Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Nexviazyme

Active ingredient: Avalglucosidase alfa

Sponsor: Sanofi-Aventis Australia Pty Ltd

December 2022

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
6MWT	Six minute walk test
ACM	Advisory Committee on Medicines
ADA	Antidrug antibody
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ARTG	Australian Register of Therapeutic Goods
ASA	Australia specific annex
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
$AUC_{0\text{-}2wk}$	Area under the concentration-time curve from time zero to 2 weeks
AUC_{last}	Area under the concentration-time curve up until the last measurable concentration
CHMP	Committee for Medicinal Products for Human Use (European Medicines Agency, European Union)
CI	Confidence interval
CK	Creatinine kinase
C_{max}	Maximum concentration
DLP	Data lock point
ECG	Electrocardiogram
EMA	European Medicines Agency (European Union)
ERT	Enzyme replacement therapy
EU	European Union
FDA	Food and Drug Administration (United States of America)
FVC	Forced vital capacity
GAA	Acid alpha-glucosidase

Abbreviation	Meaning
GLP	Good Laboratory Practice
GMFM-88	Gross Motor Function Measure (88 item)
GSD	Glycogen storage disease
GSD 2	Pompe disease (glycogen storage disease type II)
HCP	Healthcare Professional
Hex4	Hexose tetrasaccharide
IAR	Infusion-associated reaction
ICH	International Council for Harmonisation
IOPD	Infantile-onset Pompe disease
IV	Intravenous
LOPD	Late-onset Pompe disease
M6P	Mannose-6-phosphate
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intention-to-treat
MMRM	Mixed model for repeated measures
PD	Pharmacodynamics
PedsQL	Pediatric Quality of Life Inventory
PK	Pharmacokinetic(s)
PopPK	Population pharmacokinetics
PSUR	Periodic safety update report
PT	Preferred Term
QMFT	Quick Motor Function Test
RMP	Risk management plan
SD	Standard deviation
SE	Standard error
SF-12	Short-form 12 questionnaire

Abbreviation	Meaning
SOC	System Organ Class
$t_{1/2}$	Half-life
TEAE	Treatment-emergent adverse event
TGA	Therapeutic Goods Administration
US(A)	United States of America
VAS	Visual analogue score

Product submission

Submission details

Type of submission:	New biological entity
Product name:	Nexviazyme
Active ingredient:	Avalglucosidase alfa
Decision:	Approved
Date of decision:	15 November 2021
Date of entry onto ARTG:	17 November 2021
ARTG number:	346495
▼ *Black Triangle Scheme:*	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia
Sponsor's name and address:	Sanofi-aventis Australia Pty Ltd 12-24 Talavera Road Macquarie Park, NSW 2113
Dose form:	Powder for injection
Strength:	100 mg/10 mL
Container:	Vial
Pack sizes:	Single (one) vial
Approved therapeutic use:	*Nexviazyme is indicated for long-term enzyme replacement therapy for the treatment of patients one year of age and older with Pompe disease (acid α-glucosidase deficiency).*
Route of administration:	Intravenous infusion
Dosage:	Nexviazyme 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 dose of Nexviazyme is 20 mg/kg of body weight administered every other week as an intravenous infusion. Dose escalation to 40 mg/kg every other week may be considered for patients with infantile-onset Pompe disease (IOPD) who experience insufficient control or declining response at the lower dose (see Section 5.1 Pharmacodynamic Properties, Clinical Trials of the Product Information).

Nexviazyme should be administered as an intravenous infusion. 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. Vital signs should be obtained at each step, before increasing the infusion rate. Patients may be pre-treated with antihistamines, antipyretics and/or corticosteroids to prevent or reduce allergic reactions.

In the event of anaphylaxis or severe hypersensitivity reaction or severe infusion associated reactions, immediately discontinue administration of Nexviazyme and initiate appropriate medical treatment. In the event of mild to moderate hypersensitivity reactions or infusion associated reactions, the infusion rate may be slowed or temporarily stopped and/or appropriate medical treatment initiated (see Section 4.4 of the Product Information).

Symptoms may persist despite temporarily stopping the infusion; therefore, the treating physician should wait at least 30 minutes for symptoms of the reactions to resolve before deciding to stop the infusion for the remainder of the day. If symptoms subside, resume infusion rate for 30 minutes at half the rate, or less, of the rate at which the reactions occurred, followed by an increase in infusion rate by 50% for 15 to 30 minutes. If symptoms do not recur, increase the infusion rate to the rate at which the reactions occurred and consider continuing to increase the rate in a stepwise manner until the maximum rate is achieved.

Nexviazyme is for single use in one patient only. Contains no antimicrobial preservative.

For further information regarding dosage, refer to the Product Information.

Pregnancy category: Category B1

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals have not shown evidence of an increased occurrence of fetal damage.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the submission by Sanofi-Aventis Australia Pty Ltd to register Nexviazyme (avalglucosidase alfa) 100 mg/10 mL, powder for injection (vial) for the following proposed indication:

> *for long-term enzyme replacement therapy for the treatment of patients with Pompe disease (acid α-glucosidase deficiency).*

Glycogen storage diseases (GSD) are a group of metabolic disorders caused by an enzyme abnormality affecting glycogen synthesis, glycogen breakdown, or glucose breakdown, most often in muscles and/or liver cells. Most are genetic in cause, arising from an inborn error in metabolism, a class of congenital disorders affecting normal enzyme activities.

Glycogen, a carbohydrate and form of glucose storage, along with triglycerides (or fats) in adipose tissue together form the main energy stores of the body. In the human body, glycogen is mainly stored in cells of the liver and skeletal muscle. In most states, glycogen in skeletal muscle serves as an energy store for the muscle itself, whilst liver glycogen serves as a store of energy for the rest of the body, particularly the brain and central nervous system. Normally, glycogen can be rapidly broken down enzymatically to maintain blood glucose levels at a stable level, as and when needed.

Pompe disease, also known as glycogen storage disease type II (GSD2) or acid maltase deficiency, is a rare autosomal recessive neuromuscular disease caused by mutations in the *GAA* gene, which encodes an enzyme, lysosomal hydrolase acid alpha-glucosidase (GAA). Defects in both alleles of the *GAA* gene result in reduced or absent enzyme activity.[1]

The enzyme GAA is essential for the degradation of glycogen to form glucose in the lysosomes of cells. GAA degrades lysosomal glycogen by catalysing the hydrolysis of the α-1, 4- and α-1,6-glycosidic linkages. Deficiency of the enzyme results in the progressive accumulation of glycogen in the lysosomes leading to swelling and eventually rupture of the lysosome and subsequent spillage into the cytoplasm. Rupture of the lysosome and its contents results in cellular dysfunction, particularly in muscle tissue. Glycogen accumulation causes damage in a range of organs and tissues, and the symptoms are predominantly owing to damage to muscles including cardiac and skeletal muscle. The resulting damage to affected cells produces a range of symptoms that characterise Pompe disease, including metabolic myopathy leading to neuromuscular dysfunction.[2]

As over 500 mutations of *GAA* gene have been identified, including missense, nonsense, splicing defect, and frameshift mutations, each patient typically has a combination of two different affected alleles. The resultant clinical presentation of Pompe disease is heterogeneous in timing, severity, and the ranges of symptoms observed; and Pompe disease encompasses a broad range of clinical presentations, broadly based on the severity of enzyme deficiency.[1,2]

In untreated patients, un-degraded glycogen accumulates in the diaphragm and respiratory muscles, and respiratory function declines over time, leading to dependence on external ventilation and, ultimately, to respiratory failure. Glycogen also accumulates in skeletal muscles, and motor function declines over time, leading to problems with activities of daily living, reduced mobility, and eventually wheelchair dependence. Quality of life is severely affected by the burden of the disease and patients have higher mortality rates compared with the general age and gender matched healthy population.[2]

[1] Do HV, Khanna R, Gotschall R. Challenges in treating Pompe disease: an industry perspective. *Annals of Translational Medicine*. 2019 Jul;7(13):291. 16 p.
[2] Merritt JL II, et al. (2020) Lysosomal acid alpha-glucosidase deficiency (Pompe disease, glycogen storage disease II, acid maltase deficiency. *UpToDate.com*.

Although the disease manifests as a broad spectrum with a continuum of signs and symptoms, the most common classification of the condition splits Pompe disease into 'infantile-onset' Pompe disease (IOPD), characterised by a rapidly progressive infantile onset form; and 'late-onset' Pompe disease (late onset Pompe disease), a more slowly progressive form. Despite this categorisation, there is considerable variation and much overlap between these two extremes.

The classical infantile form, which represents up to one third of the cases, presents in the first months of life and is characterised by severe hypertrophic cardiomyopathy, severe generalised muscular hypotonia and respiratory failure, and without treatment, leads to death within the first year.[3] Clinical findings present at a median age of approximately four months, including cardiomegaly, respiratory distress, muscle weakness, feeding difficulties, and failure to thrive.

Patients with the late-onset form of Pompe disease generally do not develop cardiomyopathy and may present at any age, with symptoms of varying severity. Affected children usually present with delayed gross-motor development and progressive weakness in a limb-girdle distribution. Early involvement of the diaphragm is a common feature, and sleep-disordered breathing may occur. This usually leads to respiratory failure and death in the second or third decade of life. Affected adults with late-onset Pompe disease also present with progressive, proximal weakness in a limb-girdle distribution, particularly the hip flexors in the earliest stages of the disease. The weakness is accompanied by diaphragmatic involvement, leading to respiratory insufficiency early in the course of the disease.

The majority of patients with Pompe disease present after infancy with late-onset Pompe disease which takes a more variable course as compared with infantile-onset Pompe disease. Although Pompe disease manifestations vary between individuals, studies in both infantile-onset and late-onset Pompe disease patients have confirmed that respiratory failure precedes death in nearly all subjects. Indeed, the most common cause of death in patients with Pompe disease, regardless of age of disease onset and/or the severity of skeletal muscle weakness, is respiratory failure.[4,5]

The estimated global incidence of Pompe disease is 1 in 40,000, with variations in incidence reported between different ethnic groups and clinical forms. The highest incidence is in African American and Chinese populations.[4] According to the Australian Pompe Association, there are less than 70 Australians with Pompe disease, and in Australia, three infants are born with Pompe disease each year.[6]

Current treatment options

Therapeutic options for patients with Pompe disease are limited to enzyme replacement therapy (ERT) with alglucosidase alfa. The rationale for ERT in lysosomal storage disorders in general, and Pompe disease in particular, is that lysosomes are accessible to exogenous or extracellular proteins.

