5.04 AVALGLUCOSIDASE ALFA, Powder for injection 100 mg in 10 mL, Nexviazyme®, sanofi-aventis Australia Pty Ltd

1 Purpose of submission

1.1 The Category 2 submission requested a Section 100 Highly Specialised Drugs Authority Required listing for avalglucosidase alfa (AVAL) for the treatment of Pompe disease.

1.2 Listing was requested on the basis of a cost minimisation approach (CMA) versus alglucosidase alfa (ALGLU) as the main comparator. As no comparator is listed on the PBS, the submission also presented a cost effectiveness analysis (CEA) versus placebo (untreated patients) as a secondary comparator, which used ALGLU as a proxy for the survival benefits of AVAL. The key components addressed by the submission are presented in Table 1.

Table 1: Key components of the clinical issue addressed by the submission (as presented in the submission)

Component	Description
Population	Infantile-onset Pompe disease Juvenile late-onset Pompe disease Adult late-onset Pompe disease who exhibit at least one of the following criteria: impaired respiratory function, sleep disordered breathing or significant muscle weakness
Intervention	AVAL 40 mg/kg IV every other week for infantile-onset Pompe disease AVAL 20 mg/kg IV every other week for juvenile-onset and adult-onset Pompe disease
Comparator	Primary comparator: ALGLU 20 mg/kg IV every other week Supplementary comparator: Placebo, representing standard of care Near market comparator: AT-GAA (Cipaglucosidase alfa 20 mg/kg IV + miglustat 260 mg every other week)
Outcomes	FVC % predicted, 6MWT, MIP, MEP
Clinical claim	AVAL demonstrates non-inferior efficacy and safety to ALGLU [a]

Source: Table 1.1-1, p1 of the submission
Abbreviations: 6MWT = 6-minute walk test; AVAL = avalglucosidase alfa; ALGLU = alglucosidase alfa; ERT = enzyme replacement therapy; FVC = forced vital capacity; IV = intravenous; MEP = maximum expiratory pressure; MIP = maximum inspiratory pressure
Notes: [a] The clinical claim for the supplementary comparator (placebo) was superior efficacy for ERT versus no treatment in terms of overall survival, where survival benefits of ALGLU was taken as a proxy for AVAL.

2 Background

Registration status

2.1 **TGA status at time of PBAC consideration**: not registered. The submission was made under the TGA/PBAC parallel process. The requested indication was "Avalglucosidase alfa is indicated for long-term enzyme replacement therapy (ERT) for the treatment of patients with Pompe disease (acid alpha-glucosidase deficiency; GAA)". At the time of PBAC consideration, the TGA Clinical Evaluation Report (Second Round), TGA

Delegate's Overview and Advisory Committee on Medicines (ACM) minutes were available.

2.2 The TGA Delegate was "inclined to approve the registration of Nexviazyme for the population of patients with LOPD only" and sought advice of the ACM on a number of 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 LOPD (one patient aged 16) to younger patients.
- No data was provided to support efficacy or safety in treatment naïve patients with IOPD, and data for patients with IOPD who had suboptimal or declining responses to ALGLU and who had severe disease (as indicated by the presence of cardiomyopathy) was limited.
- The pharmacokinetics of AVA [avalglucosidase alfa] in adult patients with LOPD and in younger patients with IOPD appear to be different, suggesting that extrapolating data from LOPD to IOPD patients would not be appropriate.
- The sponsor intends to include information regarding the possibility of home infusions of AVA for selected patients in the product information. There are limited controlled reports of efficacy and safety outcomes of home infusions of enzyme replacement therapies (ERT) in Australia".

2.3 The ACM considered it was reasonable to extrapolate the clinical data in adults with LOPD to younger patients with LOPD. The ACM considered that, given the current lack of data for treatment-naïve IOPD and limited data for treatment-experienced IOPD, the indication should be limited to those 1 year of age and older. The ACM considered AVAL 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)". The ACM advised that stable patients with sufficient access to emergency services and with other risk mitigation strategies in place should have the option to be treated at home. The ACM advised a starting dose of 20mg/kg should be stipulated in the Product Information for all patients. The PBAC noted the draft PI provided with the pre-PBAC response recommended a dose of 20 mg/kg every other week (referred to throughout as once every two weeks, q2w), with escalation to 40 mg/kg considered for patients with IOPD who experience insufficient control or declining response at the lower dose.

Pompe Disease Expert Panel Evaluation Overview

2.4 As part of the 2014 review of the Life Saving Drugs Program (LSDP), an Expert Panel (EP) was established to provide assistance and advice to the Commonwealth Chief Medical Officer on both new medicine applications and the review of existing medicines on the LSDP. The LSDP EP recently completed a review of Pompe disease.

2.5 The Term of Reference 2 (ToR 2) of the LSDP review for Pompe disease was to 'Review evidence for the management of each type of Pompe disease and compare to the LSDP treatment guidelines, patient eligibility and testing requirements for the use of these medicines on the program (including the validity of the tests)', ToR 5 to 'Assess the value for money of ALGLU in each of the treated populations under the current funding arrangements by evaluating the benefit of the drug's treatment outcomes and cost' and ToR 6 to 'Review the utilisation of ALGLU in each of the treated populations, including storage, dispensing and evidence of patient compliance to treatment'. The following recommendations for ToR 2, ToR 5 and ToR 6 may be of particular interest within the context of the current AVAL submission:

[redacted]

3 Requested listing

3.1 The submission presented separate proposed listings for infantile-onset (IOPD), juvenile-onset (JOPD) and adult-onset (AOPD) Pompe disease. The proposed initial and continuing treatment restrictions for AVAL were adapted from the corresponding eligibility requirements for ALGLU on the LSDP.

3.2 Secretariat suggestions and additions proposed are shown in italics and deletions are in strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty (packs)	Maximum Qty (units)	No. of Rpts	Published AEMP	Proprietary name and manufacturer
Avalglucosidase alfa, infusion, 100 mg vial	1	1 [a]	12	$[redacted]	NEXVIAZYME®, Sanofi Australia

Avalglucosidase alfa (initial restriction – IOPD)

Category/Program:	Section 100 – Highly Specialised Drugs Program
PBS indication:	Infantile-onset Pompe disease (IOPD)
Treatment phase:	Initial treatment
Restriction:	Authority Required-immediate/real time assessment by Services Australia (telephone/online application avenues)
Treatment criteria:	Must not be administered concomitantly with alglucosidase alfa
Clinical criteria:	The patient must be diagnosed with infantile-onset Pompe disease AND The patient must not be on long term invasive ventilation for respiratory failure before starting ERT, which indicates a disease severity that will not benefit from treatment *AND* O~~R~~ The patient must not have another life threatening or severe disease where prognosis is unlikely to be influenced by ERT *AND* ~~OR~~ The patient must not have another medical condition that might reasonably be expected to compromise a response to ERT *AND* ~~OR~~ The patient must not be a current smoker
Population criteria:	The patient must be aged ≤ 24 months at the time of initial application
Administrative advice:	Avalglucosidase alfa is not for in-patient use

Avalglucosidase alfa (initial restriction – JOPD)

Category/Program:	Section 100 – Highly Specialised Drugs Program
PBS indication:	Juvenile-onset Pompe disease (JOPD)
Treatment phase:	Initial treatment
Restriction:	Authority Required-immediate/real time assessment by Services Australia (telephone/online application avenues)
Treatment criteria:	Must not be administered concomitantly with alglucosidase alfa
Clinical criteria:	The patient must be diagnosed with juvenile-onset Pompe disease AND The patient must not be on long-term invasive ventilation for respiratory failure before starting ERT, which indicates a disease severity that will not benefit from treatment

	AND ~~OR~~ The patient must not have another life-threatening or severe disease where prognosis is unlikely to be influenced by ERT *AND* ~~OR~~ The patient must not have another medical condition that might reasonably be expected to compromise a response to ERT *AND* ~~OR~~ The patient must not be a current smoker
Population criteria:	The patient must be aged over 24 months and under 18 years at the time of initial application

Avalglucosidase alfa (initial restriction – AOPD)

