NEO-EXT TRIAL OVERVIEW

Nexviadyme® (avalglucosidase alfa)

A multicentre, multinational, open-label study of Nexviadyme® (avalglucosidase alfa) in ERT-experienced and -naïve patients with LOPD.

Dimachkie MM, Barohn RJ, Byrne B, et al. Neurology 2022 May;99(5):e536–e548.

NEO1 (N=10)
ERT-naïve

→ **Nexviadyme® 5, 10 or 20 mg/kg qow**
(n=8; same dose as NEO1, with all patients switching to 20 mg/kg in 2016)

NEO1 (N=14)
ERT-experienced

→ **Nexviadyme® 5, 10 or 20 mg/kg qow**
(n=11; same dose as NEO1, with all patients switching to 20 mg/kg in 2016)

Open-label treatment
Up to 8 years

Outcomes

Primary

Long-term safety and pharmacokinetics

Secondary

Long-term effect of Nexviadyme® on pharmacodynamic and exploratory efficacy variables, and the time-course of response.

Key inclusion criteria

- Participated in NEO1 Phase 1 study.
  - Pena LDM, Barohn RJ, Byrne BJ, et al. Neuromuscul Disord 2019 Mar;29(3):167–186.

Results

Participants

21 of 24 adult patients with LOPD who enroled in NEO1 completed that study; 19 of them entered NEO-EXT.
As of February 2020, 17 patients remained in NEO-EXT with up to 6.5 years of data.

Safety

- Nexviadyme® was assessed, in both ERT-naïve patients and those who had previously received ERT (Myozyme®) for ≥ 9 months, with a safety profile consistent with that observed in NEO1.
- No deaths or treatment-related life-threatening SAEs were reported.
- 18 participants developed antidrug antibodies without apparent effect on clinical outcomes. No participants who were tested developed immunoglobulin E antibodies.

Exploratory efficacy

- Upright FVC (% predicted) was stable in most participants, with slope estimates (95% CIs) of −0.473 per year (−1.188 to 0.242) and −0.648 per year (−1.061 to −0.236) in the ERT-naïve and ERT-experienced patients, respectively.
- 6MWT (% predicted) was also stable for most participants, with slope estimates (95% CIs) of −0.701 per year (−1.571 to 0.169) and −0.846 per year (−1.567 to −0.125) for ERT-naïve and ERT-experienced patients, respectively.

Abbreviations: 6MWT, 6-minute walk test; CI, confidence interval; ERT, enzyme replacement therapy; FVC, forced vital capacity; LOPD, late-onset Pompe disease; qow, every other week; SAE, serious adverse event.

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Prescribing Information: Myozyme® 50mg (alglucosidase alfa) powder for concentrate for solution for infusion

Please refer to the Summary of Product Characteristics before prescribing.

