

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*

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

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Recommended Dose
- 2.2 Instructions for Use
- 2.3 Reconstitution, Dilution and Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Anaphylaxis and Hypersensitivity Reactions
- 5.2 Immune-Mediated Reactions
- 5.3 Risk of Acute Cardiorespiratory Failure
- 5.4 Risk of Cardiac Arrhythmia and Sudden Cardiac Death during General Anesthesia for Central Venous Catheter Placement
- 5.5 Risk of Antibody Development

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Immunogenicity
- 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

- 7.1 Interference with Other Drugs

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Clinical Trials in Infantile-Onset Pompe Disease
- 14.2 Clinical Trials in Late-Onset Pompe Disease

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

1 **FULL PRESCRIBING INFORMATION**

2 **WARNING: RISK OF ANAPHYLAXIS, HYPERSENSITIVITY AND**
3 **IMMUNE-MEDIATED REACTIONS, AND RISK OF**
4 **CARDIORESPIRATORY FAILURE**

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

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

22 **1 INDICATIONS AND USAGE**

23 LUMIZYME® (alglucosidase alfa) [see *Description (11)*] is a hydrolytic lysosomal glycogen-
24 specific enzyme indicated for patients with Pompe disease (acid α -glucosidase (GAA) deficiency).
25

26 **2 DOSAGE AND ADMINISTRATION**

27 **2.1 Recommended Dose**

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

30 **2.2 Instructions for Use**

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

33 The total volume of infusion is determined by the patient's body weight and should be administered
34 over approximately 4 hours. Infusions should be administered in a step-wise manner using an
35 infusion pump. The initial infusion rate should be no more than 1 mg/kg/hr. The infusion rate may
36 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.

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

$$\text{Patient weight (kg)} \times \text{dose (mg/kg)} = \text{patient dose (in mg)}$$

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.

$$\text{Example: Patient weight (68 kg)} \times \text{dose (20 mg/kg)} = \text{patient dose (1,360 mg)}$$

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).

- b. 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

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

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

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

97

98 **3 DOSAGE FORMS AND STRENGTHS**

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

102

103 **4 CONTRAINDICATIONS**

104 None.

105

106 **5 WARNINGS AND PRECAUTIONS**

107 **5.1 Anaphylaxis and Hypersensitivity Reactions**

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

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

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

128 **5.2 Immune-Mediated Reactions**

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

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

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

147 **5.3 Risk of Acute Cardiorespiratory Failure**

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

157 **5.4 Risk of Cardiac Arrhythmia and Sudden Cardiac Death During General Anesthesia 158 for Central Venous Catheter Placement**

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

166 **5.5 Risk of Antibody Development**

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

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

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

185 **6 ADVERSE REACTIONS**

186 **6.1 Clinical Trials Experience**

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

190
191 The following serious adverse reactions are described below and elsewhere in the labeling:

- 192 • Anaphylaxis and hypersensitivity reactions [see *Warnings and Precautions (5.1)*].

193
194 In clinical trials, the most common adverse reactions ($\geq 5\%$) following alglucosidase alfa treatment
195 were hypersensitivity reactions, and included anaphylaxis, rash, pyrexia, flushing/feeling hot,
196 urticaria, headache, hyperhidrosis, nausea, cough, decreased oxygen saturation, tachycardia,
197 tachypnea, chest discomfort, dizziness, muscle twitching, agitation, cyanosis, erythema,
198 hypertension/increased blood pressure, pallor, rigors, tremor, vomiting, fatigue, and myalgia.

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

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

204
205
206 The most serious adverse reactions reported with alglucosidase alfa treatment included anaphylaxis
207 and acute cardiorespiratory failure.

208
209 The most common adverse reactions requiring intervention in clinical trials were hypersensitivity
210 reactions, occurring in 20 of 39 (51%) patients treated with alglucosidase alfa, and included rash,
211 pyrexia, urticaria, flushing, decreased oxygen saturation, cough, tachypnea, tachycardia,
212 hypertension/increased blood pressure, pallor, rigors, vomiting, cyanosis, agitation, and tremor.
213 These reactions were more likely to occur with higher infusion rates. Some patients who were pre-
214 treated with antihistamines, antipyretics and/or corticosteroids still experienced hypersensitivity
215 reactions.