Category / Program:	Section 100 – Highly Specialised Drugs Program
PBS Indication:	Adult-onset Pompe disease (AOPD)
Treatment phase:	Initial treatment
Restriction:	Authority Required-immediate/real time assessment by Services Australia (telephone/online application avenues)
Treatment criteria:	Must not be administered concomitantly with alglucosidase alfa
Clinical criteria:	The patient must be diagnosed with adult-onset Pompe disease AND The patient must not be on long term invasive ventilation for respiratory failure before starting ERT, which indicates a disease severity that will not benefit from treatment *AND* ~~OR~~ The patient must not have another life threatening or severe disease where prognosis is unlikely to be influenced by ERT *AND* ~~OR~~ The patient must not have another medical condition that might reasonably be expected to compromise a response to ERT *AND* ~~OR~~ The patient must not be a current smoker AND [The patient must present with FVC, either supine or erect, < 80% of the predicted value OR The patient must have sleep disordered breathing OR The patient must have significant muscular weakness]
Population criteria:	The patient must be aged 18 years or over at the time of initial application

Avalglucosidase alfa (continuation restriction – IOPD, JOPD and AOPD)

Category / Program:	Section 100 – Highly Specialised Drugs Program
PBS Indication:	Infantile-onset, Juvenile-onset, or Adult-onset Pompe disease
Treatment phase:	Continuing treatment
Restriction:	Authority Required-immediate/real time assessment by Services Australia (telephone/online application avenues)
Treatment criteria:	Must not be administered concomitantly with alglucosidase alfa
Clinical criteria:	The patient must have received prior treatment with this drug AND [The patient must demonstrate clinical improvement OR The patient must demonstrate stabilisation of the disease condition]

Abbreviations: AOPD = adult-onset Pompe disease; IOPD; infantile-onset Pompe disease; JOPD = juvenile-onset Pompe disease; PBS = Pharmaceutical Benefits Scheme

3.3 The submission requested a special pricing arrangement (SPA) for AVAL. The proposed effective price for IOPD was $[redacted] per 100 mg vial and was not stated for JOPD or AOPD in the submission. However, the submission proposed price parity to the current

LSDP price for ALGLU for JOPD and AOPD. The ESC noted the requested price per month for JOPD was $[redacted] and for AOPD was $[redacted].

3.4 Though the requested clinical restrictions for initial treatment for JOPD and AOPD are differentiated, the clinical evidence presented in the submission combined these two populations as late-onset Pompe disease (LOPD). The ESC noted the LSDP guidelines quantitatively define respiratory function test, sleeping disorders, breathing and significant muscular weakness and considered this should be included in in the clinical criteria requested for AVAL for AOPD. However, the ESC further considered that the proposed restriction criteria will need to be reviewed to ensure people with JOPD are able to meet the criteria. The ESC noted the proposed criteria does not require evidence of a diagnosis of Pompe disease.

3.5 The Pre-Sub-Committee Response (PSCR) stated the proposed population criteria for IOPD should be amended to "the patient must be aged ≤24 months at the time of initial application for ERT", where ERT may be ALGLU or AVAL. The PBAC noted the indication supported by the ACM was limited to patients over 1 year of age and considered this criteria may need to be revised depending on the final indication approved by the TGA.

4 Population and disease

4.1 Pompe disease is a rare autosomal recessive disorder in glycogen storage caused by mutations in the GAA gene. GAA deficiency leads to accumulation of glycogen in multiple tissues resulting in progressive metabolic myopathy, respiratory dysfunction and/or cardiac impairment. Pompe disease is classified into different phenotypes based on age at onset of symptoms, extent of organ involvement and rate of progression to death. Pompe disease is classified as:

- IOPD when symptoms present before the age of 1 year (the PSCR suggested this should be 2 years), and
- LOPD for presentations in early childhood and adulthood.

4.2 IOPD is less common than LOPD, with an estimated incidence of 1 in 138,000 and 1 in 57,000 live births, respectively. IOPD is aggressive and characterised by progressive hypertrophic cardiomyopathy and muscle weakness, leading to cardiorespiratory failure. A small proportion of patients with IOPD might not present with cardiomyopathy (non-classical IOPD) and undergo a relatively more indolent disease course. IOPD can be further classified by cross-reactive immunological material (CRIM) status. CRIM positive patients synthesise a non-functional form of GAA, whilst CRIM negative patients are unable to form any kind of native enzyme. CRIM negative patients have poorer prognosis and response to ERT.

4.3 LOPD is a broad term that refers to JOPD (onset between 24 months and 18 years of age) and AOPD (onset ≥18 years of age). LOPD progresses more slowly and may present any time from early childhood to late adulthood (median age of symptom

onset: 29-33 years). Patients present with impaired respiratory function and skeletal muscle weakness, especially limb-girdle weakness. The clinical evidence presented by the submission was based on the onset of Pompe disease classified as IOPD and LOPD.

4.4 AVAL is a recombinant human GAA (rhGAA) that provides an exogenous source of GAA. AVAL is a conjugated bis-mannose-6-phosphate rhGAA engineered to increase cellular uptake of the enzyme to enhance glycogen clearance in target tissues.

5 Comparator

5.1 The submission nominated ALGLU as the main comparator. ALGLU has been available via the LSDP since 2010 for patients with IOPD and since February 2015 and September 2015 for JOPD and AOPD, respectively. In the absence of PBS listed medicines for Pompe disease, given that ALGLU was listed on the LSDP, placebo was nominated as the supplementary comparator.

5.2 AT-GAA (cipaglucosidase alfa + miglustat) was nominated as the near-market comparator and is not currently TGA approved. The submission provided an indirect treatment comparison (with ALGLU as the common comparator).

5.3 The submission stated that advantages of AVAL over ALGLU included that:

- AVAL offers advantages in terms of reconstitution time, based on a Pompe ERT pharmacy survey. The evaluation considered that the way some questions were phrased in the survey, such as “preparing a MYOZYME [alglucosidase alfa] infusion can require two-time consuming steps…”, had the potential to introduce response bias by inducing respondents towards a certain answer. It was also noted that 10 of out the 11 pharmacies prepared ALGLU infusions for one to two patients each month and that each AVAL vial contains 100 mg whereas ALGLU vials are 50mg.
- whilst ALGLU is currently only administered in specialist infusions centres, AVAL may also be administered at the patient’s home with the cost of the home-infusion service funded by Sanofi. The ESC noted the submission did not address why ALGLU was not also suitable for home-infusion services. The pre-PBAC response stated the current ALGLU PI does not include home infusion services and to include this would require a major submission to the TGA.

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician described the benefits of current ERT on the clinical progression of Pompe Disease. Of particular note, patient experience of breathlessness and difficulty walking were highlighted as two major impacts on quality of life, which PBAC noted reflected the usefulness of FVC and 6MWT as clinical measures in the trials. The clinician also described the lifestyle

benefits for a patient on long-term treatment and the independence the treatment allows.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (25), health care professionals (HCP, 2) and organisations (2) via the Consumer Comments facility on the PBS website. The HCPs described the impacts of Pompe Disease on patients' quality of life, particularly with weakness and respiratory issues, and highlighted the improvements for patients on treatment in regaining function and being active members of their community.

6.3 The PBAC noted the advice received from the Australian Pompe Association clarifying the potential benefits of using AVAL in clinical practice, in particular the reduced administrative burden with quicker reconstitution time providing more flexibility with appointment times, and home infusions providing less disruption to patients' lives. The PBAC noted the input from Rare Voices Australia which emphasised the advantages that home infusions would offer, particularly for rural and remote patients, and the reduced burden on patients and hospitals from this form of treatment delivery.

6.4 Individuals with Pompe Disease and those caring for others with Pompe Disease emphasised the quality of life impacts of the disease, the improvements from treatment, and how access to home infusions would be welcome. The PBAC noted that some individuals and organisations believed AVAL to be a more effective treatment than current ERT with ALGLU, however this was not supported by the evidence provided in the submission.

Clinical trials

Avalglucosidase alfa (AVAL) vs alglucosidase alfa (ALGLU)

6.5 Details of the trials presented in the comparison of AVAL and ALGLU for LOPD and IOPD presented in the submission are provided in Table 2.

