset disease less than 8 years of age, anaphylaxis, severe allergic reactions and severe cutaneous and systemic immune mediated reactions associated with the use Lumizyme.

CDER's current thinking is to consider the following conditions when deliberating if a proposed REMS modification to eliminate a CP-only REMS is a reasonable option:

1. All activities for the CP have been completed, and/or the CP activities have been assessed at least once; and
2. If the CP has been assessed, the goal of the CP has been met and there is no need to further assess the current CP; If the CP has not been assessed, no assessment of the current CP is necessary; and
3. There are no identified or emerging safety issues that may require continued, or new communication within the next 6 months; and
4. If the REMS include ETASU, removal of the CP has no implications for those elements.
5. The CP is no longer necessary as an element of the REMS to ensure that the benefits of the drug outweigh the risks.

While this REMS is not a CP-only REMS, the assessment of whether or not a CP was still necessary for this program includes the aforementioned considerations.

Completion of the CP

A Prescriber Introductory Letter and Healthcare Professional Introductory Letter were mailed at product launch. The CP is complete at this time.

Results from REMS Assessments

The goal of the CP has been met. The Applicant's 6-Month REMS Assessment Report indicated that prescriber survey respondents received and reported reading the Prescriber Introductory Letter. Survey results indicate prescribers have a reasonable understanding of the risks of Lumizyme and overall high knowledge scores regarding its safe use.

Identified or emerging safety issues that require new communication

The 4-Year REMS assessment report described several allergic and anaphylactic reactions that are consistent with the known safety profile, and there were no reports that met the criteria for severe cutaneous or systemic immune mediated reactions. No new safety concerns were identified in the clinical review of adverse event data submitted in efficacy supplement 136.

Implications of removing the CP on the ETASU

The CP is complete and has no further impact on introducing prescribers to the pertinent risks and REMS program.

The CP is no longer necessary as a REMS element to ensure the benefits of the drug outweigh the risks

The CP is complete. Additional CP efforts under the REMS are not necessary to ensure the benefits of Lumizyme outweigh the risks.

B. Assessment of whether ETASU are still necessary

The purpose of the ETASU for the Lumizyme REMS are to restrict distribution of Lumizyme to use in patients 8 years or greater and to ensure that the risks of anaphylaxis, severe allergic reactions and severe cutaneous and systemic immune mediated reactions associated with the use Lumizyme are communicated to prescribers and patients.

Restricted distribution

Restricted distribution of Lumizyme under a REMS is no longer necessary. Supplemental efficacy application BLA 125291/S-136 provided an evidence-based evaluation that established chemical comparability between Myozyme (160 L scale) and Lumizyme (4000 L scale), and included supportive clinical efficacy data from an open-label, single-center clinical study in treatment-naïve infantile-onset Pompe patients. The open-label study found similar overall and ventilator-free survival estimates between the patients treated with Lumizyme, in comparison with patients treated with Myozyme from the clinical trials that supported Myozyme's original approval. The safety profile of Lumizyme in the infantile-onset patients was found to be similar to the safety profile of Myozyme, which included signs and symptoms consistent with anaphylaxis, hypersensitivity reactions, immune-mediated reactions, and cardiorespiratory distress. The postmarketing safety data submitted for patients treated with Lumizyme also did not reveal new or unexpected safety signals. Based on this information, the clinical reviewer recommended approval of the efficacy supplement, which would extend the Lumizyme indication to all patients with Pompe disease. Therefore, approval of the extended indication eliminates the need for restricted distribution through the ETASU to meet the first goal of the REMS.

Although not specifically linked with the goals of the REMS, one aspect of special certification of healthcare facilities (which includes home infusion agencies) is the requirement that they attest to have measures in place for appropriate patient monitoring and are prepared to treat patients who experience severe allergic reactions including anaphylaxis. These measures are standard operating procedure for hospitals and ambulatory infusion centers, and home infusion agencies also have accreditation standards requiring policies and procedures that address these measures. Therefore, it is not necessary to continue this certification measure to ensure the benefits of the treatment outweigh the risks.

Education of prescribers and patients

Education of prescribers and patients under a REMS is no longer necessary. The requirements for special certification of prescribers and documentation of safe use conditions intends to support the second goal of the REMS, which is to communicate to prescribers and patients the known risk of anaphylaxis and severe allergic reactions, and the potential risk of severe immune mediated reactions with Lumizyme. In Genzyme's required REMS assessment for a supplemental efficacy application, the Applicant opines that the survey results have shown prescribers have effectively supplied information to inform patients about the risks associated

with Lumizyme treatment. After review of Genzyme's 4-Year REMS Assessment Report, the REMS assessment analyst concluded the survey results indicate prescribers have a reasonable understanding of the risks of Lumizyme and overall high knowledge scores regarding its safe use.

The survey results from patients/caregivers have shown a good understanding of the risks of severe allergic reactions, but relatively poor understanding of immune mediated reactions; however, patients and caregivers know the appropriate actions to take if experiencing these reactions. There were no case reports that met the criteria for severe cutaneous or systemic immune mediated reactions in the last two REMS assessment reports. Although the second goal has not been entirely met, this does not preclude releasing the REMS, as DRISK believes the risk message and survey questions may have been too complex as compared to what patients need to know to ensure safe use of the product.

Furthermore, Myozyme presents the same risks of severe allergic reactions (and severe immune mediated reactions) as Lumizyme, but was not approved with a REMS. The risks of anaphylaxis and severe allergic reactions associated with enzyme replacement therapies are well known and understood in the medical community that specializes in the treatment of rare diseases with these products. The risks of anaphylaxis and severe allergic reactions, and potential risks of severe immune mediated reactions, are communicated through the use of the Boxed Warning as well as the Warnings and Precautions sections of the Lumizyme prescribing information, and routine patient counseling provided by the prescriber can meet the needs of patients and caregivers for risk information.

6. CONCLUSION

DRISK finds the proposal to eliminate the REMS for Lumizyme acceptable upon approval of efficacy supplement 136. Approval of the supplement obviates the need for the first goal of the REMS and the ETASU that restrict distribution to patients older than 8 years of age. The CP and ETASU in the REMS have also addressed the second goal of ensuring prescribers are informed about the risks of severe allergic reactions and potential risks of severe immune mediated reactions, and patients are informed about these risks to the extent where we believe that the benefits of the drug can continue to outweigh the risks.

Therefore, a REMS is no longer required for Lumizyme to ensure the risks outweigh the benefits.

It will be necessary for the Applicant as well as the Agency to communicate the elimination of the REMS to prescribers, patients, and healthcare facilities in order to ensure there are no unnecessary delays in patient access as a result of this change in the distribution model for Lumizyme. The Agency will formulate an external communication strategy for stakeholders that informs patients, prescribers, and infusions centers that Lumizyme is now indicated for all Pompe patients, including infants. DRISK recommends external communication strategy includes a press release, collaboration with prescriber and pharmacist professional organizations, and utilization of third party services that provide medical information (e.g., MedScape), to communicate the new indication for Lumizyme and the elimination of the Lumizyme REMS.

7. RECOMMENDATIONS

Therefore, DRISK recommends the following:

- Genzyme be released from the REMS requirement for Lumizyme and the Applicant sent a Release REMS Requirement letter upon approval of BLA 125291/S-136.
- An external communication strategy be developed to notify stakeholders of the release from the REMS requirement to ensure there are no unnecessary delays in patient access to Lumizyme as a result of the change in the distribution model for Lumizyme.

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/s/

ROBERT G PRATT
07/18/2014

REEMA J MEHTA
07/20/2014

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
BLA 125291/136

OTHER REVIEW(S)

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT

Application:	BLA125291/136	Action Goal:		
Stamp Date:	30-JAN-2014	District Goal:	27-JUN-2014	
Regulatory:	01-AUG-2014			
Applicant:	(b) (4)	Brand Name:	LUMIZYME	
		Estab. Name:		
		Generic Name:		
Priority:	1Y	Product Number; Dosage Form; Ingredient; Strengths		
Org. Code:	180	001; INJECTION, POWDER, LYOPHILIZED, FOR SOLUTION; ALGLUCOSIDASE ALFA; 50MG		
Application Comment:	<p>1. REVISE THE LUMIZYME INDICATION TO TREAT ALL PATIENTS WITH POMPE DISEASE. FROM: LUMIZYME (ALGLUCOSIDASE ALFA) IS A LYSOSOMAL GLYCOGEN-SPECIFIC ENZYME INDICATED FOR PATIENTS 8 YEARS AND OLDER WITH LATE (NON-INFANTILE) ONSET POMPE DISEASE (ACID β-GLUCOSIDASE (GAA) DEFICIENCY) WHO DO NOT HAVE EVIDENCE OF CARDIAC HYPERTROPHY. THE SAFETY AND EFFICACY OF LUMIZYME HAVE NOT BEEN EVALUATED IN CONTROLLED CLINICAL TRIALS IN INFANTILE-ONSET PATIENTS, OR IN LATE (NON-INFANTILE) ONSET PATIENTS LESS THAN 8 YEARS OF AGE TO: LUMIZYME (ALGLUCOSIDASE ALFA) IS A LYSOSOMAL GLYCOGEN-SPECIFIC ENZYME INDICATED FOR PATIENTS WITH POMPE DISEASE (ACID β-GLUCOSIDASE (GAA) DEFICIENCY).</p> <p>2. RELEASE OF THE REQUIREMENT FOR THE LUMIZYME REMS. (b) (4)</p>			
FDA Contacts:	F. MILLS	Prod Qual Reviewer	(HFD-122)	3018271808
	K. BUGIN	Regulatory Project Mgr	(HFD-180)	3017962302
Overall Recommendation:	ACCEPTABLE	on 01-AUG-2014	by R. PRABHAKARA	() 3017964668
	PENDING	on 01-AUG-2014	by EES_PROD	
	PENDING	on 16-JUL-2014	by EES_PROD	

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: (b) (4)

DMF No: (b) (4) **AADA:** (b) (4)

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Establishment Comment: - SITE OF QUALITY CONTROL TESTING: DRUG SUBSTANCE
(b) (4) TESTING (b) (4)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					

SUBMITTED TO OC	16-JUL-2014				(b) (4)
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OC RECOMMENDATION	18-JUL-2014		ACCEPTABLE	PRABHAKARAR
BLA PILOT - THIS SITE WAS INSPECTED BY (b) (4) AND CLASSIFIED VAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG TESTING OPERATIONS. THE CTL PROFILE WAS UPDATED AND IS ACCEPTABLE.				

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: (b) (4)

DMF No: (b) (4)

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Establishment Comment: - SITE OF QUALITY CONTROL TESTING: DRUG SUBSTANCE
IN VITRO VIRUS TESTING
(b) (4)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					

SUBMITTED TO OC	16-JUL-2014				(b) (4)
OC RECOMMENDATION	18-JUL-2014		ACCEPTABLE		PRABHAKARAR
BLA PILOT - THIS SITE WAS INSPECTED BY (b) (4) AND CLASSIFIED VAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG TESTING OPERATIONS. THE CTX PROFILE WAS UPDATED AND IS ACCEPTABLE.					
SUBMITTED TO DO	01-AUG-2014	Extension Request			PRABHAKARAR
EXPIRED 7/25/2014. PDUFA IS TODAY.					
01-AUG-2015					
The DO is requested to clear the extension request unless the DO finds that the methods used in, or the facilities and controls used for the manufacture, processing and packing of the drug are inadequate to preserve its identity, strength, quality or purity.					
PDUFA GOAL DATE					
DO RECOMMENDATION	01-AUG-2014		ACCEPTABLE		(b) (4)
ACCEPTABLE BASED ON 1 YEAR EXTENSION REQUEST					
OC RECOMMENDATION	01-AUG-2014		ACCEPTABLE		PRABHAKARAR
THIS SITE WAS INSPECTED BY (b) (4) AND CLASSIFIED VAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG SUBSTANCE TESTING OPERATIONS. THE CTX PROFILE WAS UPDATED AND IS ACCEPTABLE. ALTHOUGH THE GMP STATUS OF THIS SITE IS OUT OF DATE, DIDQ HAS GRANTED A ONE-YEAR EXTENSION BASED ON THEIR REVIEW OF THE FACILITY AND THE PDUFA DATE FOR THIS BLA.					

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: (b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Establishment Comment: - SITE OF QUALITY CONTROL TESTING: DRUG SUBSTANCE
(b) (4)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					

SUBMITTED TO OC	16-JUL-2014				(b) (4)
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SUBMITTED TO DO	22-JUL-2014	Product Specific and GMP Inspection			PRABHAKARAR
THIS SITE HAS NO FDA INSPECTIONAL HISTORY.					

DO RECOMMENDATION	29-JUL-2014		ACCEPTABLE	(b) (4)	
SITE WAS COVERED UNDER PREVIOUS INSPECTION OF (b) (4) AND WAS CLASSIFIED VAI. ALL PROFILES ARE ACCEPTABLE.					

OC RECOMMENDATION	29-JUL-2014		ACCEPTABLE	PRABHAKARAR	
THIS SITE WAS INSPECTED BY (b) (4) AND CLASSIFIED VAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG TESTING OPERATIONS. THE CTL PROFILE WAS UPDATED AND IS ACCEPTABLE.					

FDA CDER EES

DMF No: AADA:

Establishment Comment:	SITE OF QUALITY CONTROL TESTING: DRUG SUBSTANCE AND DRUG PRODUCT (on 16-JUL-2014 by T. WILSON () 2404024226)
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<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					

OC RECOMMENDATION	18-JUL-2014	ACCEPTABLE	PRABHAKARAR
<p>BLA PILOT - THIS SITE WAS INSPECTED BY NWE-DO FROM JUNE 11 - JULY 13, 2012 AND CLASSIFIED VAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH DS TESTING OPERATIONS. THE CBI PROFILE WAS UPDATED AND IS ACCEPTABLE.</p> <p>ALTHOUGH THE CTL PROFILE WAS NOT SPECIFICALLY UPDATED FOLLOWING THIS INSPECTION, THE FACTS ENDORSEMENT TEXT INDICATES THAT LABS WERE COVERED DURING THIS INSPECTION.</p>			

FDA CDER EES

GENZYME FLANDERS BVBA

DMF No: AADA:

DRUG SUBSTANCE OTHER TESTER

FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE OTHER TESTER

- SITE OF MANUFACTURER AND STORAGE: DRUG SUBSTANCE
- QUALITY CONTROL TESTING: DRUG SUBSTANCE AND DRUG PRODUCT
- CELL BANK PREPARATION AND STORAGE
- RAW MATERIAL STORAGE
- SITE OF FORMULATION: DRUG PRODUCT (on 16-JUL-2014 by T. WILSON)

Profile:	BIOTECHNOLOGY DERIVED API (STERILE & NON-STERILE)	OAI Status:	NONE
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SUBMITTED TO OC	16-JUL-2014			WILSONT
SUBMITTED TO DO BLA PILOT - INITIAL CGMP STATUS	18-JUL-2014	10-Day Letter		PRABHAKARAR
UNDER REVIEW	24-JUL-2014			TUNGL
DO RECOMMENDATION	31-JUL-2014		ACCEPTABLE	MROSE
OC RECOMMENDATION	31-JUL-2014		ACCEPTABLE	PRABHAKARAR

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: **CFN:** 9611925 **FEI:** 3002807062

GENZYME IRELAND LTD.