216
217 *Table 2* summarizes all adverse reactions occurring in $\geq 5\%$ of patients (2 or more patients) treated
218 with alglucosidase alfa in clinical trials described above.

219
220 **Table 2: Adverse Reactions that Occurred in At Least 5% of Infantile-Onset Patients**
221 **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)

222

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

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

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

237

238 **Clinical Trials in Late-Onset Pompe Disease**

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

248

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

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

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

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

262
263 *Table 3* summarizes the most common adverse reactions that occurred in at least 3% of
264 alglucosidase alfa-treated patients and with a higher incidence than the placebo-treated patients
265 during the randomized, double-blind, placebo-controlled study described above.
266

267 **Table 3: Adverse Reactions Occurring in at Least 3% of Alglucosidase Alfa-Treated Late-**
268 **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)

269
270 In clinical trials, anaphylaxis and hypersensitivity reactions were managed with infusion
271 interruption, decreased infusion rate, administration of antihistamines, corticosteroids, intravenous
272 fluids, and/or oxygen, when clinically indicated. In some cases of anaphylactic reactions,
273 epinephrine was administered. Patients who have experienced anaphylaxis or hypersensitivity
274 reactions should be treated with caution when they are re-administered alglucosidase alfa.

275
276 **6.2 Immunogenicity**

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

281
282 In the two clinical trials in infantile-onset patients, the majority of patients (34 of 38; 89%) tested
283 positive for IgG antibodies to alglucosidase alfa. There is evidence to suggest that some patients
284 who develop high sustained titers of anti-alglucosidase alfa antibodies may experience reduced
285 clinical efficacy to alglucosidase alfa treatment [*see Warnings and Precautions (5.5)*]. Some IgG-
286 positive patients in clinical trials who were retrospectively evaluated for the presence of inhibitory
287 antibodies tested positive for inhibition of enzyme activity and/or uptake in *in vitro* assays.
288 Furthermore, CRIM-negative infants have shown reduced clinical effect in the presence of high
289 sustained IgG antibody titers with inhibitory activity. Alglucosidase alfa-treated patients who

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

292
293 In the randomized, double-blind, placebo-controlled trial in late-onset patients, all alglucosidase
294 alfa-treated patients with available samples (N=59, 100%) developed IgG antibodies to
295 alglucosidase alfa. Most patients who developed IgG antibodies did so within the first 3 months of
296 exposure (median time to seroconversion was 4 weeks). There was no apparent association
297 between mean or peak IgG antibody titers and the occurrence of adverse reactions.

298
299 None of the 59 evaluable patients tested positive for inhibition of enzyme activity. Antibody titers
300 for cellular uptake inhibition were present in 18 of 59 (31%) patients by Week 78. All other
301 patients tested negative for inhibition of cellular uptake. Patients who tested positive for uptake
302 inhibition tended to have higher IgG titers than patients who tested negative for uptake inhibition.
303 Among the 32 patients with evaluable pharmacokinetic (PK) samples, 5 patients tested positive for
304 uptake inhibition. The clinical relevance of this *in vitro* inhibition is not fully understood. The
305 clearance values for 4 of these 5 patients were approximately 1.2- to 1.8-fold greater in the presence
306 of inhibitory antibodies (Week 52) as compared to in the absence of inhibitory antibodies (Week 0)
307 [see *Clinical Pharmacology (12.3)*].

308
309 Some patients in the clinical studies or in the postmarketing setting have undergone testing for
310 alglucosidase alfa-specific IgE antibodies. Testing was performed in patients who experienced
311 moderate to severe or recurrent hypersensitivity reactions, for which mast-cell activation was
312 suspected. Some of the patients who tested positive for alglucosidase alfa-specific IgE antibodies
313 experienced anaphylactic reactions [see *Boxed Warning and Warnings and Precautions (5.1)*].

314
315 Some patients who tested positive for alglucosidase alfa-specific IgE antibodies and experienced
316 hypersensitivity reactions were able to be rechallenged with alglucosidase alfa using a slower
317 infusion rate at lower starting doses and have continued to receive treatment under close clinical
318 supervision [see *Warnings and Precautions (5.1)*]. Since patients who develop IgE antibodies to
319 alglucosidase alfa appear to be at a higher risk for developing anaphylaxis and hypersensitivity
320 reactions, these patients should be monitored more closely during administration of alglucosidase
321 alfa.