[3] Van Capelle CI, Van der Meijden JC, Van der Hout JM, Jaeken J, Baethmann M, Voit T, Kroos MA, Derks TGJ, Rubio-Gozalbo ME, Willemsen MA, Lachmann RH, Mengel E, Michelakakis H, de Jongste JC, Reuser AJJ, van der Ploeg AT. Childhood Pompe disease: clinical spectrum and genotype in 31 patients. *Orphanet Journal of Rare Diseases. 2016 May 18;11(1):65. 11 p.*

[4] Hirschhorn R, Reuser A. Glycogen storage disease type II: acid alpha-glucosidase (acid maltase) deficiency. *In: Scriver C, Beaudet A, Sly W, Valle D (eds). The metabolic and molecular bases of inherited disease. 8th ed.: New York, NY: McGraw-Hill; 2001:3389-420.*

[5] Winkel LPF, Hagemans MLC, van Doorn PA, Loonen MCB, Hop WJC, Reuser AJJ, van der Ploeg AT. The natural course of non-classic Pompe's disease; a review of 225 published cases. *Journal of Neurology. 2005 Aug;252(8):875-84.*

[6] Australian Pompe Association. Available at: https://australianpompe.org.au/

In Australia, Myozyme (alglucosidase alfa) is another product working by the same mechanism (enzyme replacement therapy) and has been registered on the Australian Register of Therapeutic Goods (ARTG) for the following approved indication: [7]

> *Myozyme (alglucosidase alfa-rch) is indicated for the long-term treatment of patients with a confirmed diagnosis of Pompe disease (acid alfa-glucosidase deficiency).*

Myozyme (alglucosidase alfa) received orphan designation in 2003 and was included on the ARTG in March 2007. At the time of this submission, treatment with Myozyme (alglucosidase alfa) is the standard treatment for GAA deficiency in Australia. The recommended dosage regimen of alglucosidase alfa is 20 mg/kg body weight once every two weeks as an intravenous infusion, irrespective of patient age or classification of Pompe disease. Some patients may require additional treatment with immunomodulation, but this is to manage the risk of hypersensitivity or infusion-associated reactions, not for the treatment of the underlying condition. Multi-disciplinary support teams may be engaged to assist with management specifically related to cardiac, respiratory, physical, rehabilitation, nutritional and other needs.

Development and approval of enzyme replacement therapy has profoundly changed the natural course of the disease, revealing new phenotypes in patients with classical infantile-onset Pompe disease who survive with enzyme replacement therapy, and considerably extending productivity and quality of life for patients with late-onset Pompe disease.

Availability of enzyme replacement therapy has extended survival in patients with classical infantile-onset Pompe disease and improved productivity and quality of life for patients with late-onset Pompe disease, and long-term benefits of alglucosidase alfa established it as the current standard-of-care for patients with Pompe disease. However, progressive decline in muscle and respiratory function is still observed in patients receiving alglucosidase alfa. This progression is attributed to suboptimal uptake of enzyme replacement therapy in skeletal muscle.

Clinical rationale

To maximise the potential benefit of enzyme replacement therapy for patients with Pompe disease, alglucosidase alfa was modified to create an investigational form of the enzyme with enhanced uptake, avalglucosidase alfa. By conjugating bis-mannose-6-phosphate (M6P) to oxidised sialic acid residues on alglucosidase alfa to create avalglucosidase alfa, it is anticipated that cellular uptake of this investigational enzyme replacement therapy, and hence, its efficacy in improving outcomes for patients with Pompe disease, would be enhanced relative to the current standard therapy.

The clinical development program for Nexviazyme (avalglucosidase alfa) was therefore designed to demonstrate higher potency of this investigational enzyme replacement therapy as compared to alglucosidase alfa.

This submission was evaluated as part of the Australia-Canada-Singapore-Switzerland-United Kingdom (ACCESS) Consortium via the New Active Substance Work Sharing Initiative (NASWSI), with work-sharing between the TGA, Health Canada, and Swissmedic (Switzerland). Each regulator made independent decisions regarding approval (market authorisation) of the new medicine.

[7] Myozyme alglucosidase alfa-rch 50 mg / 10 mL powder for concentrate for solution for infusion; Sanofi-Aventis Australia Pty Ltd. ARTG R 136005

Regulatory status

Australia regulatory status

This product is considered a new biological entity for Australian regulatory purposes.

This product received orphan drug designation on 15 September 2020 for the following indication:

> *Avalglucosidase alfa is intended for long-term enzyme replacement therapy (ERT) for the treatment of patients with Pompe disease (acid α-glucosidase deficiency).*

Overseas regulatory status

In the European Union (EU), the European Medicines Agency (EMA) approved avalglucosidase alfa (tradename Nexviadyme) on 24 June 2022, for the following indication:

> *Nexviadyme (avalglucosidase alfa) is indicated for long-term enzyme replacement therapy for the treatment of patients with Pompe disease (acid α-glucosidase deficiency).*

In the EU however, based on the EMA's Committee for Medicinal Products for Human Use (CHMP) review of the available data, considered that avalglucosidase alfa is not to be qualified as a new active substance in itself.[8]

In the United States of America (USA), on 6 August 2021, the US Food and Drug Administration (FDA) approved Nexviazyme (avalglucosidase alfa) for the following indication:

> *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).*

In the United Kingdom, on 6 July 2021, the Medicines and Healthcare products Regulatory Agency approved avalglucosidase alfa for the following indication:

> *Nexviadyme (avalglucosidase alfa) is indicated for long-term enzyme replacement therapy for the treatment of patients with Pompe disease (acid α-glucosidase deficiency).*

On 12 November 2021, Health Canada approved avalglucosidase alfa (with the tradename Nexviazyme) for the following indication:

> *for the long-term treatment of patients with late-onset Pompe disease (acid α-glucosidase deficiency).*

On 17 November 2021, Switzerland approved avalglucosidase alfa (with the tradename Nexviadyme) for the following indication:

> *for the treatment of late-onset Pompe disease (glycogen storage disease type II).*

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

[8] European Public Assessment Report for Nexviadyme, avalglucosidase alfa. Available at: Nexviadyme, INN-avalglucosidase alfa (europa.eu)

Registration timeline

The following table captures the key steps and dates for this submission.

Table 1: Timeline for Submission PM-2020-05478-1-3

Description	Date
Designation: Orphan	15 September 2020
Submission dossier accepted and first round evaluation commenced	30 November 2020
First round evaluation completed	31 March 2021
Sponsor provides responses on questions raised in first round evaluation	1 June 2021
Second round evaluation completed	19 July 2021
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	31 August 2021
Sponsor's pre-Advisory Committee response	14 September 2021
Advisory Committee meeting	31 September and 1 October 2021
Registration decision (Outcome)	15 November 2021
Completion of administrative activities and registration on the ARTG	17 November 2021
Number of working days from submission dossier acceptance to registration decision*	196 days

*Statutory timeframe for standard submissions is 255 working days

Submission overview and risk/benefit assessment

A summary of the TGA's assessment for this submission is provided below.

This section is a TGA summary of wording used in TGA's evaluation report, which discussed numerous aspects of overseas evaluation reports and included some information that was commercial-in-confidence.

Quality

Nexviazyme (avalglucosidase alfa) is a 110 kDa recombinant human alpha-glucosidase produced in Chinese hamster ovary cells (CHO) by recombinant DNA technology, which is subsequently conjugated with approximately 7 hexamannose structures, multiple copies

of a synthetic bis-mannose-6-phosphate-containing glycan (M6P) at sialic acid residues on the enzyme. The two dimensional image in Figure 1 below is a skeletal structure diagram illustrating avalglucosidase alfa with one one conjugated glycan, the second image (Figure 2) is a computer-generated model.

Figure 1: Avalglucosidase alfa structure (single conjugated glycan)

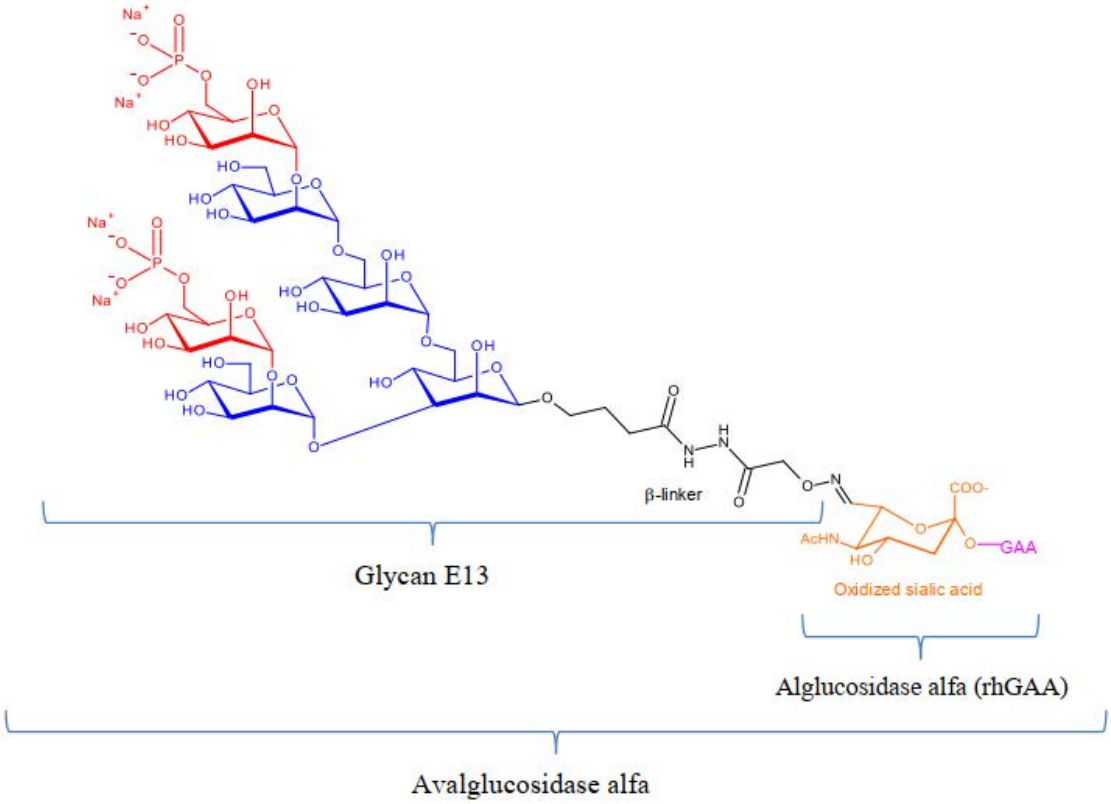
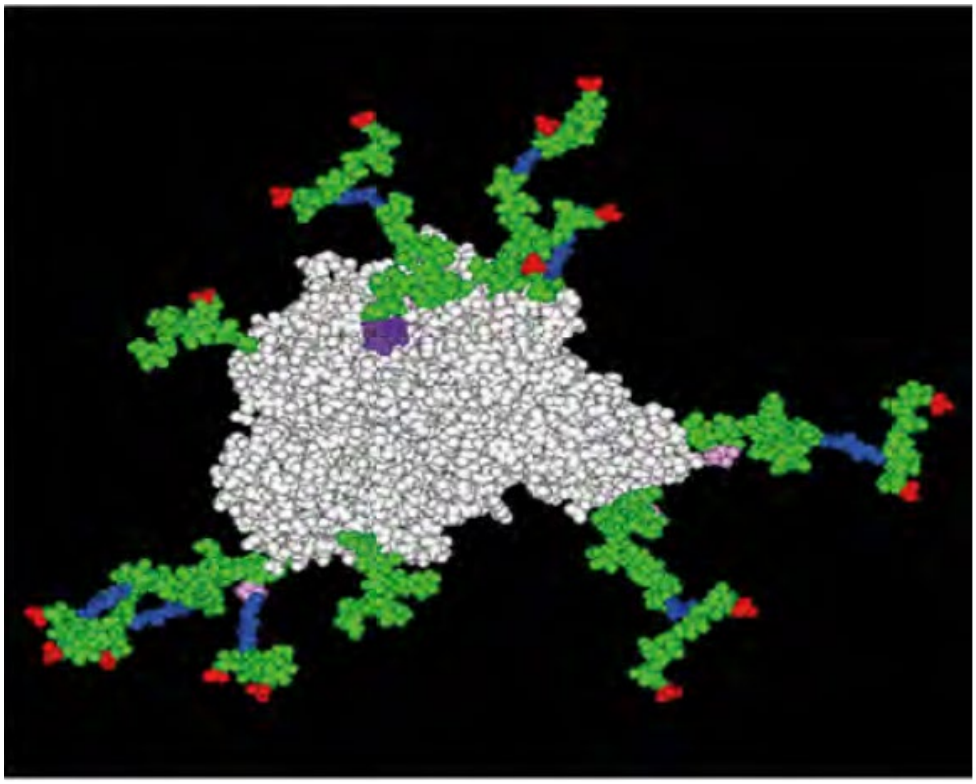