37 HOLLANDS ROAD
HAVERHILL, , UNITED KINGDOM

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE PACKAGER

Establishment Comment: - SITE OF STORAGE AND DISTRIBUTION
- LABELING AND PACKAGING
(on 16-JUL-2014 by T. WILSON () 2404024226)

Profile: SMALL VOLUME PARENTERAL, LYOPHILIZED **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					

SUBMITTED TO OC	16-JUL-2014				WILSONT
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OC RECOMMENDATION	18-JUL-2014	ACCEPTABLE	PRABHAKARAR
BLA PILOT - THIS SITE WAS INSPECTED BY IOG FROM APRIL 8-13, 2011 AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING DRUG PACKAGING AND LABELING OPERATIONS. THE NEC PROFILE (PACKAGER/LABELER FOR STERILE FILLED DRUG) WAS UPDATED AND IS ACCEPTABLE.			

FDA CDER EES

Establishment: CFN: FEI: 3003809840

GENZYME IRELAND LTD.

OLD KILMEANDEN RD
WATERFORD, , IRELAND

DMF No: AADA:

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE OTHER TESTER

Establishment Comment: FILL/FINISH: DP
- SITE OF MANUFACTURE: DRUG PRODUCT
- QUALITY CONTROL TESTING: DRUG PRODUCT
- STORAGE AND DISTRIBUTION
- LABELING AND PACKAGING (on 16-JUL-2014 by T. WILSON () 2404024226)

Profile: SMALL VOLUME PARENTERAL, LYOPHILIZED **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	16-JUL-2014				WILSONT
SUBMITTED TO DO	23-JUL-2014	10-Day Letter			PRABHAKARAR
FD MFR WITH INITIAL GMP STATUS. THE 2/2014 INSPECTION APPEARS TO HAVE BEEN A PAI THAT ONLY COVERED HARD CAPSULES (ACCORDING TO FACTS), EVEN THOUGH THE SVL PROFILE WAS UPDATED. THE LAST GMP WAS 7/2013 AND OFFERED COVERAGE OF NUMEROUS BIOTECH PRODUCTS.					
UNDER REVIEW	24-JUL-2014				TUNGL
DO RECOMMENDATION	31-JUL-2014			ACCEPTABLE	MROSE
OC RECOMMENDATION	31-JUL-2014			ACCEPTABLE	PRABHAKARAR
THIS SITE WAS INSPECTED BY IOG FROM JULY 22-30, 2013 AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG PRODUCT MANUFACTURING OPERATIONS. THE SVL PROFILE WAS UPDATED AND IS ACCEPTABLE.					

FDA CDER EES

GENZYME, A SANOFI COMPANY

DMF No: AADA:

FINISHED DOSAGE PACKAGER

Profile:	SMALL VOLUME PARENTERAL, LYOPHILIZED	OAI Status:	NONE
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SUBMITTED TO OC 16-JUL-2014 WILSONT

OC RECOMMENDATION	18-JUL-2014	ACCEPTABLE	PRABHAKARAR
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**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment:



DMF No:

AADA:

Responsibilities:

FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE OTHER TESTER

Establishment Comment:

FILL/FINISH: DP
- SITE OF MANUFACTURE: DRUG PRODUCT
- QUALITY CONTROL TESTING: DRUG PRODUCT
(on 16-JUL-2014 by (b) (4))

Profile:

SMALL VOLUME PARENTERAL, LYOPHILIZED

OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					

SUBMITTED TO OC	16-JUL-2014				(b) (4)
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SUBMITTED TO DO	18-JUL-2014	10-Day Letter			PRABHAKARAR
BLA PILOT - FD MFR. PLEASE REVIEW.					

DO RECOMMENDATION	31-JUL-2014		ACCEPTABLE		(b) (4)
A GMP EI WAS CONDUCTED (b) (4) AND COVERED THIS PROFILE CLASS. CONTACT WITH BOB WILLIFORD AT HOSPIRA FOUND THE FIRM MANUFACTURED THIS PRODUCT IN 2008 AND 2009 ON FILL LINE M-6. HE STATED THERE WASN'T ANY NEW EQUIPMENT FOR THIS PROCESS. BASED ON FILE REVIEW, KAN-DO RECOMMENDS ACCEPTABLE FOR THIS SUPPLEMENTAL APPLICATION.					

OC RECOMMENDATION	31-JUL-2014		ACCEPTABLE		PRABHAKARAR
THIS SITE WAS INSPECTED BY (b) (4) AND CLASSIFIED VAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING STERILE DRUG PRODUCT MANUFACTURING OPERATIONS. THE SVL PROFILE WAS UPDATED AND IS ACCEPTABLE.					

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/s/

RANJANI PRABHAKARA
08/01/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993

MEMORANDUM TO FILE

DATE: July 23, 2014

TO: BLA 125291/136

FROM: Vicki Moyer, MS, Senior Regulatory Project Manager

SUBJECT: Division of Gastroenterology and Inborn Errors Products (DGIEP) Consult request to PMHS, Pediatrics

DRUG: Lumizyme (alglucosidase alfa)

On March 11, 2014 DGIEP submitted a consult request to PMHS, an efficacy supplement for BLA 125291 Lumizyme (alglucosidase alfa). The Maternal Health review was performed by Tamara Johnson (see reference number 3530827).

The PMHS pediatrics team participated in several labeling meetings with the division. Labeling comments are incorporated in labeling. This memo will close out the PMHS pediatrics consult request.

PMHS Pediatrics Medical TL: Hari Cheryl Sachs
PMHS Pediatrics Reviewer: Alyson Karesh
PMHS RPM: Vicki Moyer

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/s/

VICKI A MOYER
07/23/2014

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: July 16, 2014

To: Kevin Bugin, Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products (DGIEP)

From: Adewale Adeleye, Pharm.D., MBA, Regulatory Review Officer,
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm Pharm.D., Team Leader, OPDP

Subject: BLA# 125291/ S 136 - LUMIZYME (alglucosidase alfa) for injection,
for intravenous infusion (Lumizyme)

Reference is made to DGIEP's consult request dated April 28, 2014, requesting review of the proposed Package Insert (PI) and Carton/Container Labeling for Lumizyme.

OPDP has reviewed the proposed PI entitled, "draft-labeling-text-redline.doc" that was available in the e-room on July 10, 2014. OPDP's comments on the PI are provided directly on the attached marked-up copy of the labeling (see below).

Thank you for your consult. If you have any questions please contact me at (240) 402-5039 or adewale.adeleye@fda.hhs.gov

18 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ADEWALE A ADELEYE
07/16/2014

FINAL Therapeutic Biological Establishment Evaluation

Request (TB-EER) Form

Version 1.0

Instructions:

The review team should email this form to the email account “CDER-TB-EER” to submit:

- 1) an initial TB-EER within 10 business days of the application filing date
- 2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing¹ locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA/BsUFA Action Date: August 01, 2014

Applicant Name: Genzyme Corporation
U.S. License #: 1596
STN(s): 125291/136
Product(s): Lumizyme (aglucosidase alfa)

Short summary of application:

1. Revise the Lumizyme indication to treat all patients with Pompe disease.

From: LUMIZYME (aglucosidase alfa) is a lysosomal glycogen-specific enzyme indicated for patients 8 years and older with late (non-infantile) onset Pompe disease (acid

α -glucosidase (GAA) deficiency) who do not have evidence of cardiac hypertrophy. The safety and efficacy of LUMIZYME have not been evaluated in controlled clinical trials in infantile-onset patients, or in late (non-infantile) onset patients less than 8 years of age

To: LUMIZYME (aglucosidase alfa) is a lysosomal glycogen-specific enzyme indicated for patients with Pompe disease (acid α -glucosidase (GAA) deficiency).

2. Release of the Requirement for the Lumizyme REMS.
-

¹The regulations at 21 C.F.R. § 207.3(a)(8) defines “manufacturing or processing” as “the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer.”

FACILITY INFORMATION

Manufacturing Location: Belgium
Firm Name: Genzyme Flanders bvba
Address: Ciplastraat 8, Geel, Belgium, 2440
FEI: 3003623839

Short summary of manufacturing activities performed:

- Site of Manufacturer and Storage: Drug Substance
- Quality Control Testing: Drug Substance and Drug Product
- Cell Bank Preparation and Storage
- Raw Material Storage

Manufacturing Location: Ireland
Firm Name: Genzyme Ireland Ltd
Address: Old Kilmeaden Road, Waterford, Ireland
FEI: 3003809840

Short summary of manufacturing activities performed:

- Site of Manufacture: Drug Product
- Quality Control Testing: Drug Product
- Storage and Distribution
- Labeling and Packaging

Manufacturing Location: USA
Firm Name: Hospira, Inc
Address: 1776 North Centennial Drive, McPherson, KS, US 67460
FEI: 1925262

Short summary of manufacturing activities performed:

- Site of Manufacture: Drug Product
- Quality Control Testing: Drug Product

Manufacturing Location: UK
Firm Name: Genzyme Ltd
Address: 37 Holland Road, Haverhill, Suffolk, UK CB9 8PU
FEI: 3002807062

Short summary of manufacturing activities performed:

- Site of Storage and Distribution
- Labeling and Packaging

Manufacturing Location: USA
Firm Name: Genzyme Corporation
Address: 45 & 76 New York Ave, Framingham, MA US 01701
FEI: 0001220423

Short summary of manufacturing activities performed:

- Site of Quality Control Testing: Drug Substance and Drug Product

Manufacturing Location: US

Firm Name: Genzyme Corporation

Address: 74 New York Ave, Framingham, MA US 01701

FEI: 0001220423

Short summary of manufacturing activities performed:

- Backup storage location for cell bank

Manufacturing Location: US

Firm Name: Genzyme Corporation

Address: 45 & 51 New York Ave, Framingham, MA US 01701

FEI: 0001220423

Short summary of manufacturing activities performed:

- Cell Bank Preparation and Storage

Manufacturing Location: US

Firm Name: Genzyme Northborough Operations Center

Address: 11 Forbes Road, Northborough, MA US 01532

FEI: 3009389940

Short summary of manufacturing activities performed:

- Labeling and Packaging
- Storage and Distribution

(b) (4)



(b) (4)



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KEVIN B BUGIN
07/01/2014

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: June 27, 2014

TO: Kevin Bugin, MS, RAC, Regulatory Project Manager
Juli Tomaino, M.D., Medical Officer
Division of Gastroenterology and Inborn Errors Products

FROM: Susan Leibenhaut, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan D. Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA: 125291/136

APPLICANT: Genzyme Corporation

DRUG: Lumizyme (alglucosidase alfa)

NME: No
THERAPEUTIC CLASSIFICATION: Priority

INDICATION: Expansion of indication to treat patients with infantile onset Pompe Disease

CONSULTATION REQUEST DATE: March 10, 2014
INSPECTION SUMMARY GOAL DATE: July 1, 2014
DIVISION ACTION GOAL DATE: August 1, 2014
PDUFA DATE: August 1, 2014

I. BACKGROUND:

Genzyme, the manufacturer of Lumizyme (alglucosidase alfa) a replacement therapy for Pompe disease, submitted this supplemental BLA that includes data to confirm analytical comparability between two manufacturing scales (160 L and 4000 L (b) (4)) and provides clinical data in support of expansion of the target population to patients with infantile onset Pompe Disease. The clinical data to support this indication was collected on Pompe patients in a single site, investigator sponsored study (ISS) in Taiwan with classical infantile-onset phenotype (diagnosis and clinical manifestations prior to 6 months of age with cardiac hypertrophy).

In 2006, Myozyme was approved by the FDA for replacement therapy for infantile onset Pompe disease and, in 2010; Lumizyme was approved as replacement therapy for late-onset (noninfantile) Pompe disease without evidence of cardiac hypertrophy in patients 8 years. Lumizyme and Myozyme are both alglucosidase alfa but differ in their manufacture. Myozyme is made using a 160 L bioreactor, while Lumizyme uses a 4000 L bioreactor. Because of the difference in the manufacturing process, the FDA has considered that the two products are biologically different. This current supplement is to expand the Lumizyme indication to infantile onset Pompe. Outside the US the larger scale product is marketed under the name Myozyme and is approved for all types of Pompe. The approval of the application relies heavily on the ability to establish comparability of the products manufactured by the two different processes. In addition, the sponsor submitted the single-site investigator sponsored study titled, "Interim Report of Ongoing Taiwan Investigator-Sponsored Study: A Long-Term Follow-Up of Pompe Disease" STUDY NUMBER: TAIWAN01. The study was initiated in March 2006 with the objective of documenting the long term prognosis of patients in Taiwan treated with alglucosidase alfa manufactured using the 4000-L bioreactor.

The review division chose this site for inspection because all efficacy data in this submission were collected from this single site ISS noted above.

II. RESULTS (by Site):

Sponsor/Clinical Investigator Name and Address	Protocol #/ # of Subjects	Inspection Date	Final Classification*
Wuh-Liang Hwu, MD, PhD Department of Pediatrics and Medical Genetics National Taiwan University Hospital (NTUH) 7 Chung-Shan S. Road Taipei 100, Taiwan	Taiwan01/ 18 Subjects	May 26 to 30, 2014	Pending* (preliminary NAI)

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. Wuh-Liang Hwu, MD, PhD,
Taipei 100, Taiwan

Note: Observations below for the sponsor inspection are based on e-mail communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final Establishment Inspection Report (EIR).

- a. **What was inspected:** Because this was an investigator initiated study, the study was inspected under the relevant elements of CPGM 7348.810 for sponsors and CPGM 7348.811 for clinical investigators. At this site, a total of 28 subjects were screened and 18 subjects were enrolled and followed. No subjects discontinued. Informed consent documents and source documents including and hospital records were reviewed for all 18 subjects.
- b. **General Observations/Commentary:** The study was not conducted under US IND and no Form FDA 1572 was available. All subjects were administered dosage products manufactured at the 2000 L scale until October 2009. Then in approximately November 2009, the product administered was from the 4000 L scale. There was no 160 L scale product used in this study. The data for efficacy endpoints of overall survival and invasive ventilator free survival data were verified. There was no evidence of under-reporting of adverse events. No significant regulatory violations were noted, and no Form FDA 483 was issued.

- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The sponsor investigator site was inspected for this BLA supplement. The site has the preliminary classification of NAI.

Note: Observations above for the sponsor-investigator site inspection are based on e-mail communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final EIRs.

{See appended electronic signature page}

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SUSAN LEIBENHAUT
06/27/2014

SUSAN D THOMPSON
06/30/2014

KASSA AYALEW
06/30/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
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Pediatric and Maternal Health Staff – Maternal Health Review

Date: June 20, 2014

From: Tamara Johnson, MD, MS, Medical Officer
Pediatric and Maternal Health Staff

Through: Jeanine Best, MSN, RN, PNP, Team Leader- Maternal Health
Pediatric and Maternal Health Staff

Lynne P. Yao, MD, OND Associate Director
Pediatric and Maternal Health Staff

To: Division of Gastroenterology and Inborn Errors Products (DGIEP)

BLA: 125291

Drug: Lumizyme (alglucosidase alfa)

Applicant: Genzyme Corporation

Proposed Indication: A lysosomal glycogen-specific enzyme indicated for patients with Pompe disease (acid α -glucosidase (GAA) deficiency).

Consult Request: 1. "DGIEP requests PMHS to attend team meetings for this product, and provide verbal input as appropriate."
2. Labeling review

Consult Requested: March 11, 2014

Consult Due Date: July 2, 2014

Materials Reviewed:

- Proposed labeling revision for BLA 125291 Lumizyme (alglucosidase alfa) efficacy supplement, submitted January 30, 2014
- Updated labeling, submitted April 4, 2014, in response to DGIEP information request dated March 31, 2014
- Type C Meeting Minutes for February 19, 2013

INTRODUCTION

This supplemental efficacy BLA for Lumizyme (alglucosidase alfa, 4000L scale product) was submitted, on January 30, 2014, to expand the indication and target population. Lumizyme's indication is to be changed from "indicated for patients 8 years and older with late (non-infantile) onset Pompe disease (acid α -glucosidase (GAA) deficiency) who do not have evidence of cardiac hypertrophy" to "indicated for patients with Pompe disease (acid α -glucosidase (GAA) deficiency)." Myozyme (alglucosidase alfa, 160L scale product) is approved for all patients with Pompe disease but has been in increasingly short supply. The efficacy supplement is submitted based on an agreement between Genzyme Corporation (Genzyme) and Division of Gastroenterology and Inborn Errors Products (DGIEP) from a Type C Meeting held on February 19, 2013. The intent of the agreement is to update the Lumizyme indication to include all Pompe patients and ensure a continued supply of alglucosidase alfa at the 4000 L scale for the entire Pompe patient community, including patients with infantile-onset Pompe disease and late-onset Pompe disease patients less than 8 years of age.

This efficacy supplement is presented to the Division with comparability studies between the two scales of alglucosidase alfa (Myozyme (160 L) and Lumizyme (4000 L)), evidence of clinical safety and immunogenicity, as well as data from ongoing postmarketing studies.

DGIEP requests meeting attendance and input from the Pediatric and Maternal Health Staff - Maternal Health Team (PMHS-MHT) for the proposed full prescribing information of Lumizyme, as well as any additional assistance as necessary. This review, therefore, provides recommended revisions and structuring of existing information related to the Pregnancy and Nursing Mothers labeling in order to provide clinically relevant information for prescribing decisions and to comply with current regulatory requirements.

BACKGROUND

Pompe Disease

Pompe disease (glycogen storage disease type II, acid alpha-glucosidase deficiency, acid maltase deficiency, or glycogenosis type II) is a rare, autosomal recessive, life-threatening muscle disorder caused by genetic mutations to the gene for lysosomal enzyme acid α -glucosidase (GAA). With deficient or nonfunctional GAA, patients are unable to appropriately metabolize glucose, leading to accumulation of glycogen in muscle cells. This leads to irreversible muscle damage, and a range of systemic manifestations including respiratory insufficiency and skeletal muscle weakness. Incidence of Pompe disease ranges from 1:33,000 to 1:300,000 depending on geographic region and ethnicity.¹ There are two main phenotypes of Pompe disease; the severe and rapidly progressive infantile-onset and the more slowly progressive juvenile/adult onset. Patients with the infantile-onset Pompe disease present in the first months of life with failure to thrive, respiratory insufficiency, frequent lung infections, cardiac hypertrophy,

¹ Toscano A, Schoser B. Enzyme replacement therapy in late-onset Pompe disease: a systematic literature review. J Neurol. 2013 Apr;260(4):951-9.

and hypotonia. These patients generally die before two years of age of cardiomyopathy. Patients with juvenile/adult onset Pompe disease present as early as the first decade of life to as late as the fifth decade of life. Their main clinical manifestations are respiratory insufficiency and limb-girdle muscular dystrophy.² Death is often due to respiratory failure. There is often no cardiac involvement with juvenile/adult onset Pompe.

Lumizyme (alglucosidase alfa)

- Molecular weight = 109,000 Daltons
- Administration route = intravenous infusion
- Dosing regimen = 20 mg/kg body weight IV, every 2 weeks

Lumizyme is a recombinant human enzyme acid α -glucosidase (GAA), produced in a Chinese hamster ovary cell line, and intended for enzyme replacement therapy for Pompe disease patients.

There are two FDA-approved drug products for Pompe disease: Myozyme (produced on a 160L bioreactor scale) and Lumizyme (produced on a 4000L scale). Both products are manufactured by Genzyme and are recombinant alglucosidase alfa; however, due to glycosylation differences, chemical comparability between these two production scales could not be established. These critical product quality attributes have the potential to affect clinical performance of the products and, therefore, FDA determined that these scales were not interchangeable. The two products were also approved for different populations. Drug shortages of Myozyme (approved for infantile-onset Pompe disease) limited the availability of the product for older pediatric and adult patients. However, Lumizyme was approved for juvenile/adult onset Pompe disease patients eight years of age or older. Outside of the US, the Myozyme tradename is used for the 4000 L product and all ages of Pompe patients are treated with the 4000 L product. The 160 L scale product was never approved outside the US.

LABELING

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DISCUSSION

PMHS-MHT has been working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates “the spirit” of the Proposed Pregnancy and Lactation Labeling Rule (PLLR) (published on May 29, 2008). As part of the labeling review, the PMHS-MHT reviewer conducts a literature search to determine if relevant published pregnancy and lactation data are available that would add clinically useful information to the Pregnancy and Nursing Mothers labeling subsections. In addition, the PMHS-MHT works with the pharmacology/toxicology reviewers to present

animal data, in the Pregnancy and Nursing Mothers subsections, to make it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, animal dose including human dose equivalents (with the basis for calculation), and outcomes for dams and offspring. The first paragraph in the pregnancy subsection of labeling summarizes available data from published literature, outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. For the Nursing Mothers subsection, when animal data are available, only the presence or absence of drug in milk is presented in the label. The goal of this restructuring is to make the pregnancy and lactation section of labeling a more effective communication tool for clinicians.

Pregnancy Data and Literature Review

Adequate animal reproduction studies for alglucosidase alfa were completed and submitted with the original marketing application for Lumizyme. Teratogenicity was not observed in the embryo-fetal toxicity studies performed in mice and rabbits. The current labeling, however, does not reflect the results of the pre- and postnatal developmental study in mice. In the pre- and postnatal developmental study, mice pups demonstrated an increased incidence of mortality during lactation days 15 to 21. No maternal toxicity was observed. The DGIEP Pharmacology/Toxicology team proposes revision to the Lumizyme labeling that would describe the results of this study and change the Pregnancy Category classification from “B” to “C”.

No adequate and well-controlled studies of Lumizyme treatment in pregnant Pompe disease patients have been conducted. There are three case reports in the literature that describe successful pregnancies in Pompe disease patients.^{3, 4, 5} Common to these three patients was worsening of Pompe disease manifestations such as respiratory insufficiency requiring ventilation and limb-girdle weakness reducing ambulation. One patient received enzyme replacement therapy (ERT) with Lumizyme before, during, and after pregnancy.⁴ Another patient, who received no ERT, experienced severe preeclampsia in two pregnancies.³ Pompe disease manifestations contributed to unproductive labor in all three patients, requiring infants to be delivered by Caesarean section. Table 1 (below) describes the specific pregnancy experiences of the three Pompe disease patients.

Aside from the three successful pregnancies in Pompe disease patients, as described above, the Applicant reports three pregnancy outcomes as serious adverse events in their postmarketing safety database. Two of the three pregnancies resulted in spontaneous abortion. The third pregnancy outcome was a premature rupture of membranes. The

³ Cilliers HJ, Yeo ST, Salmon NP. Anaesthetic management of an obstetric patient with Pompe disease. *Int J Obstet Anesth.* 2008 Apr;17(2):170-3.

⁴ De Vries JM, Brugma JD, Ozkan L, Steegers EA, Reuser AJ, van Doorn PA, van der Ploeg AT. First experience with enzyme replacement therapy during pregnancy and lactation in Pompe disease. *Mol Genet Metab.* 2011 Dec;104(4):552-5

⁵ Weida J, Hainline BE, Bodkin C, Williams MK. Management of a pregnancy complicated by Pompe disease. *Case Rep Obstet Gynecol.* 2012;2012:137861.

patients were categorized as late-onset Pompe disease (n=1) or unknown phenotype (n=2). The postmarketing safety data is sparse and reports only those pregnancies with adverse outcomes

In summary, while there is evidence of harm in animal reproduction studies, there is a scarcity of clinical information in the scientific literature and the postmarketing database regarding the effects of alglucosidase alfa treatment during pregnancy. Pompe disease manifestations worsen during pregnancy and may lead to chronic maternal hypoxia, fetal hypoxia, and maternal death.⁵ On the other hand, Lumizyme requires a large volume infusion and some clinicians are concerned about fluid overload in a patient with respiratory compromise. It is not clear whether there are adverse effects associated with the use of alglucosidase alfa during pregnancy; however, the mother with Pompe disease may wish to continue treatment despite potential risks. PMHS-MHT agrees with the DGIEP Pharmacology/Toxicology team to modify the pregnancy category classification of Lumizyme to reflect the results of the pre- and postnatal development study. PMHS-MHT has revised and reformatted Section 8.1 to comply with the proposed PLLR.

Table 1: Case Reports of Pregnancies in Pompe Disease Patients

Journal article	Age (years), Gravidity Parity*	Pompe disease phenotype and manifestations	Pregnancy complications	Pregnancy outcome	Enzyme replacement therapy?
Cilliers HJ, <i>et al.</i> 2008.	31, G2P1	Adult-onset; Muscle weakness, including diaphragmatic weakness	Severe pre-eclampsia, urgent Caesarean section at 37 weeks EGA	Live infant, BW 1980 grams, Apgar scores of 9 and 9 at 1 and 5 minutes	None
	28, G1P0 (same patient)	Adult-onset; Muscle weakness, including diaphragmatic weakness	Severe pre-eclampsia, intrauterine growth retardation, fetal distress at 27 weeks EGA required an emergent Caesarean section	Infant died at age 3 days due to complications of prematurity	None
De Vries JM, <i>et al.</i> 2011.	40, G1P0	Adult-onset; limb-girdle weakness, nocturnal ventilation	Caesarean section at 37 weeks EGA due to worsening maternal respiratory status	Live infant, BW “normal”, Apgar scores of 8, 9, and 10 at 1, 5, and 10 minutes – normal development at 1 year of age; Patient’s respiratory function improved postpartum	Lumizyme 20 mg/kg IV every other week started 17 months before pregnancy and continued through breastfeeding
Weida J, <i>et al.</i> 2012.	23, G1P0	Juvenile-onset; worsening ambulation to require powered wheelchair and nursing care for ADLs, pulmonary insufficiency due to neuromuscular weakness (nocturnal, then continuous BiPAP)	Caesarean section at 33 weeks EGA due to worsening maternal respiratory status	Live infant, BW 3080 grams, Apgar scores of 6, 3, and 9 at 1, 5, and 10 minutes – normal development; Patient’s respiratory function returned to pre-pregnancy values at ten months postpartum, but she still requires assistance with ADLs	Declined experimental ERT treatment during pregnancy due to unknown risks to fetus and mother; however, patient started Lumizyme at one year postpartum.

*G = gravidity, P = parity

Lactation Data and Literature Review

Many, but not all, drugs transfer to breast milk. The transport of a drug into breast milk is largely a function of the drug’s physicochemical properties and its concentration in

maternal plasma.⁶ All of the following factors influence the amount of drug transfer into human milk: plasma and milk protein binding, molecular weight, mechanism of transport, degree of ionization, and clearance pathways. Factors that tend to produce higher human milk levels of drugs include: higher maternal plasma concentration, higher lipid solubility, higher pKa, lower protein binding, and lower molecular weight. The mean pH of human milk is 7.2, about 0.2 units lower than that of plasma. This difference influences the transfer of drugs into milk, more so for drugs that are weak bases with pKa values in that range. Drugs that are more lipid soluble may accumulate in the lipid fraction of the milk, leading to higher concentrations of drug in human milk than in maternal plasma. Most drugs move between maternal serum and human milk based on equilibrium forces. Drugs with higher molecular weights, especially those with weights greater than 800 Daltons (Da), must generally be actively transported or dissolved in the cells lipid membranes. Protein drugs with very high molecular weights (e.g., Insulin MW 5808 Da, Heparin MW 5000 Da) are usually excluded from breast milk.

No formal lactation studies of Lumizyme treatment in nursing mothers has been conducted by the Applicant; however, there is a case report in the scientific literature which provides some information on the presence of Lumizyme in breastmilk. De Vries, *et al.*, describe an adult-onset Pompe disease patient who received Lumizyme 20 mg/kg IV infusion every other week during pregnancy and lactation.⁷ The Lumizyme activity levels measured in the patient's breastmilk prior to infusion were found to be 3 nmol/h.ml, 10% of what was measured in breastmilk of an unaffected woman. The enzyme activity levels in breastmilk peaked at 2.5 hours after the end of infusion at 245 nmol/h.mL, which was 0.3% of the peak plasma value. The enzyme activity levels then dropped to undetectable levels at 24 hours after the end of infusion. Both mother's and infant's sera had low anti-alglucosidase alfa antibody titer (1:800 and 1:400, respectively) at three days postpartum, and appeared to remain at this level at 77 days postpartum. The authors caution that this is a singular report of pregnancy and lactation during treatment with Lumizyme, but, recommend withholding breastfeeding for 24 hours after each infusion as a precaution.

