Policy Number	**RX501.189**
Policy Effective Date	**7/21/2026**

Enzyme Replacement Therapy for Pompe Disease

Table of Contents

Related Policies (if applicable)
RX501.067 Enzyme Replacement Therapy for lysosomal storage disorders (excluding Gaucher and Pompe Disease)
RX501.190 Enzyme Replacement Therapy for Gaucher Disease

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of care developed by: nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

Enzyme replacement therapy when utilized for the treatment of Pompe disease **may be considered medically necessary** for the specific indications noted under each of the following enzyme-replacements therapies:

Product	Criteria For Use
Avalglucosidase alfa-ngpt (Nexviazyme®)	Avalglucosidase alfa-ngpt (Nexviazyme®) **may be considered medically necessary** for the treatment of individuals 1 year of age and older with a diagnosis of late-onset Pompe disease (lysosomal acid alpha-glucosidase [GAA] deficiency). Avalglucosidase alfa-ngpt (Nexviazyme®) **is considered experimental, investigational, and/or unproven** for all other non-Food and Drug Administration (FDA) approved indications.
Alglucosidase alfa (Lumizyme®; formerly known as Myozyme)	Alglucosidase alfa (Lumizyme®, formerly known as Myozyme) **may be considered medically necessary** for individuals with Pompe disease (GAA deficiency). Alglucosidase alfa (Lumizyme®; formerly known as Myozyme) **is considered experimental, investigational, and/or unproven** for the treatment of all other non-FDA approved indications.
Cipaglucosidase alfa-atga (Pombiliti™)	Cipaglucosidase alfa-atga (Pombiliti™) **may be considered medically necessary** for the treatment of late-onset Pompe disease when **ALL** the following criteria are met: • Individual is 18 years of age or older; and • Individual weighs greater than or equal to 40 kg; and • Will be taken in combination with Opfolda; and • Individual is not improving on current enzyme replacement therapy (ERT). Cipaglucosidase alfa-atga (Pombiliti™) **is considered experimental, investigational, and/or unproven** for all other non-FDA approved indications.

Policy Guidelines

None.

Description

Lysosomal storage disorders are a group of inherited metabolic diseases that are characterized by the accumulation of waste products in the body's cells due to an enzyme deficiency. There are more than 70 lysosomal disorders and additional disorders continue to be identified. These individual

disorders are rare inborn errors of metabolism, which results in the absence or deficiency of an enzyme which causes cellular deficiency. LSDs affect different parts of the body, including but not limited to the skeleton, brain, skin, heart, and central nervous system. As a group, lysosomal storage diseases are believed to have an estimated frequency of about 1 in 40,000-60,000. Although individual diseases are rare, the group together affects many people globally. (4, 5)

There is no cure for lysosomal storage disorders; however, enzyme-replacement therapy can greatly improve the quality of life in select patients. The decision to start enzyme-replacement therapy is based on the patient's symptoms or deterioration in each affected patient. (4, 5)

Pompe Disease (acid alpa-glucosidase [GAA] deficiency, acid maltase deficiency [AMD], or Glycogen Storage Disease Type II)

Pompe disease is considered a lysosomal storage disease. Pompe disease is a rare, inherited autosomal recessive trait that is characterized by a mutation in the gene that makes an enzyme called acid alpha-glucosidase (GAA). The GAA enzyme is required to metabolize the complex carbohydrate glycogen and convert it into simple glucose. Failure to properly break down glycogen results in accumulation of lysosomal glycogen in cells throughout the body, particularly in cardiac, smooth, and skeletal muscle cells. The onset of Pompe disease varies from birth to adulthood, and it progresses rapidly with greater disease severity. There are 2 relatively distinct clinical forms of Pompe disease which include (6, 7):

- Early onset (Infantile) Pompe disease: This disease is a result of a complete or near complete deficiency of GAA and typically occurs within the first few months of life. Symptoms may include but are not limited to hypertrophic cardiomyopathy, hepatomegaly due to heart failure, weakness of skeletal muscle (especially proximal muscles), and progressive diaphragm weakness resulting in respiratory difficulties. Patients with this form of Pompe disease are the most severely affected. Infants may present with feeding difficulties due to an enlarged tongue. Infants typically do not meet or have a severe delay in meeting developmental milestones. Without treatment, progressive cardiac and respiratory failure usually causes life-threatening complications within the first year of life.
- Late-onset Pompe disease (also known as juvenile/adult Pompe disease): This disease is a result of a partial deficiency of GAA and can be present at any age. The extent of organ involvement varies among affected individuals. Symptoms include progressive muscle weakness mainly involving the shoulders and hips, progressive diaphragm weakness leading to respiratory failure, difficulty with balance, swallowing difficulties, and ptosis. Late-onset Pompe disease typically does not involve cardiac problems. Initial symptoms of late-onset Pompe disease may be subtle and may go unrecognized for years. Typically, the later the onset, the slower the progression of the disease.