322
323 The detection of antibody formation is highly dependent on the sensitivity and specificity of the
324 assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity
325 in an assay may be influenced by several factors including assay methodology, sample handling,
326 timing of sample collection, concomitant medications, and underlying disease. For these reasons,
327 comparison of the incidence of antibodies to alglucosidase alfa with the incidence of antibodies to
328 other products may be misleading.

329

330 **6.3 Postmarketing Experience**

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

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

339
340 Recurrent reactions consisting of flu-like illness or a combination of events such as pyrexia, chills,
341 myalgia, arthralgia, pain, or fatigue occurring after completion of infusions and lasting usually for 1
342 - 3 days have been observed in some patients treated with alglucosidase alfa. The majority of
343 patients were able to be rechallenged with alglucosidase alfa using lower doses and/or pretreatment
344 with anti-inflammatory drugs and/or corticosteroids and were able to continue treatment under close
345 clinical supervision.

346
347 In addition to the hypersensitivity reactions reported in clinical trials [see *Adverse Reactions*
348 *(6.1)*], the following hypersensitivity reactions have been reported in at least 2 patients and
349 included: anaphylactic shock, respiratory failure, respiratory arrest, cardiac arrest, hypoxia,
350 dyspnea, wheezing, convulsions, peripheral coldness, restlessness, nervousness, back pain, stridor,
351 pharyngeal edema, abdominal pain, apnea, muscle spasm, and conjunctivitis. In addition, one case
352 of hyperparathyroidism has been reported.

353
354 Systemic and cutaneous immune-mediated reactions, including proteinuria and nephrotic syndrome
355 secondary to membranous glomerulonephritis, and necrotizing skin lesions have been reported in
356 postmarketing safety experience with alglucosidase alfa [see *Warnings and Precautions (5.2)*].
357

358 **7 DRUG INTERACTIONS**

359 **7.1 Interference with Other Drugs**

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

361

362 **8 USE IN SPECIFIC POPULATIONS**

363 **8.1 Pregnancy**

364 **Pregnancy Category C**

365 There is a registry for Pompe disease patients that monitors the outcomes of women and their
366 offspring exposed to alglucosidase alfa during pregnancy. Patients or their physicians should call
367 1-800-745-4447 or visit www.pomperegistry.com to enroll [see *Patient Counseling Information*
368 *(17)*].

369

370 Risk Summary

371 There are no studies of alglucosidase alfa in pregnant women. In animal reproduction studies, no
372 effects on embryo-fetal development were observed in mice or rabbits given daily administration of
373 alglucosidase alfa up to 0.4 or 0.5 times the human steady-state AUC (area under the plasma
374 concentration-time curve), respectively, at the recommended human bi-weekly dose during the
375 period of organogenesis. An increase in pup mortality was observed when alglucosidase alfa was
376 administered every other day in mice during the period of organogenesis through lactation at a dose
377 0.4 times the human steady-state AUC at the recommended human bi-weekly dose. Alglucosidase

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

380

381 Animal Data

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

391

392 **8.3 Nursing Mothers**

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

399

400 **8.4 Pediatric Use**

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

403

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

407

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

411

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

416

417 **8.5 Geriatric Use**

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

421

422 **11 DESCRIPTION**

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

428
429 Alglucosidase alfa is a glycoprotein with a calculated mass of 99,377 daltons for the polypeptide
430 chain, and a total mass of approximately 109,000 daltons, including carbohydrates. Alglucosidase
431 alfa has a specific activity of 3.6 to 5.4 units/mg (one unit is defined as that amount of activity that
432 results in the hydrolysis of 1 micromole of synthetic substrate per minute under specified assay
433 conditions). Alglucosidase alfa is intended for intravenous infusion. It is supplied as a sterile,
434 nonpyrogenic, white to off-white, lyophilized cake or powder for reconstitution with 10.3 mL
435 Sterile Water for Injection, USP. Each 50 mg vial contains 52.5 mg alglucosidase alfa, 210 mg
436 mannitol, 0.5 mg polysorbate 80, 9.9 mg sodium phosphate dibasic heptahydrate, 31.2 mg sodium
437 phosphate monobasic monohydrate. Following reconstitution as directed, each vial contains 10.5
438 mL reconstituted solution and a total extractable volume of 10 mL at 5 mg/mL alglucosidase alfa.
439 Alglucosidase alfa does not contain preservatives; each vial is for single use only.

