ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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1. NAME OF THE MEDICINAL PRODUCT

Nexviazyme 100mg for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Avalglucosidase Alfa for Injection for Intravenous Infusion

Each vial contains 100mg of avalglucosidase alfa

Avalglucosidase alfa is a hydrolytic lysosomal glycogen- specific recombinant human α-glucosidase enzyme conjugated with multiple synthetic bis-mannose-6-phosphate (bis-M6P)-tetra-mannose glycans resulting in approximately 15 moles of M6P per mole of enzyme (15 M6P) and is produced in Chinese hamster ovary cells (CHO).

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Injection

Sterile white to pale-yellow lyophilized powder for intravenous use after reconstitution and dilution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pompe disease

NEXVIAZYME is indicated for the treatment of patients 1 year of age and older with late-onset Pompe disease (lysosomal acid alpha-glucosidase [GAA] deficiency).

4.2 Posology and method of administration

Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of conditions for which Nexviazyme is indicated (see section 4.1)

Premedication
Prior to Nexviazyme administration, consider pretreating with antihistamines, antipyretics, and/or corticosteroids.

NEXVIAZYME must be reconstituted and diluted prior to use.

Posology

NEXVIAZYME is administered as intravenous infusion. For patients weighing:
o ≥30 kg, the recommended dosage is 20 mg/kg (of actual body weight) every two weeks.
o <30 kg, the recommended dosage is 40 mg/kg (of actual body weight) every two weeks.

The initial recommended infusion rate is 1 mg/kg/hour. Gradually increase the infusion rate every 30 minutes if there are no signs of infusion-associated reactions (IARs)

Special population

Pediatric use
The safety and effectiveness of NEXVIAZYME for the treatment of late-onset Pompe disease have been established in pediatric patients 1 year of age and older.

Elderly
The recommended dosage in elderly patients is the same as the recommended dosage in younger adult patients

Method of administration

Reconstitution and Dilution Instructions
Reconstitute and dilute NEXVIAZYME in the following manner. Use aseptic technique during preparation.

Reconstitute the Lyophilized Powder
1. Determine the number of vials to be reconstituted based on individual patient's weight and the recommended dose
2. Remove the required number of vials needed for the infusion from the refrigerator and set aside for approximately 30 minutes to allow them to reach room temperature.
3. Reconstitute each vial by injecting 10 mL of Sterile Water for Injection, USP, into each vial by a slow drop-wise addition of the diluent down the inside of the vial and not directly onto the lyophilized powder. Tilt and roll each vial gently. Avoid forceful impact of the diluent on the lyophilized powder and avoid foaming. Do not invert, swirl, or shake. Allow the solution to become dissolved. After reconstitution, each vial will yield 100 mg/10 mL (10 mg/mL) of avalglucosidase alfa .
4. Perform an immediate visual inspection of the reconstituted solution in vials for particulate matter and discoloration. The reconstituted solution is clear, colorless to pale-yellow. If upon immediate inspection, particles are observed or if the solution is discolored, do not use.

Storage of the Reconstituted Solution

Dilute the reconstituted solution without delay. If immediate use is not possible, the reconstituted solution can be stored up to 24 hours in a refrigerator, 36°F to 46°F (2°C to 8°C). Do not freeze.

Dilute the Reconstituted Solution
1. Slowly withdraw the volume of reconstituted solution from each vial (calculated according to patient's weight).

2. Add the reconstituted solution slowly and directly into 5% Dextrose Injection. See Table 1 for the recommended total infusion volume based on the patient's weight. Avoid foaming or agitation of the infusion bag and avoid air introduction into the infusion bag. Discard any unused reconstituted solution remaining in the vial.

3. Mix the contents of the infusion bag by gently inverting or massaging the infusion bag. Do not shake. After dilution, the solution will have a final concentration of 0.5 to 4 mg/mL of Avalglucosidase alfa .

4. Administer the diluted solution without delay. The recommended infusion duration is between 4 to 7 hours. Discard any unused diluted solution after 9 hours.