Regulatory Status

The following enzyme-replacement therapies are U.S. Food and Drug Administration (FDA) approved for the treatment of specific Lysosomal Storage Disorders:

- Avalglucosidase alfa-ngpt (Nexviazyme®) was U.S. FDA approved in 2021 for the treatment of individuals 1 year of age and older with late-onset Pompe disease (lysosomal acid alpha-glucosidase [GAA] deficiency). The safety and effectiveness of Nexviazyme® has not been established in pediatric patients less than 1 year of age. (1)
- Alglucosidase alfa (Lumizyme®; formerly known as Myozyme) was approved in 2010 by the U.S. FDA for the use in individuals 8 years of age and older with late-onset Pompe disease that has

not shown evidence of cardiac hypertrophy. In August 2014, the U.S. FDA label was modified to state that alglucosidase alfa is indicated for all individuals with Pompe disease. The restrictions on age and cardiac hypertrophy were removed. The FDA also reviewed available information and determined that Lumizyme and Myozyme are chemically and biochemically comparable; therefore, the safety and effectiveness of Lumizyme and Myozyme are expected to be comparable. (2, 8)

- Cipaglucosidase alfa-atga (Pombiliti™) was approved in September 2023 by the U.S. FDA when used in combination with Opfolda, an enzyme stabilizer, for the treatment of adults with late-onset Pompe disease (lysosomal acid alpha-glucosidase [GAA] deficiency) in individuals weighing ≥40 kg who are not improving on their current enzyme replacement therapy (ERT). Per the FDA label, the safety and effectiveness of Pombiliti in combination with Opfolda has not been established in pediatric patients with late-onset Pompe disease. (3)

NOTE 1: Per the FDA labels, when receiving ERT, individuals should be monitored closely for hypersensitivity reactions, including anaphylaxis. Appropriate medical monitoring and support measures, including cardiopulmonary resuscitation equipment, should be readily available when ERT is administered. Please refer to the U.S. FDA label for precautions for each individual ERT therapy.

Rationale

This policy is based on the U.S. Food and Drug Administration (FDA) labeled indications for enzyme replacement therapy for Pompe disease.

Avalglucosidase alfa-ngpt (Nexviazyme®)

Late-Onset Pompe Disease

Study 1 (NCT02782741) was a randomized, double-blinded, multinational, multicenter trial comparing the efficacy and safety of Nexviazyme to alglucosidase alfa in treatment-naive patients with late-onset Pompe disease. One hundred patients (51 in Nexviazyme and 49 in alglucosidase alfa) were randomized in a 1:1 ratio based on baseline forced vital capacity ([FVC] % predicted; <55% or ≥55%), sex, age (<18 years or ≥18 years), and country (Japan or not-Japan) to receive 20 mg/kg of Nexviazyme or alglucosidase alfa administered intravenously (IV) once every two weeks for 49 weeks. After 49 weeks, all randomized patients in Study 1 had the option to enter an open-label extension treatment period to receive Nexviazyme and continue treatment up to at least Week 145. (1)

Demographic and Disease Characteristics

Of the 100 randomized patients, 52 were males, the baseline median age was 49 years old (range from 16 to 78), median baseline weight was 76.4 kg (range from 38 to 139 kg), median length of time since diagnosis was 6.9 months (range from 0.3 to 328.4 months), mean age at diagnosis was 46.4 years old (range from 11 to 78), mean FVC (% predicted) at baseline was 62.1% (range from 32 to 85%), and mean 6 Minute Walk Test (6-MWT) at baseline was 388.9 meters (range from 118 to 630 meters). The racial groups for the patients consisted of 94 White (94%), 3 Black or African American (3%), and 3 Asian (3%). Fifteen patients were Hispanic/Latino (15%), 76 non-Hispanic/Latino (76%) and 9 were not reported. Five patients (all in the alglucosidase alfa arm) discontinued the study prior to Week 49: four due to adverse events (acute myocardial infarction, arthritis, dyspnea, and

urticaria), and one due to withdrawal of consent. All 95 patients who did not discontinue the study prior to Week 49 entered the open-label period (51 from the Nexviazyme arm and 44 from the alglucosidase alfa arm). Of the 95 patients, 77 patients had follow-up data on FVC (% predicted) at Week 145 (44 from the Nexviazyme arm and 33 from the alglucosidase alfa arm) and 80 patients had follow-up data on 6-MWT at Week 145 (45 from the Nexviazyme arm and 35 from the alglucosidase alfa arm). Fourteen (14%) patients (7 in each group) discontinued treatment during the extension treatment period (5 for adverse events, 1 for poor compliance to protocol and 8 for other reasons).

Primary Efficacy Results from the 49-Week Active-Controlled Period and Open-Label Period up to Week 145 in Study 1