The LactMed database states that the transfer of alglucosidase alfa to breastmilk is predicted to be very low because of the high molecular weight of the drug product (109,000 Da). LactMed further states that "absorption is unlikely because the molecule is probably destroyed in the infant's gastrointestinal tract." The LactMed database provides information for FDA-approved drugs when available on maternal levels in breastmilk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered, and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

Although Lumizyme is associated with serious adverse events, the nursing mother with Pompe disease will continue to use this therapy because the benefits outweigh the risks.

⁶ Hale T. Medications and Mothers' Milk, 15th Ed, Hale Publishing, 2012.

⁷ de Vries JM, Brugma JD, Ozkan L, Steegers EA, Reuser AJ, van Doorn PA, van der Ploeg AT. First experience with enzyme replacement therapy during pregnancy and lactation in Pompe disease. *Mol Genet Metab.* 2011 Dec;104(4):552-5

Lumizyme is labeled for the serious adverse events of anaphylaxis, hypersensitivity, immune-mediated reactions, and the risk of cardiorespiratory failure. Patients are also at risk of developing anti-alglucosidase alfa antibodies. However, if Lumizyme treatment were discontinued in a nursing mother, she would experience worsening respiratory function and/or muscular function that may affect her ability to care for herself and her infant. The limited information on Lumizyme treatment during lactation does not describe potential risks to the breastfed infant that support a recommendation to discontinue breastfeeding. Lumizyme is present in breastmilk, but it may not be absorbed by the infant and may not be clinically relevant for the infant. Healthcare practitioners should use caution when administering Lumizyme to a nursing woman.

Until more clinical data are available regarding alglucosidase alfa (and maternal anti-alglucosidase alfa antibodies) transfer via breastmilk, PMHS-MHT recommends nursing mothers to wait 24 hours before resuming breastfeeding. During this short period, nursing mothers should pump and discard breastmilk. The infant may be temporarily fed with previously stored breastmilk or formula. This 24-hour pump-and-discard period is feasible because the dosing for Lumizyme is once every two weeks.

CONCLUSIONS

There is limited information available on pregnancy and lactation in Pompe disease patients with Lumizyme treatment. With evidence of harm in animal reproduction studies, the few reports of pregnancy in non-infantile Pompe disease patients do not lend to a clear determination about the risks of Lumizyme treatment over those risks already known from the underlying disease.

The singular case report of alglucosidase alfa enzyme activity levels in breastmilk provides evidence that Lumizyme is present in breastmilk. Therefore, with Lumizyme dosing once every two weeks, a 24-hour period for cessation of breastfeeding after maternal Lumizyme infusion is sufficient and acceptable to minimize exposure to an infant through breastmilk. The potential risks of Lumizyme treatment during lactation have not been demonstrated in the published literature. Healthcare practitioners should exercise caution when administering Lumizyme to a nursing woman.

PMHS-MHT structured the Pregnancy and Nursing Mothers subsections of the Lumizyme labeling in the spirit of the proposed PLLR, while complying with current labeling regulations. PMHS-MHT participated in the team and labeling meetings with DGIEP held between March and July 2014. Final labeling will be negotiated with the Applicant and may not fully reflect changes recommended here.

RECOMMENDATIONS

PMHS-MHT recommends revisions to the Applicant's proposed labeling. These labeling revisions are shown below; deleted text has a strikethrough, while new text is underlined. Labeling recommendations made by the DGIEP Pharmacology/Toxicology Review team, Dr. F. Cai and Dr. D. Joseph are included in this version of the labeling.

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TAMARA N JOHNSON
06/24/2014

JEANINE A BEST
06/24/2014

LYNNE P YAO
06/30/2014



**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research**

Division of Therapeutic Proteins
Office of Biotechnology Products

FINAL LABEL AND LABELING REVIEW

Date: June 23, 2014

Reviewer: Jibril Abdus-Samad, PharmD
Division of Therapeutic Proteins (DTP)

Through: Juhong Liu, PhD

Application: BLA 125291/136

Product: Lumizyme (alglucosidase alfa)

Applicant: Genzyme Corporation

Submission Date(s): January 30, 2014; April 4, 2014; and May 23, 2014

Executive Summary

The prescribing information for Lumizyme (alglucosidase alfa) was reviewed and found not to comply with the following regulations: 21 CFR 201.57(a)(2), 21 CFR 201.57(c)(3)(iv), 21 CFR 201.57(c)(4), and CDER's best labeling practices. The label and labeling submitted on May 23, 2014 is unacceptable and requires revisions.

Background and Summary Description

The Applicant, Genzyme Corporation, submitted this efficacy supplemental BLA in support of updating the Lumizyme indication to include all Pompe patients. The prescribing information was revised to include the safety and efficacy data. There is no change in dosage form and strength, thus no container label or carton labeling was submitted in this supplement.

Materials Reviewed:

Prescribing Information submitted May 23, 2014.

- Highlights
- Dosage and Administration
- Dosage Forms and Strengths
- How Supplied/Storage and Handling

Review:Product Title

The product title does not contain the dosage form (for injection) and route of administration (for intravenous use) per 21 CFR 201.57(a)(2). Additionally, CDER's best labeling practices recommend included all this information on one line.

Section 2.3 - Reconstitution, Dilution, and Administration

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Section 3 - Dosage Forms and Strengths

The partial instructions for product reconstitution that appear

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The correct strength of Lumizyme is 50 mg/vial.

Section 16 - How Supplied/Storage and Handling

Additionally, this section contains the

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**Recommendations for Prescribing Information:**

DTP's recommendations for revising the deficiencies noted above for the Prescribing Information appear below in red color font.

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Conclusions

We recommend revising the Prescribing Information as detailed above to comply with 21 CFR 201.57(a)(2), 21 CFR 201.57(c)(3)(iv), 21 CFR 201.57(c)(4), and CDER's best labeling practices.

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/s/

JIBRIL ABDUS-SAMAD
06/23/2014

JUHONG LIU
06/23/2014

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	June 20, 2014
Requesting Office or Division:	Division of Gastroenterology and Inborn Error Products (DGIEP)
Application Type and Number:	BLA 125291/S-136
Product Name and Strength:	Lumizyme (alglucosidase alfa) Lyophilized powder for solution for intravenous infusion 5 mg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Genzyme Corporation
Submission Date:	January 30, 2014
OSE RCM #:	2014-860
DMEPA Primary Reviewer:	Sherly Abraham, R.Ph.
DMEPA Associate Director:	Lubna Merchant, M.S., Pharm D.

1 REASON FOR REVIEW

This review is in response to a request by DGIEP to review proposed prescribing information (Instructions for Use under Dosage and Administration section) for any areas that may cause medication errors. Genzyme Corporation submitted an efficacy supplement to expand the current indication to all pediatric patients.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews	C
Human Factors Study	D (N/A)
ISMP Newsletters	E
Other	F(N/A)
Labels and Labeling	G(N/A)

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Genzyme Corporation submitted an efficacy supplement to expand the current indication to all pediatric patients. We reviewed proposed prescribing information (Instructions for Use under Dosage and Administration section), and found the proposed changes acceptable. We defer to the Division for the appropriateness of the pediatric dosing information in the label.

Additionally, we did not identify any medication error concerns from our search of the FAERS database, previous DMEPA reviews, and ISMP Newsletters

4 CONCLUSION & RECOMMENDATIONS

The revised PI is acceptable from a medication error perspective and we have no further comments.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Lumizyme that Genzyme Corporation submitted on January 30, 2014.

Table 2. Relevant Product Information for Product Name	
Initial Approval Date	May 24, 2010
Active Ingredient	Alglucosidase alfa
Indication	Treatment of Pompe disease for all patients including pediatrics.
Route of Administration	Intravenous infusion
Dosage Form	Lyophilized powder for solution
Strength	5 mg/mL
Dose and Frequency	20 mg/kg body weight administered every 2 weeks as intravenous infusion
How Supplied	Carton of one single-use vial and carton of ten single-use vials
Storage	Refrigeration between 2° to 8° C (36° to 46° F). The reconstituted and diluted solution should be administered without delay. If immediate use is not possible, the reconstituted and diluted solution is stable for up to 24 hours at 2° to 8° C (36° to 46° F).
Container Closure	The vial closure consists of a (b) (4) butyl stopper and an aluminum seal with a plastic flip-off cap.

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on May 16, 2014, using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter²

² The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

Table 3: FAERS Search Strategy	
Date Range	June 29, 2012 to May 16, 2014. Last FAERS search was on June 29, 2012, for OSE review 2012-1469 (BLA 125291/S-063), dated July 6, 2012.
Product	Lumizyme [product name]
Event (MedDRA Terms)	Medication Errors [HLGT] Product Packaging Issues [HLT] Product Label Issues [HLT] Product Quality Issues (NEC)[HLT]

B.2 Results

Our search identified one case; this case was excluded because it did not describe a medication error.

B.3 List of FAERS Case Numbers

N/A

B.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L: Drive on June 12, 2014, using the term Lumizyme, to identify reviews previously performed by DMEPA.

C.2 Results

DMEPA has reviewed Lumizyme labels and labeling in the following OSE reviews:

2008-1214 for BLA 125291, dated November 14, 2008

2008-1215 for BLA 125291, dated February 13, 2009

2009-1030 for BLA 125291, dated September 9, 2009

2009-2422 for BLA 125291, dated December 29, 2009

2009-2422-1 for BLA 125291, dated March 24, 2010

2012-1469 for BLA 125291, dated July 6, 2012

The FAERS searches performed for these reviews did not retrieve any relevant cases. Finally, all of DMEPA's recommendations from these reviews have been implemented.

APPENDIX E. ISMP NEWSLETTERS

E.1 Methods

We searched the Institute for Safe Medication Practices (ISMP) newsletters on June 13, 2014 using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute care, Community and Nursing
Search Strategy and Terms	Match Exact Word or Phrase: Lumizyme

E.2 Results

No articles associated with medication errors or relevant to labels and labeling were retrieved from the above searches.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHERLY ABRAHAM
06/20/2014

LUBNA A MERCHANT
06/20/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # BLA#	NDA Supplement #:S- BLA Supplement # 125291/136	Efficacy Supplement Type SE-
Proprietary Name: Lumizyme Established/Proper Name: alglucosidase alfa Dosage Form: Lyophilized powder for injection Strengths: 50 mg per vial		
Applicant: Genzyme Corporation Agent for Applicant (if applicable):		
Date of Application: January 30, 2014 Date of Receipt: January 30, 2014 Date clock started after UN:		
PDUFA Goal Date: July 30, 2014		Action Goal Date (if different):
Filing Date: March 31, 2014		Date of Filing Meeting: March 6, 2014
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): 1. Revise the Lumizyme indication to treat all patients with Pompe disease. <div style="margin-left: 40px;"> From: LUMIZYME (alglucosidase alfa) is a lysosomal glycogen-specific enzyme indicated for patients 8 years and older with late (non-infantile) onset Pompe disease (acid α-glucosidase (GAA) deficiency) who do not have evidence of cardiac hypertrophy. The safety and efficacy of LUMIZYME have not been evaluated in controlled clinical trials in infantile-onset patients, or in late (non-infantile) onset patients less than 8 years of age To: LUMIZYME (alglucosidase alfa) is a lysosomal glycogen-specific enzyme indicated for patients with Pompe disease (acid α-glucosidase (GAA) deficiency). </div> 2. Release of the Requirement for the Lumizyme REMS.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<div style="display: flex; flex-direction: column;"> <div> <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) </div> <div> <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) </div> </div>	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		
Type of BLA <i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	<input checked="" type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)	
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.</i>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher submitted	

Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): IND10780 BLA125141				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>				
Are the proprietary, established/proper, and applicant names correct in tracking system?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, ask the document room staff to make the appropriate entries.</i>				
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p> <input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required </p>
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p> <input type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears </p>

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>				
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm </p>				
If yes, please list below:				
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>				
Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (NDAs only)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Exclusivity expired 4/28/2013

Format and Content	
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?	

Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: <input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only) If no, explain.	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input type="checkbox"/>		
<u>Proprietary Name</u>	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<u>REMS</u>	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Sponsor is proposing to remove the REMS requirement with this efficacy supplement.
<u>Prescription Labeling</u>	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide)			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Consults to be submitted by D60.
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	PMHS notified 2/19/2014. Consult in DARRTS 3/11/2014.
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 2/19/2013, 7/3/2013 (WRO)	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 6, 2014

BLA/NDA/Supp #: sBLA 125291/136

PROPRIETARY NAME: Lumizyme

ESTABLISHED/PROPER NAME: alglucosidase alfa

DOSAGE FORM/STRENGTH: Lyophilized powder for injection /50 mg per vial

APPLICANT: Genzyme Corporation

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

1. Revise the Lumizyme indication to treat all patients with Pompe disease.

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

To: LUMIZYME (alglucosidase alfa) is a lysosomal glycogen-specific enzyme indicated for patients with Pompe disease (acid α -glucosidase (GAA) deficiency).

2. Release of the Requirement for the Lumizyme REMS.

BACKGROUND: There are two approved enzyme replacement therapies for Pompe disease in the United States, Myozyme and Lumizyme, both are recombinant alglucosidase alfa. Myozyme is produced on a 160L bioreactor scale and Lumizyme is produced on a 4000L scale. Myozyme was approved in 2006 for Pompe patients of all ages, while Lumizyme was approved in 2010 for juvenile/adult onset Pompe patients 8 years and older. At the time of approval, a REMS was required to mitigate the risk of rapid disease progression in infantile-onset Pompe disease patients and patients with late (non-infantile) onset disease less than 8 years of age, the risk of anaphylaxis and severe allergic reactions, and potential risks of severe cutaneous and systemic immune mediated reactions as listed in the labeling.

Due to drug shortages and manufacturing challenges, Myozyme was restricted to Pompe patients under 12 months of age. As of March 30, 2012, Genzyme stopped shipping Myozyme to patients over 12 months of age and enrolled these patients in the Lumizyme ADVANCE study to continue treatment with Lumizyme. Genzyme is submitting sBLA 125291/136 in support of updating the Lumizyme indication to include all Pompe patients, and proposing to release the REMS requirement for Lumizyme.