Table 2: Trials associated reports presented in the submission (AVAL versus ALGLU)

Trial ID	Protocol title/ Publication title	Publication citation
LOPD		
COMET	COMET CSR. A Phase 3 randomized, multicenter, multinational, double blinded study comparing the efficacy and safety of repeated biweekly infusions of avalglucosidase alfa (neoGAA, GZ402666) and alglucosidase alfa in treatment-naïve patients with late-onset Pompe disease. *Interim Clinical Study Report EFC 14028*	1 September 2020
NEO1	NEO1 CSR. An open-label, multicenter, multinational, ascending dose study of the safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory efficacy of repeated biweekly infusions of neoGAA in naïve and alglucosidase alfa treated late-onset Pompe disease patients. *Clinical Study Report GZ402666 - TDR12857*	28 July 2015
NEO-EXT	NEO-EXT CSR. An open-label, multicenter, multinational extension study of the long-term safety and pharmacokinetics of repeated biweekly infusions of avalglucosidase alfa (neoGAA, GZ402666) in patients with Pompe disease. *Interim Clinical Study Report LTS13769*	12 August 2020
IOPD		
Mini-COMET	Mini-COMET CSR. An open-label ascending dose cohort study to assess the safety, pharmacokinetics, and preliminary efficacy of avalglucosidase alfa (neoGAA, GZ402666) in patients with infantile-onset Pompe disease treated with alglucosidase alfa who demonstrate clinical decline or sub-optimal clinical response. Clinicaltrials.gov NCT03019406. *Interim Clinical Study Report GZ402666-ACT14132*	16 April 2020

Source: Table 2(a).2-1, 2(b).2-1 pp26,88-89 of the submission
Abbreviations: IOPD = infantile-onset Pompe disease; LOPD = late-onset Pompe disease.

LOPD

6.6 The submission presented the results from COMET (N = 100), a head-to-head randomised non-inferiority trial comparing the efficacy and safety of AVAL (N=51) and ALGLU (N=49) in treatment naïve patients. The extended phase was COMET-EXT, where patients on ALGLU switched to AVAL.

6.7 The results of COMET were supplemented by NEO1/NEO-EXT, where NEO1 was a non-randomised open-label ascending dose study with patients who were treatment naïve at baseline (Group 1; n = 10) or had previously received ALGLU for a minimum of nine months (Group 2– switch group; n = 14). NEO-EXT was a long-term extension study, where patients who were treated with ALGLU in NEO1 were switched to AVAL.

6.8 Only one patient in the AVAL arm of the COMET study was < 18 years and the NEO1 study only enrolled patients ≥ 18 years of age. The clinical evidence presented did not sufficiently capture the Australian JOPD population.

IOPD

6.9 The submission presented the results from mini-COMET (N = 22), a phase 2, open-label, multi-stage ascending dose, cohort trial where children with IOPD were treated with repeated infusions of AVAL. Patients recruited in Stage 1 required demonstration of clinical decline whilst receiving ALGLU (Cohort 1; AVAL dose 20mg/kg q2w and Cohort 2: AVAL dose 40mg/kg q2w) and Stage 2 required patients to show suboptimal response to ALGLU (Cohort 3: AVAL dose 40mg/kg q2w).

6.10 Patients in Stage 1 (Cohort 1 and 2; n=11) did not undergo randomisation. Patients enrolled in Stage 2 (Cohort 3) were randomised 1:1 to receive AVAL 40 mg/kg q2w (n = 5) or ALGLU at their current stable dose (n = 6). Only one of the six patients received the TGA approved ALGLU dose (20 mg/kg q2w), all other patients received a higher dose (range: 20 mg/kg q2w to 40 mg/kg weekly). The low number of patients potentially impacted the even distribution of characteristics between the arms despite randomisation such as mean age at diagnosis (1.54 versus 5.12 months) and time from first symptom to first dose of ALGLU (1.94 versus 4.46 months).

6.11 The mean age at study entry in mini-COMET ranged from 5.7-8.1 years across all three cohorts, with time from Pompe disease diagnosis to first infusion of study drug ranging between 4.29-7.80 years.

6.12 The key features of COMET, NEO1 and mini-COMET are summarised in Table 3.

Table 3: Key features of the included evidence (AVAL versus ALGLU)

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s) [a]
LOPD					
COMET	100	Phase III, R, DB (49-week) [a]	Low	Treatment-naïve patients with LOPD	Primary: FVC % predicted Key secondary: 6MWT Additional Secondary: MIP/MEP % predicted, HHD, QMFT, HRQoL (SF-12) [c]
NEO1	24	Phase I, OL (25-weeks) [d]	High	Treatment naïve (Group 1; n = 10) and ALGLU treated (Group 2; n = 14) patients with LOPD [e]	Primary: safety secondary: Hex4 levels Exploratory: PFT (MIP/MEP % predicted), 6MWT [f]
IOPD					
Mini-COMET	22	Phase II, OL (25-weeks) [g]	Moderate to high	Patients with IOPD treated with ALGLU who demonstrated clinical decline (Stage 1; n = 11) or sub-optimal clinical response (Stage 2; n = 11)	Primary: safety Secondary: Motor function (GMFCS-E&R, GMFM-88 and QMFT, Pompe-PEDI: mobility domain), cardiomyopathy, ptosis, eyelid position measurements, biomarkers (CK, Hex4) Tertiary: PFT (FVC), 6MWT

Source: Tables 2(a).4-1, 2(b).4-2, pp40,99 of the submission

Abbreviations: 6MWT = 6-minute walk test; AVAL = avalglucosidase alfa; ALGLU = alglucosidase alfa; CK = creatine kinase; DB = double blind; EQ-5D-5L = Euro Quality of life 5D-5L; FVC = forced vital capacity; GMFCS-E&R = Gross Motor Function Classification System - Expanded and Revised; GMFM-88 = gross motor function measure-88; GSGC = gait, stair Gowers' manoeuvre, chair; Hex4 = glucose tetrasaccharide; HHD = handheld dynamometry; HRQoL = health related quality of life; LOPD = late-onset Pompe disease; MEP = maximum expiratory pressure; MIP = maximum inspiratory pressure; MRI = magnetic resonance imaging; n = total participants in group; OL = open label; PedsQL = paediatric quality of life inventory; PFT = pulmonary function test; QMFT = quick motor function test;; R = randomised.

Notes: [a] Outcomes that were presented within the submission are stated here

[b] COMET-EXT was the extension treatment period for COMET after the 49-weeks, where patients received open-label avalglucosidase alfa for up to week 293 (approximately 5.6 years).

[c] Exploratory efficacy outcomes in COMET included: GSGC composite functional assessment, GMFM-88/GMFCS, HHD of upper extremity muscle groups, EQ-5D-5L and PedsQL

[d] 13 infusions (which was approximately 25-weeks). NEO-EXT was the long-term extension study, where patients continue to receive the same dose of avalglucosidase alfa. The duration of the study was 6 years.

[e] Patients previously treated with alglucosidase alfa require a minimum of 9 months treatment

f Other secondary outcomes in NEO1/NEO-EXT included skeletal muscle MRI and glycogen content. Other exploratory outcomes included GSGC and GMFM-88, QMFT, HHD and PedsQL fatigue scale

[g] After the 25-week treatment period, patients were eligible to enter the follow-up extension treatment period for a total of 3 years.

6.13 Overall survival (OS) as an efficacy outcome was not measured in COMET, NEO/NEO-EXT, and mini-COMET nor in their respective extended treatment periods (ETP). Thus,

PBAC's previous view for ALGLU, where the PBAC expressed concerns about the uncertainty associated with assuming that short-term surrogate outcomes (i.e., forced vital capacity; FVC; and six-minute walk test; 6MWT) can be extrapolated to improvement in patient's morbidity and mortality in a chronic disorder for patient survival (ALGLU Public Summary Document (PSD), July 2011 PBAC meeting), would be applicable to AVAL.

Alglucosidase alfa (ALGLU) (as a proxy for avalglucosidase alfa (AVAL)) vs placebo

6.14 Details of the trials presented in the comparison of ALGLU (as a proxy for AVAL) to placebo for LOPD and IOPD presented in the submission are provided in Table 4.