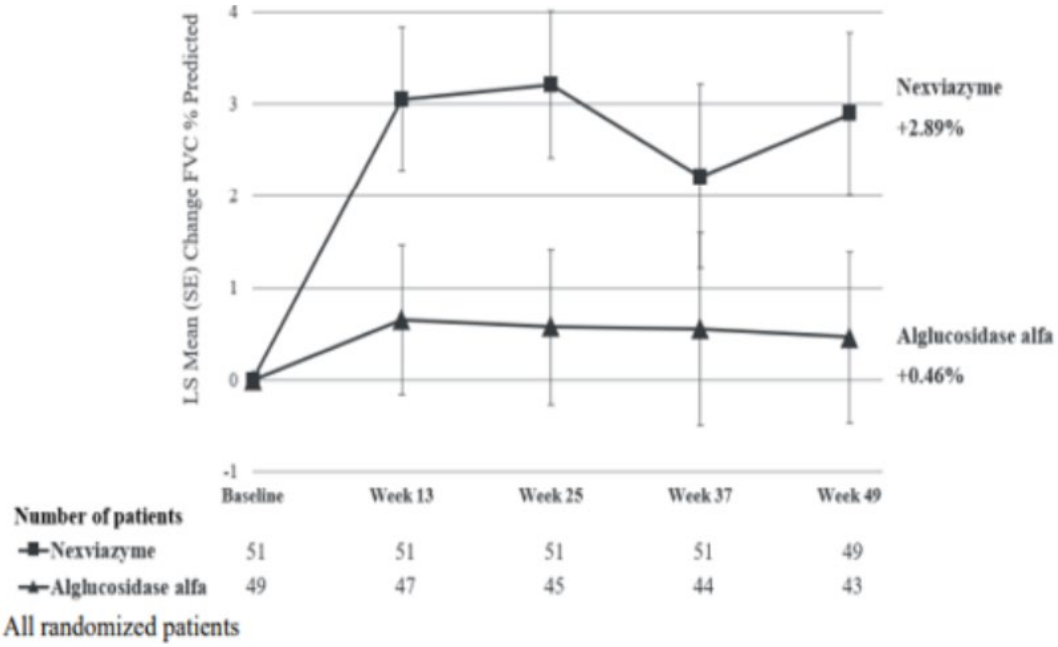
The primary endpoint of Study 1 was the change in FVC (% predicted) in the upright position from baseline to Week 49. At Week 49, the least squares (LS) mean change in FVC (% predicted) for patients treated with Nexviazyme and alglucosidase alfa was 2.9% and 0.5%, respectively. The estimated treatment difference was 2.4% (95% confidence interval [CI]: -0.1, 5.0) favoring Nexviazyme (see Table 1). Figure 1 presents the LS mean change from baseline in FVC (% predicted) over time by treatment group up to Week 49.

Table 1: Summary Results of FVC (% predicted) in Upright Position in ERT-Treatment-Naive Patients with LOPD (Study 1)*

		Nexviazyme (n=51)	**Alglucosidase Alfa (n=49)**
Pretreatment baseline	Mean (SD)	62.5 (14.4)	61.6 (12.4)
Week 49	Mean (SD)	65.5 (17.4)	61.2 (13.5)
Estimated change from baseline to week 49	LS mean (SE)	2.9† (0.9)	0.5† (0.9)
Estimated difference between groups in change from baseline to week 49	LS mean (95% CI)	2.4†‡ (-0.1, 5.0)	

CI: confidence interval; LOPD: Late-onset Pompe disease; LS: Least squares; SD: standard deviation.
*All randomized patients,
† Estimated using a mixed model for repeated measures (MMRM) including baseline FVC (% predicted,
as continuous), sex, baseline age (years), treatment group, visit, and treatment-by-visit interaction term as fixed effects.
‡ Noninferiority margin of 1.1% (p=0.0074). Statistical superiority of Nexviazyme over alglucosidase alfa was not achieved (p=0.06).

Figure 1: Plot of LS Mean (SE) Change From BaseLine of FVC (% predicted) in Upright Position over Time in ERT-Naïve Patients with LOPD (Study 1)



For patients who continued to receive Nexviazyme after Week 49 the mean change from baseline to Week 145 in FVC (% predicted) was 1.7 (SD=8.6, 95% CI: -0.9, 4.2), and the mean change from Week 49 to Week 145 was -0.8 (SD=6.2, 95% CI: -2.7, 1.0). For patients who switched from alglucosidase alfa to Nexviazyme after Week 49 the mean change from baseline to Week 145 was 0.5 (SD=8.3, 95% CI: -2.3, 3.4), and the mean change in FVC (% predicted) from Week 49 to Week 145 was 0.8 (SD=6.9) (95% CI: -1.6, 3.1).

Efficacy Results for Total Distance Walked in 6 Minutes from the 49-Week Active-Controlled Period and Open-Label Period up to Week 145 in Study 1