Figure 2: Avalglucosidase alfa structure (computer generated model)



Key to Figure 2:

Purple: active site of the enzyme.

Green: multiple N-linked glycosylation sites.

Blue: amino-oxy linkers.

Red: terminal glycan phosphates.

The avalglucosidase alfa drug substance is manufactured as a single process starting from cell bank vial thaw, through the upstream cell culture, downstream purification of alglucosidase alfa, conjugation of synthetic glycan E13 to generate avalglucosidase alfa, subsequent purification, and final formulation to generate the drug substance. In the drug product manufacturing process, the drug substance is sterile filled into vials with direct filtration, lyophilised, capped and labelled into the final product. The final formulation is 100 mg powder for injection, to be made up to 10 mL.

Each single-use vial contains 100 mg of avalglucosidase alfa as a powder for injection. The powder for injection is reconstituted with 10 mL sterile water for injection. Each vial contains an overfill to compensate for liquid loss during preparation. Following reconstitution, each vial contains 10.3 mL reconstituted solution and a total extractable volume of 10 mL. Each 1 mL of the reconstituted solution contains 10 mg of avalglucosidase alfa.

Along with the active pharmaceutical substance (avalglucosidase alfa), the Nexviazyme drug product is formulated with the excipients histidine, histidine hydrochloride monohydrate, glycine, mannitol and polysorbate 80.

The drug product container closure system is a 20 mL Type I clear glass vial closed with a siliconized Type I grey elastomeric stopper. The stoppers are crimped to the vials with an aluminium seal with plastic flip-off cover. The stability studies were conducted using the actual container.

The proposed shelf life for the drug product is 48 months when stored at 2 to 8°C.

The real time stability summary and conclusions supported the drug product shelf life of 24 months when stored at 2 to 8°C.

The drug product has the following proposed storage instructions: Do not use Nexviazyme after the expiration date on the vial. The reconstituted and diluted solution should be administered without delay.

The reconstituted product can be stored up to 24 hours when refrigerated at 2°C to 8°C and diluted product can be stored up to 24 hours when refrigerated at 2°C to 8°C and up to 9 hours (including infusion time) when stored at room temperature (up to 27 °C).

Recommendations and conclusions

The administrative, product usage, pharmaceutical, microbiological and biopharmaceutic data submitted in support of this submission have been fully evaluated and the TGA has confirmed that the product satisfies Australian legislative, pharmacopoeial and relevant technical requirements.

There are no objections on quality grounds to the registration of Nexviazyme (avalglucosidase alfa).

Proposed conditions of registration

Laboratory testing & compliance with Certified Product Details (CPD):

> *All batches of Nexviazyme supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).*
>
> *When requested by the TGA, the sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the Product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index and periodically in testing reports on the TGA website.*

Nonclinical

The following is a summary of the non-clinical evaluation for this submission.

The submitted nonclinical data was in accordance with the relevant International Council for Harmonisation (ICH) guideline for the nonclinical assessment of biotechnology products.[9] The overall quality of the nonclinical dossier was high, and all pivotal safety-related studies were Good Laboratory Practice (GLP) compliant.[10]

Four *in vivo* pharmacology studies were conducted in acid alpha-glucosidase (GAA) knockout mice. Avalglucosidase alfa at 12 and 20 mg/kg IV (that is, similar to the minimum clinical dose) resulted in reduced glycogen content in the heart, skeletal muscle (quadriceps and triceps), diaphragm, and psoas; in contrast, 4 mg/kg doses reduced

[9] ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals. EMA/CPMP/ICH/286/1995. December 2009.

[10] **Good Laboratory Practice** (**GLP**) is intended to promote the quality and validity of test data. It is a managerial concept covering the organisational process and the conditions under which laboratory studies are planned, performed, monitored, recorded and reported (OECD GLP Guideline). The closely related **Good Clinical Laboratory Practice** (**GCLP**) applies those principles established under GLP for data generation used in regulatory submissions relevant to the analysis of samples from a clinical trial. At the same time it ensures that the objectives of the GCP principles are carried out. This ensures the reliability and integrity of data generated by analytical laboratories.

glycogen in heart tissues only. The presence of at least three glycan moieties was found to be of sufficient efficacy (glycogen clearance), with inclusion of additional moieties providing no significant improvement in efficacy. Antidrug antibodies and hypersensitivity reactions were seen in all repeat-dose studies. The pharmacology studies support the proposed indication and dose in late onset Pompe disease patients.

No secondary pharmacodynamics or pharmacodynamic drug interaction studies were conducted with avalglucosidase alfa, which is reasonable, given it is an enzyme replacement therapy.

No dedicated safety pharmacology studies were conducted. Cardiovascular, respiratory, and central nervous system evaluations were included in the 26-week toxicity study in monkeys. No effects on electrocardiogram (ECG), heart rate, body temperature, neurobehavioural and/or respiratory rate parameters were reported at doses up to 200 mg/kg IV, administered every other week (19-fold the maximum concentration (C_{max}) in late onset Pompe disease patients).

Overall, the avalglucosidase alfa pharmacokinetic (PK) profile in mice and cynomolgus monkeys was comparable with the PK in humans, characterised by short half-life ($t_{1/2}$) values (0.5 to 2.7 hours), low clearance, and volume of distribution values lower than total body water. There were no sex differences in PK parameters in mice and monkeys. the area under the concentration-time curve (AUC) in serum, $t_{1/2}$ and volume of distribution following a single dose of avalglucosidase alfa were significantly lower in mice compared with alglucosidase alfa (Myozyme),[7] possibly owing to increased tissue uptake of the modified enzyme. Tissue distribution of avalglucosidase alfa in mice was largely restricted to the liver, with much lower levels seen in the heart, skeletal muscle and bone marrow. *In vitro*, there was no evidence of cleavage of the linker from the protein component of avalglucosidase alfa. Hydrazine-containing compounds from metabolism of the linker are not expected to occur *in vivo*.

Single-dose toxicity studies with avalglucosidase alfa were not conducted.

While repeat-dose toxicity studies were conducted in mice and monkeys (2 studies, respectively), only the pivotal 26-week monkey study was GLP-compliant. With the exception of hypersensitivity in mice, which may not be predictive of the clinical response, no organ toxicity was observed at doses up to 120 mg/kg, IV, every other day, or weekly (3.7-fold the mean area under the curve over 2 weeks ($AUC_{0\text{-}2wk}$) in late onset Pompe disease patients). No avalglucosidase alfa-related toxicological findings were observed in the pivotal monkey study up to 200 mg/kg, IV, fortnightly (23-fold the mean $AUC_{0\text{-}2wk}$ in late onset Pompe disease patients). Lower heart weights were seen in some animals, which may be associated with the pharmacological activity of avalglucosidase alfa (depletion of glycogen content).

No dedicated genotoxicity and carcinogenicity studies with avalglucosidase alfa were conducted; this is consistent with the relevant ICH guideline.[11] However, an exploratory micronucleus study in *GAA* knockout mice revealed no increase in micronucleated reticulocytes or normochromatic erythrocyte compared with controls, and a carcinogenicity risk assessment was conducted based on Myozyme and Lumizyme (both alglucosidase alfa drug products);[7] data review and literature searches, and through evaluating the potential release of the linker moiety of Genz-669342 (Bis-M6P-Man6 hydroxylamine) and other hydrazine compounds in avalglucosidase alfa. Taken together, the carcinogenicity potential of avalglucosidase alfa appears minimal.

Fertility was unaffected in mice treated with avalglucosidase alfa at exposure levels 50 mg/kg IV, every second day (9.4-fold the clinical dose for late onset Pompe disease patients). In a mouse embryofetal development study, a higher incidence of

[11] ICH S1A: guideline on the need for carcinogenicity studies of pharmaceuticals. July 1996.

post-implantation loss was noted at doses > 20 mg/kg/day IV (subclinical exposures). However, since placental transfer of avalglucosidase alfa was not evident in mice, the effect was considered to be secondary to maternal toxicity arising from the immunological response. There was no evidence of fetal damage at 50 mg/kg/day IV (17-fold the $AUC_{0\text{-}2wk}$ in late onset Pompe disease patients. In rabbits, embryofetal development was unaffected at doses up to 100 mg/kg/day IV (91-fold the mean $AUC_{0\text{-}2wk}$ in late onset Pompe disease patients). No pre-/postnatal developmental effects were observed in mice at doses up to 50 mg/kg IV, every second day (9.4-fold the clinical dose for late onset Pompe disease patients). A pregnancy category of B1;[12] the same category as Myozyme,[7] was proposed by the sponsor, which is acceptable.