440
441 **12 CLINICAL PHARMACOLOGY**

442 **12.1 Mechanism of Action**

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

446
447 Alglucosidase alfa provides an exogenous source of GAA. Binding to mannose-6-phosphate
448 receptors on the cell surface has been shown to occur via carbohydrate groups on the GAA
449 molecule, after which it is internalized and transported into lysosomes, where it undergoes
450 proteolytic cleavage that results in increased enzymatic activity. It then exerts enzymatic activity in
451 cleaving glycogen.

452
453 **12.2 Pharmacodynamics**

454 Clinical pharmacodynamic studies have not been conducted for alglucosidase alfa.

455
456 **12.3 Pharmacokinetics**

457
458 The pharmacokinetics of alglucosidase alfa were evaluated in 13 patients with infantile-onset
459 Pompe disease, aged 1 month to 7 months, who received 20 mg/kg (approximately as a 4-hour
460 infusion) or 40 mg/kg (approximately as a 6.5-hour infusion) of alglucosidase alfa every 2 weeks.
461 The measurement of alglucosidase alfa plasma concentration was based on an activity assay using
462 an artificial substrate. Systemic exposure was approximately dose proportional between the 20 and
463 40 mg/kg doses. Based on the pharmacokinetic blood samples collected for 12 hours after a 4-hour
464 intravenous infusion of 20 mg/kg (n=5), the estimated mean AUC was 811 mcg•hr/mL with 17%

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

467
468 The pharmacokinetics of alglucosidase alfa were also evaluated in a separate trial of 14 patients
469 with infantile-onset Pompe disease, aged 6 months to 3.5 years, who received 20 mg/kg of
470 alglucosidase alfa as a 4-hour infusion every 2 weeks. The pharmacokinetic parameters were
471 similar to those observed for the infantile-onset Pompe disease patients aged 1 month to 7 months
472 who received the 20 mg/kg dose.

473
474 Nineteen of 21 patients who received treatment with alglucosidase alfa and had pharmacokinetics
475 and antibody titer data available at Week 12 developed antibodies to alglucosidase alfa. Five
476 patients with antibody titers $\geq 12,800$ at Week 12 had an average increase in clearance of 50%
477 (range 5% to 90%) from Week 1 to Week 12. The other 14 patients with antibody titers $< 12,800$ at
478 Week 12 had similar average clearance values at Week 1 and Week 12.

479

480 **13 NONCLINICAL TOXICOLOGY**

481 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

484

485 Intravenous administration of alglucosidase alfa every other day in mice at doses up to 40 mg/kg
486 (0.4 times the human AUC at the recommended bi-weekly dose) had no effect on fertility and
487 reproductive performance.

488

489 **14 CLINICAL STUDIES**

490 **14.1 Clinical Trials in Infantile-Onset Pompe Disease**

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

493

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

501

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

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

511
512 Other outcome measures in this study included unblinded assessments of motor function by the
513 Alberta Infant Motor Scale (AIMS), a measure of infant motor performance that assesses motor
514 maturation of the infant through age 18 months. Although gains in motor function were noted in 13
515 patients, the motor function was substantially delayed compared to normal infants of comparable
516 age in the majority of patients. Two of 9 patients who had initially demonstrated gains in motor
517 function after 12 months of alglucosidase alfa treatment regressed despite continued treatment.

518
519 Changes from baseline to Month 12 in left ventricular mass index (LVMI), a measure of
520 pharmacodynamic effect, were evaluated by echocardiography. Fifteen patients who underwent
521 both baseline and Month 12 echocardiograms demonstrated decreases from baseline in LVMI
522 (mean decrease 118 g/m², range 45 to 193 g/m²). However, the magnitude of the decrease in LVMI
523 did not correlate with the clinical outcome measure of ventilator-free survival.

524
525 Study 2 was an international, multicenter, non-randomized, open-label clinical trial that enrolled 21
526 infantile-onset patients aged 3 months to 3.5 years at first infusion. Eighteen patients were CRIM-
527 positive and 3 patients were CRIM-negative. All patients received 20 mg/kg alglucosidase alfa
528 every other week for up to 104 weeks. Five of 21 patients were receiving invasive ventilatory
529 support at the time of first infusion.