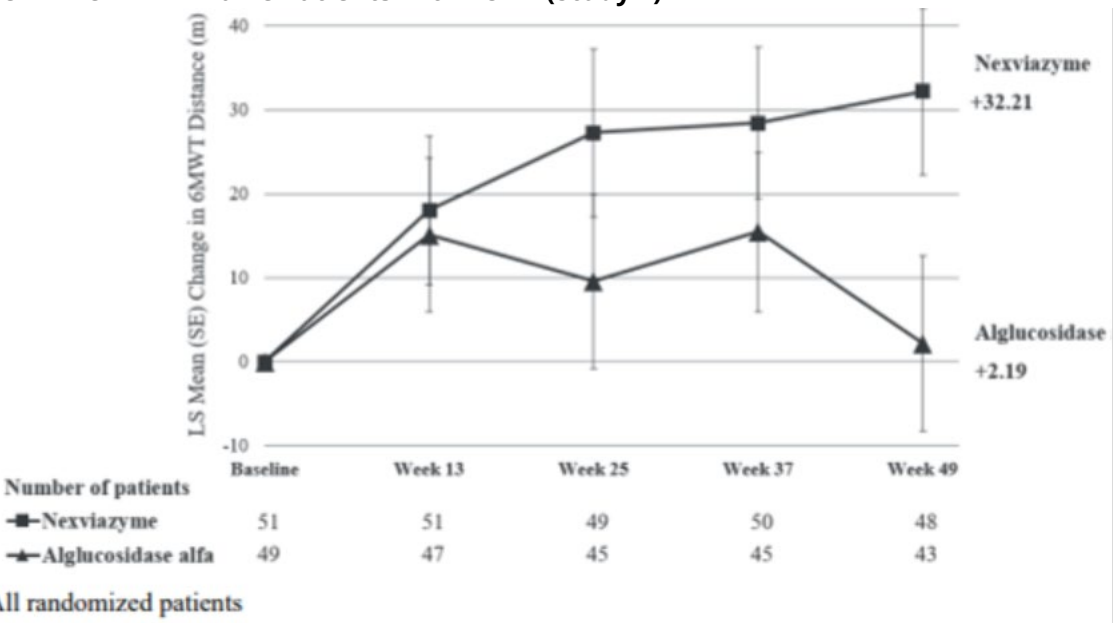
The key secondary endpoint of Study 1 was change in total distance walked in 6 minutes (6 Minute Walk Test, 6-MWT) from baseline to Week 49. At Week 49, the LS mean change from baseline in 6-MWT for patients treated with Nexviazyme end alglucosidase alfa was 32.2 meters and 2.2 meters. The estimated treatment difference was 30 meters (95% CI: 1.3, 58.7) favoring Nexviazyme (Table 2). Figure 2 presents the LS mean change from baseline in 6MWT distance over time by treatment group.

Table 2: Summary Results of 6-MWT in ERT-Naive Patients with LOPD (Study 1)*

		Nexviazyme (n=51)	**Alglucosidase Alfa (n=49)**
Pretreatment baseline	Mean (SD)	399.3 (110.9)	378.1 (116.2)
Week 49	Mean (SD)	441.3 (109.8)	383.6 (141.1)
Estimated change from baseline to week 49	LS mean (SE)	32.2† (9.9)	2.2† (10.4)
Estimated difference between groups in change from baseline to week 49	LS mean (95% CI)	30.0†‡ (1.3, 58.7)	

6-MWT: 6-Minute Walk Test; CI: confidence interval; ERT: Enzyme replacement therapy; LOPD: Late-onset Pompe disease; SD: standard deviation; SE: standard error.
*All randomized patients.
† The mixed model for repeated measures (MMRM) model for 6-MWT distance adjusts for baseline FVC (% predicted), baseline 6-MWT (distance walked in meters), baseline age (years), gender, treatment group, visit, and treatment-by-visit interaction as fixed effects.
‡ p-value at nominal level, without multiplicity adjustment (p=0.04).

Figure 2: Plot of LS Mean (SE) Change from Baseline of 6-MWT (distance walked, in meters) over Time in ERT-Naïve Patients with LOPD (Study 1)



For patients who continued to receive Nexviazyme after Week 49, the mean change from baseline to Week 145 in 6MWT was 24.9 (SD=68.6, 95% CI: 4.8, 44.9), and the mean change from Week 49 to Week 145 was -11.0 (SD=33.5, 95% CI: -20.8, -1.2). For patients who switched from alglucosidase alfa to Nexviazyme after Week 49 the mean change from baseline to Week 145 in 6-MWT was -4.1 (SD=90.4, 95% CI: -34.1, 25.8), and the mean change from Week 49 to Week 145 was -7.7 (SD=50.3, 95% CI: -24.4, 9.0).

Alglucosidase alfa (Lumizyme®, formerly known as Myozyme)

Infantile-Onset Pompe Disease

The safety and effectiveness of alglucosidase alfa in the treatment of patients with infantile-onset Pompe disease (IOPD) were assessed in 57 treatment-naive infantile-onset Pompe disease patients, aged 0.2 month to 3.5 years at first alglucosidase alfa infusion, in three separate open label, single-arm clinical trials (Trials 1, 2, and 3). (2)

Trial 1 (Patients with IOPD)

Trial 1 was an international, multicenter, open-label, clinical trial of 18 patients with IOPD. This trial was conducted between 2003 and 2005. Patients were randomized 1:1 to receive either 20 mg/kg or 40 mg/kg of IV 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 trial 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 patients with IOPD with similar age and disease severity. In the historical cohort, 61 untreated patients with IOPD 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 trial 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/m^2, range 45 to 193 g/m^2). However, the magnitude of the decrease in LVMI did not correlate with the clinical outcome measure of ventilator-free survival.

Trial 2 (Patients with IOPD)
Trial 2 was an international, multicenter, non-randomized, open-label clinical trial that enrolled 21 patients with IOPD aged 3 months to 3.5 years at first infusion. Eighteen patients were CRIM positive and 3 patients were CRIM negative. All patients received IV 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 the 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.

Trial 3 (Patients with IOPD)
Trial 3 was an open-label, single-center trial in 18 patients with IOPD who had a confirmed diagnosis of Pompe disease as identified through a newborn screening program. All patients were CRIM positive. Patients were treated with IV 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.