Storage of the Diluted Solution

• If the diluted solution is not used immediately, refrigerate at 36°F to 46°F (2°C to 8°C) for up to 24 hours. Do not freeze.
• Completely infuse the diluted solution within 9 hours after removal from the refrigerator.
• If the diluted solution is removed from the refrigerator, it must not be restored in the refrigerator.
• Discard the diluted solution if refrigerated more than 24 hours or if the diluted solution is not able to be completely infused within 9 hours after removal from the refrigerator.

Table 1: Projected Intravenous Infusion Volume for NEXVIAZYME Administration According to Patient Weight

Patient Weight Range (kg)	Total Infusion Volume (mL) for 20 mg/kg	Total Infusion Volume (mL) for 40 mg/kg
5 to 9.9	N/A	100
10 to 19.9	N/A	200
20 to 29.9	N/A	300
30 to 34.9	200	N/A
35 to 49.9	250	N/A
50 to 59.9	300	N/A
60 to 99.9	500	N/A
100 to 119.9	600	N/A
120 to 140	700	N/A

Administration Instructions

1. It is recommended to use an in-line, low protein binding, 0.2 micrometer filter to administer NEXVIAZYME.

2. Administer the infusion incrementally, as determined by the patient's response and comfort.

When the recommended dose is 20 mg/kg

o *Initial and Subsequent Infusions:* The recommended starting infusion rate is 1 mg/kg/hour. If there are no signs of infusion-associated reactions (IARs), gradually increase the infusion rate every 30 minutes in each of the following three steps: 3 mg/kg/hour, 5 mg/kg/hour, and then 7 mg/kg/hour; then, maintain the infusion rate at 7 mg/kg/hour until the infusion is complete. The approximate total infusion duration is 4 hours to 5 hours.

When the recommended dose is 40 mg/kg

o *Initial Infusion:* The recommended starting infusion rate is 1 mg/kg/hour. If there are no signs of IARs, gradually increase the infusion rate every 30 minutes in each of the following three steps: 3 mg/kg/hour, 5 mg/kg/hour, and then 7 mg/kg/hour; then, maintain the infusion rate at 7 mg/kg/hour until the infusion is complete (4-step process). The approximate total infusion duration is 7 hours.

o *Subsequent Infusions:* The recommended starting infusion rate is 1 mg/kg/hour, with gradual increase in infusion rate every 30 minutes if there are no signs of IARs. The process may use either the above 4-step process or the following 5-step process:

3 mg/kg/hour, 6 mg/kg/hour, 8 mg/kg/hour, and then 10 mg/kg/hour; then, maintain the infusion rate at 10 mg/kg/hour until the infusion is complete. The approximate total 5-step infusion duration is 5 hours.

3. After the infusion is complete, flush the intravenous line with 5% Dextrose Injection.
4. Discard any unused diluted product after 9 hours.
5. Do not infuse NEXVIAZYME in the same intravenous line with other products.

4.3 Contraindications

None

4.4 Special warnings and precautions for use

Hypersensitivity Reactions Including Anaphylaxis

Prior to NEXVIAZYME administration, consider pretreating with antihistamines, antipyretics, and/or corticosteroids. Appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be readily available during NEXVIAZYME administration.
• If a *severe* hypersensitivity reaction (e.g., anaphylaxis) occurs, NEXVIAZYME should be discontinued immediately and appropriate medical treatment should be initiated. The risks and benefits of readministering NEXVIAZYME following severe hypersensitivity reaction (including anaphylaxis) should be considered. Some patients have been rechallenged using slower infusion rates at a dosage lower than the recommended dosage. In patients with severe hypersensitivity reaction, a desensitization procedure to NEXVIAZYME may be considered. If the decision is made to readminister NEXVIAZYME, ensure the patient tolerates the infusion. If the patient tolerates the infusion, the dosage (dose and/or the rate) may be increased to reach the approved recommended dosage.
• If a *mild or moderate* hypersensitivity reaction occurs, the infusion rate may be slowed or temporarily stopped.