A juvenile toxicity study was conducted in mice aged from postnatal Day 21 to Day 77 or Day 91 (corresponds to children/adolescents of between 2 and 16 years). At doses up to 100 mg/kg IV every other week (2 to 3-fold the highest mean $AUC_{0\text{-}2wk}$ value in infantile onset Pompe disease patients), no significant growth or development effects were reported. The only notable finding was an immunological response, similar to that seen in adult mice.

The limit for glycan is above the ICH Q3B qualification threshold of 0.15% (15 µg/mL).[13] The limit was qualified using genotoxicity studies (Ames test and chromosome aberration) and a 13-week repeat-dose toxicity study in monkeys (up to 5-fold the maximum amount of residual glycan at specification limit). The impurity, E11, was classified as potentially mutagenic (ICH M7 Class 3);[14,15] due to a hydrazine structural alert. However, the proposed limit is considered acceptable based on the permissible daily exposure for hydrazine.

Results and conclusions drawn from the nonclinical program for avalglucosidase alfa detailed in the sponsor's risk management plan are in general concordance with those of the TGA's nonclinical evaluation

There were no major deficiencies identified. Hypersensitivity reactions may be seen in patients.

The TGA review made recommendations specific to the wording of the Australian Product Information, which were accepted by the sponsor. Changes were made in Section 4.6 Use in pregnancy, to specify the avalglucosidase alfa exposure ratios for the developmental and reproductive toxicity studies.

Conclusion

The nonclinical data submitted was in accordance with the relevant ICH guideline for the nonclinical assessment of biotechnology products.

The overall quality of the nonclinical dossier was high, and all pivotal safety-related studies were GLP compliant.

[12] **Pregnancy Category B1**: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals have not shown evidence of an increased occurrence of fetal damage.
[13] ICH guideline Q3B (R2) Impurities in new drug products. CPMP/ICH/2738/99. June 2006.
[14] ICH guideline M7 (R1) Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk. EMA/CHMP/ICH/83812/2013. February 2018.
[15] Class 3 definition (ICH M7 (R1)): Alerting structure, unrelated to the structure of the drug substance; no mutagenicity data. Proposed action: Control at or below acceptable limits (appropriate threshold of toxicological concern (TTC)) or conduct bacterial mutagenicity assay. If non-mutagenic = Class 5, treat as non-mutagenic impurity. If mutagenic = Class 2, control at or below acceptable limits (appropriate TTC).

There were no objections to the registration of Nexviazyme (avalglucosidase-alfa) on nonclinical grounds.

Clinical

Summary of clinical data

Summary of clinical studies

This submission documented a full clinical development program of pharmacology, efficacy and safety studies appropriate for an orphan drug.

The submission contained the following:

- three clinical pharmacology studies providing pharmacokinetic, pharmacodynamic and safety pharmacology data: Study TDR12857, Study ACT14132 including one pharmacokinetic and pharmacokinetic, Report POH0817, an analysis of data from Study EFC14028.
- one population PK (popPK) analysis, Report POH0703
- one pivotal efficacy/safety study: Study EFC14028 (also called the COMET trial) in late-onset Pompe disease patients
- two other efficacy/safety studies: Study LTS13769, an extension study to Study TDR12857, and Study ACT14132 (also called the mini-COMET trial), in infantile-onset Pompe disease patients)
- six other reports: an integrated summary of efficacy and safety, a home infusion study, literature review of immunology for Study EFC14028 and updated tabulated data for efficacy outcomes for Study EFC14028
- Literature references

Paediatric data

Paediatric data was provided for patients from the age of one year and older, up to the age of 17 years.

The sponsor indicated that there is a proposed study that has not yet been started for the age ranges: infants and toddlers (28 days to 23 months) and preterm and term newborn infants (less than 28 days).

The sponsor indicated that they have an agreed Paediatric Investigation Plan (PIP) in Europe. The sponsor indicated that there is a proposed study which has not yet started, Study EFC14462 (also called the Baby-COMET trial). The study is part of the EU agreed PIP and will include naive infantile-onset Pompe disease patients less than or equal to 6 months of age with infantile-onset Pompe disease (IOPD). A PIP modification to also include two patients aged from 7 to 12 months into Study EFC14462;[16] was agreed by the EMA's paediatric committee (PDCO) on 23 July 2020. The clinical trial protocol will therefore be amended in the very near future to allow inclusion of these patients. First patient enrolment is expected before end of 2021.

[16] Study EFC14462 (Baby-COMET trial): An open-label, multinational, multicenter, intravenous infusion study of the efficacy, safety, pharmacokinetics, and pharmacodynamics of avalglucosidase alfa in treatment naïve pediatric participants with infantile-onset Pompe disease (IOPD). ClinicalTrials.gov Identifier: NCT04910776

The sponsor stated that they do not have an agreed Paediatric Plan under the Paediatric Research Equity Act (PREA) in the USA as this legislation does not apply to any drug for an indication for which orphan designation has been granted.

Good Clinical Practice

The sponsor states that all studies were conducted:

> *In accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, and the ICH guidelines for Good Clinical Practice (GCP), all applicable laws, rules and regulations*.

All studies were reviewed by appropriate ethics committees and informed consent from adults and assent for children was obtained prior to the conduct of any study related procedures.

No notable Good Clinical Practice (GCP) deviations were noted in any of the study documentation.

Guidance

The Delegate listed the following guidance as being applicable to this submission:

- Guideline on the Role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population. EMEA/CHMP/EWP/147013/2004 Corr.

  Effective from 24 August 2009

- Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population. CPMP/ICH/2711/99.

  Effective from 19 April 2001

- Reflection Paper on the Use of Extrapolation in the Development of Medicines for Paediatrics. EMA/189724/2018.

  Effective from 1 August 2014

- Guideline on Clinical Trials in Small Populations. CHMP/ICH/375/95.

  Effective from 1 December 2006

- Note for Guidance on Population Exposure: The extent of Population Exposure to Assess Clinical Safety. CHMP/ICH/375/95.

  Effective from 12 February 2002

- Guideline on Immunogenicity Assessment of Biotechnology Derived Therapeutic Proteins. EMEA/CHMP/BMWP/14327/2006.

  Effective from 22 June 2009

Pharmacology

Pharmacokinetics

Studies providing pharmacokinetic data included Studies TDR12857/LTS13769, Study EFC14028 and Study ACT14132. The pharmacokinetic (PK) studies separately reported data for patients naïve to enzyme-replacement therapy (ERT) and patients who had previously been treated with alglucosidase alfa. Two population pharmacokinetic (PopPK) models were provided by the sponsor: one included data collected only from children and adults with late-onset Pompe disease (Study POH0703); the second, which was prepared on request of the US FDA, included data from patients with infantile-onset Pompe disease.

Avalglucosidase alfa is administered as an intravenous solution and predominantly cleared by cellular uptake and subsequent catabolism. There is unlikely to be significant hepatic or renal clearance. The pharmacokinetics appear to be linear over the dose range of 5 mg/kg to 40 mg/kg. There was no evidence of accumulation with multiple doses in studies up to 48 weeks, and there was no obvious effect of previous exposure to alglucosidase alfa on avalglucosidase alfa pharmacokinetics.

At the usual late-onset Pompe disease dose of 20mg/kg every second week, the PopPK studies estimated a mean maximum concentration (C_{max}) of 273 µg/mL and the area under the concentration versus time curve from time zero to 2 weeks ($AUC_{0\text{-}2wk}$) of 1220 µg.h/mL, an average central volume of distribution of 3.4 L, and linear clearance following each dose of 0.87 L/h. There was no apparent effect of age on the pharmacokinetics of avalglucosidase alfa in patients with late-onset Pompe disease, noting that only one treated patient was aged less than 18 years, and 10 were 65 years or older.

The pharmacometrics evaluation confirmed that the modelling supported extrapolation of PK data from adult patients to children with late-onset Pompe disease.

In the infantile-onset Pompe disease patients, PK parameters for avalglucosidase alfa were derived from studies with patients who had either suboptimal response or declining response to previous treatment with alglucosidase alfa (Study ACT14132). Five patients with declining responses were treated with 20 mg/kg avalglucosidase alfa every second week, and five patients with declining responses were treated with 40 mg/kg avalglucosidase alfa every second week. A third group of five patients with suboptimal responses to alglucosidase alfa were treated with 40mg/kg avalglucosidase alfa every second week. At the lower dose of 20mg/kg avalglucosidase alfa every other week, the pharmacokinetics in patients with infantile-onset Pompe disease demonstrated both lower clearance and lower exposure to avalglucosidase alfa compared to patients with late-onset Pompe disease who were alglucosidase alfa experienced. Mean C_{max} was 175 to 189 µg/mL, area under the concentration versus time curve up until the last measurable concentration (AUC_{last}) was 805 to 923 µg.h/mL, volume at steady state of 3.5 to 3.6 L and clearance was 0.67 to 0.70 L/h in the small infantile onset Pompe disease population. At the higher dose, in declining responders the mean C_{max} was 297 to 403 µg/mL, AUC_{last} was 1930 to 2630 µg.h/mL, volume at steady state was 4.5 to 5.3 L and clearance was 0.56 to 0.68 L/h, and in suboptimal responders mean C_{max} was 250 to 356 µg/mL, AUC_{last} was 1720 to 2200 µg.h/mL, volume at steady state was 4.0 to 4.3 L and clearance was 0.53 L/h.

The PopPK analysis that included infantile-onset Pompe disease patient data was not able to support extrapolation of PK data from adults with late-onset Pompe disease to infants with infantile-onset Pompe disease.

No studies have been completed in patients with infantile-onset Pompe disease naïve to alglucosidase alfa. The sponsor states that an efficacy/safety/PK study in treatment-naïve infants, less than or equal to 6 months of age, with infantile-onset Pompe disease (Study EFC14462, also called the Baby-COMET trial)[16] is planned, from which they expect to report final clinical results in 2027.

No PK studies were conducted in patients with significantly impaired hepatic or renal function. Only six patients with mild renal impairment (estimate glomerular filtration rate (eGFR) of 60 to 89 mL/min) were included in the late-onset Pompe disease studies and there was insufficient data to conclude a clinical effect.

Pharmacodynamics

Limited pharmacodynamic (PD) data was collected in the efficacy and safety studies. Avalglucosidase alfa was developed as a modification of alglucosidase alfa, with additional mannose-6-phosphate (M6P) moieties to increase cellular uptake of the active protein. Urinary hexose tetrasaccharide (Hex4) levels (used as a biomarker for glycogen storage in

skeletal and cardiac muscle) were measured to assess glycogen accumulation, whereas creatinine kinase (CK), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were used as PD measures of muscle damage. A small number of patients had muscle biopsies taken. Urinary Hex4 levels declined and remained low with regular avalglucosidase alfa treatment in patients with late-onset Pompe disease both naïve to alglucosidase alfa and in patients who had previously been treated with alglucosidase alfa.