Clinical Trials in Late-Onset Pompe Disease

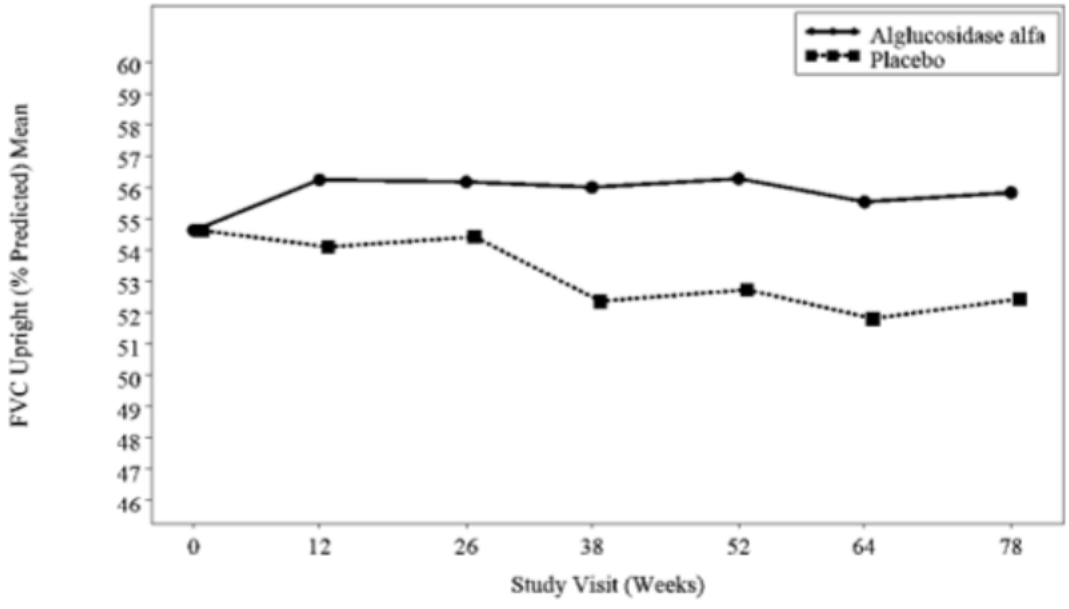
The safety and efficacy of alglucosidase alfa were assessed in 90 patients with late-onset Pompe disease (LOPD), aged 10 to 70 years, in a randomized, double-blind, placebo-controlled trial (Trial 4). All patients were naive to ERT. Patients were allocated in a 2:1 ratio and received 20 mg/kg of IV alglucosidase alfa (n=60) or IV placebo (n=30) every other week for 78 weeks (18 months).

The youngest alglucosidase alfa-treated patient was 16 years of age, and the youngest placebo treated patient was 10 years of age. The trial 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 trial 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 3).

Figure 3: Mean FVC Upright (% Predicted) over Time in Patients with LOPD (Trial 4)

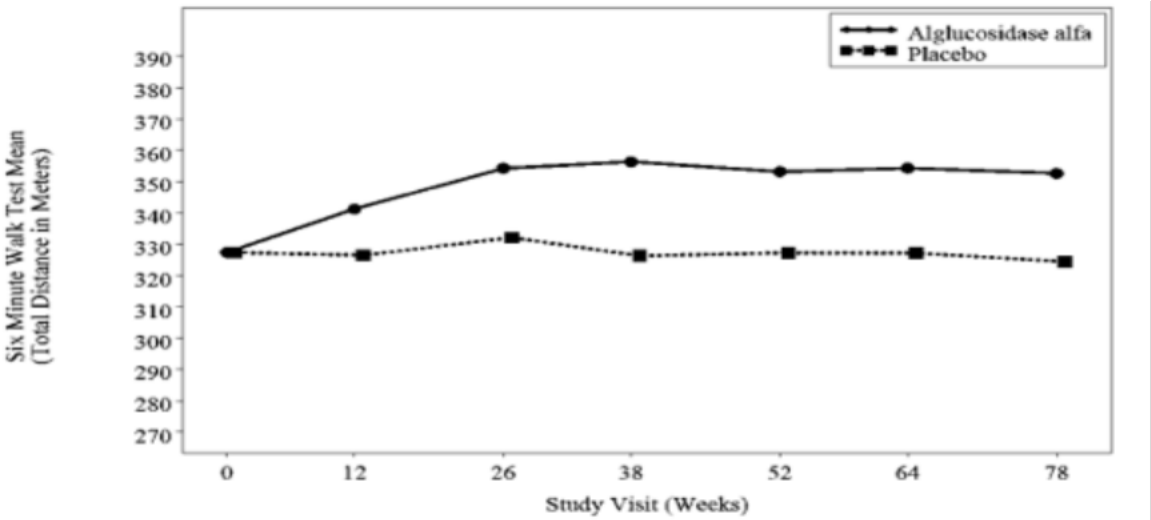


Note: ANCOVA least squares means adjusting for baseline values

FVC: forced vital capacity; LOPD: late-onset Pompe disease.

At trial entry, the mean 6-MWT among all patients was about 330 meters. After 78 weeks, the mean 6-MWT 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% CI: [-1 to 52 meters]; p=0.06) (see Figure 4).