Life-threatening hypersensitivity reactions, including anaphylaxis, have been reported in NEXVIAZYME-treated patients. In clinical studies, 67 (48%) NEXVIAZYME-treated patients experienced hypersensitivity reactions, including 6 (4%) patients who reported severe hypersensitivity reactions and 3 (2%) additional patients who experienced anaphylaxis; 1 (1%) patient experiencing anaphylaxis discontinued from the study. Some of the hypersensitivity reactions were IgE mediated. Anaphylaxis signs and symptoms included respiratory distress, chest discomfort, flushing, cough, erythema, lip swelling, pruritus, swollen tongue, dysphagia, and rash. Symptoms of severe hypersensitivity reactions included respiratory distress, erythema, urticaria, tongue edema, and rash. Increased incidence of hypersensitivity reactions was observed in patients with higher antidrug antibody (ADA) titers.

Infusion-Associated Reactions

Antihistamines, antipyretics, and/or corticosteroids can be given prior to NEXVIAZYME administration to reduce the risk of infusion-associated reactions (IARs). However, IARs may still occur in patients after receiving pretreatment.
If *severe* IARs occur, consider immediate discontinuation of NEXVIAZYME, initiation of appropriate medical treatment, and the benefits and risks of readministering NEXVIAZYME following severe IARs. Some patients have been rechallenged using slower infusion rates at a dose lower than the recommended dose. Once a patient tolerates the infusion, the dose may be increased to reach the recommended approved dose.
If *mild or moderate* IARs occur regardless of pretreatment, decreasing the infusion rate or temporarily stopping the infusion may ameliorate the symptoms.
In clinical studies, IARs were reported to occur at any time during and/or within a few hours after the NEXVIAZYME infusion and were more likely to occur with higher infusion rates. IARs were reported in 48 (34%) NEXVIAZYME-treated patients in clinical studies. In these studies, 5 (4%) NEXVIAZYME-treated patients reported 10 severe IARs including symptoms of chest discomfort, nausea, dysphagia, erythema, respiratory distress, tongue edema, urticaria, and increased blood pressure. The majority of IARs were assessed as mild to moderate. IARs that led to treatment discontinuation were chest discomfort, cough, dizziness, erythema, flushing, nausea, ocular hyperemia, and respiratory distress. Increased incidence of IARs was observed in patients with higher ADA titers.
Patients with an acute underlying illness at the time of NEXVIAZYME infusion appear to be at greater risk for IARs.

Patients with advanced Pompe disease may have compromised cardiac and respiratory function, which may predispose them to a higher risk of severe complications from IARs.

Risk of Acute Cardiorespiratory Failure in Susceptible Patients

Patients susceptible to fluid volume overload, or those with acute underlying respiratory illness or compromised cardiac or respiratory function for whom fluid restriction is indicated may be at risk of serious exacerbation of their cardiac or respiratory status during the NEXVIAZYME infusion. More frequent monitoring of vitals should be performed during NEXVIAZYME infusion in these patients. Some patients may require prolonged observation times.

4.5 Interaction with other medicinal products and other forms of interaction

In the absence of compatibility studies Nexviazyme should not be mixed with other medicinal products.

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk Summary
Available data from case reports of NEXVIAZYME use in pregnant women are insufficient to evaluate for a drug associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. However, available data from postmarketing reports and published case reports on alglucosidase alfa (another hydrolytic lysosomal glycogen-specific enzyme replacement therapy) use in pregnant women have not identified a drug-associated risk of adverse pregnancy outcomes. The continuation of treatment for Pompe disease during pregnancy should be individualized to the pregnant woman. Untreated Pompe disease may result in worsening disease symptoms in pregnant women.
Embryo-fetal toxicity studies performed in pregnant mice resulted in maternal toxicity related to an immunologic response (including an anaphylactoid response) and embryo-fetal loss at 17 times the human steady-state AUC at the recommended biweekly dose of 20 mg/kg for LOPD patients weighing ≥30 kg or 10 times the human steady-state AUC at the recommended biweekly dose of 40 mg/kg for LOPD patients weighing <30 kg. Avalglucosidase alfa did not cross the placenta in mice, therefore, the adverse effects were likely related to the immunologic response in the mothers.
Embryo-fetal toxicity studies performed in pregnant rabbits showed no adverse effects on the fetuses at exposure up to 91 times the human steady-state AUC at the recommended biweekly dosage of 20 mg/kg for LOPD patients weighing ≥30 kg or 50 times the human steady-state AUC at the recommended biweekly dose of 40 mg/kg for LOPD patients weighing <30 kg