In Study EFC14028, the decrease in urinary Hex4 after 48 weeks of treatment was some five-fold greater with avalglucosidase alfa than with alglucosidase alfa at the same dose of 20 mg/kg every two weeks. Similarly, CK levels declined to a greater extent with avalglucosidase alfa than with alglucosidase alfa given at the same dose.

In the infantile-onset Pompe disease study (Study ACT14132), patients who had suboptimal responses or declining responses to alglucosidase alfa subsequently treated with avalglucosidase alfa 40 mg/kg every other week had numerically greater decreases in urinary Hex4 over 25 weeks than did patients treated with avalglucosidase alfa 20 mg/kg every other week or patients with declining responses to alglucosidase alfa who remained on treatment with alglucosidase alfa. Similar trends to improvement were seen in blood CK, ALT and AST levels. Owing to the small numbers in the studies, confidence intervals were overlapping.

Efficacy

Study EFC14028

Study EFC14028 was considered to be the pivotal efficacy trial for this submission.

Study EFC14028 was a Phase III randomised, multicentre, multinational, double blinded study comparing the efficacy and safety of repeated infusion of avalglucosidase alfa and alglucosidase alfa in 100 treatment-naïve patients with late-onset Pompe disease.

Patients were randomised in a 1:1 ratio with stratification by baseline forced vital capacity (FVC) percentage predicted;[17] (less than 55%, or 55% or more), gender, and age (under 18 years, or 18 years and older). Statistical analysis methods were appropriate, and a hierarchical testing strategy was applied. Treatment groups were reasonably well balanced with regard to demographic factors at baseline, although patients with Hispanic or Latino ethnicity contributed to 24.5% of the alglucosidase alfa treatment arm, and only 5.9% in the avalglucosidase alfa arm. There was no evidence that this imbalance in the patient population influenced the outcomes. All but one patient (aged 16) were adults.

The mean time from diagnosis to first infusion of study drug was 15.60 (standard deviation (SD) 32.06) months in the avalglucosidase alfa arm and 26.52 (SD 59.86) months in the alglucosidase alfa arm, and the difference in duration from first symptom of Pompe disease to first infusion of study drug was 160.36 ±131.71 months in the avalglucosidase alfa arm, compared to 151.78 ±120.90 months in the alglucosidase group.

The least square mean (LSM) change (± standard error (SE)) from Baseline to Week 49 in FVC percentage predicted in the modified intention-to-treat (mITT) population was 2.89 (0.88) in the avalglucosidase alfa group and 0.46 (0.93) in the alglucosidase alfa group. The difference of 2.43 with lower boundary of 95% confidence interval (CI) of -0.13

[17] **Forced vital capacity** (**FVC**) is the maximal volume of gas that can be expired as forcefully and rapidly as possible after a maximal inspiration to total lung capacity. An FVC test is lung/pulmonary function test normally conducted via spirometry and is commonly given a percentage predicted where a patient's FVC recorded during the test is compared to an average of the normal total volume for a person of the same gender, height, and age. This is expressed as a percentage, with normal test values falling between 80% and 120% of the average (predicted) values.

exceeded the predefined non-inferiority margin of -1.1 and thus achieved statistical non-inferiority (p = 0.0074), meeting the primary objective.

The test for superiority of avalglucosidase alfa over alglucosidase alfa at Week 49 was not statistically significant (p = 0.0626). The sponsor claims the difference between the two treatments is clinically meaningful based on the greater values of change from Baseline in percent predicted FVC being observed at each time point.

Table 2: Study EFC14028 Forced vital capacity (percent (%) predicted) in upright body position: Estimates and hypothesis tests of change from Baseline by visit (Primary analysis, in PAP, using modified intention to treat population)

	Statistics[a]	Avalglucosidase alfa (N = 51)	Alglucosidase alfa (N = 49)	Difference
Week 13	Estimate	3.05	0.65	2.40
	SE	0.78	0.81	1.13
	95% CI	1.50, 4.59	-0.95, 2.26	0.16, 4.63
	p-value for non-inferiority [b]			0.0026
	p-value for superiority			0.0363
Week 25	Estimate	3.21	0.57	2.64
	SE	0.80	0.84	1.17
	95% CI	1.62, 4.80	-1.10, 2.24	0.32, 4.96
	p-value for non-inferiority [b]			0.0018
	p-value for superiority			0.0259
Week 37	Estimate	2.21	0.55	1.66
	SE	1.00	1.05	1.45
	95% CI	0.23, 4.19	-1.53, 2.64	-1.22, 4.54
	p-value for non-inferiority [b]			0.0603
	p-value for superiority			0.2556
Week 49	Estimate	2.89	0.46	2.43
	SE	0.88	0.93	1.29
	95% CI	1.13, 4.65	-1.39, 2.31	-0.13, 4.99
	p-value for non-inferiority [b]			0.0074
	p-value for superiority			0.0626

Abbreviations: CI = confidence intervals; FVC = forced vital capacity; SE = standard error;

a) Based on mixed model repeats model (MMRM) model, the model includes baseline FVC (% predicted, as continuous), sex, age (in years at baseline), treatment group, visit, interaction term between treatment group and visit as fixed effects.

b) Non-inferiority margin is -1.1%

Secondary efficacy outcomes, except the SF-12 questionnaire;[18] showed similar improvements or trends to improvement with avalglucosidase alfa over those with

[18] The **SF-12** is a 12 question self-reported outcome measure assessing the impact of health on an individual's everyday life. It is often used as a quality of life measure. The SF-12 is a condensed and shortened version of it's predecessor, the SF -36.

alglucosidase alfa at Week 49, supporting the primary efficacy outcome. Patients who switched from alglucosidase alfa to avalglucosidase alfa in the extended treatment period demonstrated improved FVC percent-predicted, which was comparable to that in the avalglucosidase alfa arm, by Week 97.

Study ACT14132 was the only study submitted for patients with infantile-onset Pompe disease, enrolling 22 patients who had demonstrated clinical decline or sub-optimal clinical response to treatment with alglucosidase alfa. There were some notable demographic imbalances in the different cohorts, which could be partially attributed to the small group sizes. Most notable was that in Cohort 3, one patient receiving avalglucosidase alfa was diagnosed at 15.9 months and commenced treatment considerably later than the remaining patients in the cohort (who were diagnosed at ≤ 6.5 months and commenced treatment between 1.94 and 4.63 months later). Although the study was primarily a safety study, some secondary efficacy outcomes are presented here. The data are derived from an interim report with outcomes for all enrolled patients after six months of treatment (Week 25). Following treatment for 25 weeks, all patients could continue long-term avalglucosidase alfa treatment with follow-up for up to 7 years in an extended treatment period. A summary of the efficacy outcomes as evaluated during evaluation are given below.

- Five patients were receiving ventilation at baseline and few changes were observed in ventilation use during the timeframe.
- Despite heterogeneity of functional levels at baseline within and across cohorts, a trend of improvement in GMFM-88 total percent score;[19] was observed across all cohorts. All patients showed unchanged score or improved score, except 2 patients in Cohort 1 who demonstrated a worsening in this score.
- The greatest degree of change on the GMFM-88 was observed in the alglucosidase alfa group. This may be attributed to younger patient age and a smaller proportion of subjects within the group with suboptimal motor response at baseline. Three of six patients were included in Cohort 3 based on the sole inclusion criterion of new onset of ptosis.
- All cohorts except Cohort 1 showed improvement in QMFT total score;[20] while the mean score in Cohort 1 (that is, the 20 mg/kg group) remained stable. In general, correlation between the GMFM-88 and the 16-item QMFT, which is more specific to Pompe disease, were nominally significant.
- Despite high inter-patient variability in the 6MWT distance walked;[21] the plot of means by cohort showed more improvement in the patients treated with 40 mg/kg avalglucosidase alfa every other week. For the 5 patients with reliable tests (that is, > 5 years of age) from Cohort 2 and Cohort 3 avalglucosidase alfa arm, all improved.

[19] The **Gross Motor Function Measure (GMFM)** is an observational clinical tool originally designed to evaluate change in gross motor function in children with cerebral palsy. The original 88-item measure (the **GMFM-88**) was designed for use in children with cerebral palsy aged between 5 months to 16 years whose motor skills is delayed compared to those of the same age, however the GMFM-88 has also been validated for other populations. The scoring system consists of a 4-point scale with each item scored as 0, 1, 2, 3, or 'not tested'. Scores translate as: zero: does not initiate, 1: initiates task, 2: partially completes task, and 3: task completed. Some items involve parameters such as distance, time, support provided, accuracy, counts, and tasks will determine specific item scores.

[20] The **Quick Motor Function Test** (**QMFT**) was constructed on the basis of the clinical expertise of several physicians involved in the care of Pompe patients; the Gross Motor Function Measure and the IPA/Erasmus MC Pompe survey. The test comprises 16 items. The Quick Motor Function Test can rate clinical severity and motor function in children and adults with Pompe disease.

[21] The **6 Minute Walk Test** (6MWT) is a sub-maximal exercise test used to assess aerobic capacity and endurance. The distance covered over a time of 6 minutes is used as the outcome by which to compare changes in performance capacity.

- Assessment of Health-related quality of life through PedsQL[22], and pain through PedsQL and a Pain visual analogue score (VAS) reflected the impact of the underlying chronic disease, with trends of stable or improved assessments up to last available time points in most patients, although inter-individual high variability.

Based on the limited exploratory data and the mechanism of action, it is possible that further studies with avalglucosidase alfa in infantile-onset Pompe disease may confirm comparable efficacy outcomes to those reported for alglucosidase alfa.

Safety

Safety information for avalglucosidase alfa was collected and reported from Studies EFC14028 and TDR12857/LTS13769, and Study ACT14132 separately. Furthermore, a combined summary of clinical safety for five patient populations as follows:

- all patients;
- alglucosidase alfa-naïve patients;
- patients previously treated with alglucosidase alfa;
- adult patients; and
- paediatric patients

There was no placebo-controlled comparative data available, although Studies EFC14028 and TDR12857 provided some comparisons against alglucosidase alfa.

As may be expected for a rare disease such as Pompe disease, the total duration of exposure to avalglucosidase alfa in the clinical trials was relatively low. The total exposure time for the 19 patients treated with avalglucosidase alfa in the infantile-onset Pompe disease study was 1120.6 person-weeks, and for the 119 patients treated with avalglucosidase alfa in the late-onset Pompe disease studies was 13182.9 person-weeks.