Figure 4: Mean Six Minute Walk Test Total Distance Walked Over Time In Patients with LOPD (Trial 4)



LOPD: late-onset Pompe disease.

Use in the Pediatric Population

Per the FDA label, the safety and effectiveness of alglucosidase alfa (Lumizyme) has been established in pediatric patients with Pompe disease. The use of Lumizyme for this pediatric indication is supported by evidence from an adequate and well-controlled trial in 57 treatment-naive pediatric patients with IOPD treated with alglucosidase alfa, aged 0.2 month to 3.5 years at first infusion, (Trials 1, 2, and 3) and 90 adult and pediatric patients with LOPD in a randomized, double-blind, placebo-controlled trial including 2 patients 16 years of age or less.

Anaphylaxis, hypersensitivity reactions, and acute cardiorespiratory failure have occurred in pediatric patients (see Boxed Warning, Warnings and Precautions on label). Additionally, cardiac arrhythmia and sudden cardiac death have occurred in pediatric patients during general anesthesia for central venous catheter placement.

Cipaglucosidase alfa-atga (Pombiliti™)

Trial 1 was a randomized, double-blind, active-controlled, international, multi-center clinical trial (NCT03729362) in patients ≥18 years old diagnosed with late-onset Pompe disease (LOPD). Patients were randomized 2:1 to receive Pombiliti (20 mg/kg by IV infusion) in combination with Opfolda (260 mg orally for those ≥50 kg or 195 mg orally for those ≥40 kg to <50 kg) or a non-U.S.-approved alglucosidase alfa product with placebo every other week for 52 weeks. The efficacy population included a total of 123 patients of whom 95 (77%) had received prior treatment with U.S.-approved

alglucosidase alfa or a non-U.S.-approved alglucosidase alfa product (ERT-experienced) and 28 (23%) were ERT-naïve. More than two thirds (n=64, 67%) of ERT experienced patients had been on ERT treatment for more than 5 years prior to entering Trial 1 (mean of 7.4 years). (3)

Demographics, baseline sitting forced vital capacity (FVC) (% predicted), and 6-MWD were generally similar between the 2 treatment groups (see Table 3 for baseline sitting FVC [percent predicted] values). Of the 123 randomized patients, 56 were males, baseline mean age was 47 years old (range from 19 to 74 years old), and mean age at diagnosis was 39 years old (range from 1 to 66). The racial groups for the patients consisted of 104 White (85%), 6 Japanese (5%), 6 Other racial group (5%), 4 Asian (3%), 1 Native Hawaiian or other Pacific Islander (1%), 1 American Indian or Alaska Native (1%), and 1 African American (1%).

Key efficacy endpoints included assessment of sitting FVC (% predicted) and 6-MWD (Table 3 and Table 4).

Sitting FVC (Percent-Predicted) at 52 Weeks

Patients treated with Pombiliti in combination with Opfolda showed a mean change in sitting FVC from baseline at Week 52 of -1.1% as compared with patients treated with a non-U.S.-approved alglucosidase alfa product with placebo of -3.3%; the estimated treatment difference was 2.3% (95% CI: 0.02, 4.62).

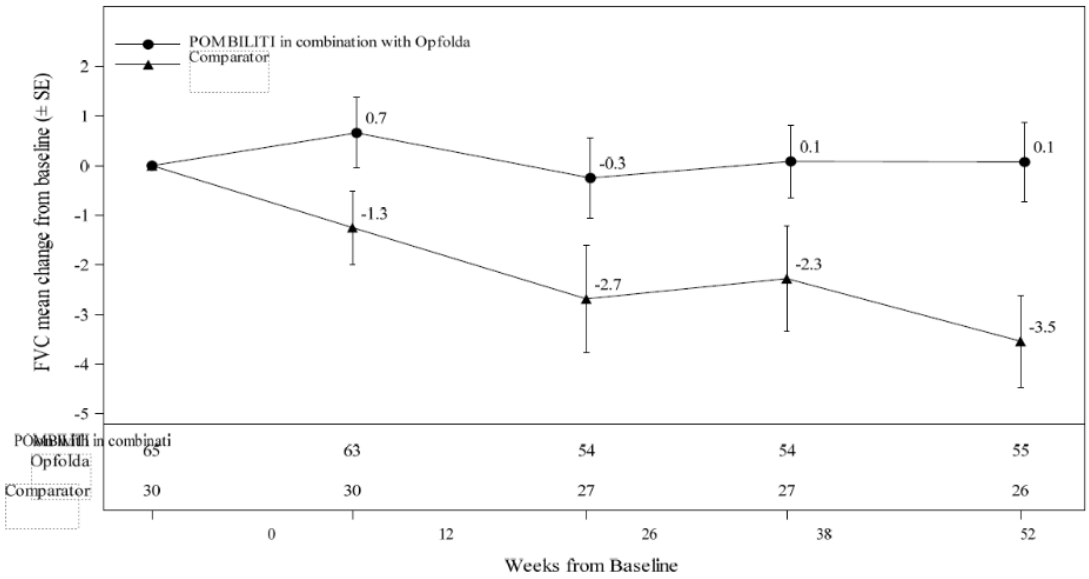
The ERT-experienced patients treated with Pombiliti in combination with Opfolda showed a numerically favorable change in sitting FVC from baseline at Week 52 (Table 3 and Figure 5).