The estimated background risk of major birth defects and miscarriage in the indicated population is unknown. All pregnancies have a background risk of birth defect, miscarriage, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Pregnant women exposed to NEXVIAZYME, or their healthcare providers, should report NEXVIAZYME exposure

Lactation

Risk Summary
There are no data on the presence of avalglucosidase alfa in human or animal milk, the effects on the breastfed infant, or the effects on milk production. Available published literature suggests the presence of alglucosidase alfa (another hydrolytic lysosomal glycogen-specific enzyme replacement therapy) in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NEXVIAZYME and any potential adverse effects on the breastfed child from NEXVIAZYME or from the underlying maternal condition. Lactating women exposed to NEXVIAZYME, or their healthcare providers, should report NEXVIAZYME exposure.

Fertility

The effects of Nexviazyme on fertility were evaluated in male and female mice following the administration of 0, 10, 20 or 50 mg/kg IV every other day before cohabitation, through conception to Gestation Day 7. There were no effects on fertility. The NOAEL was 50 mg/kg/dose[1]

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Because dizziness, hypotension, and fatigue have been reported as IARs, this may affect the ability to drive and use machines on the day of the infusion

4.8 Undesirable effects

Serious adverse reactions reported in 2 or more NEXVIAZYME-treated patients were respiratory distress, chills, and pyrexia. Serious adverse events were similar across both adult and pediatric populations.

A total of 5 NEXVIAZYME-treated patients in clinical trials permanently discontinued NEXVIAZYME due to adverse reactions, including 2 of these patients who discontinued the treatment because of a serious adverse reaction.
The most frequently reported adverse reactions (>5%) in the pooled safety population were headache, diarrhea, nausea, fatigue, arthralgia, myalgia, dizziness, rash, vomiting, pyrexia, abdominal pain, pruritus, erythema, abdominal pain upper, chills, cough, urticaria, dyspnea, hypertension, and hypotension.

IARs were reported in 48 (34%) NEXVIAZYME-treated patients. IARs reported in more than 1 patient included chills, cough, diarrhea, erythema, fatigue, headache, influenza-like illness, nausea, ocular hyperemia, pain in extremity, pruritus, rash, rash erythematous, tachycardia, urticaria, vomiting, chest discomfort, dizziness, hyperhidrosis, lip swelling, oxygen saturation decreased, pain, palmar erythema, swollen tongue, abdominal pain upper, burning sensation, eyelid edema, feeling cold, flushing, respiratory distress, throat irritation, and tremor.

<u>Adverse Reactions from Clinical Trials in Late-Onset Pompe Disease (LOPD)</u>
In Study 1, 100 patients aged 16 to 78 years of age with LOPD (naive to enzyme replacement therapy) were treated with either 20 mg/kg of NEXVIAZYME (n=51) or 20 mg/kg of alglucosidase alfa (n=49) given every other week as an intravenous infusion for 49 weeks followed by an open-label extension period.
During the double-blind active-controlled period of 49 weeks, serious adverse reactions were reported in 1 (2%) patient treated with NEXVIAZYME and in 3 (6%) patients treated with alglucosidase alfa. The most frequently reported adverse reactions in (>5%) NEXVIAZYME-treated patients were headache, fatigue, diarrhea, nausea, arthralgia, dizziness, myalgia, pruritus, vomiting, dyspnea, erythema, paresthesia, and urticaria.
IARs were reported in 13 (25%) of the NEXVIAZYME-treated patients. IARs reported in more than 1 patient on NEXVIAZYME were mild to moderate and included headache, diarrhea, pruritus, urticaria, and rash. None of them were severe IARs. IARs were reported in 16 (33%) patients treated with alglucosidase alfa. IARs reported in more than 1 patient on alglucosidase alfa were mild to severe and included dizziness, flushing, dyspnea, nausea, pruritis, rash, erythema, chills, and feeling hot. Severe IARs were reported in 2 patients treated with alglucosidase alfa.
Table 2 summarizes the adverse reactions that occurred in at least 3 NEXVIAZYME-treated patients (≥6%) in Study 1. Study 1 was not designed to demonstrate a statistically significant difference in the incidence of adverse reactions in the NEXVIAZYME and the alglucosidase alfa treatment groups.