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: 125291/136

Application Type: Efficacy Supplement

Name of Drug/Dosage Form: Lumizyme (alglucosidase alfa) intravenous infusion

Applicant: Genzyme Corporation

Receipt Date: January 30, 2014

Goal Date: August 1, 2014

1. Regulatory History and Applicant's Main Proposals

There are two approved enzyme replacement therapies for Pompe disease in the United States, Myozyme and Lumizyme; both are recombinant alglucosidase alfa. Myozyme is produced on a 160L bioreactor scale and Lumizyme is produced on a 4000L scale. Myozyme was approved in 2006 for Pompe patients of all ages, while Lumizyme was approved in 2010 for juvenile/adult onset Pompe patients 8 years and older. At the time of approval, a REMS was required to mitigate the risk of rapid disease progression in infantile-onset Pompe disease patients and patients with late (non-infantile) onset disease less than 8 years of age, the risk of anaphylaxis and severe allergic reactions, and potential risks of severe cutaneous and systemic immune mediated reactions as listed in the labeling.

Due to drug shortages and manufacturing challenges, Myozyme was restricted to Pompe patients under 12 months of age. As of March 30, 2012, Genzyme stopped shipping Myozyme to patients over 12 months of age and enrolled these patients in the Lumizyme ADVANCE study to continue treatment with Lumizyme. Genzyme is submitting sBLA 125291/136 in support of updating the Lumizyme indication to include all Pompe patients, and proposing to release the REMS requirement for Lumizyme.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 60-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by April 21, 2014. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.
- YES** 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).
- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.
- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.
- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.
- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.
- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional

Selected Requirements of Prescribing Information

• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **“HIGHLIGHTS OF PRESCRIBING INFORMATION”**.

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: **“These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).”** The name of drug product should appear in UPPER CASE letters.

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement **“Initial U.S. Approval:”** followed by the **4-digit year**.

Boxed Warning (BW) in Highlights

- YES** 12. All text in the BW must be **bolded**.

- YES** 13. The BW must have a heading in UPPER CASE, containing the word **“WARNING”** (even if more than one warning, the term, **“WARNING”** and not **“WARNINGS”** should be used) and other words to identify the subject of the warning (e.g., **“WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE”**). The BW heading should be centered.

- YES** 14. The BW must always have the verbatim statement **“*See full prescribing information for complete boxed warning.*”** This statement should be centered immediately beneath the heading and appear in *italics*.

- YES** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement **“*See full prescribing information for complete boxed warning.*”**).

Recent Major Changes (RMC) in Highlights

- YES** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

- YES** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date

Selected Requirements of Prescribing Information

(month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Contraindications in Highlights

- N/A** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:
- If a product **does not** have FDA-approved patient labeling:
- “**See 17 for PATIENT COUNSELING INFORMATION**”
- If a product **has** FDA-approved patient labeling:
- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
 - “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
- YES** 26. The following heading must appear at the beginning of the TOC: **“FULL PRESCRIBING INFORMATION: CONTENTS”**. This heading should be in all UPPER CASE letters and **bolded**.
- YES** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[see *Warnings and Precautions (5.2)*]” or “[see *Warnings and Precautions (5.2)*]”.

- NO** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Selected Requirements of Prescribing Information

Comment: Applicant should place vertical lines to Boxed Warning, Indications and Usage, and Warnings and Precautions sections.

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

BOXED WARNING Section in the FPI

- YES** 36. In the BW, all text should be **bolded**.
- YES** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

- YES** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

PATIENT COUNSELING INFORMATION Section in the FPI

- N/A** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

- N/A** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME] (nonproprietary name) dosage form, route of administration, controlled substance symbol]

Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

- [text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELIZABETH A FORD
03/26/2014

BRIAN K STRONGIN
03/26/2014

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Elizabeth Ford	Y
	CPMS/TL:	Brian Strongin	N
Cross-Discipline Team Leader (CDTL)	Jessica Lee		
Clinical	Reviewer:	Juli Tomaino	Y
	TL:	Jessica Lee	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	
	TL:	N/A	

Clinical Pharmacology	Reviewer:	Christine Hon	Y
	TL:	Jie Wang	N
Biostatistics	Reviewer:	Freda Cooner	Y
	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Fang Cai	Y
	TL:	David Joseph	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	Cecilia Tami	Y
	TL:	Daniela Verthelyi (TL) Susan Kirshner (tertiary)	Y
Product Quality (CMC)	Reviewer:	Christopher Downey	Y
	TL:	Juhong Liu	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	N/A	
	TL:	N/A	
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	N/A	
	TL:	N/A	
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:	Kendra Worthy	Y
	TL:	Reema Mehta	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:	N/A	

Bioresearch Monitoring (OSI)	Reviewer:	N/A	
	TL:	N/A	
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers	Alyson Karesh, M.D., PMHS		N
Other attendees	Joyce Korvick, M.D., DDS, DGIEP Chantal Phillips, SRPM, DGIEP		Y

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues: <ul style="list-style-type: none"> Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies): 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? If no, explain: 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments List comments: 	<input type="checkbox"/> Not Applicable
CLINICAL Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? If no, explain: 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<u>Environmental Assessment</u> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? Comments:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Quality Microbiology (for sterile products)</u> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Facility Inspection</u> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? Comments: TB-EER to be submitted by OBP.	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments: CMC reviewer will review CMC labeling.</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<p><input checked="" type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p align="center">REGULATORY PROJECT MANAGEMENT</p>	
<p>Signatory Authority: To be determined</p>	

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): N/A 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input checked="" type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input checked="" type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and

	the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://erom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELIZABETH A FORD
03/19/2014

BRIAN K STRONGIN
03/19/2014

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
BLA 125291/136

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # BLA # 125291	NDA Supplement # BLA Supplement # 136	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Lumizyme Established/Proper Name: alglucosidase alfa Dosage Form: Injectable for intravenous infusion		Applicant: Genzyme Agent for Applicant (if applicable):
RPM: Kevin Bugin		Division: ODEIII/DGIEP
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input checked="" type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <div style="margin-left: 20px;"> <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>) Date of check: </div> <p style="margin-top: 10px;"><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>08/01/2014</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input checked="" type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

NDAs: Subpart H

- ☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)

Subpart I

- ☐ Approval based on animal studies

- ☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- ☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)

Subpart H

- ☐ Approval based on animal studies

- REMS: ☐ MedGuide
☐ Communication Plan
☒ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments: Submission requests REMS Release

❖ BLAs only: Ensure RMS-BLA Product Information Sheet for TBP and RMS-BLA Facility Information Sheet for TBP have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input checked="" type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s) 08/01/2014
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
• Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	<input checked="" type="checkbox"/> Included
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
• Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	<input type="checkbox"/> Included
• Original applicant-proposed labeling	<input type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
• Most-recent draft labeling	<input type="checkbox"/> Included
❖ Proprietary Name	
• Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i>	
• Review(s) <i>(indicate date(s))</i>	
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input checked="" type="checkbox"/> None 03/26/2014 DMEPA: <input checked="" type="checkbox"/> None 06/20/2014 DMPP/PLT (DRISK): <input type="checkbox"/> None OPDP: <input checked="" type="checkbox"/> None 07/16/2014 SEALD: <input type="checkbox"/> None CSS: <input type="checkbox"/> None Other: <input checked="" type="checkbox"/> None DTP: 06/23/2014
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	03/19/2014
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>orphan designation</u> 	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	ROC Minutes 06/04/2014
❖ Minutes of Meetings	
<ul style="list-style-type: none"> If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 07/03/2014 (WRO)
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg
<ul style="list-style-type: none"> Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A
<ul style="list-style-type: none"> Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A
<ul style="list-style-type: none"> Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 08/01/2014
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 07/22/2014
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None
Clinical	
❖ Clinical Reviews	
<ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> Clinical review(s) (<i>indicate date for each review</i>) 	07/24/2014; 07/08/2014; 03/10/2014;
<ul style="list-style-type: none"> Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See Clinical Review: 07/08/2014;
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None 07/23/2014 Peds; 06/30/2014 Maternal;
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A

❖ Risk Management	
<ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	06/16/2014; 08/01/2014; <input type="checkbox"/> None 7/29/14; 07/20/2014;
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested 06/30/2014;
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 07/18/2014; 3/10/14
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 07/08/2014; 03/12/2014;
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
<ul style="list-style-type: none"> ADP/T Review(s) (<i>indicate date for each review</i>) Supervisory Review(s) (<i>indicate date for each review</i>) Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review <input checked="" type="checkbox"/> No separate review <input type="checkbox"/> None 07/08/2014; 03/07/2014;
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 8/1/14; 07/17/14; 07/14/2014; 03/31/2014; 3/26/14
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	07/25/2014;
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input checked="" type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) <i>(original and supplemental BLAs)</i>	Date completed: 08/01/2014; <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁵ i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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/s/

RICHARD W ISHIHARA

08/05/2014

Signing for Kevin Bugin.

From: [Bugin, Kevin](#)
To: jennifer.eaddy@genzyme.com
Cc: [Bugin, Kevin](#)
Subject: sBLA 125291/136 Lumizyme - Final Prescribing Information - July 30, 2014
Date: Wednesday, July 30, 2014 7:11:07 PM
Attachments: [sBLA 125291-136 PI FDA Version Jul 30 REDLINE.docx](#)
[sBLA 125291-136 PI FDA Version Jul 30 CLEAN.docx](#)

Hi Jennifer,

Please refer to your supplemental Biologics License Application (sBLA) submitted on January 30, 2014, under section 351(a) of the Public Health Service Act for Lumizyme.

Attached please find a clean word copy of the Final FDA version of the prescribing information. To facilitate your review, I have also attached the redlined version of the label, with changes from your prior version of labeling (submitted on July 29, 2014, via email) marked with tracked changes. Please use the clean copy of labeling for your final submission.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
P-301-796-2302

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/s/

KEVIN B BUGIN
07/30/2014

From: [Bugin, Kevin](#)
To: jennifer.eaddy@genzyme.com
Cc: [Bugin, Kevin](#)
Subject: sBLA 125291/136 Lumizyme - Advice - July 30, 2014
Date: Wednesday, July 30, 2014 2:49:16 PM

Hi Jennifer,

Please refer to your supplemental Biologics License Application (sBLA) submitted on January 30, 2014, under section 351(a) of the Public Health Service Act for Lumizyme.

We have reviewed your communication plan regarding the Lumizyme label expansion and have the following comments for your consideration.

- 1) We recommend notifying patients, prescribers, and facilities currently enrolled in the ACE Program that they may continue using Lumizyme without taking further actions in the program.
- 2) We recommend specifying in the Myozyme Dear HealthCare Provider letter that Lumizyme is now an approved treatment option for all patients with Pompe disease.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
P-301-796-2302

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KEVIN B BUGIN
07/30/2014

From: [Bugin, Kevin](#)
To: jennifer.eaddy@genzyme.com
Cc: [Bugin, Kevin](#)
Subject: sBLA 125291/136 Lumizyme - Labelling Comments - July 28, 2014
Date: Monday, July 28, 2014 10:52:49 AM

Hi Jennifer,

Please refer to your supplemental Biologics License Application (sBLA) submitted on January 30, 2014, under section 351(a) of the Public Health Service Act for Lumizyme.

We have the following additional comment regarding the prescribing information. We request that you respond to this request no later than July 30, EOD.

- 1) In Table 2, Section 6, the following three terms were combined into one adverse reaction for rash: rash maculo-papular (2 patients), rash macular (2 patients), and rash (4 patients). However, only 7 patients are listed in the combined term, "rash (including rash erythematous, rash macular and maculo-papular)". Please provide your rationale for including 7 patients instead of 8 patients.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
P-301-796-2302

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KEVIN B BUGIN
07/28/2014

From: [Bugin, Kevin](#)
To: jennifer.eaddy@genzyme.com
Cc: [Bugin, Kevin](#)
Subject: sBLA 125291/136 Lumizyme - Labeling Comments - July 24, 2014
Date: Thursday, July 24, 2014 9:02:42 PM
Attachments: [sBLA 125291-136 PI FDA Version Jul 24 Redlined.docx](#)
[sBLA 125291-136 PI FDA Version Jul 24 Clean.docx](#)

Hi Jennifer,

Please refer to your supplemental Biologics License Application (sBLA) submitted on January 30, 2014, under section 351(a) of the Public Health Service Act for Lumizyme.

Attached please find a clean word copy of the revised FDA version of the prescribing information. To facilitate your review, I have also attached the redlined version of the label, with changes from your prior version of labeling (submitted on July 21, 2014) marked with tracked changes. Please use the clean copy of labeling for further revisions and comments.

We have the following focused comments and request regarding the labeling for your review.

- Additionally, while reviewing the Lumizyme label, received on July 21, 2014, and have the following comments on Table 3, in Section 6, of the label. (b) (4)
[REDACTED]
[REDACTED] However, we recommend that Table 3 be revised to include adverse reactions that occurred in at least 3% (2 or more patients) of the Lumizyme-treated patients and with a higher incidence than the placebo group. The 3% incidence rate should not represent the difference in adverse reaction rates between the treated and placebo patients. The revised approach will be consistent with the manner in which the adverse reactions are presented for the infantile-onset patients.

- [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

(b) (4) we recommend including Myozyme (160 L) PK information for the infantile-onset disease patients into the Lumizyme labeling (b) (4)

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

We request that you respond no later than August 30, 2014, EOD. In the spirit of efficiently and amicably resolving the remaining labeling issues prior to the PDUFA goal date, I am currently holding time with the clinical and clinical pharmacology team members on July 29, 2014, from 9:00 to 9:30 AM, ET, for a teleconference discussion. Please confirm that you would like to participate in this teleconference, no later than 2 PM, July 25, 2014.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
P-301-796-2302

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/s/

KEVIN B BUGIN
07/24/2014

From: [Bugin, Kevin](#)
To: jennifer.eaddy@genzyme.com
Cc: [Bugin, Kevin](#)
Subject: sBLA 125291/136 - Labeling Comments (OPDP) - July 17, 2014
Date: Thursday, July 17, 2014 2:09:19 PM
Attachments: [sBLA 125291-136 FDA PI-OPDP Revisions.docx](#)

Hi Jennifer,

Please refer to your supplemental Biologics License Application (sBLA) submitted on January 30, 2014, under section 351(a) of the Public Health Service Act for Lumizyme.

Attached please find a redlined version of the revised FDA prescribing information, which is based on feedback from our Office of Prescription Drug Promotion. Please incorporate these revisions into the labeling you are currently working on from our communication dated July 16, 2014.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
P-301-796-2302

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/s/

KEVIN B BUGIN
07/17/2014

From: [Bugin, Kevin](#)
To: jennifer.eaddy@genzyme.com
Cc: [Bugin, Kevin](#)
Subject: sBLA 125291/136 - Labeling Comments - July 16, 2014
Date: Wednesday, July 16, 2014 12:44:34 PM
Attachments: [sBLA125291-136 Lumizyme PI FDA Version 2 Clean.docx](#)
[sBLA125291-136 Lumizyme PI FDA Version 2 Redlined.docx](#)

Hi Jennifer,

Please refer to your supplemental Biologics License Application (sBLA) submitted on January 30, 2014, under section 351(a) of the Public Health Service Act for Lumizyme.