Presentation: Each vial contains 50mg of the active ingredient alglucosidase alfa. Following reconstitution each vial contains 5mg/ml alglucosidase alfa. **Indication:** Myozyme is indicated for long-term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of Pompe disease (acid α-glucosidase deficiency). Myozyme is indicated in adults and paediatric patients of all ages. **Dosing and Administration:** Myozyme treatment should be supervised by a physician experienced in the management of patients with Pompe disease or other inherited metabolic or neuromuscular diseases. The recommended dosage regimen for Myozyme is 20 mg/kg of body weight administered once every 2 weeks as an intravenous infusion. Infusions should be administered incrementally: it is recommended that the infusions begin at an initial rate of 1 mg/kg/hr and, if there are no signs of infusion associated reactions (IARs), are gradually increased by 2 mg/kg/hr every 30 minutes, until a maximum rate of 7 mg/kg/hr is reached. Before administration determine the number of vials to be reconstituted based on the individual patient's dose regimen (mg/kg) and remove the required vials from the refrigerator in order to allow them to reach room temperature (approx. 30 mins). Each vial of Myozyme is for single use only. There is no evidence for special considerations when Myozyme is administered to children, adolescents, adults or elderly patients. The safety and efficacy of Myozyme in patients with renal or hepatic insufficiency have not been evaluated and no specific dosage regimen can be recommended for these patients. *Refer to SmPC for full guidance on reconstitution of Myozyme.* **Contraindications:** Life-threatening hypersensitivity to the active substance or to any of the excipients confirmed by re-challenge. **Warnings and Precautions:** *Hypersensitivity/Anaphylactic reactions:* Serious and life-threatening anaphylactic reactions, including anaphylactic shock, have been reported in infantile and late onset patients during Myozyme infusions. Because of the potential for severe IARs, appropriate medical support measures, including cardiopulmonary resuscitation equipment should be readily available when Myozyme is administered and patients should be closely monitored. If severe hypersensitivity or anaphylactic reactions occur, immediate discontinuation of Myozyme infusion should be considered, and appropriate medical treatment should be initiated. *IARs:* Patients who have experienced IARs (and in particular anaphylactic reactions) should be treated with caution when re-administering Myozyme. Mild and transient effects may not require medical treatment or discontinuation of the infusion. Reduction of the infusion rate, temporary interruption of the infusion or pre-treatment, generally with oral antihistamine and/or antipyretics and/or corticosteroids, has effectively managed most reactions. *Immunogenicity:* In clinical studies, most patients are expected to develop IgG antibodies to rhGAA, typically within 3 months of starting treatment. Immune-mediated reactions: Severe cutaneous reactions, possibly immune-mediated, have been reported with alglucosidase alfa, including ulcerative and necrotizing skin lesions. Nephrotic syndrome was observed in a few Pompe patients treated with alglucosidase alfa and who had high IgG antibody titres (≥102,400). Immunomodulation: Immunogenicity data from clinical trials and published literature in CRIM-negative infantile-onset patients (IOPD) suggests that the administration of immune tolerance induction (ITI) regimen given to alglucosidase alfa naive patients (prophylactic ITI) may be effective in preventing or reducing the development of High Sustained Antibody Titer (HSAT) against alglucosidase alfa. ITI regimens may need to be tailored to individual patient needs. Patients with Pompe disease are at risk of respiratory infections due to the progressive effects of the disease on the respiratory muscles. Treating patients with immunosuppressive agents may further increase the risk of developing severe respiratory infections and vigilance is recommended. Fatal and life-threatening respiratory infections have been observed in some of these patients. **Interactions:** No drug interaction studies have been carried out with Myozyme. Recombinant human protein, alglucosidase alfa is an unlikely candidate for cytochrome P450 mediated drug-drug interactions. Pregnancy and Lactation: There is limited data from the use of alglucosidase alfa in pregnant women. Studies in animals have shown reproductive toxicity. Myozyme should not be used during pregnancy unless the clinical condition of the woman requires treatment with alglucosidase alfa. Myozyme is excreted in breast milk in very low concentrations. No clinical effect is expected in a breastfed infant due to low breast milk transfer and poor bioavailability. Breast-feeding during treatment with Myozyme may therefore be considered. As a precautionary measure, breast- feeding interruption for the first 24 hours after treatment may be considered. Fertility: There is too limited clinical data on the effects of alglucosidase alfa on fertility to evaluate its impact. Preclinical data did not reveal any significant adverse findings. **Adverse effects:** Infantile-onset Pompe Disease: Serious infusion reactions including urticaria, rales, tachycardia, decreased oxygen saturation, bronchospasm, tachypnoea, periorbital oedema and hypertension have been reported. *Very common (≥ 1/10):* tachycardia, flushing, tachypnoea, cough, vomiting, urticaria, rash, pyrexia and decreased oxygen saturation. *Common (≥ 1/100 to <1/10):* agitation, tremor, cyanosis, hypertension, pallor, retching, nausea, erythema, rash maculopapular, rash macular, rash papular, pruritus, irritability, chills, increased heart rate, increased blood pressure and increased body temperature. Late-onset Pompe disease: Serious adverse reactions reported in 4 patients treated with Myozyme were: angioedema, chest discomfort, throat tightness, non-cardiac chest pain and supraventricular tachycardia. Reactions in 2 of these patients were IgE-mediated hypersensitivity reactions. *Common (≥ 1/100 to <1/10):* Hypersensitivity, dizziness, paraesthesia, headache, flushing, throat tightness, diarrhoea, vomiting, nausea, urticaria, rash papular, pruritus, hyperhidrosis, muscle spasms, muscle twitching, myalgia, pyrexia, chest discomfort, peripheral oedema, local swelling, fatigue, feeling hot and increased blood pressure. *Prescribers should consult the SmPC in relation to other adverse reactions.*