Table 4: Trials associated reports presented in the submission (ALGLU versus placebo)

Trial ID	Publication Details	Publication citation
LOPD		
Alglucosidase alfa studies		
Hahn *et al* (2018) (ADVANCE)	Efficacy, safety profile, and immunogenicity of alglucosidase alfa produced at the 4,000-liter scale in US children and adolescents with Pompe disease: ADVANCE, a phase IV, open-label, prospective study.	Genet Med 2018; 20 (10): 1284-1294.
Nagura *et al* (2019)	Long-term observation of the safety and effectiveness of enzyme replacement therapy in Japanese patients with Pompe disease: results from the post-marketing surveillance.	Neurol Ther 2019; 8: 397-409.
Güngör *et al* (2013) [a]	Impact of enzyme replacement therapy on survival in adults with Pompe disease: results from a prospective international observational study.	Orphanet J Rare Dis 2013; 8: 49.
Natural history studies		
Güngör *et al* (2011) [b]	Survival and associated factors in 268 adults with Pompe disease prior to treatment with enzyme replacement therapy.	Orphanet J Rare Dis 2011; 6: 34.
Winkel *et al* (2005)	The natural course of non-classic Pompe's disease; a review of 225 published cases.	J Neurol 2005; 252: 875-884.
Systematic review		
Schoser *et al* (2017) [c]	Survival and long-term outcomes in late-onset Pompe disease following alglucosidase alfa treatment: a systematic review and meta-analysis.	J Neurol 2017; 264: 621-630.
IOPD		
Alglucosidase alfa treated patients		
Kishnani *et al* (2007); Kishnani *et al* (2009)	Recombinant human acid α-glucosidase. Major clinical benefits in infantile-onset Pompe disease.	Neurol 2007; 68: 99-109.
	Early treatment with alglucosidase alfa prolongs long-term survival of infants with Pompe disease.	Pediatr Res 2009; 66 (3): 329-335.
Nicolino *et al* (2009)	Clinical outcomes after long-term treatment with alglucosidase alfa in infants and children with advanced Pompe disease.	Genet Med 2009; 11 (3): 210-219.
Hahn *et al* (2018) (ADVANCE)	Efficacy, safety profile, and immunogenicity of alglucosidase alfa produced at the 4,000-liter scale in US children and adolescents with Pompe disease: ADVANCE, a phase IV, open-label, prospective study.	Genet Med 2018; 20 (10): 1284-1294.
Broomfield *et al* (2016)	Response of 33 UK patients with infantile-onset Pompe disease to enzyme replacement therapy.	J Inherit Metab Dis 2016; 39: 261-271
Parini *et al* (2018)	Long term clinical history of an Italian cohort of infantile-onset Pompe disease treated with enzyme replacement therapy.	Orphanet J Rare Dis 2018; 13: 32.
Chien *et al* (2015)	Long-term prognosis of patients with infantile-onset Pompe disease diagnosed by newborn screening and treated since birth.	J Pediatr 2015; 166: 985-991.
Nagura *et al* (2019)	long-term observation of the safety and effectiveness of enzyme replacement therapy in Japanese patients with Pompe disease: results from the post-marketing surveillance.	Neurol Ther 2019; 8: 397-409.
Untreated natural history cohort		
Kishnani *et al* (2006)	A retrospective, multinational, multicenter study on the natural history of infantile-onset Pompe disease.	J Pediatr 2006; 148: 671-676.
van den Hout *et al* (2003)	The natural course of infantile Pompe's disease: 20 original cases compared with 133 cases from the literature.	Pediatr 2003; 112: 332-340.

Source: Table 2(c).2-1, 2(d).2-1 pp136,171 of the submission

Abbreviations: EMC = Erasmus Medical Centre; IOPD = infantile-onset Pompe disease; IPA = International Pompe Association; LOPD = late-onset Pompe disease.

Notes: [a] Previously considered by PBAC in the alglucosidase alfa submission November 2012 (unpublished), March 2013 (published)

[b] The PBAC had reviewed data from the IPA/EMC based on the EMC Pompe survey February 2011 and Güngör et al (2013), but not this particular study.

[c] The LOTS trial was identified and included in the meta-analysis. LOTS was considered in the alglucosidase alfa submission in several PBAC submissions. This meta-analysis (Shoser et al 2017) has not been previously considered by the PBAC.

LOPD

6.15 The submission presented results for three studies of ALGLU treated LOPD patients, one meta-analysis of ALGU treated patients, and two studies in untreated natural history cohort patients and survival information from patients who had received ALGLU through the LSDP. The survival benefit of ALGLU as a proxy for AVAL, is based on non-inferiority in terms of respiratory function, motor function and muscle strength. All studies were non-randomised.

6.16 Overall, there was high variability in baseline disease and demographic variability within and between the trials, which may potentially confound the interpretation of trial results. For example, differences were identified in terms of median age at diagnosis and duration of disease at study entry.

IOPD

6.17 The submission presented results from seven studies of ALGLU treated IOPD patients, and two natural history cohort studies of untreated patients and survival information from patients that had received ALGLU through the LSDP. The survival benefit of ALGLU as a proxy for AVAL, was based on non-inferiority in terms of motor and respiratory function, and cardiomyopathy. All the studies were non-randomised except for Kishnani 2007, where patients were randomised to either ALGLU 20 or 40 mg/kg q2w.

Comparative effectiveness

Avalglucosidase alfa (AVAL) vs alglucosidase alfa (ALGLU)

LOPD

COMET/COMET-EXT

6.18 At the time of the COMET-EXT interim analysis (data cut-off 19 March 2020), all patients had competed the 49-week randomised period and the median duration of treatment for the extended open-label treatment period in patients originally randomised to AVAL and those to ALGLU was similar (10.58 and 10.46 months respectively).

6.19 A summary of the change in FVC (primary outcome) predicted in the upright position from baseline to week 49, and to week 97 are presented in Table 5, and graphically represented in Figure 1.

Table 5: Change in FVC % predicted in the upright position (COMET/COMET-EXT)

	AVAL (N = 51)	ALGLU (N = 49)
COMET (49-week randomised period) [a]		
Baseline, mean (SD)	62.55 (14.39)	61.56 (12.40)
Week 49, mean (SD)	65.49 (17.42)	61.16 (13.49)
Change from baseline to week 49, LSM (SE)	2.89 (0.88)	0.46 (0.93)
Mean difference, LSM difference (95% CI)	2.43 (-0.13, 4.99)	
p-value for non-inferiority [b]	**0.0074**	
p-value for superiority	0.0626	
COMET-EXT (extended treatment period)		
Patients who switched from ALGLU to AVAL [c]		
Number of patients with a measurement at weeks 49 and 97	20	
Change from week 49 to 97, LSM (95% CI)	0.15 (-1.95, 2.25)	
p-value	0.8854	

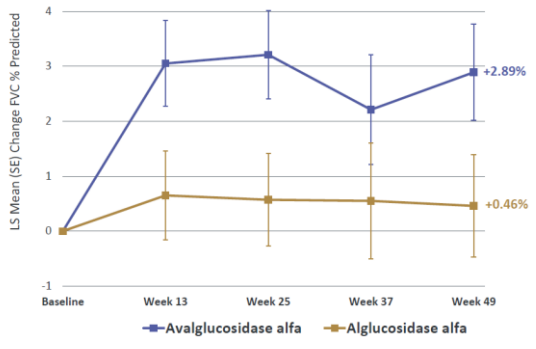
Source: Table 2(a).5-1, Table 2(a).5-10, pp48,58 of the submission
Abbreviations: ALGLU = alglucosidase alfa; AVAL=avalglucosidase alfa; CI = confidence interval; ETP = extended treatment period; FVC = forced vital capacity; LSM = least squares mean; MMRM = mixed model repeated measures; SD = standard deviation; SE = standard error.
[a] Statistics based on MMRM, 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%
[c] Patients who switched from ALGLU in primary analysis period to AVAL in ETP. Due to sequential enrolment, only 20 of the 43 patients who switched from ALGLU to AVAL completed their week 97 visit.
Bold text indicates a statistically significant difference.

6.20 The difference in least squared mean (LSM) change from baseline to Week 49 of 2.43 with lower boundary of 95% CI of -0.13 exceeded the predefined non-inferiority margin of -1.1 and thus supported the non-inferiority claim.

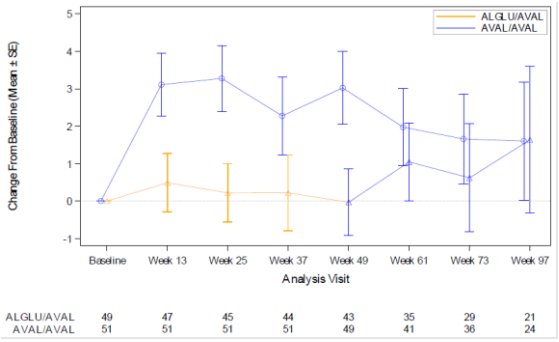
6.21 In the ETP, due to sequential enrolment, only 20 of the 43 patients who switched from ALGLU to AVAL completed their week 97 visit. Change in FVC % predicted from week 49 to 97 was 0.15 (95% CI: -1.95, 2.25). These results were not statistically significant.