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

536 Study 3 was an open-label, single-center trial in 18 infantile-onset Pompe disease patients who had
537 a confirmed diagnosis of Pompe disease as identified through a newborn screening program. All
538 patients were CRIM-positive. Patients were treated with alglucosidase alfa prior to 6 months of age
539 (0.2 to 5.8 months at first infusion). Sixteen patients reached 18 months of age at the time of
540 analysis, and all (100%) were alive without invasive ventilator support.

541 542 **14.2 Clinical Trials in Late-Onset Pompe Disease**

543 The safety and efficacy of alglucosidase alfa were assessed in 90 patients with late-onset Pompe
544 disease, aged 10 to 70 years, in a randomized, double-blind, placebo-controlled trial. The youngest
545 alglucosidase alfa-treated patient was 16 years of age, and the youngest placebo-treated patient was
546 10 years of age. All patients were naïve to enzyme replacement therapy. Patients were allocated in
547 a 2:1 ratio and received 20 mg/kg alglucosidase alfa (n=60) or placebo (n=30) every other week for
548 78 weeks (18 months). The study population included 34 males and 26 females (n=60) in the
549 alglucosidase alfa group and 11 males and 19 females (n=30) in the placebo group. At baseline, all
550 patients were ambulatory (some required assistive walking devices), did not require invasive
551 ventilator support or non-invasive ventilation while awake and sitting upright, and had a forced
552 vital capacity (FVC) between 30 and 79% of predicted in the sitting position. Patients who could
553 not walk 40 meters in 6 minutes or were unable to perform appropriate pulmonary and muscle
554 function testing were excluded from the study.

555

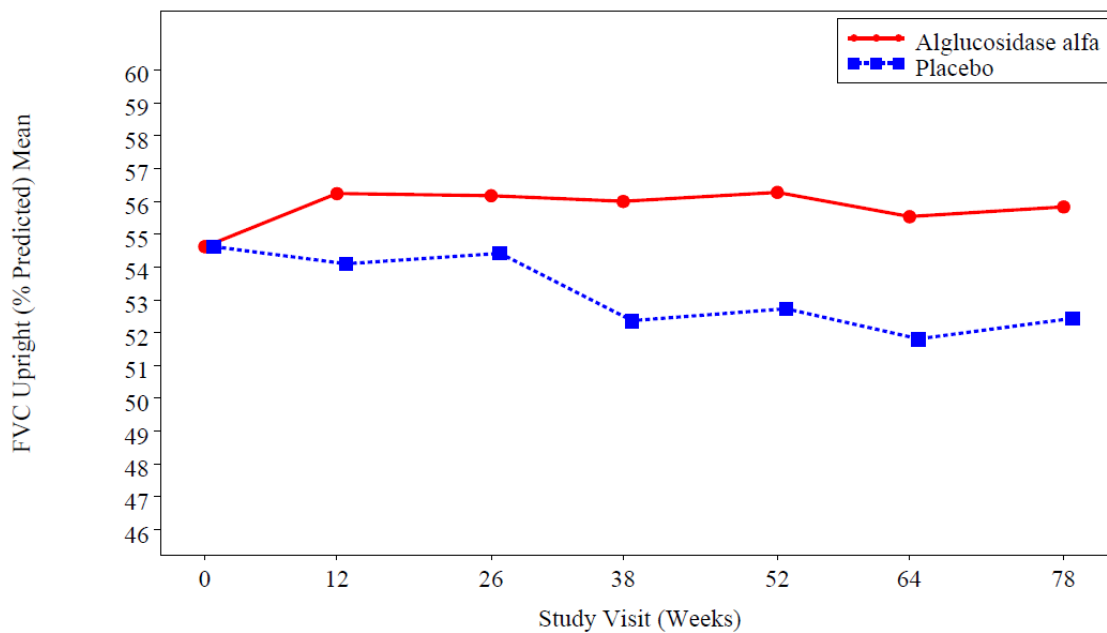
556 A total of 81 of 90 patients completed the trial. Of the 9 patients who discontinued, 5 were in the
557 alglucosidase alfa group and 4 were in the placebo group. Three patients discontinued the study
558 due to an adverse event, two patients were in the alglucosidase alfa treatment group and one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

560

561 At study entry, the mean % predicted FVC in the sitting position among all patients was about
562 55%. After 78 weeks, the mean % predicted FVC increased to 56.2% for alglucosidase alfa-treated
563 patients and decreased to 52.8% for placebo-treated patients indicating an alglucosidase alfa
564 treatment effect of 3.4% (95% confidence interval: [1.3% to 5.5%]; p=0.004). Stabilization of %
565 predicted FVC in the alglucosidase alfa-treated patients was observed (*see Figure 1*).
566