Legal Category: POM. **UK List Price** £356.06 per vial. **Marketing Authorisation Number:** PLGB 04425/0770. **Marketing Authorisation Holder:** Sanofi, 410 Thames Valley Park Drive, Reading, Berkshire, RG6 1PT. **Further information available from:** Medical Information, Sanofi, 410 Thames Valley Park Drive, Reading, Berkshire, RG6 1PT, UK or uk-medicalinformation@sanofi.com

Date of Preparation: March 2024

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Adverse events should also be reported to the Sanofi Drug Safety department on Tel: 0800 0902314.

Alternatively, send via email to UK-drugsafety@sanofi.com

Prescribing Information: Nexviadyme▼(avalglucosidase alfa) 100 mg powder for concentrate for solution for infusion
Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Presentation: Each vial contains 100 mg of avalglucosidase alfa. After reconstitution, each vial contains a total extractable volume of 10.0 ml at a concentration of 10 mg of avalglucosidase alfa* per ml.
*Avalglucosidase alfa is a human acid α-glucosidase produced in Chinese hamster ovary cells (CHO) by recombinant DNA technology.
Indication: Nexviadyme is indicated for long-term enzyme replacement therapy for the treatment of patients with Pompe disease (acid α-glucosidase deficiency).
Dosage and Administration: Nexviadyme treatment should be supervised by a physician experienced in the management of patients with Pompe disease or other inherited metabolic or neuromuscular diseases. Patients may be pretreated with antihistamines, antipyretics and/or corticosteroids to prevent or reduce allergic reactions. The recommended dose of avalglucosidase alfa is 20 mg/kg of body weight administered once every 2 weeks. Nexviadyme vials are for single use only and the medicinal product should be administered as an intravenous infusion. The infusion should be administered incrementally as determined by patient response and comfort. It is recommended that the infusion begins at an initial rate of 1 mg/kg/hour and is gradually increased every 30 minutes if there are no signs of infusion- associated reactions (IARs); see SmPC for infusion rate schedule. *Home infusion:* Infusion of Nexviadyme at home may be considered for patients who are tolerating their infusions well and have no history of moderate or severe IARs for a few months. The decision to have a patient move to home infusion should be made after evaluation and upon recommendation by the treating physician. The healthcare professional should be available at all times during the home infusion and a specified time after infusion, depending on patient's tolerance prior to starting home infusion. (See SmPC section 4.2 for full guidance).
Dose modification for Infantile-Onset Pompe Disease (IOPD) patients: For IOPD patients who experience lack of improvement or insufficient response in cardiac, respiratory, and/or motor function while receiving 20 mg/kg, a dose increase to 40 mg/kg every other week should be considered in the absence of safety concerns (e.g., severe hypersensitivity, anaphylactic reactions, or risk of fluid overload). In patients who do not tolerate avalglucosidase alfa at 40 mg/kg every other week (e.g., severe hypersensitivity, anaphylactic reactions, or risk of fluid overload), consider decreasing the dose to 20 mg/kg every other week.
Special Populations: ***Elderly patients:*** No dose adjustment is required in patients >65 years. ***Hepatic impairment:*** The safety and efficacy of avalglucosidase alfa in patients with hepatic impairment have not been evaluated. ***Renal impairment:*** No dose adjustment is required in patients with mild renal impairment. The safety and efficacy of avalglucosidase alfa in patients with moderate or severe renal impairment have not been evaluated.
Paediatric population (patients 6 months of age and younger): The safety and efficacy of avalglucosidase alfa in children 6 months of age and younger have not yet been established. There are no data available in patients 6 months of age and younger.
Contraindications: Life-threatening hypersensitivity to the active substance or to any of the excipients.