[22] The Pediatric Quality of Life Inventory (**PedsQL**) is a brief measure of health-related quality of life in children and young people. It may either be completed by parents/guardians (the Proxy Report) and/or children and young people themselves (the Self-Report). The 23 items in the PedsQL comprise four Generic Core Scales: physical functioning (8 items), emotional functioning (5 items), social functioning (5 items) and school functioning (5 items)

Table 3: Duration of exposure, and by disease subtype across four studies

Duration of exposure	Infantile onset Pompe disease		Late onset Pompe disease	
	Patients n (%)	Person time (person-weeks)	Patients n (%)	Person time (person-weeks)
< 12 weeks	0	0	9 (7.6)	37.3
≥ 12 to < 24 weeks	3 (15.8)	39.3	6 (5.0)	94.1
≥ to < 48 weeks	5 (26.3)	177.6	14 (11.8)	464.4
≥ 48 to < 96 weeks	8 (42.1)	605.3	37 (31.1)	2615.6
≥ 96 to < 144 weeks	3 (15.8)	298.4	24 (20.2)	2754.6
≥ 144 to < 192 weeks	0		12 (10.1)	1936.3
≥ 192 to < 240 weeks	0		0	
≥ 240 weeks	0		17 (14.3)	5280.6
Total	19 (100.0)	1120.6	119 (100.0)	13182.9

Note: Study TDR12857 is completed. For the other 3 on-going studies, only data up to cut-off dates will be included: 30 September 2019 for Study ACT14132; 27 February 2020 for Study LTS13769 and 19 March 2020 for Study EFC14028.

Infantile-onset Pompe disease: Study ACT14132.

Late-onset Pompe disease: Studies TDR12857/LTS13769 and Study EFC14028

Note: Only exposure to avalglucosidase alfa data are included.

Person time is defined as the sum of the treatment exposure of all patients in each category.

In the pooled studies, the proportion of treatment-emergent adverse events (TEAE) potentially related to avalglucosidase alfa ranged between 30% in all paediatric patients to 50% in all adult patients (47.1% overall), and treatment-emergent severe adverse events potentially related to avalglucosidase alfa were reported only in alglucosidase alfa-naïve adult patients (3.6% of all patients).

One patient was reported to have a TEAE resulting in death, not related to avalglucosidase alfa (pancreatic adenocarcinoma), and four patients were reported to have permanently discontinued avalglucosidase alfa owing to a TEAE: respiratory distress and chest discomfort in one patient, and ocular hyperaemia and erythema in a second patient were considered related to study drug; whereas acute myocardial infarction in the third patient, and pregnancy in a fourth patient were not considered related to the study drug.

Treatment-emergent adverse events (TEAEs) reported in ≥ 20% of all patients included nasopharyngitis, headache, diarrhoea, back pain, fall and nausea. In the much smaller paediatric cohort, upper respiratory tract infection (30%), rash (30%), pyrexia (30%), fall (25%) and pneumonia (25%) were most frequently recorded. TEAE were comparable between avalglucosidase alfa and alglucosidase alfa treated arms where comparative data was collected. The most common TEAE in Study ACT14132 Cohort 3 (avalglucosidase alfa versus alglucosidase alfa) are tabulated below.

Table 4: Study ACT14132 Most common treatment-emergent adverse events, in PAP, by primary System Organ Class and Preferred Term (safety population)

Primary System Organ Class Preferred Term n (%)	Cohort 3	
	Avalglucosidase alfa (N = 5)	Alglucosidase alfa (N = 6)
Patients with at least one TEAE	5 (100)	5 (83.3)
Infections and Infestations	2 (40.0)	3 (50.0)
Upper respiratory tract infection	2 (40.0)	1 (16.7)
Urinary tract infection	0	1 (16.7)
Otitis media	0	1 (16.7)
Pneumonia	0	1 (16.7)
Viral infection	0	2 (33.3)
Nervous System Disorders	2 (40.0)	0
Headache	2 (40.0)	0
Eye Disorders	2 (40.0)	0
Eye irritation	2 (40.0)	0
Eyelid ptosis	0	0
Ear and labyrinth disorders	1 (20.0)	2 (33.3)
Excessive cerumen production	0	1 (16.7)
Middle ear effusion	1 (20.0)	1 (16.7)
Respiratory, thoracic and mediastinal disorders	2 (40.0)	1 (16.7)
Cough	2 (40.0)	0
Oropharyngeal pain	0	0
Rhinorrhoea	2 (40.0)	1 (16.7)

Primary System Organ Class Preferred Term n (%)	Cohort 3	
	Avalglucosidase alfa (N = 5)	Alglucosidase alfa (N = 6)
Gastrointestinal disorders	3 (60.0)	3 (50.0)
Diarrhoea	2 (40.0)	0
Vomiting	2 (40.0)	3 (50.0)
Abdominal pain	1 (20.0)	0
Toothache	0	0
Nausea	1 (20.0)	1 (16.7)
Skin and subcutaneous tissue disorders	2 (40.0)	1 (16.7)
Rash	2 (40.0)	1 (16.7)
Musculoskeletal and connective tissue disorders	1 (20.0)	0
Pain in extremity	1 (20.0)	0
General disorders and administration site conditions	2 (40.0)	1 (16.7)
Pyrexia	2 (40.0)	1 (16.7)
Injury, poisoning and procedural complications	0	0
Fall	0	0
Product issues	2 (40.0)	0
Device occlusion	2 (40.0)	0

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; SOC = System Organ Class; TEAE = treatment-emergent adverse event;

Note: Most common TEAEs are defined as those preferred terms which occur in at least 2 patients

Adverse Events are coded using MedDRA = MedDRA 22.0

Note: Sorted by SOC internationally agreed order and decreasing frequency of PT within a SOC in the groups of avalglucosidase patients (Cohort 1, Cohort2 and Cohort 3 avalglucosidase arm).

Source: Study ACT14132 CSR Table 22 (amended to include only Cohort 3).

Adverse events of special interest (AESI) included a long list of protocol-defined infusion-associated reactions (IARs), increases in liver transaminases (aspartate and alanine aminotransaminase (AST and ALT)) and increases in serum creatinine. The most frequent IARs reported in the pooled studies were pruritis (13/138 patients), rash (10/138, and 2 additional 'rash erythematous'), urticaria (8/138) and headache (8/138).

Pregnancy was also considered an event of special interest. Two pregnancies in women taking avalglucosidase alfa were reported, both resulting in live births with no further information provided. Three pregnancies in two partners were reported with no further information provided.

Eight reports of anaphylactic reactions were identified across the studies, of which two patients were considered to satisfy the clinical diagnosis of anaphylaxis. A 51 year-old woman discontinued the study after experiencing Grade 2 respiratory distress, chest pressure, flushing, cough, dizziness and nausea three minutes into an infusion of avalglucosidase alfa. She recovered with standard treatment for anaphylaxis.
A 44 year-old female experienced two episodes of symptoms including erythema, angioedema, flushing and oxygen desaturation, and was treated with standard treatment for anaphylaxis although not requiring adrenalin.

Hypersensitivity reactions included rash, pruritus, erythema, urticaria, respiratory failure, seasonal allergy, rhinitis allergic and infusion site rashes, with one or more symptoms reported by a total of 60 patients. In six patients the events were considered serious and/or severe, including respiratory failure, respiratory distress or severe rash. No event was considered to be consistent with immune-complex mediated disease.

Reports of anti-drug antibody (ADA) development against avalglucosidase alfa were recorded in both adult and paediatric populations and occurred in treatment-naïve and alglucosidase alfa experienced patients.

Table 5: Anti-avalglucosidase alfa antibody response for alglucosidase alfa-naïve patients (antidrug antibody evaluable population)

	Alglucosidase alfa-naïve patients (N = 61)
Antidrug antibody status, n (%)	
Always negative	3 (4.9)
Positive at Baseline	2 (3.3)
Positive post-Baseline	56 (91.8)
Treatment-induced ADA[a] n (%)	56 (94.9)
Transient response	1 (1.7)
Persistent response	49 (83,1)
Low response	8 (13.6)
Intermediate response	28 (47.5)
High response	13 (22.0)

	Alglucosidase alfa-naïve patients (N = 61)
Tolerised	6 (10.2)
Indeterminate response	0
Treatment-boosted ADA[b], n (%)	2 (100)
Treatment emergent ADA[c], n (%)	58 (95.1)

Abbreviation: ADA = antidrug antibody.

The percentage calculations are based on denominator of total number of patients in ADA evaluable population of each group if not specified.

a) Treatment induced ADA incidence is defined as 100 x (treatment induced ADA positive patients) / (number of evaluable patients with ADA negative at baseline).

b) Treatment boosted ADA incidence is defined as 100 x (treatment boosted ADA positive patients)/ (number of evaluable patients with ADA positive at baseline).

c) Treatment emergent ADA incidence is defined as 100 x (treatment boosted + treatment induced ADA positive patients)/ (number of evaluable patients).

Positive at baseline = pre-existing ADA and Positive post baseline = negative at baseline, and seroconverted ADA evaluable population in avalglucosidase alfa safety set will be used for the immunogenicity analyses. It is defined as all randomised or enrolled patients who received at least one infusion (partial or completed) of avalglucosidase alfa and had at least one ADA sample taken post-baseline after avalglucosidase alfa infusion that is appropriate for ADA testing with a reportable result.

Naïve-patients (from Studies TDR12857, LTS13769, and EFC14028).

Table 6: Anti-avalglucosidase alfa antibody response for alglucosidase alfa experienced patients (antidrug antibody evaluable population)

ADA status	Alglucosidase alfa-experienced patients, n (%)		
	Adult (N = 55)	Paediatric (N = 18)	All (N = 73)
Always negative	6 (10.9)	10 (55.6)	16 (21.9)
Positive at baseline	40 (72.7)	3 (16.7)	43 (58.9)
Positive post baseline	9 (16.4)	5 (27.8)	14 (19.2)
Treatment-induced ADA[a], n (%)	9 (60.0)	5 (33.3)	14 (46.7)
Transient response	3 (20.0)	1 (6.7)	4 (13.3)
Persistent response	5 (33.3)	3 (20.0)	8 (26.7)
Low response	5 (33.3)	1 (6.7)	6 (20.0)
Intermediate response	0	2 (13.3)	2 (6.7)
High response	0	0	0

ADA status	Alglucosidase alfa-experienced patients, n (%)		
	Adult (N = 55)	Paediatric (N = 18)	All (N = 73)
Tolerised	1 (6.7)	0	1 (3.3)
Indeterminate response	0	1 (6.7)	1 (3.3)
Treatment-boosted ADA[b], n (%)	18 (45.0)	0	18 (41.9)
Treatment emergent ADA[c], n (%)	27 (49.1)	5 (27.8)	32 (43.8)

Abbreviation: ADA = antidrug antibody

The percentage calculations are based on denominator of total number of patients in ADA evaluable population of each group if not specified.

a) Treatment induced ADA incidence is defined as 100 x (treatment induced ADA positive patients)/(number of evaluable patients with ADA negative at baseline).

b) Treatment boosted ADA incidence is defined as 100 x (treatment boosted ADA positive patients)/(number of evaluable patients with ADA positive at baseline).

c) Treatment emergent ADA incidence is defined as 100 x (treatment boosted + treatment induced ADA positive patients)/(number of evaluable patients).