Attached please find a clean word copy of the revised FDA version of the prescribing information. To facilitate your review, I have also attached the redlined version of the label, with changes from your prior version of labeling (submitted on June 25, 2014) marked with tracked changes. Please use the clean copy of labeling for further revisions and comments, to preserve formatting and ensure no FDA edits are overlooked, as we have identified some issues in the past with the redlined copies.

Given the PDUFA goal date, we request that you respond by July 23, 2014 or earlier.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin B Bugin, MS, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
P-301-796-2302

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/s/

KEVIN B BUGIN
07/16/2014

From: [Bugin, Kevin](#)
To: jennifer.eaddy@genzyme.com
Cc: [Bugin, Kevin](#)
Subject: sBLA 125291/136 Lumizyme - Request for Informatino (Safety) - July 10, 2014
Date: Thursday, July 10, 2014 9:22:31 AM

Hi Jennifer,

Please refer to your supplemental Biologics License Application (sBLA) submitted on January 30, 2014, under section 351(a) of the Public Health Service Act for Lumizyme.

We also refer to the teleconference held on July 07, 2014, where you indicated that Genzyme would be performing certain communication activities to support the expansion of the Lumizyme indication and ensure all eligible patients would understand the new changes. We request that you submit your communication plans for review. We request that you respond to this request no later than July 18, 2014.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
P-301-796-2302

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/s/

KEVIN B BUGIN
07/10/2014

From: [Bugin, Kevin](#)
To: jennifer.eaddy@genzyme.com
Cc: [Bugin, Kevin](#)
Subject: sBLA 125291/136 - Lumizyme - Request for Information (Quality) - June 20, 2014
Date: Friday, June 20, 2014 10:01:00 AM

Hi Jennifer,

Please refer to your supplemental Biologics License Application (sBLA) submitted on January 30, 2014, under section 351(a) of the Public Health Service Act for Lumizyme.

We are reviewing the quality information contained in your sBLA and have the following requests for additional information. We request that you respond to this request no later than June 23, 2014, close of business.

For your analytical comparison of three lots each of 160 L and 4000 L process-scale drug substance, it is not clear which data are from side-by-side assays and which are from independent release and characterization testing. We acknowledge that the proposed battery of side-by-side testing was discussed in the May 6, 2013 meeting briefing and in our July 3, 2013 response, but this information should be provided explicitly in the current supplement. Please provide a table stating which tests you performed side-by-side (i.e. in the same assay or same assay occasion) for the 160 L and 4000 L lots as part of your comparability study. In addition, provide an updated Table 5 for CTD Section 1.11 that either highlights, flags, or otherwise conveys which test results (if any) are from your side-by-side analyses and which are from routine release and characterization testing.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
P-301-796-2302

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/s/

KEVIN B BUGIN
06/20/2014

From: [Bugin, Kevin](#)
To: jennifer.eaddy@genzyme.com
Cc: [Bugin, Kevin](#)
Subject: sBLA 125291/136 - Labeling Comments - June 12, 2014
Date: Thursday, June 12, 2014 4:49:17 PM
Attachments: [sBLA125291-136_Prescribing_Information_FDA_Version_1_12Jun2014_Redline.doc](#)
[sBLA125291-136_Prescribing_Information_FDA_Version_1_12Jun2014_Clean.doc](#)

Hi Jennifer,

Please refer to your supplemental Biologics License Application (sBLA) submitted on January 30, 2014, under section 351(a) of the Public Health Service Act for Lumizyme.

Attached please find a clean word copy of the final FDA version of the prescribing information. To facilitate your review, I have also attached the redlined version of the label, with all changes from your prior version of labeling (submitted on May 23, 2014) marked with tracked changes. Please use the clean copy of labeling for further revisions and comments, to preserve formatting. We request that you respond by June 30, 2014.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
P-301-796-2302

45 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

KEVIN B BUGIN
06/12/2014

From: [Bugin, Kevin](#)
To: jennifer.eaddy@genzyme.com
Cc: [Bugin, Kevin](#)
Subject: sBLA 125291/136 - Request for Information - Safety (REMS) - June 11, 2014
Date: Wednesday, June 11, 2014 9:43:11 AM

Hi Jennifer,

Please refer to your supplemental Biologics License Application (BLA) dated January 30, 2014, submitted under section 351 of the Public Health Service Act for Lumizyme.

We are reviewing your submission and, in accordance with section 505-1(g)(2)(A) of the FDCA, you are required to submit an assessment of the REMS when you submit an efficacy supplement for a new indication for use. Therefore, please provide the additional information listed below in addition to your rationale for your proposal to release the REMS:

- a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
- b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
- c) *If the new indication for use introduces unexpected risks:* A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
- d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* A statement about whether the REMS was meeting its goals at the time of that the last assessment and if any modifications of the REMS have been proposed since that assessment.
- e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
- f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use:* provide the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. If you are not proposing REMS modifications for the new indication of use, provide a rationale for why the REMS does not need to be modified

If you have any questions, please do not hesitate to contact me.

Best,
Kevin

Kevin Bugin, MS, RAC

Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
P-301-796-2302

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/s/

KEVIN B BUGIN
06/11/2014

**REMS Oversight Committee
Minutes of Meeting
June 4, 2014**




Attendance: Doris Auth, Abigail Brandel (OCC), Kevin Bugin, Jason Bunting, Igor Cerny, Chrissy Cochran, Gerald Dal Pan, Kathleen Davies, Nancy Dickinson, Phong Do, Kristen Everett, Liz Everhart, Donna Griebel, LaShawn Griffiths, Nancy Hayes, Michie Hunt, John Jenkins, Alyson Karesh, Mwango Kashoki, Joyce Korvick, Cynthia LaCivita, Jessica Lee, Elaine Lippmann, Claudia Manzo, Reema Mehta, Megan Moncur, Mary Park, Jamie Wilkins Parker, Chantal Phillips, Robert Pratt, Haley Seymour, Gary Slatko, Danielle Smith, Terry Toigo (chairman), Julie Tomaino (presenter)

Purpose: to obtain the ROC's concurrence with DGIEP's and DRISK's plan to grant Lumizyme's sponsor a release from the REMS upon approval of the efficacy supplement currently under review.

Action Items:

- DGIEP will write a memorandum explaining the rationale for the decision to release the REMS.
- DRISK will write a review explaining the rationale for release of the REMS
- DGIEP will work with the press office to develop a communication strategy, including a press release and a set of Q&As to be used at the time when the REMS is released.

Background Materials:

<ul style="list-style-type: none">• Agenda	 Agenda 6-4-2014 ROC Meeting Lumizyr
<ul style="list-style-type: none">• Background Document	 Lumizyme attachment.pdf
<ul style="list-style-type: none">• Presentation, Juli Tomaino	 ROC meeting June 4 Lumizyme sB...

Questions from the Committee

Question 1: Who proposed eliminating the REMS, the sponsor or FDA?

Response: The sponsor proposed eliminating the REMS.

Question 2: Does FDA anticipate that the sponsor will withdraw Myozyme from the US market if the REMS is eliminated?

Response: FDA does not know what the sponsor plans to do, although it is reasonable to expect that it would withdraw Myozyme and market Lumizyme. Outside the US, the sponsor markets Lumizyme under the name, “Myozyme,” so the name under which a unique product would be marketed is unclear as well.

Question 3: What rationale will FDA provide for eliminating a REMS altogether?

Response: The DRISK review will provide the rationale, which is articulated in the presentation.

Question 4: What strategy does the sponsor have for telling patients that they are no longer enrolled in the REMS, once it has been eliminated?

Response: The sponsor will send a communication to the patients outside the REMS to inform them.

Question 5: Does OCC concur with elimination of the REMS?

Response: OCC agrees with elimination of the REMS so long as FDA maintains a paper trail that explains why it is taking this action.

Question 6: Should FDA have an external communication plan ready to use when the Efficacy Supplement is approved and the REMS released?

Response: Yes, FDA should have an external communication plan, including a press release stating that the agency has concluded that all Pompe patients, including infants, can benefit from the Lumizyme product. The press release might stress that FDA wants to make sure that infants do not lose the benefits of Lumizyme, that Lumizyme and Myozyme are physiochemically comparable, thanks to some improvements in the manufacturing process for Lumizyme, and most importantly, that the clinical data indicate that they are equally effective treatments for Pompe disease.

Question to the Committee: Does the Committee concur with DGIEP’s proposal to release Lumizyme’s sponsor from the REMS upon approval of the efficacy supplement

Response: Yes, the committee concurs. However, the ROC emphasized that it is important that DGIEP write a memorandum explaining the rationale for the release and work with the press office to develop a communication plan to use when the efficacy supplement is approved. Because of the history of shortages of Myozyme, the release of the REMS will be important news to the families of infants and children who were affected and thus warrant a press release. It would also be prudent to prepare a set of reactive Questions and Answers to be used as needed if and when FDA receives inquiries about the decision.

From: Bugin Kevin
To: Jennifer Eaddy@qenzyme.com
Cc: Bugin Kevin
Subject: sBLA 125291/136 - Request for Information (Clinical+Clinical Pharmacology+Immunogenicity) - May 08, 2014
Date: Thursday, May 08, 2014 2:18:55 PM

Hi Jennifer,

Please refer to your supplemental Biologics License Application (BLA) dated January 30, 2014, submitted under section 351 of the Public Health Service Act for Lumizyme.

We are reviewing the clinical information contained in your sBLA and have the following requests for information. We request that you provide a response to these requests on or before May 23, 2014, COB. If you are unable to meet this timeline, please let us know.

Clinical

1. (b) (4)
(b) (4) are not well defined and may encompass a wide range of clinical events, including anaphylaxis. Therefore, we recommend that you avoid using the term (b) (4) in the label, and instead, include a description of the adverse reactions and the timing of signs and symptoms (e.g., post-administration reaction characterized by acute hypotension and pulmonary edema). We also recommend that anaphylaxis and hypersensitivity reactions be separated out as distinct events, whenever possible. Refer to the definitions of anaphylaxis described in the Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products, dated February 2013, available at:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM338856.pdf>.
2. In the safety analysis, replace the term (b) (4) with “anaphylaxis” or “hypersensitivity reaction” for the Taiwan01 (full analysis set) and ADVANCE trials, and provide the information listed below.
 - a) Patient identification numbers and the narratives of all patients who experienced anaphylaxis or hypersensitivity reactions, if not previously included in the January 30, 2014 supplemental BLA submission.
 - b) Updated Table 14.3.2.2.1 located on pages 491-493/851 of the AGLU09411 Clinical Study Report.
 - c) Updated Table 11-5 located on page 50/138 of the Taiwan01 Abbreviated Synoptic Clinical Study Report.
3. Provide all available information on patient 10378 from the Taiwan01 trial who experienced bradycardia. Based on the narrative provided in the Taiwan01 Clinical Study Report (page 138/158), it appears that the event of bradycardia may have been related to pneumothorax. However, the narrative contains insufficient details to determine whether the bradycardia was related to pneumothorax or represents a symptom of anaphylaxis, since the timing of the Lumizyme infusion is not included in the narrative.
4. Provide the narrative that describes the events of urticaria for patient 10530 in the Taiwan01 trial. Based on the “ADAE” dataset, this patient experienced urticaria that was deemed not to be an “infusion-associated reaction,” as defined in the protocol. Provide the rationale as to why this event was not characterized as an “infusion-associated reaction” since urticaria could be a symptom of anaphylaxis or hypersensitivity reaction.
5. Since all of the patients from the Taiwan01 trial are CRIM positive, we are requesting additional information on clinical outcomes of CRIM negative, classic infantile-onset patients (onset of symptoms < 6 months of age and evidence of cardiac hypertrophy) who were treated exclusively with Lumizyme (4000 L). Using the Pompe Registry data, please provide the requested information in the following table for CRIM negative, classic infantile-onset patients treated exclusively with commercial Lumizyme (4000 L) since the most recent manufacturing changes to the product.

Table 1: Demographic and clinical characteristics of CRIM negative, classic infantile-onset Pompe patients in the Pompe Registry who were treated exclusively with Lumizyme (4000 L) since [date]

		Infantile-onset, CRIM-negative patients treated exclusively with Lumizyme 4000 L
Number of patients	n (%)	

Male gender	n (%)	
Race		
Asian	n (%)	
Black	n (%)	
Caucasian	n (%)	
Hispanic	n (%)	
Other	n (%)	
Unknown	n (%)	
Age at diagnosis (months)	Mean \pm SD	
	Median (min, max)	
Age at first infusion with Lumizyme (months)	Mean \pm SD	
	Median (min, max)	
Duration of therapy with Lumizyme (years)	Mean \pm SD	
	Median (min, max)	
Number of patients who required invasive-ventilation	n (%)	
Age at first invasive-ventilation	Mean \pm SD	
	Median (min, max)	
Number of deaths	n (%)	
Age at time of death (years)	Mean \pm SD	
	Median (min, max)	

Clinical Pharmacology

6. We noted that in the ADVANCE (AGLU09411) trial, optional pharmacokinetic (PK) sample collections are to be performed at scheduled visits throughout the study treatment period. Clarify how many patients have enrolled in this optional PK study. We request that you provide for our review the available PK data from these patients, including a summary of PK findings, along with the original PK data, PK analysis datasets, and PK parameter datasets. We remind you that the availability of these PK data will impact the labeling of Section 12.3 Pharmacokinetic section as well as the future clinical development program of Lumizyme.