Precautions and Warnings: ***Hypersensitivity reactions (including anaphylaxis):*** Hypersensitivity reactions, including anaphylaxis, have been reported in Nexviadyme-treated patients. Appropriate medical support measures, including cardiopulmonary resuscitation equipment especially for patients with cardiac hypertrophy and patients with significantly compromised respiratory function, should be readily available when Nexviadyme is administered. If severe hypersensitivity or anaphylaxis occur, Nexviadyme should be discontinued immediately, and appropriate medical treatment should be initiated. The risks and benefits of re-administering Nexviadyme following anaphylaxis or severe hypersensitivity reaction should be considered. ***Infusion associated reactions (IARs):*** In clinical studies, IARs were reported to occur at any time during and/or within a few hours after the infusion of Nexviadyme and were more likely with higher infusion rates. Patients with an acute underlying illness at the time of Nexviadyme 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. If severe IARs occur, immediate discontinuation of the administration of Nexviadyme should be considered and appropriate medical treatment should be initiated. The benefits and risks of re- administering Nexviadyme following severe IARs should be considered. ***Immunogenicity:*** Treatment emergent anti-drug antibodies (ADA) were reported in both treatment naïve (95%) and treatment experienced patients (49%). Adverse-event-driven immunologic testing, including IgG and IgE ADA, may be considered for patients who have risk for allergic reaction or previous anaphylactic reaction to alglucosidase alfa.
Risk of acute cardiorespiratory failure: Caution should be exercised when administering Nexviadyme to patients susceptible to fluid volume overload or patients with acute underlying respiratory illness or compromised cardiac and/or respiratory function for whom fluid restriction is indicated. These patients may be at risk of serious exacerbation of their cardiac or respiratory status during infusion. Appropriate medical support and monitoring measures should be readily available during Nexviadyme infusion. ***Cardiac arrhythmia and sudden death during general anaesthesia for central venous catheter placement.*** Cardiac arrhythmia, including ventricular fibrillation, ventricular tachycardia, and bradycardia, resulting in cardiac arrest or death, or requiring cardiac resuscitation or defibrillation, have been associated with the use of general anaesthesia in IOPD patients with cardiac hypertrophy.
Interactions: No interaction studies have been performed. Because it is a recombinant human protein, avalglucosidase alfa is an unlikely candidate for cytochrome P450 mediated drug-drug interactions. ***Fertility and Lactation:*** There are no available data on the use of Nexviadyme in pregnant women. The potential risk for humans is unknown. Nexviadyme should be used during pregnancy only if the potential benefits to the mother outweigh the potential risks, including those to the foetus. ***Breast-feeding:*** There are no available data on the presence of Nexviadyme in human milk or the effects of Nexviadyme on milk production or the breastfed infant. **Adverse Reactions**: Serious adverse reactions reported in patients treated with Nexviadyme were respiratory distress, chills, headache, dyspnoea, hypoxia, tongue oedema, nausea, pruritus, urticaria, skin discoloration, chest discomfort, pyrexia, blood pressure increased or decreased, body temperature increased, heart rate increased, oxygen saturation decreased, hypersensitivity reactions and anaphylaxis. ***Very common (≥1/10):*** Hypersensitivity, headache, nausea, pruritus, rash. ***Common (≥1/100 to<1/10):*** Anaphylaxis, dizziness, tremor, somnolence, burning sensation, ocular hyperaemia, conjunctival hyperaemia, eye pruritus, eyelid oedema, tachycardia, flushing, hypertension, hypotension, cyanosis, hot flush, pallor, cough, dyspnoea, Respiratory distress, throat irritation, oropharyngeal pain, diarrhoea, vomiting, lip swelling, swollen tongue, abdominal pain, abdominal pain upper, dyspepsia, urticaria, erythema, palmer erythema, hyperhidrosis, rash erythematous, rash pruritic, skin plaque, muscle spasms, myalgia, pain in extremity, flank pain, fatigue, chills, chest discomfort, pain, influenza like illness, infusion site pain, pyrexia, asthenia, face oedema, feeling cold, feeling hot, sluggishness, blood pressure increased, oxygen saturation decreased and body temperature increase. Prescribers should consult the SmPC in relation to other adverse reactions.
List price: (UK list price): £783.33/Vial **Legal Category:** POM **Marketing Authorisation Number**: PLGB 04425/0893 **Marketing Authorisation Holder:** Sanofi, 410 Thames Valley Park Drive, Reading, Berkshire, RG6 1PT, UK.
Further information is available from: Medical Information, Sanofi, 410 Thames Valley Park Drive, Reading, Berkshire, RG6 1PT, UK. uk-medicalinformation@sanofi.com
Date of preparation: January 2024

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Alternatively, send via email to UK-drugsafety@sanofi.com