Figure 1: Change from baseline in FVC % predicted in the upright position in COMET (A) and COMET-EXT (B)

(A) COMET



(B) COMET-EXT

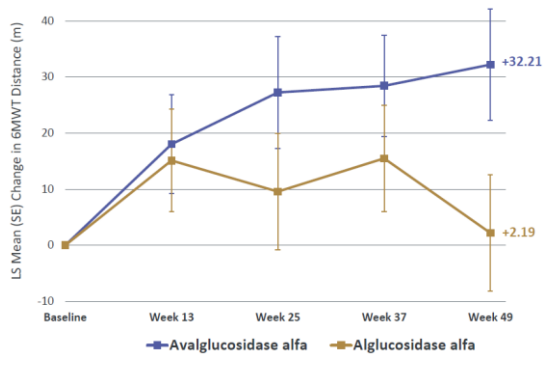


Source: Figure 2(a).5-1, Figure 2(a).5-7 pp,48,58 of the submission
Abbreviations: AVAL = avalglucosidase alfa; ALGLU = alglucosidase alfa; FVC = forced vital capacity, SE = standard error

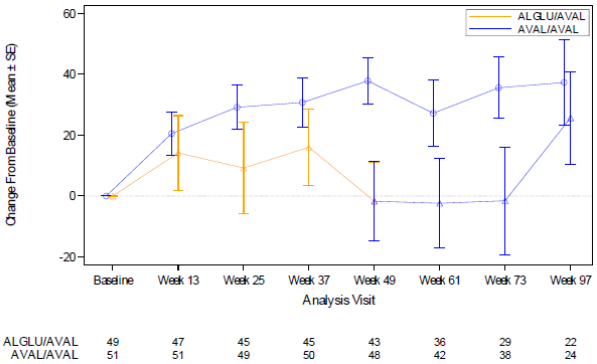
6.22 A summary of the change in 6MWT (secondary outcome) from baseline to week 49, and to week 97 is presented in Figure 2.

Figure 2: Change in 6MWT in COMET (A) and COMET-EXT (B)

(A) COMET **(B) COMET-EXT**



AVAL	51	51	49	50	48
ALGLU	49	47	45	45	43



ALGLU/AVAL	49	47	45	45	43	36	29	22
AVAL/AVAL	51	51	49	50	48	42	38	24

Source: Figure 2(a).5-3, Figure 2(a).5-8 pp,51,59 of the submission
Abbreviations: 6MWT = 6-minute walk text; AVAL = avalglucosidase alfa; ALGLU = alglucosidase alfa; LS mean = least squares mean

6.23 The LSM change from baseline to week 49 in 6MWT was 32.21 metres (SE = 9.93) in the AVAL group and 2.19 metres (SE = 10.40) in the ALGLU group. The difference from baseline to week 49 of 30.01 metres was statistically significant (p = 0.0405) however the 95% CI was wide due to the small sample size (95%CI: 1.33, 58.69).

NEO1/NEO-EXT

6.24 At the time of the NEO1-EXT interim analysis (data cut-off 27 February 2020), 17 patients remained on AVAL. The median duration of treatment for the ETP was 67.7 months for Group 1 (naïve group) and 70.2 months for patients in Group 2 (switch group).

6.25 Overall, it is difficult to draw meaningful conclusions from the results presented in NEO1/NEO-EXT as changes from baseline at various time points did not follow linear improvement or decline which made it difficult to determine trends. Furthermore, NEO1 recruited few patients, and even fewer patients remained at week 312 (6 years) (i.e., 2 patients in the naïve group and 3 patients in the switch group), thus it is difficult to determine whether outcomes observed were due to the disease natural history or indeed could be attributed to the effects of AVAL.

IOPD

6.26 At the time of the mini-COMET interim analysis (data cut-off 30 September 2019), the last patient in Cohort 3 had completed 6 months of treatment (week 25). The TGA CER stated that the efficacy outcomes presented below were positive in IOPD patients who had previously showed clinical decline or suboptimal response with prior ALGLU treatment. However, the numbers were too small to allow for statistical analysis and definitive conclusions (p65, TGA Clinical Evaluation Report).

6.27 In mini-COMET, motor functions were measured using the gross motor function classification system expanded and revised (GMFCS E&R), gross motor function measure-88 (GMFM 88), quick motor function test (QMFT) and the Pompe paediatric evaluation of disability inventory (Pompe-PEDI): mobility Domain as secondary efficacy outcomes.

- For GMFCS-E&R during the primary analysis and ETP, all patients that were Levels I, II, and V (where a higher level is indicative of further functional limitations) at baseline remained at the same level throughout the study, except for one patient from Cohort 2 (increased from Level II to Level I at week 73). Of the eight patients with baseline classifications III and IV, five remained unchanged, two had a lower score (both from Cohort 1) and one had a higher score (Cohort 3, AVAL arm; p59, Mini-COMET CSR).
- In general, the ETP showed that changes in GMFM-88 and QMFT followed the individual patient trajectory observed from baseline to week 25 with a few exceptions.
- Pompe-PEDI improvement from baseline to week 25 in patients in Cohort 1 and 2 was 4.9% and 3.3%, respectively. In Cohort 3, at Week 25, improvement in Pompe-PEDI score was lower for the AVAL arm compared to the alglucosidase arm (4.4% vs 19.0% improvement).

6.28 Cardiomyopathy was measured based on changes in left ventricular mass (LVM) M-mode Z-score. Overall, patients from Cohort 3 remained stable and their Z-scores remained within normal ranges up to week 25.

Alglucosidase alfa (ALGLU) (as a proxy for avalglucosidase alfa (AVAL)) vs placebo

6.29 The clinical claim is superior efficacy for ERT versus no treatment in terms of OS. The submission relied on ALGLU as a proxy to present the survival benefit of AVAL compared to placebo. The PSCR stated that AVAL is a second generation ERT which is the same active enzyme as ALGLU with a better cellular uptake, both catalyse the breakdown of glycogen to glucose, and replace the same enzyme that is deficient in patients with Pompe disease. The PSCR considered it is therefore reasonable to assume AVAL generates a similar clinical benefit in terms of surrogate outcomes with this translating to at a minimum the same OS benefit as ALGLU due to the higher cellular uptake of AVAL.

6.30 The submission presented the in-trial data for the individual studies in LOPD and IOPD. Only studies where the Kaplan-Meier (KM) data were pooled to allowed comparison between ALGLU (as a proxy for AVAL) and placebo (untreated natural history patients) are presented below.

LOPD

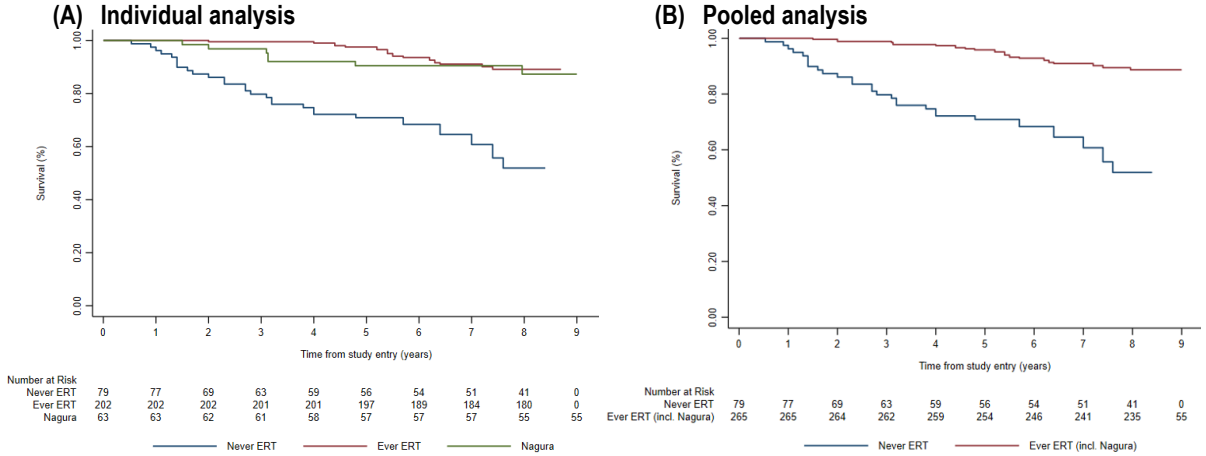
Pooled analysis

6.31 Erasmus Medical Centre (EMC) Pompe Survey February 2011: The PBAC had previously reviewed the clinical evidence from this survey (July 2011 submission). The trial enrolled patients 18 years or older treated with ALGLU (ever ERT) and untreated (never ERT) patients. During the follow up, 41 patients died of which 15 deaths were in the ever ERT arm (7%) and 26 (33%) in the never ERT arm. The submission stated that the difference in survival between the two groups were statistically significant (HR= 0.141, 95% CI: 0.074, 0.268, p < 0.001). However, PBAC previously considered that the differences in death between treatment groups cannot necessarily be simply attributed to ALGLU due to potentially confounding factors that may mean that there is systematic difference between the ever-treated and never-treated groups (ALGLU PSD, July 2011 PBAC meeting).