Immunogenicity

7. Table 14.3.4.2.1 of the Abbreviated Clinical Study Report for AGLU09411 study shows that of the 31 patients who were seronegative at baseline, 21 remained seronegative throughout the entire study period. The number of patients who remained seronegative in AGLU09411 study is higher than the number of patients who remained seronegative in the Taiwan01 study (1 out of 18) or the Myozyme (AGLU1602/2403) study (2 out of 18). Please provide an explanation for this observation.
8. In your response to our information request dated March 19th 2014, you provided tabular data on CRIM status, phenotype, dose, and IgG titers over time for patients who participated in Study AGLU09411 (when they switched over to the 4000L product). In order to facilitate our evaluation of the data, we request that you

provide graphical presentations of the data showing antibody formation over time by CRIM status, phenotype and dose. In addition, please provide a table that summarizes IgG titers at baseline and seroconversion over time by CRIM and phenotype statuses.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
P-301-796-2302

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/s/

KEVIN B BUGIN
05/08/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO (Division/Office): Mail: OSE			FROM: Elizabeth Ford/ODE III/DGIEP/301-796-0193	
DATE: 4/28/2014	IND NO.	NDA NO: BLA 125291/136	TYPE OF DOCUMENT: sBLA	DATE OF DOCUMENT: 1/30/2014
NAME OF DRUG Lumizyme		PRIORITY CONSIDERATION Priority	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE: 6/23/2014
NAME OF FIRM: Genzyme				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input checked="" type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH	
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):	
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST	
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS	
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL	
COMMENTS/SPECIAL INSTRUCTIONS: Lumizyme has submitted a sBLA (efficacy supplement) expanding the age range of the current indication to include all patients with Pompe disease, and removal of the REMS. There are multiple labeling changes, including one change to Instructions for use (Section 2.2) to include infusion volumes and rates for younger and lighter weighing patients, and an annual reportable change to How supplied (section 16). This BLA SUPPLEMENT DCC Login ID 60022452 is now available in the EDR. This is an eCTD submission. Select the link to access the .enx file: < http://cberedweb.fda.gov:8080/esp/cberedr.jsp?folderObjId=0bbcaea6813bf95a > DESCRIPTION: Applicant: GENZYME CORPORATION / 1596 Product: ALGLUCOSIDASE ALFA2 Indication: treatment of late-onset Pompe's disease Proprietary Name: LUMIZYME APPLICATION INFORMATION: Application Number: 125291/136 eCTD Sequence Number: 0294 CBER Receipt Date: 30-Jan-2014				
SIGNATURE OF REQUESTER			METHOD OF DELIVERY (Check all that apply) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> DARRTS <input type="checkbox"/> HAND	
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER	

06/18/2013

Reference ID: 3497012

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/s/

ELIZABETH A FORD
04/28/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION **Please send immediately following the Filing/Planning meeting**				
TO: CDER-OPDP-RPM		FROM: (Name/Title, Office/Division/Phone number of requestor) Elizabeth Ford/ODE III/DGIEP/301-796-0193				
REQUEST DATE 4/28/2014	IND NO.	NDA/BLA NO. 125291/136	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)			
NAME OF DRUG Lumizyme	PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE June 23, 2014			
NAME OF FIRM: Genzyme		PDUFA Date: August 1, 2014				
TYPE OF LABEL TO REVIEW						
<table style="width: 100%; border: none;"> <tr> <td style="width: 33%; vertical-align: top;"> TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE (IFU) </td> <td style="width: 33%; vertical-align: top;"> TYPE OF APPLICATION/SUBMISSION <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input checked="" type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION </td> <td style="width: 33%; vertical-align: top;"> REASON FOR LABELING CONSULT <input type="checkbox"/> INITIAL PROPOSED LABELING <input checked="" type="checkbox"/> LABELING REVISION For OSE USE ONLY <input type="checkbox"/> REMS </td> </tr> </table>				TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE (IFU)	TYPE OF APPLICATION/SUBMISSION <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input checked="" type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	REASON FOR LABELING CONSULT <input type="checkbox"/> INITIAL PROPOSED LABELING <input checked="" type="checkbox"/> LABELING REVISION For OSE USE ONLY <input type="checkbox"/> REMS
TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE (IFU)	TYPE OF APPLICATION/SUBMISSION <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input checked="" type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	REASON FOR LABELING CONSULT <input type="checkbox"/> INITIAL PROPOSED LABELING <input checked="" type="checkbox"/> LABELING REVISION For OSE USE ONLY <input type="checkbox"/> REMS				
EDR link to submission: This is an eCTD submission. Select the link to access the .enx file: < http://cberedrweb.fda.gov:8080/esp/cberedr.jsp?folderObjId=0bbcaea6813bf95a >						
<p>Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.</p> <p>OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.</p>						
COMMENTS/SPECIAL INSTRUCTIONS: Mid-Cycle Meeting: May 2, 2014 Labeling Meetings: May 12, 15, 22, 27; June 23, 30 Wrap-Up Meeting: June 26, 2014						
SIGNATURE OF REQUESTER						
SIGNATURE OF RECEIVER		METHOD OF DELIVERY (Check one) <input type="checkbox"/> eMAIL <input type="checkbox"/> HAND				

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/s/

ELIZABETH A FORD

04/28/2014



BLA 125291/136

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Genzyme Corporation
Attention: Jennifer Eaddy
Associate Director, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Ms. Eaddy:

Please refer to your Supplemental Biologics License Application (sBLA) dated January 30, 2014, received January 30, 2014, submitted under section 351 of the Public Health Service Act for Lumizyme (alglucosidase alfa).

We have completed our filing review and have determined that your supplemental application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this supplemental application is considered filed 60 days after the date we received your supplemental application. The review classification for this supplemental application is **Priority**. Therefore, the user fee goal date is August 1, 2014.

We are reviewing your supplemental application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by July 2, 2014.

At this time, we have not identified any potential review issues. Our filing review is only a preliminary review, and deficiencies may be identified during substantive review of your supplement. Following a review of the supplement, we will advise you in writing of any action we have taken and request additional information if needed.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

1. The Highlights section of the package insert (PI) identifies Recent Major Changes (RMCs) to the Boxed Warning, Indications and Usage, and Warnings and Precautions sections of the PI. Amend the PI such that the corresponding new or modified text in the Full Prescribing Information (FPI) sections or subsections are marked with a vertical line on the left edge.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by April 21, 2014. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the biological product for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Elizabeth Ford, Regulatory Project Manager, at (301) 796-0193.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

DONNA J GRIEBEL
03/31/2014



BLA 125291/136

INFORMATION REQUEST

Genzyme Corporation
Attention: Jennifer Eaddy
Associate Director, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Ms. Eaddy:

Please refer to your Supplemental Biologics License Application (sBLA) dated January 30, 2014, received January 30, 2014, submitted under section 351 of the Public Health Service Act for Lumizyme (alglucosidase alfa).

We are reviewing your submission and have the following comments and information requests. We request a response to these requests by April 2, 2014.

1. Submit your rationale for assuming the applicability of foreign data (obtained from Taiwan) to the U.S. population and practice of medicine for infantile-onset patients with Pompe disease.
2. The narrative for Patient 10528 in Section 14.3.3 (Narratives of deaths, serious adverse events and other significant adverse events) of the Abbreviated-Synoptic Clinical Study Report for Taiwan01 study (page 146 of 158) states that a detailed study report is pending. Submit a detailed follow-up narrative report for this patient's death.
3. In "Post-Marketing Tables and Listings" in Module 5.3.6 (Reports of Postmarketing Experience), the number of adverse events is presented without the number of patients. Resubmit the following tables including the number and percentage of patients who experienced the adverse events.
 - a. Table 14.3.1.1: Table of SAEs- Post-Marketing by Phenotype and Overall (Infantile-Onset, Late-Onset, and Unknown-Phenotype)
 - b. Table 14.3.1.2: Table of Adverse Events Resulting in Death- Post-Marketing by Phenotype and Overall (Infantile-Onset, Late-Onset, and Unknown-Phenotype)
 - c. Table 14.3.1.3: Table of Serious IARs- Post-Marketing by Phenotype and Overall (Infantile-Onset, Late-Onset, and Unknown-Phenotype)
4. For Study AGLU09411, provide the Adverse Event Analysis Dataset "adae" that includes the following three additional columns for each patient:
 - a. Phenotype (i.e., infantile-onset or late-onset)

- b. CRIM status
 - c. Genotype and mutational analysis
5. Complete the following table for both infantile-onset and late-onset patients less than 8 years of age who participated in Study AGLU09411. In addition, provide a separate dataset that includes all the variables listed in the following table and was used to complete the requested analysis.

Table 1: Demographic and clinical characteristics of Pompe patients who enrolled in Study AGLU09411

		Infantile-onset, CRIM-negative patients	Infantile-onset, CRIM-positive patients	Late-onset patients, treated at < 8 years of age
Number of patients	n (%)			
Male gender	n (%)			
Age at diagnosis (years)	Mean \pm SD			
	Median (min, max)			
Age at start of 160 L product (years)	Mean \pm SD			
	Median (min, max)			
Age at switch-over to 4000 L product (years)	Mean \pm SD			
	Median (min, max)			
Length of time treated with 4000 L product (months)	Mean \pm SD			
	Median (min, max)			
Length of time treated with 160 L product (months) at switch over to 4000L product				
Number of patients who required invasive ventilation <i>prior to</i> switch	n (%)			
Number of patients who were on invasive ventilation <i>at time of</i> switch-over	n (%)			
Number of patients who required invasive ventilation <i>after</i> switch-over	n (%)			
Number of deaths <i>after</i> switch-over	n (%)			
Age at time of death (years)	Mean \pm SD			
	Median (min, max)			

6. Table 14.3.1.2.2 of the Abbreviated-Synoptic Clinical Study Report for Taiwan01 study summarizes the spontaneous adverse events and IgG anti-rhGAA antibody titers. Provide your rationale for dividing patients based on peak antibody below or above 1600 when

performing this analysis. In addition, present the spontaneous adverse event data stratified by quartiles of peak IgG antibody responses.

7. In the Abbreviated-Synoptic Clinical Study Report for Taiwan01 study, you state that none of the patients from the Taiwan01 study had high sustained IgG antibody titers to alglucosidase alfa (page 53, Section 11.5.1 of the Taiwan01 study report). However, antibody titers for Patient 10381 remained high after seroconversion and increased over time. Similarly, the antibody titers for Patients 10375, 10377, and 10328 increased over time after seroconversion (refer to Listing 16.2.8.2 and Figure 14.3.1 of the report). Provide your definition of “high sustained antibody titers” and your rationale for not classifying antibody responses observed in Patients 10381, 10375, 10377, and 10328 as high sustained responses.
8. The Abbreviated-Synoptic Clinical Study Report for Taiwan01 study provides individual patient data on IgG antibody titers for patients with infantile-onset Pompe disease (Listing 16.2.8.2) as well as a graphical presentation showing antibody formation over time by clinical outcome (Figure 14.3.1). We request that you provide similar tabular and graphical data for patients who participated in Study AGLU09411 (when they switched over to the 4000L product) and for patients who received exclusively the 160L product (AGLU1602/2403 studies). Patients from AGLU1602/2403 studies should be analyzed separately based on their CRIM status. These data will allow a comparison of the immunogenicity profile and clinical outcome between patients receiving the 4000L product and those receiving the 160L product.
9. The Abbreviated-Synoptic Clinical Study Report for Taiwan01 study states that the presence of IgG inhibitory antibodies to rhGAA was tested only if requested by the Genzyme Global Pharmacovigilance and Epidemiology Department as a result of an adverse event (page 15 of the Taiwan01 study report). Three patients (10381, 10529 and 10530) were tested for the presence of IgG inhibitory antibodies to rhGAA. Explain what triggered testing of inhibitory antibodies in these three patients.

If you have questions, call Elizabeth Ford, Regulatory Project Manager, at (301) 796-0193.

Sincerely,

{See appended electronic signature page}

Brian K. Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

BRIAN K STRONGIN
03/19/2014

OSI/DGCPC CONSULT: Request for Clinical Inspections

Date: March 7, 2014

To: Ann Meeker-O'Connell, Acting Division Director, DGCPC
Constance Lewin, M.D., M.P.H, Branch Chief, GCPEB*
Susan Thompson, M.D., Acting Branch Chief, GCPAB
Janice Pohlman, M.D., M.P.H., Team Leader GCPAB
Susan Leibenhaut, M.D. Acting Team Leader, GCPAB
CDER OSI PM Track
Name of DSI Primary Reviewer (if known)
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance/CDER

Through: *Juli Tomaino, MD, DGIEP*
Jessica Lee, MD, DGIEP
Donna J. Griebel, MD, Division Director, Division of Gastroenterology and Inborn Errors Products

From: *Elizabeth Ford, Regulatory Health Project Manager/DGIEP*

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: BLA 125291/136

IND#:

Applicant/ Applicant contact information (to include phone/email): Jennifer Eaddy,
Jennifer.Eaddy@genzyme.com, 617-768-6245

Drug Proprietary Name: Lumizyme

Generic Drug Name: alglucosidase alfa

NME or Original BLA (Yes/No/Not Applicable*): No

Review Priority (Standard or Priority or Not Applicable*): Priority

Study Population includes < 17 years of age (Yes/No): Yes

Is this for Pediatric Exclusivity (Yes/No/Not Applicable*): No

**For inspection requests not connected to a PDUFA timeline (i.e., for-cause when marketing application is not pending for product)*

Proposed New Indication(s): Sponsor proposes to expand the Lumizyme indication to treat all patients with Pompe disease.

From: Lumizyme (alglucosidase alfa) is a lysosomal glycogen-specific enzyme indicated for patients 8 years and older with late (non-infantile) onset Pompe disease (acid α -glucosidase (GAA) deficiency) who do OSI/DGCPC Consult
version: 09/12/2013

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

To: Lumizyme (alglucosidase alfa) is a lysosomal glycogen-specific enzyme indicated for patients with Pompe disease (acid α -glucosidase (GAA) deficiency).

PDUFA: August 1, 2014

Action Goal Date: August 1, 2014

Inspection Summary Goal Date: May 2, 2014

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table (Note: ALL items listed are required, to process inspection request. Failure to provide complete information will result in delay of inspection process).

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication/Primary endpoint and other endpoints for verification
Site study code: Taiwan01 Wuh-Liang Hwu, M.D., Ph.D. Department of Pediatrics and Medical Genetics National Taiwan University Hospital (NTUH) 7 Chung-Shan S. Road, Taipei 100, Taiwan Phone: (886) 2-23123456 ext 71938 Fax: (886) 2-23314518 E-mail: hwuwlntu@nut.edu.tw	Protocol title: "Interim Report of Ongoing Taiwan Investigator-Sponsored Study: A Long-Term Follow-Up of Pompe Disease" (Taiwan01)	25 total patients (18 patients that meet the inclusion criteria for primary efficacy endpoint)	Indication: Treatment of infantile-onset Pompe disease. Primary endpoint: Overall survival and ventilator-free survival

III. Site Selection/Rationale

DGIEP rationale for OSI Audit:

The approval of this application will rely heavily on the ability to establish chemical comparability between Lumizyme (4000 L) and Myozyme (160 L). All efficacy data in this submission were

collected from one foreign site in Taiwan through an investigator-sponsored study and will be primary source of clinical data to support an efficacy claim. The trial was conducted for academic research purposes, not under an IND; however, the study appears to have been conducted under IRB/ethics committee purview. The submission contains domestic data; however, the domestic data will be reviewed primarily for safety.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- ☐ Enrollment of large numbers of study subjects
- ☐ High treatment responders (specify):
- ☐ Significant primary efficacy results pertinent to decision-making
- ☐ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- ☐ Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

- ☒ There are insufficient domestic data
- ☐ Only foreign data are submitted to support an application
- ☐ Domestic and foreign data show conflicting results pertinent to decision-making
- ☐ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- ☒ Other (specify): The data from the ongoing trial in Taiwan are the supportive efficacy data for this submission. The submission contains domestic data; however, the domestic data will be reviewed for safety primarily. Therefore, the data submitted from the investigator-sponsored trial in Taiwan will be primary source of data to support an efficacy claim. In addition, the approval will rely heavily on the ability to establish chemical comparability between Lumizyme (4000 L) and Myozyme (160 L).