Positive at baseline = pre-existing ADA and Positive post baseline = negative at baseline, and seroconverted

ADA evaluable population in avalglucosidase alfa safety set will be used for the immunogenicity analyses. It is defined as all randomised or enrolled patients who received at least one infusion (partial or completed) of avalglucosidase alfa and had at least one ADA sample taken post-baseline after avalglucosidase alfa infusion that is appropriate for ADA testing with a reportable result.

Experienced patients: previously treated with alglucosidase alfa (in Studies TDR12857, LTS13769, EFC14028, and ACT14132), CRIM negative paediatric patients excluded.

Overall, the safety profile of avalglucosidase alfa is consistent with that of the registered formulation of alglucosidase alfa.

Home infusions

The sponsor has requested that recommendations for home infusion are included in the Product Information. This was based on a retrospective review of home-based infusions for adults with late-onset Pompe disease being treated with alglucosidase alfa in the Netherlands. No data was presented by the sponsor regarding the applicability of home infusions in Australia, and the clinical evaluation noted that there is a requirement for a doctor or nurse practitioner to be in attendance during the infusion period (up to six hours).

As part of a response to a request for more information, the sponsor explained that eight patients in Study EFC14028 (late-onset Pompe disease), two patients in Study LTS13769 (late-onset Pompe disease) and one patient in Study ACT14132 (infantile-onset Pompe disease) had received avalglucosidase alfa at home under healthcare professional supervision during the COVID-19 pandemic. These 11 patients received up to 27 home infusions each for a total of 154 infusions in the home setting. There have been no reports of medication errors, however one 32 year old female experienced eyelid oedema and flushing during one treatment which was treated with methylprednisolone and dexchlorpheniramine. Subsequent infusions were given at the study site. There is no reported experience of home infusion of avalglucosidase alfa nor alglucosidase among Australian patients.

The sponsor also provided a 'consensus document' signed by 10 Australian clinicians from major tertiary hospitals in Australia. The document indicated that home infusions are particularly appropriate during the COVID-19 pandemic, and that other enzyme replacement therapies have been given as home infusions at the discretion of the treating specialist physician. The evaluator has noted that two of the three therapies for which home infusion is apparently common practice do not contain information in the PI.

The clinical evaluation has recommended that, should home infusions of Nexviazyme be supported, it should be made clear that guidance in the PI and in any educational material should not override specialist recommendations and guidelines.

Clinical recommendation

The clinical evaluation found the submission to be approvable for the following modified indication:

> *Nexviazyme is indicated for long term enzyme replacement therapy for the treatment of patients with late onset Pompe disease (LOPD) (acid α-glucosidase deficiency).*

The recommendation for approval came with the following proposed conditions of registration.

Proposed conditions of registration

The sponsor should submit final study reports for any ongoing or planned clinical studies, as were detailed in the sponsor's response to TGA questions for the sponsor. These included final reports for ongoing studies: Study LTS13769, Study EFC14028 (the COMET trial) and Study ACT14132 (the Mini-COMET trial), as well as the planned study in treatment-naïve infants with infantile onset Pompe disease, Study EFC14462 (the Baby-COMET trial).[16]

Risk management plan

The sponsor has applied to register a new biological entity, avalglucosidase alfa in the drug product Nexviazyme. Nexviazyme is proposed to be used as a long-term enzyme replacement therapy for the treatment of patients with Pompe disease (acid alpha-glucosidase deficiency). The proposed dosing regimen involves weekly intravenous infusion of 20 mg/kg of body weight for late-onset Pompe disease or 40 mg/kg body weight for infantile-onset Pompe disease. Avalglucosidase alfa was granted Orphan Drug Designation by the TGA on 15 September 2020 for the treatment of Pompe disease.

The sponsor submitted draft EU-RMP (risk management plan) version 1.0 (date 26 August 2020; data lock point (DLP) 19 March 2020) and Australia Specific Annex (ASA) version 1.0 (October 2020) in support of this application. In the sponsor's response to TGA questions, the sponsor informed that a further EU-RMP version 1.2 is under development to address European Medicine Agency (EMA) recommendations and will be supplied to TGA in association with an updated ASA after June 2021. At the third round, draft EU-RMP version 1.2 (date 14 June 2021; DLP 19 Mar 2020) and ASA version 1.2 are supplied in support of a decision on product registration.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 8. Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach.

Table 7: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies	✓[3]	✓[5,6]	✓	✓[10]
Important potential risks	Immunogenicity leading to loss of response (high sustained IgG antibody titres and/or neutralising antibodies)	✓	✓[5]	✓	✓[11]
	Medication errors in the home infusion setting [1]	✓	✓[5,6]	✓	✓[12]
	Immune complex related reactions [1]	✓	✓[5]	–	–
Missing information	Use in pregnant and lactating women	✓[4]	✓[7]	✓	–
	Use in patients with renal or hepatic insufficiency [1]	✓	✓[8]	✓	–
	Use in children below 6 months of age [2]	✓	✓[9]	–	–

Abbreviations: IgE: Immunoglobulin E; IgG: Immunoglobulin G;

[1] Added at Round 3 in EU-RMP v1.2 and ASA v1.2.

[2] Australia-specific safety concern added in ASA v1.2 (TGA request)

[3] Targeted follow-up questionnaire – hypersensitivity reactions

[4] Targeted follow-up questionnaire – Pregnancy / Drug Exposure Via Parent (DEVP) Data Collection Form

[5] Clinical trials: ongoing LTS13769, EFC14028(COMET), ACT14132 (Mini-COMET); and planned EFC14462

[6] Post-authorisation safety study (PASS)

[7] AGLU03506 (Pompe Disease Pregnancy Sub-registry)

[8] DIREGC07005 (Pompe Disease Registry)

[9] EFC14462

[10] Educational materials -HCP guide for immunosurveillance service, Home infusion guide

[11] Educational material -HCP guide for immunosurveillance service

[12] Educational material – Home Infusion Guide

At the third round of evaluation, the summary of safety concerns in the RMP and ASA is considered acceptable. EU-RMP version 1.2 has been produced to address questions from EMA's Committee for Medicinal Products for Human Use (CHMP) and Pharmacovigilance Risk Assessment Committee (PRAC) at an advanced stage (Day 180);[23] of the initial

[23] The evaluation of medicines, step-by-step | European Medicines Agency (europa.eu) https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/evaluation-medicines-step-step

marketing authorisation application evaluation for avalglucosidase alfa (EMEA/H/C/005501); including addition of further safety concerns which also address earlier TGA requests (see Table 8 above). On request, use in children below 6 months of age is included by sponsor in the ASA as Australia-specific missing information item for follow-up.

Routine and additional pharmacovigilance activities are proposed. The EMA-required additional activities include three ongoing studies and one planned clinical study to further characterise risks associated with of Nexviazyme use. At the third round of RMP evaluation, a further three EMA-required activities are added in the RMP and all are in planning phase:

1. DIREGC07005 - Collection of data from the Pompe Disease Registry to provide assessment on the missing information 'Use in patients with renal and hepatic insufficiency';
2. AGLU03506 - Use of Pregnancy sub-registry to provide further characterization of the missing information 'Use in pregnant and lactating women'; and
3. Addition of a new Post-Authorisation Safety Study to further characterise the risks 'Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development'. The studies in EU-RMP are applicable to Australian use of Nexviazyme and all are included in the ASA. Should the results of these studies identify any new safety concerns, or change the status of existing safety concerns, the ASA will be updated with this information in the post-market setting. The pharmacovigilance plan is considered acceptable.

Routine risk minimisation activities are proposed. Pack insert for Nexviazyme will be identical to the PI and this is considered an appropriate measure for injectable products. At the third round of RMP evaluation, educational programme for Nexviazyme is added into the EU-RMP and ASA consisting of following educational materials to minimise the important risks indicated in table above: A Healthcare Professional (HCP) guide for immunosurveillance service, and a Home infusion guide. The programme will be implemented in post-market setting and will be ongoing by sponsor from first use of Nexviazyme in Australia. Draft materials have been supplied, but are subject to final acceptance by TGA prior to use. The risk minimisation plan is considered acceptable.

Following acceptance of EU recommendations and earlier TGA RMP evaluation requests, sponsor commits to implement an educational materials to support Nexviazyme use. ASA v1.2 has been supplied as accompanying document to EU-RMP v1.2 to support the decision on product registration and this includes acceptable risk management strategies. Drafts of the Australian additional risk minimisation materials have also been supplied to the TGA as follows:

- *HCP guide for immunosurveillance service* (v1.0 10 August 2021), for management of the following safety concerns:
  - Important identified risk: *'Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies'.*
  - Important potential risk: *'Immunogenicity leading to loss of response (High Sustained IgG Antibody Titres and/or neutralising antibodies'.*
- *HCP Guide - Home infusion for Nexviazyme*, for management of the following safety concerns:
  - Important identified risk: *'Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies'.*
  - Important potential risk: *'Medication errors in the home infusion setting'.*

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

> *The Nexviazyme EU-Risk Management Plan (RMP) (version 1.2, dated 14 June 2021; DLP 19 Mar 2020), with Australian Specific Annex (version 1.2, dated 10 August 2021), included with submission PM-2020-05478-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.*

The following wording is recommended for the PSUR requirement:

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

> *Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.*
>
> *If the product is approved in the EU during the three years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter.*
>
> *The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.*

As Nexviazyme is a new biological entity it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

> *Nexviazyme (Avalglucosidase alfa) is to be included in the Black Triangle Scheme. The PI and CMI for Nexviazyme must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.*

Risk-benefit analysis

Delegate's considerations

Indication

Data supporting the efficacy and safety of avalglucosidase alfa in adult patients with late-onset Pompe disease is adequate for this rare disease, but extremely limited in younger populations, particularly in newly diagnosed, treatment naïve patients with infantile-onset Pompe disease. Population pharmacometrics studies support extrapolation of data from

adult patients with late-onset Pompe disease to younger patients with late-onset Pompe disease. No significant safety concerns have been identified with Nexviazyme.

In response to requests arising from the clinical evaluation, the sponsor argued that Nexviazyme should also be approved for use in infantile-onset Pompe disease. The arguments presented included that Nexviazyme is a modification of alglucosidase alfa (Myozyme);[7] which has been extensively used in patients with infantile-onset Pompe disease, confirming long term safety and effectiveness in clinical practice.