Table 3: Summary of Sitting FVC in Adults with LOPD by ERT Status at 52 Weeks in Trial 1

Efficacy Endpoint	**ERT-experienced**		**ERT-naïve***	
Sitting FVC (% predicted)	**Pombiliti in Combination with Opfolda**	**A Non-U.S.-Approved Alglucosidase alfa Product† with Placebo**	**Pombiliti in Combination with Opfolda**	**A Non-U.S.-Approved Alglucosidase alfa Product† with Placebo**
Baseline				
n	n=65	n=30	n=20	n=8
Mean (SD)	67.9 (19.1)	67.5 (21.0)	80.2 (18.7)	79.6 (21.0)
Median	68.0	69.0	82.3	88.5
Change from baseline at Week 52				
n	n=55	n=26	n=19	n=7
Mean (SD)	0.1 (5.9)	-3.5 (4.7)	-4.7 (6.2)	-2.4 (6.3)
Median	0.5	-2.5	-4.5	-3.0
Change to Week 52				
Diff of means (SE)	3.5 (1.3)		-1.9 (2.7)	
(95% CI)	(1.0, 6.0)‡		(-7.3, 3.6)	

CI: confidence interval; Diff: difference; ERT: enzyme replacement therapy; FVC: forced vital capacity; LOPD: late-onset Pompe disease; SD: standard deviation; SE: standard error; U.S.: United States.
*Pombiliti in combination with Opfolda is not approved for use in ERT-naïve patients with LOPD. The
ERT-naïve patient subgroup enrolled too few patients to conclusively interpret the data. For the ERT-naïve group, the treatment difference was estimated using a 2-sample t-test.
† A U.S.-approved alglucosidase alfa product was not used in this clinical trial. Conclusions cannot be drawn from this clinical trial regarding comparative effectiveness between a U.S.-approved alglucosidase alfa product and Pombiliti in combination with Opfolda for the treatment of adult patients with LOPD weighing ≥40 kg and who are not improving on their current ERT.
‡ For the ERT-experienced group, the treatment difference of the mean was estimated by analysis of covariance which included treatment, gender, baseline FVC, age, weight, height in the model. Nominal p=0.006. Missing data at Week 52 was imputed using last observed values.

Figure 5: Mean Change (± SE) in Sitting FVC (% Predicted) From Baseline to Week 52 in ERT-Experienced Adults with LOPD in Trial 1*



SE: standard error; FVC: forced vital capacity; ERT: enzyme replacement therapy; LOPD: late-onset Pompe disease.
*A U.S.-approved alglucosidase alfa product was not used in this clinical trial. Conclusions cannot be drawn from this clinical trial regarding osidase alfa product and POMBILITI in combination with Opfolda for the treatment adult patients with LOPD weighing ≥40 kg and who are not improving on their current ERT.

6-Minute Walk Distance (6-MWD) at 52 Weeks

Patients treated with Pombiliti in combination with Opfolda walked on average 21 meters farther from baseline as compared to those treated with a non-U.S.-approved alglucosidase alfa product with placebo who walked 8 meters farther from baseline; the estimated treatment difference was 14 meters (95% CI: -1, 28).

The ERT-experienced patients treated with Pombiliti in combination with Opfolda showed a numerically favorable change in 6-MWD from baseline at Week 52 (Table 4 and Figure 6).

Table 4: Summary of 6MWD in Adults with LOPD by ERT Status at 52 Weeks in Trial 1

Efficacy Endpoint	**ERT-experienced**		**ERT-naïve***	
6MWD	**Pombiliti in Combination with Opfolda**	**A Non-U.S.-Approved Alglucosidase alfa Product† with Placebo**	**Pombiliti in Combination with Opfolda**	**A Non-U.S.-Approved Alglucosidase Product† with Placebo**
Baseline n Mean (SD) Median	 n=65 347 (110) 353	 n=30 335 (114) 344	 n=20 394 (112) 375	 n=7 421 (136) 386
Change from baseline at Week 52 n Mean (SD) Median	 n=61 16 (39) 10	 n=29 1 (40) -9	 n=20 33 (49) 24	 n=7 38 (29) 34
Change to Week 52 Diff. of means (SE) (95% CI)	 17 (8) (0.2, 33) ‡		 -5 (20) (-45, 36)	