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DGCPC.

IV. Tables of Specific Data to be Verified (if applicable)

Please evaluate the general conduct of the trial and verify that the survival data were collected appropriately.

Should you require any additional information, please contact Juli Tomaino, medical officer DGIEP, at 301-796-8812.

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/s/

ELIZABETH A FORD
03/10/2014

JULI A TOMAINO
03/10/2014

JESSICA J LEE
03/10/2014

DONNA J GRIEBEL
03/10/2014



BLA 125291/136

**PRIOR APPROVAL SUPPLEMENT -
ACKNOWLEDGEMENT**

Genzyme Corporation
Attention: Jennifer Eaddy
Associate Director, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Ms. Eaddy:

We have received your Supplemental Biologics License Application (sBLA) submitted under section 351(a)/351(k) of the Public Health Service Act for the following:

BLA SUPPLEMENT NUMBER: 125291/136

PRODUCT NAME: LUMIZYME (alglucosidase alfa)

DATE OF SUBMISSION: JANUARY 30, 2014

DATE OF RECEIPT: JANUARY 30, 2014

This supplemental application proposes the following change(s):

1. Revise the Lumizyme indication to treat all patients with Pompe disease.
From: LUMIZYME (alglucosidase alfa) is a lysosomal glycogen-specific enzyme indicated for patients 8 years and older with late (non-infantile) onset Pompe disease (acid α -glucosidase (GAA) deficiency) who do not have evidence of cardiac hypertrophy. The safety and efficacy of LUMIZYME have not been evaluated in controlled clinical trials in infantile-onset patients, or in late (non-infantile) onset patients less than 8 years of age

To: LUMIZYME (alglucosidase alfa) is a lysosomal glycogen-specific enzyme indicated for patients with Pompe disease (acid α -glucosidase (GAA) deficiency).
2. Release of the Requirement for the Lumizyme REMS.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 31, 2014 in accordance with 21 CFR 601.2(a).

CONTENT OF LABELING

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology and Inborn Errors Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size.

Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

If you have questions, call me, at (301) 796-0193.

Sincerely,

{See appended electronic signature page}

Elizabeth A.S. Ford, R.N.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

ELIZABETH A FORD
02/27/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125291/119

**MEETING REQUEST-
WRITTEN RESPONSES**

Genzyme Corporation
Attention: Jennifer Eaddy
Associate Director, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Ms. Eaddy:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for Lumizyme (alglucosidase alfa).

We also refer to your submission dated May 6, 2013, containing a pre-sBLA meeting request. The purpose of the requested meeting was to discuss the clinical data content and format of a proposed sBLA.

Further reference is made to our Meeting Granted letter dated May 24, 2013, wherein we agreed to provide written responses to your questions in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your May 6, 2013 background package.

If you have any questions, call me at (301) 796-0193.

Sincerely,

{See appended electronic signature page}

Elizabeth A.S. Ford, R.N.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Written Responses



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

WRITTEN RESPONSES

Meeting Type: B
Meeting Category: Pre sBLA

Application Number: 125291/119
Product Name: Lumizyme
Indication: The applicant is proposing expansion of the Lumizyme indication from: Lumizyme is a lysosomal glycogen-specific enzyme indicated for patients 8 years and older with late (non-infantile) onset Pompe disease (acid α -glucosidase (GAA) deficiency) who do not have evidence of cardiac hypertrophy. The safety and efficacy of Lumizyme have not been evaluated in controlled clinical trials in infantile-onset patients, or in late (non-infantile) onset patients less than 8 years of age.

To: Lumizyme is a lysosomal glycogen-specific enzyme indicated for the treatment of patients with a confirmed diagnosis of Pompe disease (acid α -glucosidase (GAA) deficiency).

Sponsor/Applicant Name: Genzyme Corporation
Regulatory Pathway: §351 of the Public Health Service Act

1.0 BACKGROUND

There are two approved enzyme replacement therapies for Pompe disease in the United States. Both are recombinant α -glucosidase alfa (rhGAA): Myozyme is produced on a 160 L bioreactor scale and Lumizyme is produced on a 4000 L scale. The pivotal trial leading to approval of Myozyme (160 L) included 18 patients with infantile-onset Pompe disease and demonstrated markedly improved survival and ventilator-free survival compared to an untreated historical cohort. Lumizyme was approved in 2010 for juvenile/adult onset Pompe patients and approved for treatment in patients over the age of eight years old. Since the approval of Myozyme in 2006 for Pompe patients of all ages, there have been drug shortages and manufacturing challenges. Currently, Myozyme (160 L) is restricted to Pompe patients under 12 months of age. As of March 30, 2012, Genzyme stopped shipping Myozyme 160 L to patients over 12 months of age and enrolled these patients in the ADVANCE study to continue treatment with Lumizyme (4000 L).

Genzyme and FDA met on February 19, 2013, to discuss Genzyme's plans to expand the Lumizyme indication to include patients with infantile-onset Pompe disease as well as patients under the age of 8 with late-onset Pompe disease. On May 6, 2013, Genzyme submitted a

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Written Response

meeting request for written feedback, seeking agreement from the Agency on the overall clinical data content and format for a planned Lumizyme sBLA.

2. QUESTIONS AND RESPONSES

2.1. Regulatory

Question 1: Does the Agency agree that the pathway as proposed by the Agency and the data package as outlined in this submission supports this proposed indication?

FDA Response: In general, we agree with the data package and the proposed pathway discussed during the February 19, 2013 Type C meeting (i.e., determination of analytical comparability between the 160 L and 4000 L products and establishing that the 4000 L product is associated with ventilator-free survival in classic infantile-onset Pompe disease patients in Taiwan). However, we need to review the data before we can agree that the data support the proposed indication. In addition, clarify whether the 4000 L drug product lots used in the Taiwan trial were manufactured using the 4000 L process with (b) (4) to allow assessment of physicochemical comparability.

Question 2: Does the Agency agree that the restricted distribution element of the REMS ETASU is no longer required if the Lumizyme indication is updated for all Pompe patients and the REMS safety surveillance can be transitioned to the annual periodic safety reporting for alglucosidase alfa?

FDA Response: The appropriateness of eliminating or modifying the REMS ETASU will be determined during the review of the sBLA. It is possible that a REMS may continue to be required to ensure appropriate communication of the important risks to patients and prescribers and/or to restrict the use in certain populations due to safety concerns (e.g., CRIM-negative patients). Include in your sBLA submission your request to modify or eliminate the REMS ETASU and justification(s) to support this request. In addition, clarify what components of the “REMS safety surveillance” you are proposing to transition to annual periodic safety reporting.

2.2. CMC

Question 3: Based on the overall data package (both clinical and CMC) as outlined in this proposal: Does the Agency believe that the supplement would qualify as prior approval CMC supplement with supportive clinical data?

FDA Response:

No, we do not agree. The proposed supplement would constitute a prior approval efficacy supplement since it proposes a significant modification to an existing indication, including removal of a limitation to use. A request for approval of a new indication or a modification

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of a previously approved indication should be submitted individually in a separate supplement to an approved original application. Therefore, separate indications or claims should be submitted in separate supplements. Please see *Guidance for Industry – Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees*.

Question 4: Does the FDA agree on the specific lot selection, the assays for the side-by-side analyses, the design of the degradation pathway studies, and the historical data comparison as outlined in the comparability proposal?

FDA Response: We agree with your plan to evaluate 3 lots each of the 160 L and 4000 L (b) (4) products. However, you will need to provide justification for selecting specific lots for your studies.

We recommend that you add the (b) (4) to your side-by-side analyses.

With regard to your proposed degradation pathway study, your previously approved submissions have demonstrated that (1) lots produced at the 160 L and 4000 L (b) (4)

We agree with your proposed historical data comparison of 160 L and 4000 L commercial lots manufactured with (b) (4). Provide a summary comparing available real time/real temperature stability data for 160 L and 4000 L lots (b) (4)

Question 5: Does the Agency agree that the degradation pathway study can be submitted during the review of the supplement if provided in a timely manner?

FDA Response: As stated in response to Question 4, (b) (4) However, if accelerated stability data are not available for the 4000 L scale product with (b) (4)

2.3. Clinical

Question 6: Does the Agency agree with the overall clinical content of the Lumizyme sBLA?

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Written Response

FDA Response: Yes, we agree with the proposed clinical content of the sBLA, which will include (1) a clinical study report and data on the safety and efficacy of alglucosidase alfa (at the larger scales) in patients with infantile-onset Pompe disease treated in Taiwan, (2) a clinical study report and safety data from the ongoing AGLU09411 (ADVANCE) study in infantile-onset patients ≥ 12 months of age who previously received the 160 L product and switched to the 4000 L product, and (3) the post-marketing safety data on all patients treated with the larger scale alglucosidase alfa product (including the scales of all products received and treatment duration).

In addition to the proposed clinical content, provide any available outcome data (if not previously submitted in the AGLU01602 and AGLU02403 study reports) that describe a longer term follow-up of survival beyond 18 months.

Question 7: Does the Agency agree with Genzyme's proposal for the content and planned analyses of the Taiwan data?

FDA Response: In addition to the data you plan to submit, we recommend that you also include available data on patient genotype, CRIM status, enzyme activity level, type and duration of tolerizing regimen, and muscle biopsy results. We recommend that you assess the association between clinical outcome and the CRIM status, antibody response (binding and neutralizing antibody titers), genetic mutations, and enzyme activity level in patients who received the 4000 L product. In addition, we recommend that you assess the impact of anti-drug antibody titers on the safety and efficacy of the 4000 L scale product and compare the results to those of patients who received the 160 L product exclusively (Study AGLU01602 and extension study AGLU02403).

Although we agree with the overall objectives of comparing the proportions of patients who are alive at 18 months of age and of comparing the proportions of subjects who are alive at 18 months of age and free of invasive ventilator support, we cannot agree with your planned analyses until we have reviewed a detailed statistical analysis plan. We recommend that you submit a statistical analysis plan for concurrence prior to submission of the sBLA. The plan must include a detailed description of the Kaplan-Meier methods that will be used to estimate the proportions of overall survival and of ventilator-free survival. The methods must account for staggered entry into the studies and for left-truncated data. For these reasons, the previously submitted graphs and tables of the overall survival results and ventilator-free survival results for Study AGLU01602 will need to be recalculated.

The study report should include a comparison of clinical outcome (i.e., ventilator-free survival and overall survival) between infantile-onset Taiwan patients treated with a larger scale alglucosidase alfa product, patients treated with the 160 L product (from Studies AGLU01602 / AGLU02403), and untreated patients (AGLU00400). Provide two separately labeled analysis datasets that correspond to "patients enrolled set" and "full analysis set"

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Written Response

to distinguish between the infantile-onset Taiwan patients and all patients who were enrolled in the Taiwan study.

Question 8: Does the Agency agree with Genzyme's proposal for the content of the clinical summary of safety and planned analyses? Specifically, does the Agency agree to the 6 months prior to approximate submission data cut-off (30June2013) and the studies proposed for inclusion?

FDA Response: We agree with the proposed content of the clinical summary of safety, which will include the safety data from completed and ongoing studies using the 4000 L product in patients with infantile-onset and late-onset Pompe disease younger than 8 years of age. However, we recommend that you include the following additional analysis:

- In the ADVANCE Study, compare the impact of antibody response (anti-drug antibody titers, inhibitory and neutralizing antibody status) on safety before and after switching from the 160 L to the 4000 L product.

The data cut-off date that is approximately 6 months prior to the sBLA submission appears reasonable. However, you will need to submit a 120-day safety update.

2.4. Submission Content and Format

Question 9: Does the Agency agree with the dataset format proposal as contained in the Electronic Data Submission Planning Template document?

FDA Response: Yes, the proposed content as described in Section 3.4 and in Attachment 2: Electronic Data Submission Plan appears reasonable. From a technical standpoint (not content-related), the proposed format for the planned sBLA is acceptable. However, we have the following additional comments:

- Provide a linked reviewer's guide in module 1.2, as a separate document from the cover letter, to briefly describe where the information can be found throughout the application.
- For archival purposes, submit a PDF file of any word document and include "word" in the leaf title, so that the reviewers can quickly identify the word version of the document.
- Provide the tabular listing in module 5.2 in a tabular format that is linked to the referenced studies in m5.
- Study Tagging Files (STF) are required for submissions to the FDA when providing study information in modules 4 and 5 with the exception of the following modules: 4.3 Literature References, 5.2 Tabular Listing, 5.4 Literature References and 5.3.6 Reports of Postmarketing Experience, if the Periodic Report is a single PDF document (not granular format). Each study should have a separate STF, and all components of each study should be tagged and placed under the study's STF including the case report forms (CRFs).

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Written Response

- Please refer to The eCTD Backbone File Specification for Study Tagging Files 2.6.1 (PDF - 149KB) (6/3/2008) for additional details:
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>
- FDA does not use the module heading 5.3.7 CRFs. Instead, the case report forms should be referenced in the appropriate study's STF, organized by site, tagged as “case report form” and placed with the study's information. Do not use 5.3.7 as a heading element in the index.xml
- When submitting the PADER/PSUR descriptive portion in eCTD format, provide a single PDF file with bookmarks, table of contents and hyperlinks in the eCTD section, module 5.3.6. The leaf title of the report should include the reporting period, since each report covers a specific time period. When the leaf title follows a standard format, the reviewers are able to quickly differentiate one year's report from another.
- Across the pooled analysis datasets, ensure that each subject has a unique patient identifier.
- Ensure that variable names and definitions are consistent across the analysis datasets.

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Further, under the Food and Drug Administration Safety and Innovation ACT (FDASIA), sponsors must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements.

4.0 PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57. In particular, please note the following formatting requirements:

- Each summarized statement in the Highlights (HL) must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.

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- The section headings and subheadings (including title of the Boxed Warning) in the Table of Contents must match the headings and subheadings in the FPI.
- The preferred presentation for cross-references in the in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "[see *Warnings and Precautions (5.2)*]".

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

5.0 MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

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Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELIZABETH A FORD
07/03/2013