Table 2: Adverse Reactions Reported in at Least 6% of NEXVIAZYME-Treated Patients with LOPD in Study 1

Adverse Reaction	NEXVIAZYME (N=51) n (%)	Alglucosidase Alfa (N=49) n (%)
Headache	11 (22%)	16 (33%)
Fatigue	9 (18%)	7 (14%)
Diarrhea	6 (12%)	8 (16%)
Nausea	6 (12%)	7 (14%)
Arthralgia	5 (10%)	8 (16%)
Dizziness	5 (10%)	4 (8%)
Myalgia	5 (10%)	7 (14%)
Pruritus	4 (8%)	4 (8%)
Vomiting	4 (8%)	3 (6%)
Dyspnea	3 (6%)	4 (8%)
Erythema	3 (6%)	3 (6%)
Paresthesia	3 (6%)	2 (4%)
Urticaria	3 (6%)	1 (2%)

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. 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 in the studies described below with the incidence of antibodies in other studies or to other avalglucosidase alfa products may be misleading.

The incidence of anti-avalglucosidase alfa-ngpt antibodies (antidrug antibodies, ADA) in NEXVIAZYME-treated patients with Pompe disease is shown in Table 3. In NEXVIAZYME-treated patients (mean of 26 months, up to 85 months of treatment), the incidence of IAR was 62% (8/13) in those with an ADA peak titer ≥12,800, compared with incidences of 19% (8/43) in those with ADA peak titer <12,800 and 33% (1/3) in those who were ADA-negative *[see Warnings and Precautions (5.2)]*. Increased incidence of hypersensitivity reactions was observed in patients with higher ADA titers (4/13, 31%) compared to lower ADA titers (2/14, 14%). In enzyme replacement therapy (ERT)–experienced adult patients, the occurrences of IARs and hypersensitivity reactions were higher in patients who developed ADA compared to patients who were ADA-negative. One (1) treatment-naive patient (ADA peak titer 3,200) and 2 treatment-experienced patients (ADA peak titers; 800 and 12,800, respectively) developed anaphylaxis *[see Warnings and Precautions (4.4)]*.

The median time to seroconversion was 8 weeks. No clear trend of ADA impact on pharmacokinetics was observed. A trend toward decreased pharmacodynamic response as measured by percent change of urinary glucose tetrasaccharides from baseline was observed in patients with ADA peak titer ≥12,800. The development of ADA did not have an apparent impact on clinical efficacy.

ADA cross-reactivity studies showed that antibodies to avalglucosidase alfa-ngpt were cross-reactive to alglucosidase alfa.

Table 3: Incidence of Anti-Avalglucosidase Alfa-ngpt Antibodies in Patients with Pompe Disease

	NEXVIAZYME			
	Treatment-Naive Patients Avalglucosidase alfa-ngpt ADA* (N=61)†	Treatment-Experienced Patients Avalglucosidase alfa-ngpt ADA (N=74)‡		
	Adults/Pediatrics 20 mg/kg every two weeks (N=61)†	Adults 20 mg/kg every two weeks (N=58)	Pediatrics 20 mg/kg every two weeks (N=6)	Pediatrics 40 mg/kg every two weeks (N=10)
	n (%)	n (%)	n (%)	n (%)
ADA at baseline	2 (3%)	43 (74%)	1 (17%)	1 (10%)
ADA after treatment	58 (95%)	32 (55%)	1 (17%)	5 (50%)
Neutralizing Antibody (NAb)				
Both NAb types	13 (21%)	3 (5%)	0	0
Inhibition of enzyme activity	17 (28%)	10 (18%)	0	0
Inhibition of enzyme cellular uptake	24 (39%)	12 (21%)	0	1 (10%)

* Includes one pediatric patient
† Treatment naive: only treated with avalglucosidase alfa-ngpt
‡ Treatment experienced: previously treated with alglucosidase alfa. Treatment-experienced patients received alglucosidase alfa treatment within a range of 0.9-9.9 years for adult patients and 0.5-11.7 years for pediatric patients before receiving NExviazyme.