The underlying pathophysiology of Pompe disease is common to infantile-onset Pompe disease and late-onset Pompe disease, with symptoms developing based only on the differing levels of residual enzyme activity. The sponsor also argued comparable pharmacokinetic profiles in infantile-onset Pompe disease and late-onset Pompe disease, but this does not appear to be supported by the population PK/PD models. Even applying a pragmatic approach as may be justified in some very rare conditions, approving a new medical therapy for a section of the treatment population in the absence of any direct clinical data presents its own risks.

On the other hand, infantile-onset Pompe disease is the most severely affected population with rapidly progressive disease who arguably stand to benefit the most from the modified enzyme-replacement therapy. The delegate notes that the sponsor does not intend to cease manufacturing the currently registered therapy, and that an additional paediatric study in treatment-naïve patients is planned, in accordance with EU requirements. It may be a more considered approach to await the results of the proposed study before registering Nexviazyme for patients with infantile-onset Pompe disease.

Home infusions

Home infusions are accepted practice in some overseas jurisdictions, and may have a place in the Australian context, where 'hospital in the home' approaches to treatment are becoming more common.

In the opinion of this Delegate, the major concern with regard to home infusions of enzyme-replacement therapy in general, and Nexviazyme in particular, is likely to lie with the risk of significant hypersensitivity reactions and anaphylaxis, and subsequently a need for attendance by a health care practitioner with appropriate training and equipment to deal with unexpected adverse events.

Resolution of these issues lie within the realm of clinical practice, rather than with the TGA. The major issue with including recommendations for home infusions in the product information is that some health care workers may understand that the TGA have received and evaluated high standard evidence supporting the practice. Reference to home infusions has been included in the product information for other registered enzyme-replacement therapy. This alone does not indicate that such advice should be included for another enzyme-replacement therapy.

Efficacy and safety

The evidence provided for efficacy and safety of Nexviazyme in adults with late-onset Pompe disease is sufficient to support registration in this population, and the sponsor has provided a reasonable case for extrapolation to a younger population with late-onset Pompe disease. The clinical evidence provided to support the use of Nexviazyme in infantile-onset Pompe disease, and in particular in treatment naïve patients with infantile-onset Pompe disease, is immature and does not meet the accepted standards generally applied by the TGA. While there is a bridging argument based on the mechanism of action of Nexviazyme in late-onset Pompe disease and infantile-onset Pompe disease populations, it would be appropriate to continue to support treatment of patients with the registered therapy until sufficient evidence of efficacy and safety becomes available.

Summary of data

There was one pivotal efficacy/safety study (Study EFC14028) comparing outcomes with avalglucosidase alfa and current registered treatment alglucosidase alfa in 100 patients with late-onset Pompe disease. This was supported by two primarily safety studies with secondary efficacy outcomes in 24 patients with late-onset Pompe disease and 26 patients with infantile-onset Pompe disease who were suboptimal responders or experienced declining responses to alglucosidase alfa. Among adult patients with late-onset Pompe disease, avalglucosidase alfa was at least non-inferior to alglucosidase alfa with regard to the primary efficacy outcome, and secondary efficacy outcomes were supportive. In the small population of patients with infantile-onset Pompe disease with poor responses to alglucosidase alfa, secondary efficacy outcomes trended to improvement. There is no clinical trial data in treatment-naïve patients with infantile-onset Pompe disease. Adverse events in patients treated with avalglucosidase alfa were comparable to those experienced by patients treated with alglucosidase alfa.

Outstanding issues

Few patients with Pompe disease aged below 18 years were included in the submitted studies, and the submission relies upon population pharmacometrics to support extrapolation of efficacy outcomes reported in adults with late-onset Pompe disease (one patient aged 16 years) to younger patients.

No data was provided to support efficacy or safety in treatment naïve patients with infantile-onset Pompe disease, and data for patients with infantile-onset Pompe disease who had suboptimal or declining responses to alglucosidase alfa, and who had severe disease as indicated by the presence of cardiomyopathy was limited.

The pharmacokinetics of avalglucosidase alfa in adult patients with late-onset Pompe disease, and in younger patients with infantile-onset Pompe disease appear to be different, suggesting that extrapolating data from late-onset Pompe disease to infantile-onset Pompe disease patients would not be appropriate.

The sponsor intends to include information regarding the possibility of home infusions of avalglucosidase alfa for selected patients in the product information. There are limited controlled reports of efficacy and safety outcomes of home infusions of enzyme replacement therapies in Australia.

Proposed action

While the Delegate's decision was yet to be made, at this stage the Delegate was inclined to approve the registration of Nexviazyme for the population of patients with late onset Pompe disease only.

Advisory Committee considerations

The Advisory Committee on Medicines (ACM) considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

1. What is the opinion of the committee regarding the extrapolation of data from adult patients with late onset Pompe disease to patients aged between 12 and 18 years?

The ACM advised this data could be extrapolated for late-onset Pompe disease, patients aged between 12 and 18 years. The data provided demonstrates there is no apparent age effect of pharmacokinetics in late onset Pompe disease. The ACM were satisfied that the

disease mechanisms in adolescent late-onset Pompe disease and adult late onset Pompe disease, are the same when consideration is given to the spectrum of enzyme deficiency.

2. What is the opinion of the committee regarding the extrapolation of data from adult patients with lateonset Pompe disease to children aged younger than 12 years?

The ACM advised there is no biological reason why this data cannot be extrapolated for late-onset Pompe disease patients younger than 12 years. The severity of disease is reflected as a spectrum of enzyme deficiency rather than age related parameters.

The ACM noted that it is unlikely that late onset Pompe disease will be diagnosed before the age of one.

3. What is the opinion of the committee regarding the efficacy of avalglucosidase alfa in the treatment of paediatric patients with infantile-onset Pompe disease?

The ACM noted that the Mini-COMET trial (Study ACT14132) was the only study submitted for patients with infantile-onset Pompe disease and was primarily a safety study, with efficacy as a secondary endpoint.

The ACM discussed this study and while noting that this study is ongoing, were of the view that the diversity in age, gender and baseline prior treatments made the assessment of efficacy challenging but that it did provide some support of treatment efficacy.

The ACM also noted that treatment duration can be finite if the disease has progressed beyond reversibility, in which case neither avalglucosidase alfa nor Myozyme[7] would improve symptoms. The ACM noted no patients' disease worsened throughout the study, which may be interpreted as evidence of some effectiveness.

4. In the absence of clinical data regarding the efficacy and safety of avalglucosidase alfa in treatment-naïve patients with infantile-onset Pompe disease, what is the opinion of the committee regarding the generalisability of clinical information from patients with late-onset Pompe disease and/or treatment-experienced infant patients with infantile-onset Pompe disease to this population?

While the ACM noted that no efficacy data specific to the treatment naïve infantile-onset Pompe disease patients was provided. The ACM advised that infantile-onset Pompe disease and late-onset Pompe disease is a spectrum of the same disease and considered that based on the data provided and the understanding of the disease, treatment naïve infantile-onset Pompe disease patients could be expected to respond to avalglucosidase therapy in a similar manner to treatment-experienced patients. The ACM noted that this is an extremely rare and devastating disease and the demand for improved treatment options for infantile-onset Pompe disease patients was also acknowledged.

The ACM noted that infantile-onset Pompe disease is usually diagnosed at a young age. Given the current lack of data for treatment-naïve infantile-onset Pompe disease and limited data for treatment-experienced infantile-onset Pompe disease, the ACM recommended that the indication be limited to those aged above one year old, noting that additional data will be available from the proposed Baby-COMET trial (Study EFC14462)[16] which is due to end in 2027.

5. What is the opinion of the committee regarding the safety of home infusions of avalglucosidase alfa in the home environment?

The ACM advised that stable patients with sufficient access to emergency services and other risk mitigation strategies in place should have the option to be treated at home. Data in the literature further supports enzyme therapy administration in the home as long as appropriate supports are in place.

6. If home infusions are to be supported in the product information, what is the advice of the committee regarding the availability of clinical support during the infusion period?

The ACM advised that the comprehensive checklist outlined in the clinical evaluation report should be used to support home infusion administration. This includes patient specific parameters such as stable disease, no prior infusion-associated reactions (IAR) in the clinical setting, and strict adherence to the prescribed regimen. Health care providers administering home infusions must also be sufficiently trained to recognise IARs, perform cardiopulmonary resuscitation (CPR) and have ready access to emergency medical services. The ACM also noted that reconstitution of this product is complex, so should be undertaken in a sterile manufacturing pharmacy onsite before being transported to the patient.

7. The ACM is requested to provide any other advice applicable to this submission.

The ACM also discussed the potential clinical benefit of the dosing suggested by the sponsor for infantile-onset Pompe disease patients (40 mg/kg every 2 weeks) in late-onset Pompe disease patients, compared with dosing used in the late-onset Pompe disease clinical trials (20 mg/kg every 2 weeks). This was considered based on the theory that higher doses are required for sufficient skeletal muscle penetration. The ACM advised, however, that a regulatory decision must be taken from the data submitted in the dossier, rather than clinical judgement and extrapolation. The ACM advised a starting dose of 20 mg/kg should be stipulated in the PI, in line with the clinical trial data.

Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

> *Nexviazyme is indicated for long-term enzyme replacement therapy for the treatment of patients one year of age and older with Pompe disease (acid α-glucosidase deficiency).*

Outcome

Based on a review of quality, safety, and efficacy, the TGA approved the registration of Nexviazyme, avalglucosidase alfa, powder for injection 100 mg/10 mL (vial), indicated for:

> *Nexviazyme is indicated for long-term enzyme replacement therapy for the treatment of patients one year of age and older with Pompe disease (acid α-glucosidase deficiency).*

Specific conditions of registration applying to these goods

- The Nexviazyme EU-Risk Management Plan (EU-RMP), version 1.2, dated 16 June 2021, data lock point 19 March 2020, with Australian Specific Annex (version 1.2, dated 10 August 2021), included with submission PM-2020-04578-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

- Nexviazyme (avalglucosidase alfa) is to be included in the Black Triangle Scheme. The PI and CMI for Nexviazyme must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

- The sponsor should provide to the TGA the final study reports for any ongoing or planned clinical studies, as were detailed in the response to second round clinical questions submitted, as they become available. These include final reports for ongoing studies: Study LTS13769, Study EFC14028 (the COMET trial) and Study ACT14132 (the Mini-COMET trial), as well as the planned study in treatment-naïve infants with infantile-onset Pompe disease, Study EFC14462 (the Baby-COMET trial).
- All batches of Nexviazyme supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

Attachment 1. Product Information

The PI for Nexviazyme approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

Therapeutic Goods Administration

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