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

568



569

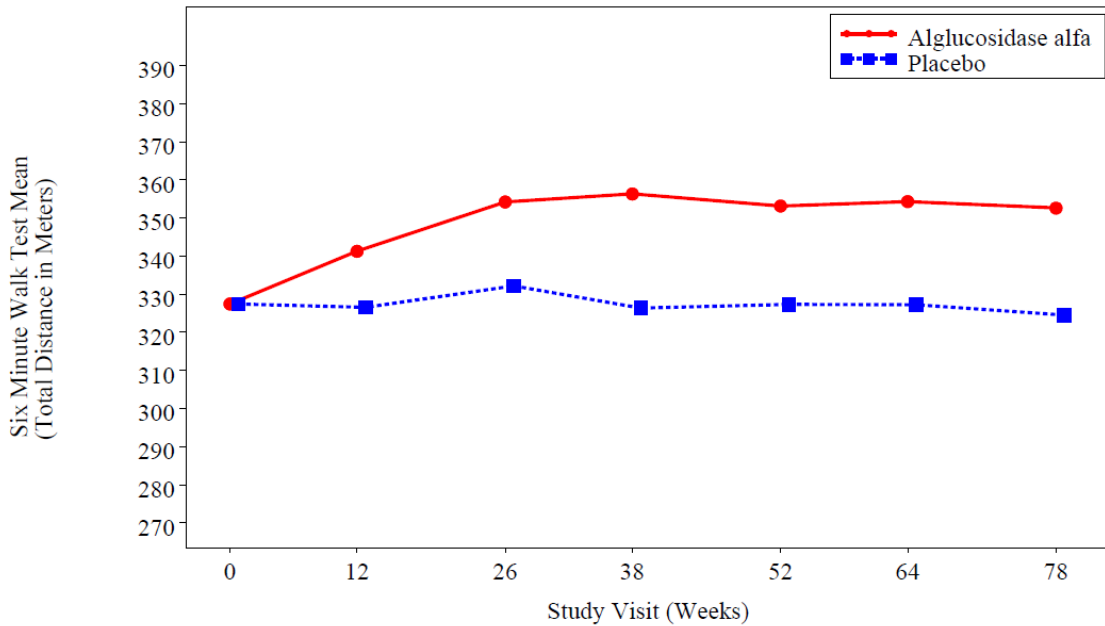
Note: ANCOVA least squares means adjusting for baseline values

570

571 At study entry, the mean 6 minute walk test (6MWT) among all patients was about 330 meters.
572 After 78 weeks, the mean 6MWT increased by 25 meters for alglucosidase alfa-treated patients and
573 decreased by 3 meters for placebo-treated patients indicating an alglucosidase alfa treatment effect
574 of 28 meters (95% confidence interval: [-1 to 52 meters]; p=0.06) (*see Figure 2*).
575

576

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



578 Note: ANCOVA least squares means adjusting for baseline values

579

580 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

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

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

585

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

588

589 **17 PATIENT COUNSELING INFORMATION**

590 Anaphylaxis, Hypersensitivity and Immune-Mediated Reactions

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

598

599 Risk of Acute Cardiorespiratory Failure

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

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

604

605 Pompe Registry

606 Inform patients and their caregivers that the Pompe Registry has been established in order to better
607 understand the variability and progression of Pompe disease, and to continue to monitor and
608 evaluate long-term treatment effects of alglucosidase alfa. The Pompe Registry will also monitor
609 the effect of alglucosidase alfa on pregnant women and their offspring [*see Use in Specific*
610 *Populations (8)*]. Patients and their caregivers should be encouraged to participate in the Pompe
611 Registry and advised that their participation is voluntary and may involve long-term follow-up. For
612 more information regarding the registry program, visit www.pomperegistry.com or call 1-800-745-
613 4447.

614

615 LUMIZYME is manufactured and distributed by:

616 Genzyme Corporation

617 500 Kendall Street

618 Cambridge, MA 02142

619 1-800-745-4447 (phone)

620

621 US License Number: 1596

622 LUMIZYME and GENZYME are registered trademarks of Genzyme Corporation.