To report any side effect(s):

- **Saudi Arabia:**

- The National Pharmacovigilance Centre (NPC):
- SFDA call center : 19999
- E-mail: npc.drug@sfda.gov.sa
- Website: https://ade.sfda.gov.sa/

- Sanofi- Pharmacovigilance: KSA_Pharmacovigilance@sanofi.com

4.9 Overdose

IARs are more likely to occur with higher infusion rates. In a clinical study, pediatric patients received doses up to 40 mg/kg of body weight every other week.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Enzymes, ATC code: A16AB

Mechanism of Action
Pompe disease (also known as glycogen storage disease type II, acid maltase deficiency, and glycogenosis type II) is an inherited disorder of glycogen metabolism caused by a deficiency of the lysosomal enzyme acid α-glucosidase (GAA), which results in intralysosomal accumulation of glycogen in various tissues.
Avalglucosidase alfa provides an exogenous source of GAA. The M6P on avalglucosidase alfa mediates binding to M6P receptors on the cell surface with high affinity. After binding, it is internalized and transported into lysosomes where it undergoes proteolytic cleavage that results in increased GAA enzymatic activity. Avalglucosidase alfa then exerts enzymatic activity in cleaving glycogen

Pharmacodynamics effects
In patients with Pompe disease, excess of glycogen is degraded to hexose tetrasaccharide (Hex4) which is then excreted in urine. The urinary Hex4 assay measures its major component, glucose tetrasaccharide (Glc4). In clinical studies, treatment with NEXVIAZYME resulted in reductions of urinary Glc4 concentrations (normalized by urine creatinine and reported as mmol Glc4/mol creatinine) in patients with Pompe disease.
In Study 1, the baseline mean urinary Glc4 concentration was 12.7 mmol/mol and 8.7 mmol/mol in NEXVIAZYME and alglucosidase alfa treatment groups, respectively, in treatment-naive LOPD patients *[see Clinical Studies (14.1)]*. The mean percentage (SD) change in urinary Glc4 concentrations from baseline to Week 49 was -54% (24) and -11% (32) in the NEXVIAZYME and alglucosidase alfa treatment groups, respectively.

CLINICAL STUDIES
Clinical Trial in Patients with 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 100 treatment-naive patients with LOPD. Patients were randomized in a 1:1 ratio based on baseline forced vital capacity (FVC), gender, age, and country to receive 20 mg/kg of NEXVIAZYME or alglucosidase alfa administered intravenously once every two weeks for 49 weeks. The trial included an open-label, long-term, follow-up phase of up to 5 years, in which patients in the alglucosidase alfa arm were switched to NEXVIAZYME treatment. 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 6MWT at baseline was 388.9 meters (range from 118 to 630 meters).
Endpoints and Results from the 49-Week Active-Controlled Period 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% CI: -0.1, 5.0) favoring NEXVIAZYME (see Table 4). Figure 1 presents the LS mean change from baseline in FVC (% predicted) over time by treatment group up to Week 49.

Table 4: Summary Results of FVC (% predicted) in Upright Position in Treatment-Naive Patients with LOPD (Study 1)*

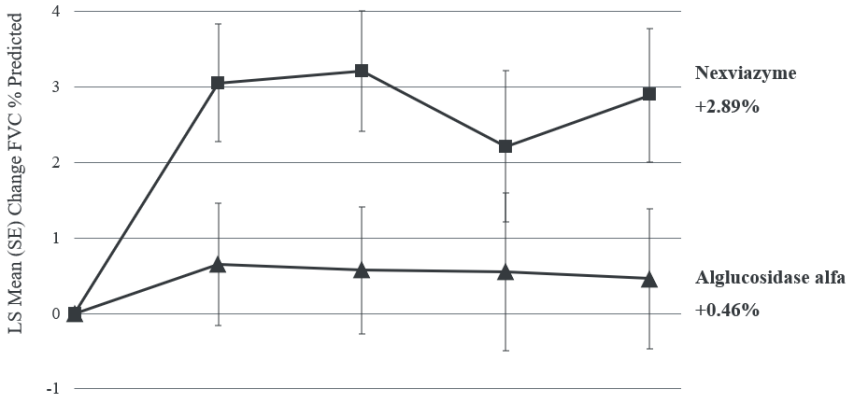
NEXVIAZYME (n=51)		**Alglucosidase Alfa (n=49)**	
Pretreatment baseline	Mean (SD)	62.5 (14.4)	61.6 (12.4)
Week 49	Mean (SD)	65.5 (17.4)	61.2 (13.5)
Estimated change from baseline to week 49	LS mean (SE)	2.9† (0.9)	0.5† (0.9)
Estimated difference between groups in change from baseline to week 49	LS mean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