6.32 Nagura 2019: This analysis included 73 Japanese ERT-treated patients, of which 42 (57.5%) had JOPD, 21 (28.8%) had AOPD and the remaining had IOPD. During the study 6 patients died (2 patients with JOPD and 4 patients with AOPD). The cause of death was documented in 5 of the 6 cases: progression of the primary disease (n = 3), complications (n = 1) and severe pneumonia (n = 1). The survival rate for JOPD after 9 years of ERT was 95.2% (95% CI: 82.1, 98.8) and for AOPD was 70.2% (95% CI: 37.2, 88.1).

6.33 The data from the individual KM curves were digitised and pooled. The individual and pooled KM survival curves are presented in Figure 3. The submission presented a naïve comparison of the KM curves analyses for survival between ALGLU treated and untreated patients. KM curves from EMC Pompe Survey and the JOPD and AOPD arms of Nagura 2019, were presented based on the closest time definition for measuring survival.

Figure 3: KM survival curves for Individual (A) and Pooled (B) analyses EMC Pompe Survey February 2011 and Nagura 2019)



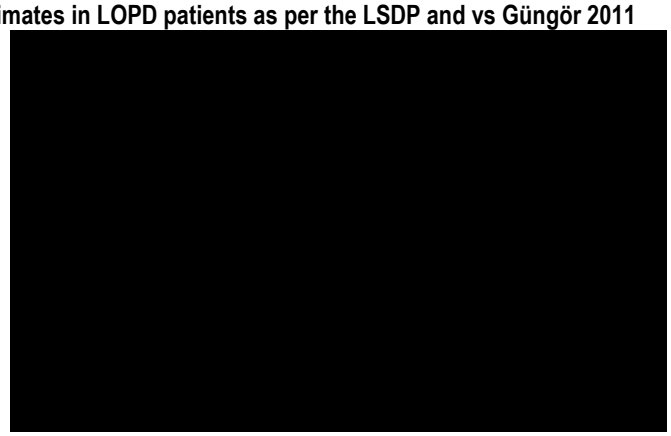
Source: Figure 2(c).6-1, Figure 2(c).6-2, pp163, 164 of the submission
Abbreviations: EMC = Erasmus Medical Centre; ERT = enzyme replacement therapy

6.34 Some applicability issues were identified in Nagura 2019, mainly regarding the diagnosis criteria defined in the Japanese guideline for Pompe disease compared to the Australian guideline. A direct comparison of KM survival curves between the EMC Pompe Survey and Nagura 2019 may be subject to transitivity issues, and thus, not appropriate. The pooled analysis formed the basis of the economic evaluation for LOPD.

LSDP Population

6.35 The LSDP analysis is presented in Figure 4. In the analysis, patients with JOPD (n=< 500) and AOPD (n=< 500) were combined and compared with patients in Güngör 2011 (natural history study, n=< 500).

Figure 4: KM survival estimates in LOPD patients as per the LSDP and vs Güngör 2011



Source: Figure 2(c).5-8, p160 of the submission
Abbreviations: CI = confidence interval; KM = Kaplan-Meier; LOPD = late-onset Pompe disease; lsdp = Life Saving Drugs Program

6.36 In the LSDP population, < 500 were reported in patients with AOPD and none in the JOPD population died. Baseline characteristics from patients in the LSDP and Gungor 2011 could not be compared due to insufficient information and inconsistencies on how the information was reported. The ESC noted the wide confidence intervals and low patient numbers included in the comparison and considered the results were difficult to interpret.

IOPD

Treated patients

6.37 Kishnani 2007 and Kishnani 2009: The PBAC had previously reviewed the clinical evidence from these studies (referred to as Study 1602 and Study 2403) in the ALGLU submission from July 2008. The PBAC had previously considered that the results of these studies suggest that ALGLU prolongs survival in infants but does not appear to extend the lifespan beyond early childhood (ALGLU PSD, July 2008 PBAC meeting). This study was subsequently published with additional follow-up data by Nicolino 2009. The KM estimate for OS at 104 weeks was 71.1% (95% CI: 51.6, 90.6) for ALGLU treated patients, and 26.3% (95% CI: 6.5, 46.1) for the historical control group. Cox

regression analysis showed that ALGLU treatment reduced the risk of death by 79% (p = 0.0009).

6.38 Broomfield 2016: OS at 42 months was 54% and ventilator free survival was 30.6%. In the 13 patients who died, the median age of death was 12 months (range: 6 months to 5 years 5 months).

6.39 Parini 2018: The probability of OS at 6 years of age was 58.8% (SE 9.8) and for ventilator free survival was 31.8% (SE 8.6). At the last clinical examination, there were 19 long-term surviving patients of whom only 6 patients (31%) were free of ventilation support, 3 patients (15%) needed non-invasive ventilation and 10 patients (52%) were ventilated through tracheostomy.

6.40 Chien 2015: This study was focused on improving the prognosis of IOPD by newborn screening (NBS) and early treatment. However, as Australia does not currently have a NBS program for Pompe disease, data from Chien 2015 that informed the pooled data analysis was from the clinically diagnosed patient cohort.

Untreated natural history cohort

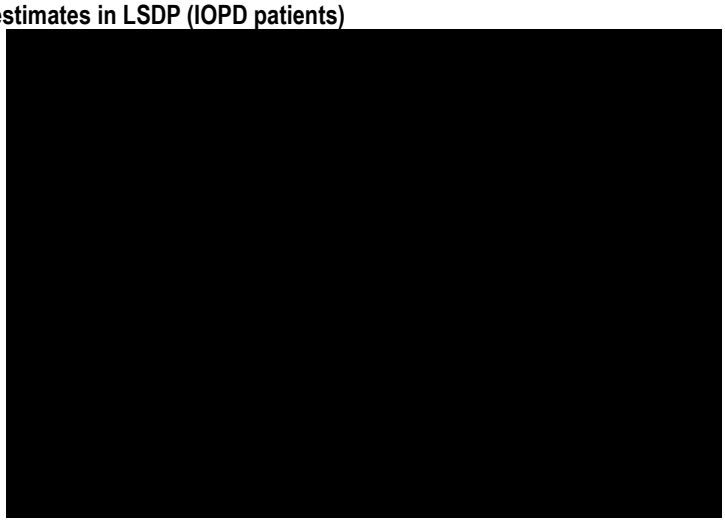
6.41 Kishnani 2006: A total of 144 (85.7%) deaths were reported at a median age of 8.7 months (range: 0.3, 73.4 months). Overall, 36 (25.0%) infants survived beyond their first birthday, 19 (13.2%) survived beyond 18 months of age and 12 (8.3%) survived beyond 24 months of age. The cause of death was documented in 85 patients (59.0%), most commonly cardiorespiratory complications (57.6%) and cardiorespiratory plus other causes (27.1%). Patients presenting with their first symptoms within 6 months of age were associated with significantly greater risk of death compared with those presenting after 6 months of age (RR = 2.89; 95%CI: 1.58, 5.29; p < 0.001). Similarly, a diagnosis of Pompe disease within 6 months of age was also associated with a greater risk of death (RR = 2.13; 95%CI: 1.47, 3.08; p < 0.001).

6.42 Van den Hout 2003: The median time from diagnosis to death was 2.0 months for both the Dutch patients (n=20) and the patients identified through the literature (n=133). The median age of death was 7.7 months and 6.0 months respectively. Only one patient in the Dutch population and 10 patients reported in the literature, survived beyond the age of 1 year. Of the 10 cases in the literature who survived beyond 1 year, only two patients reported ages of death above 1.5 years (range: 29 and 34.5 months).

LSDP Population

6.43 The KM curve for OS in IOPD patients on the LSDP is presented in Figure 5. Thirteen IOPD patients have commenced ALGLU treatment and < 500 patients have died since ALGLU was listed on the LSDP. The mean age of death of patients with IOPD receiving ALGLU in Australia is currently 42 months.