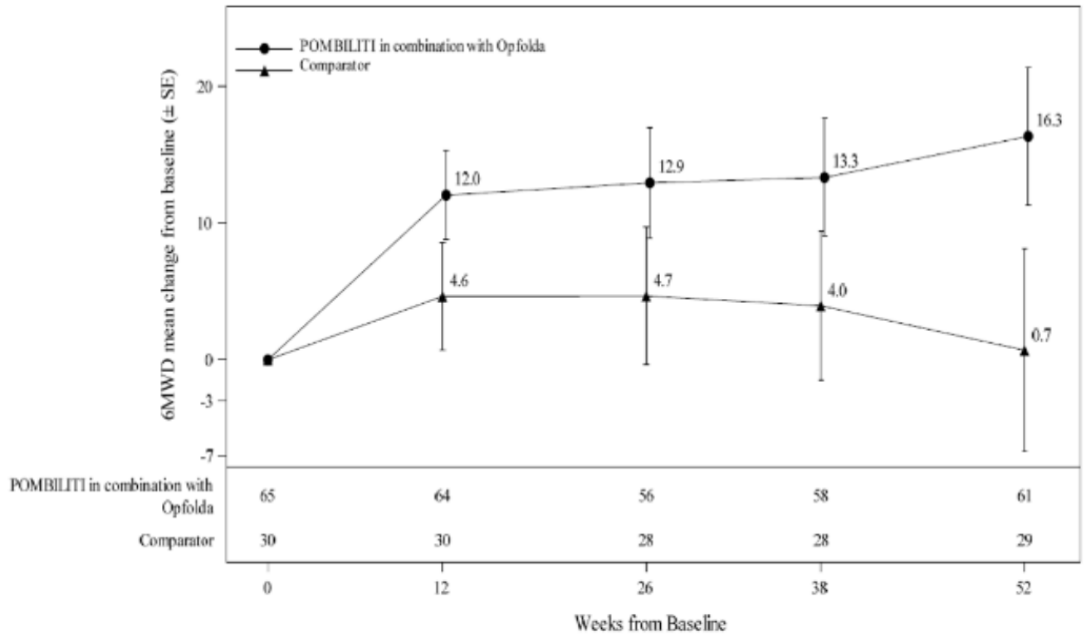
6-MWD: 6-minute walk distance; LOPD: late-onset Pompe disease; ERT: enzyme replacement therapy; SD: standard deviation; Diff.: difference; SE: standard error; CI: confidence interval.

* POMBILITI in combination with Opfolda is not approved for use in ERT-naïve patients with LOPD. The ERT-naïve patient subgroup enrolled too few patients to conclusively interpret the data. For the ERT-naïve group, the treatment difference was estimated using a 2-sample t-test. One ERT-naïve subject in the control arm was excluded from this table because their change of 355 meters in 6MWD from baseline at Week 52 was a statistical outlier and not considered clinically plausible.

† A U.S.-approved alglucosidase alfa product was not used in this clinical trial. Conclusions cannot be drawn from this clinical trial regarding comparative effectiveness between a U.S.-approved alglucosidase alfa product and POMBILITI in combination with Opfolda for the treatment of adult patients with LOPD weighing ≥40 kg and who are not improving on their current ERT.

‡ For the ERT-experienced group, the treatment difference of the mean was estimated by nonparametric analysis of covariance which included gender, baseline 6MWD, age, weight, and height in the model. Nominal p=0.047. Missing data at Week 52 was imputed using last observed values.

Figure 6: Mean Change (± SE) of 6-MWD From Baseline to week 52 in ERT-experienced Adults with LOPD in Trial 1*



SE: standard error; 6MWD: 6-minute walk distance; ERT: enzyme replacement therapy; LOPD: late-onset Pompe disease.
*A U.S.-approved alglucosidase alfa product was not used in this clinical trial. Conclusions cannot be drawn from this clinical trial regarding comparative effectiveness between a U.S. approved alglucosidase alfa product and Pombiliti in combination with Opfolda for the treatment adult patients with LOPD weighing ≥40 kg and who are not improving on their current ERT.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	G0138, J0219, J0220, J0221, J1203

*Current Procedural Terminology (CPT®) ©2025 American Medical Association: Chicago, IL.

References

U.S. Food and Drug Administration Labels:

1. Nexviazyme®) for injection, for intravenous use. September 2023. Available at: https://www.accessdata.fda.gov (accessed Feb. 19, 2026).
2. Prescribing Label: Lumizyme® (alglucosidase alfa) for injection, for intravenous use. December 2024. Available at: https://www.accessdata.fda.gov (accessed Feb. 20, 2026).
3. Prescribing Label: Pombiliti™ (cipaglucosidase alfa-atga) for injection, for intravenous use. July 2024. Available at: https://www.accessdata.fda.gov (accessed Feb. 20, 2026).

Other:

4. National Organization of Rare Disorders. Rare disease database: Lysosomal storage disorder. (March 2008). Available at: https://www.rarediseases.org (accessed Feb. 25, 2026).
5. Cleveland Clinic. Lysosomal storage diseases (June 2022). Available at: https://my.clevelandclinic.org (accessed Feb. 25, 2026).
6. Cleveland Clinic. Pome disease (September 2023). Available at: https://my.clevelandclinic.org (accessed Feb. 25, 2026).
7. National Organization of Rare Disorders. Pompe Disease. (January 2024). Available at: https://www.rarediseases.org (accessed Feb. 25, 2026).
8. FDA expands approval of drug to treat Pompe disease to patients of all ages. (Aug 2014) Available at: https://www.drugs.com (accessed Feb. 25, 2026).

Centers for Medicare & Medicaid Services

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare & Medicaid Services does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at https://www.cms.hhs.gov.

Policy History/Revision

Date	Description of Change
7/21/2026	New medical document. Enzyme replacement therapy when utilized for the treatment of Pompe disease may be considered medically necessary for the specific indications noted under each of the enzyme-replacements therapies in Coverage.