* 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 Treatment-Naive Patients with LOPD (Study 1)*



Number of patients					
Nexviazyme	51	51	51	51	49
Alglucosidase alfa	49	47	45	44	43

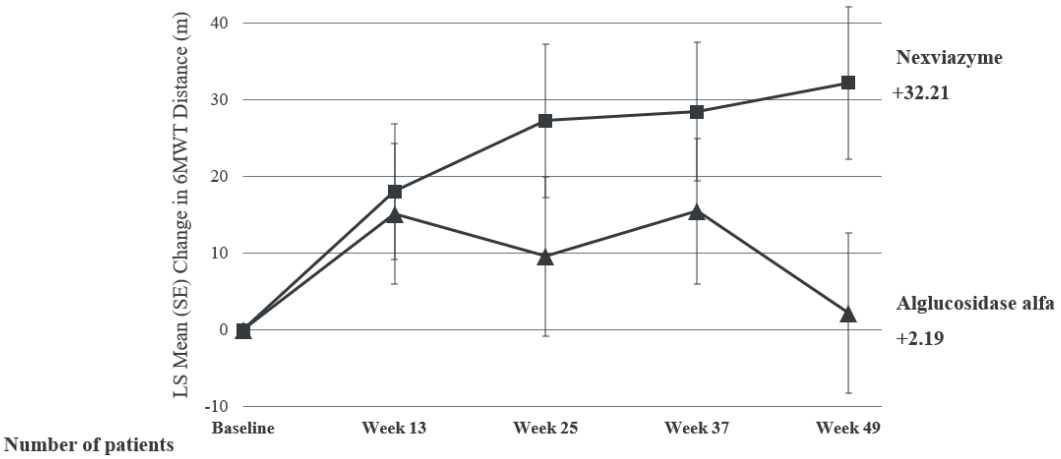
* All randomized patients

The key secondary endpoint of Study 1 was change in total distance walked in 6 minutes (6-Minute Walk Test, 6MWT) from baseline to Week 49. At Week 49, the LS mean change from baseline in 6MWT for patients treated with NEXVIAZYME and alglucosidase alfa was 32.2 meters and 2.2 meters, respectively. The estimated treatment difference was 30 meters (95% CI: 1.3, 58.7) favoring NEXVIAZYME (Table 5). Figure 2 presents the LS mean change from baseline in 6MWT distance over time by treatment group.

Table 5: Summary Results of 6-Minute Walk Test in Treatment-Naive Patients with LOPD (Study 1)*

16 **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)	

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



Number of patients					
Nexviazyme	51	51	49	50	48
Alglucosidase alfa	49	47	45	45	43

* All randomized patients

5.2 Pharmacokinetic properties

The avalglucosidase alfa-ngpt exposure increases in an approximately proportional manner with increasing doses over a range from 5 to 20 mg/kg (0.25 to 1 time the approved recommended dosage in LOPD patients weighing ≥30 kg or 0.125 to 0.5 times the approved recommended dosage in LOPD patients weighing <30 kg). No accumulation was observed following every two weeks dosing. Following intravenous infusion of 20 mg/kg of NEXVIAZYME every two weeks in LOPD patients weighing ≥30 kg, the mean ± SD plasma Cmax of avalglucosidase alfa-ngpt at Week 1 and Week 49 was 259 ± 72 µg/mL and 242 ± 81 µg/mL, respectively; the mean ± SD plasma AUC of avalglucosidase alfa-ngpt at Week 1 and Week 49 was 1,290 ± 420 µg·h/mL and 1,250 ± 433 µg·h/mL, respectively. Patients weighing <30 kg are expected to have similar AUC following intravenous infusion of 40 mg/kg of NEXVIAZYME every two weeks.