Figure 5: KM survival estimates in LSDP (IOPD patients)



Source: Figure 2(d).5-13, p199 of the submission
Abbreviations: CI = confidence interval; IOPD = infantile-onset Pompe disease; KM = Kaplan Meier; LSDP = Life Saving Drugs Program

Pooled analysis

6.44 The individual and pooled KM survival curves are presented in Figure 6 and 7. The same method used to pool data for the LOPD population was used for IOPD. The submission stated that OS was measured at different timepoints in Nagura 2019 (from the time of treatment initiation) and Hahn 2018 (from the time of switch to a different manufacturing process), rather than from birth like the other ALGLU studies. Thus, these studies were excluded from the pooled analysis. The natural history cohorts from Kishnani 2009 and 2015 were not included in the pooled data as they were subsets of the Kishnani 2006 patient population.

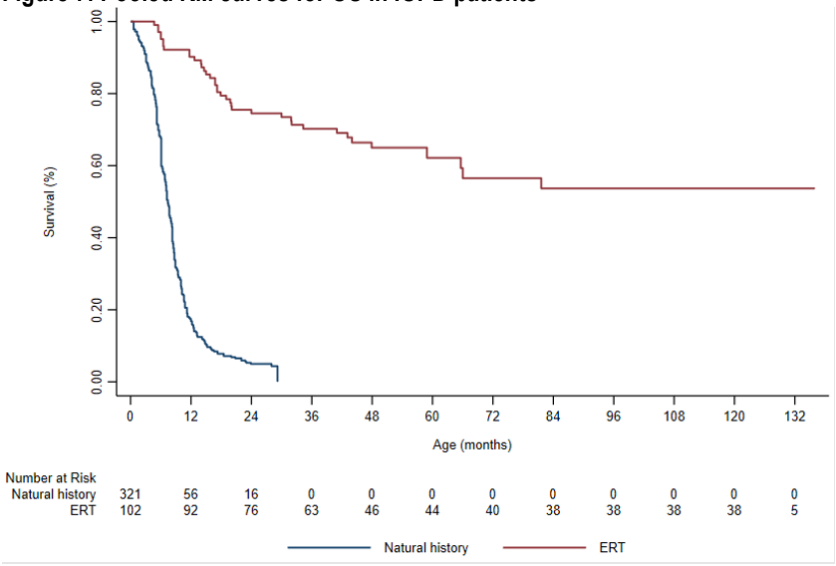
Figure 6: Individual KM curves for OS in IOPD patients treated with ERT (A) and untreated patients (B)

(A) Patients treated with ERT **(B) Untreated patients**

Source: Figure 2(d).6-1, Figure 2(d).6-2, pp203-204 of the submission
Abbreviations: ERT = enzyme replacement therapy; IOPD = infantile-onset Pompe disease; KM = Kaplan-Meier; LSDP = Life Saving Drugs Program; OS = overall survival

6.45 The OS KM curves for the patients treated with ERT vary between the studies, as well as the length of data observation. Overall, the trends appear to be consistent with the PBAC's previous view that ALGLU prolongs survival in infants. The additional evidence from Kishnani 2009, Broomfield 2016 and Parini 2018 showed survival benefits beyond early childhood which had been PBAC's previous concern (ALGLU PSD, July 2008 PBAC meeting).

Figure 7: Pooled KM curves for OS in IOPD patients [a]



Source: Figure 2(d).6-4, p205 of the submission
Abbreviations: ERT = enzyme replacement therapy; IOPD = infantile-onset Pompe disease; KM = Kaplan Meier; OS = overall survival
Note: [a] The individual Kaplan Meier curves for the ERT treated patients (Kishnani 2009, Broomfield 2016, Parini 2018, Chien 2015 and the LSDP population) and those for the natural history patients (van den Hout 2003 and Kishnani 2006) were combined and the resulting analysis

6.46 According to the submission, in the updated analysis, the median OS was 7.4 months (95% CI: 5.2, 10.2) in the untreated natural history cohort and was not reached in the ERT treated patients. Treatment with ALGLU led to a 91% reduction in the risk of death (HR = 0.09; 95% CI: 0.06, 0.13) compared with no treatment. The HR for the pooled KM curves was considered by the submission to be similar to that in the ALGLU March 2008 submission (HR 0.05; 95% CI: 0.02, 0.14), and that the updated analysis comprises up to 11 years of ALGLU treatment compared with 3 years in the ALGLU March 2008 submission. The HR for the pooled ALGLU treated patients could not be verified during the evaluation. The study duration and duration of follow-up could not be ascertained for Broomfield 2016, Parini 2018 and the clinically diagnosed cohort from Chien 2015.

6.47 There were variations in the ALGLU dose received by patients in the pooled analyses, ranging from 20 to 40 mg/kg q2w. Thus, the effect of dosage on survival outcomes is unclear. Furthermore, the proposed IOPD dose of avalglucosidase alfa is 40 mg/kg q2w whilst the TGA dose for ALGLU is 20 mg/kg. It is therefore unclear, in the absence of AVAL survival data, how the data for ALGLU (as a proxy for AVAL) should be interpreted, and whether effects may be potentially impacted by the dose conversion

between ALGLU and AVAL. The PSCR stated that ALGLU at higher doses and/or more frequent dosing is associated with a greater treatment benefit in terms of respiratory and motor function than that obtained at 20 mg/kg q2w (Chien et al, 2020, Khan et al, 2020). The PSCR stated that as the proposed IOPD dose of AVAL is 40 mg/kg and is the same active enzyme as ALGLU, the survival benefit of a pooled analysis of ALGLU from 20 - 40 mg/kg is likely an underestimate of the survival benefit of AVAL.

Comparative harms

Avalglucosidase alfa (AVAL) vs alglucosidase alfa (ALGLU)

LOPD

6.48 A summary of the adverse events (AEs) during the 49-week randomised period of COMET is presented in Table 6. The safety population included randomised patents who received at least one infusion.

Table 6: Summary of adverse events in COMET (safety population)

	AVAL (N = 51)	ALGLU (N = 49)	RR (95% CI) [a]	RD (95% CI) [a]	OR (95% CI) [a]
TEAEs	44 (86.3)	45 (91.8)	0.94 (0.82, 1.08)	-0.06 (-0.18, 0.07)	0.56 (0.15, 2.04)
TEAEs potentially related to treatment	23 (45.1)	24 (49.0)	0.92 (0.61, 1.40)	-0.04 (-0.23, 0.16)	0.86 (0.39, 1.88)
Serious TEAEs	8 (15.7)	12 (24.5)	0.64 (0.29, 1.43)	-0.09 (-0.24, 0.07)	0.57 (0.21, 1.55)
Serious TEAEs potentially related to treatment	1 (2.0)	3 (6.1)	0.32 (0.03, 2.98)	-0.04 (-0.12, 0.04)	0.31 (0.03, 3.05)
Severe TEAEs	6 (11.8)	7 (14.3)	0.82 (0.30, 2.28)	-0.03 (-0.16, 0.11)	0.80 (0.25, 2.57)
TEAEs leading to discontinuation	0	4 (8.2)	0.11 (0.01, 1.93)	-0.08 (-0.17, 0.00)	0.10 (0.01, 1.87)
TEAEs leading to death	0	1 (2.0) [c]	0.19 (0.01, 3.91)	-0.04 (-0.11, 0.03)	0.18 (0.01, 3.94)
IARs (protocol-defined) [b]	13 (25.5)	16 (32.7)	0.78 (0.42, 1.45)	-0.07 (-0.25, 0.11)	0.71 (0.30, 1.68)

Source: Table 2(a).5-15 p74 of the submission

Abbreviations: ALGLU = alglucosidase alfa; AVAL = avalglucosidase alfa; CI = confidence interval; IAR = infusion-associated reaction; OR = odds ratio; RD = risk difference; RR = relative risk; TEAEs = treatment-emergent adverse event

Notes: [a] Calculated using RevMan v5.3 for the purpose of this submission

[b] defined as an adverse event that occurred during either the infusion or observation period following the infusion, related or possible related to the investigational treatment

[c] SAE of acute myocardial infarction (unrelated to treatment).

6.49 TEAEs were predominantly of moderate intensity in both the avalglucosidase alfa (45.1%) and ALGLU (55.1%) arms (p105, COMET CSR). Serious TEAEs and TEAEs leading to permanent treatment discontinuation were lower in the AVAL arm compared to ALGLU. Overall, the differences in safety profile were not significantly different.

6.50 Commonly reported TEAEs (≥20%) were nasopharyngitis (23.5%), back pain (23.5%), and headache (21.6%) in the AVAL group and headache (32.7%), nasopharyngitis (24.5%), and falls (20.4%) in the ALGLU group.