Distribution
The volume of distribution of avalglucosidase alfa-ngpt was 3.4 L in LOPD patients.

Elimination
The mean avalglucosidase alfa-ngpt plasma elimination half-life was 1.6 hours in LOPD patients. The mean avalglucosidase alfa-ngpt clearance was 0.9 L/hour.

Metabolism
The metabolic pathway of avalglucosidase alfa-ngpt has not been characterized. The protein portion of avalglucosidase alfa-ngpt is expected to be metabolized into small peptides and amino acids via catabolic pathways.
Antidrug Antibody Effects on Pharmacokinetics
In treatment-naive LOPD patients who received NEXVIAZYME 20 mg/kg every two weeks, 96% (49/51) of patients developed treatment emergent ADA. The exposure (e.g., AUC) in the two ADA-negative patients was within the range of that in patients who developed ADA. Among the patients who developed ADA, the median AUC was similar between Week 1 and Week 49 irrespective of titer values and neutralizing activities of the ADA. Increased incidence of IARs was observed in patients with sustained higher ADA peak titers (>12,800)

Specific Populations
Population pharmacokinetic analyses indicated that age and sex did not significantly influence the pharmacokinetics of avalglucosidase alfa-ngpt in patients with Pompe disease aged 1 to 78 years.

Pediatric patients
In 16 patients aged 1 to 12 years with Pompe disease, following a 4-hour intravenous infusion of NEXVIAZYME 20 mg/kg every two weeks and 7-hour intravenous infusion of NEXVIAZYME 40 mg/kg every two weeks, the

mean Cmax ranged from 175 to 189 µg/mL and 250 to 403 µg/mL, respectively. The mean AUClast ranged from 805 to 923 µg·hr/mL for 20 mg/kg every two weeks and 1,720 to 2,630 µg·hr/mL for 40 mg/kg every two weeks

5.3 Preclinical safety data

Nonclinical Toxicology
Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate the carcinogenic potential or studies to evaluate mutagenic potential have not been performed with avalglucosidase alfa-ngpt.
Intravenous administration of avalglucosidase alfa-ngpt every other day at doses up to 50 mg/kg (exposure not evaluated) had no adverse effects on fertility in male or female mic

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-Histidine
L-Histidine hydrochloride Monohydrate
Glycine
Mannitol
Polysorbate 80
Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

4 years.

A reconstituted product shelf life of 24 hours when stored refrigerated (2 - 8°C) is Recommended.

A diluted product shelf life of 24 hours when stored refrigerated (2 - 8°C) and 9 hours (Including infusion time) when stored at room temperature (up to 27°C) is recommended.

6.4 Special precautions for storage

Refrigerate vials of NEXVIAZYME at 36°F to 46°F (2°C to 8°C). Do not use NEXVIAZYME after the expiration date on the vial.

6.5 Nature and contents of container

NEXVIAZYME (avalglucosidase alfa) for injection is supplied as a sterile, white to pale-yellow lyophilized powder in single-dose vials.
One 100 mg vial in a carton.

6.6 Special precautions for disposal and other handling

If immediate use is not possible, the reconstituted solution can be stored up to 24 hours in a refrigerator, 36°F to

46°F (2°C to 8°C). Do not freeze.

- Completely infuse the diluted solution within 9 hours after removal from the refrigerator.

• If the diluted solution is removed from the refrigerator, it must not be restored in the refrigerator.
• Discard the diluted solution if refrigerated more than 24 hours or if the diluted solution is not able to be completely infused within 9 hours after removal from the refrigerator.

7. MARKETING AUTHORISATION HOLDER

Genzyme Europe B.V
Paasheuvelweg 25, Amsterdam, Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

N/A

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

NA

10. DATE OF REVISION OF THE TEXT Aug 2021

This is a Medicament

− Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.

− Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.

− The doctor and the pharmacist are the experts in medicines, their benefits and risks.

− Do not by yourself interrupt the period of treatment prescribed for you.