6.51 In the extension treatment phase, 51 patients continued to receive AVAL and 44 patients entered the ETP and switched from ALGLU to AVAL. The rates of serious TEAEs (15.7% AVAL vs 11.4% switched group), severe TEAEs (15.7% AVAL vs 11.4% switched group), and TEAEs leading to permanent treatment discontinuation (3.9% AVAL vs none in the switched group), were numerically higher in patients who continued AVAL compared to patients who had switched.

6.52 A summary of AEs in NEO1 (13 infusions, approximately 25 weeks) and its ETP in NEO-EXT are presented in Table 7. In NEO1, most patients reported at least one TEAE (≥ 80%) and over half of the patients (50-60%) reported drug related TEAE. No deaths occurred due to TEAEs.

Table 7: Summary of adverse events in NEO1/NEO-EXT (safety population)

Adverse events, n (%)	NEO1		NEO-EXT
	Naïve group	Switch group	Combined group
	N = 10	N = 14	N = 24
Any TEAE	8 (80.0)	12 (85.7)	24 (100)
Drug-related TEAE	6 (60.0)	7 (50.0)	NR
TESAE	1 (10.0)	1 (7.1)	9 (37.5)
TEAE leading to death	0	0	0
TEAE leading to discontinuation	1 (10.0)	0	1 (4.2)

Source: Table 2(a).5-1, p75 of the submission
Abbreviations: TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event

IOPD

6.53 A summary of the AEs during the 25-week primary analysis period and its ETP is presented in Table 8. In the ETP, the median duration of study drug exposure was 70 and 44.6 weeks for Cohort 1 and 2 respectively, and 10 and 13 weeks for the ALGLU and AVAL arms respectively, of Cohort 3.

Table 8: Summary of adverse events in mini-COMET (Safety Population)

Adverse events, n (%)	Primary analysis period					Extended treatment period		
	Cohort 1 [a]	Cohort 2 [a]	Cohort 3		Pooled AVAL [d]	AVAL/AVAL 20 mg/kg [e]	AVAL/AVAL 40 mg/kg [e]	ALGLU/AVAL
			AVAL [b]	ALGLU [c]				
	N = 6	N = 5	N = 5	N = 6	N = 16	N = 6	N = 10	N = 3
TEAEs	5 (83.3)	5 (100)	5 (100)	5 (83.3)	15 (93.8)	6 (100)	7 (70.0)	3 (100)
TEAEs potentially related to study treatment	0	2 (40.0)	1 (20.0)	1 (16.7)	3 (18.8)	1 (16.7)	3 (30.0)	1 (33.3)
Serious TEAEs	1 (16.7)	3 (60.0)	0	2 (33.3)	4 (25.0)	4 (66.7)	2 (20.0)	1 (33.3)
Severe TEAEs	0	2 (40.0)	0	1 (16.7)	2 (12.5)	2 (33.3)	1 (10.0)	1 (33.3)
AESI [f]	0	2 (40.0)	1 (20.0)	1 (16.7)	3 (18.8)	1 (16.7)	3 (30.0)	0
Protocol-defined IARs	0	2 (40.0)	1 (20.0)	1 (16.7)	3 (18.8)	1 (16.7)	3 (30.0)	0
Algorithm-defined IARs	0	2 (40.0)	1 (20.0)	1 (16.7)	3 (18.8)	1 (16.7)	3 (30.0)	0

Source: Table 2(b).5-11, p119 of the submission
Abbreviations: AESI = adverse event of special interest; ALGLU = alglucosidase alfa; AVAL = avalglucosidase alfa; IAR = infusion associated reaction; q2w = once every two weeks; TEAE = treatment emergent adverse event
Notes: [a] Cohort 1 received avalglucosidase alfa 20 mg/kg q2w; Cohort 2 received AVAL 40 mg/kg q2w
[b] The AVAL arm of Cohort 3 received AVAL 40 mg/kg q2w
[c] ALGLU dose was at the patient's current stable dose defined by dose of ALGLU administered regularly for a minimum of 6 months immediately prior to study entry. The doses administered for ALGLU was 20 mg/kg q2w (n = 1), 40 mg/kg q2w (n = 2), 20 mg/kg qw (n = 1), 30 mg/kg qw (n = 1) and 40 mg/kg qw (n = 1)
[d] Calculated by adding patients on AVAL from Cohorts 1, 2 and 3
[e] Initial planned dose. Two patients in Cohort 1 increased dose from 20 mg/kg q2w to 40 mg/kg q2w during the extended treatment period, which was allowed by the protocol
[f] An AESI was defined as an AE (serious or nonserious) of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the sponsor is required. This included IAR, pregnancy, symptomatic overdose, and clinical laboratory changes from baseline (p77, mini-COMET CSR).

6.54 The submission presented comparisons between the pooled AVAL arm, which consisted of patients on AVAL from Cohorts 1, 2 and 3; and the ALGLU arm of Cohort

3. However, these percentages represent small numbers (16 patients in the pooled AVAL arm and 6 patients in the ALGLU arm) in which to draw any conclusions based on the safety information provided.

Avalglucosidase alfa (AVAL) vs placebo

6.55 The submission did not present any safety data associated with the comparison of ALGLU (as a proxy for AVAL) in comparison to placebo (natural history).

Benefits/harms

6.56 A summary of the benefits and harms was not presented for LOPD and IOPD based on:

- the non-inferiority nature of the claim between AVAL versus ALGLU, and
- the pooled analysis of ALGLU (as a proxy for AVAL) compared to placebo (natural history), which did not allow for a quantitative comparison.

Clinical claim

Avalglucosidase alfa (AVAL) vs alglucosidase alfa (ALGLU)

6.57 For the primary clinical claim, the submission described AVAL as non-inferior in patients with LOPD and IOPD in terms of effectiveness and safety to ALGLU. However, the evaluation considered the following issues need to be considered when examining the claim:

- OS was not measured in COMET, NEO1/NEO-EXT, nor mini-COMET nor in their respective ETP. Thus, consistent with the previous PBAC view, it is unclear whether the effects of these surrogate outcomes can be extrapolated to improvements in patients' overall survival in a chronic disorder (ALGLU PSD, March 2009 PBAC meeting).
- In COMET, results for the key secondary outcome (6MWT) had broad 95% confidence intervals that crossed the zero mark which may suggest that the data for AVAL is comparable to, rather than non-inferior, compared to ALGLU.
- The clinical evidence presented in COMET and NEO1/NEO-EXT did not sufficiently capture the proposed PBS JOPD population (24 months to < 18 years of age). Only one patient in the AVAL arm of COMET was <18 years of age. The PSCR stated this should be viewed in the context that there are only < 500 JOPD patients in Australia based on the LSDP review.
- The clinical evidence from mini-COMET did not reflect the requested restriction for IOPD. The mean age at study entry ranged from 5.7 to 8.1 years across the three cohorts and all patients had previous treatment with ALGLU. This is different to the requested PBS listing for IOPD, where patients must be aged ≤ 24 months at the time of initial application, and there are no restrictions specifying prior

treatment. The PSCR revised the clinical criteria related to IOPD age (see paragraph 3.5).

- The ALGLU dosing of the comparator arm in mini-COMET was higher in 5 of the 6 patients compared to the TGA approved dose, while only one patient received the TGA approved dose. This difference introduces transitivity issues of the claim in the Australian context.
- In mini-COMET the clinical claim was informed by Cohort 3, however formal statistical analyses were not undertaken for efficacy outcomes due to the imbalance in the patient characteristics in the randomised treatment arms. This, coupled with the small sample in both arms (n = 5 AVAL and n = 6 ALGLU) introduces high uncertainty in the interpretation of the results.

6.58 Overall, the evaluation considered the differences in safety between AVAL and ALGLU were not significant based on COMET and NEO1/NEO-EXT.

6.59 The ESC considered the claim that AVAL is non-inferior to ALGLU in terms of efficacy for IOPD was not adequately supported by the clinical data presented in the submission. The PBAC agreed with the ESC that the data does not adequately support non-inferiority; however, the PBAC considered that, overall, AVAL was likely to provide similar health outcomes to ALGLU for the treatment of IOPD.

6.60 The PBAC agreed with the ESC that the claim that AVAL is non-inferior to ALGLU in terms of efficacy for LOPD may be reasonable based on a comparison of surrogate outcomes but noted there was no OS data provided.

6.61 The PBAC agreed with the ESC that the safety of AVAL and ALGLU appears comparable and considered that, overall, the claim of non-inferior safety for IOPD and LOPD is likely to be reasonable.

Alglucosidase alfa (ALGLU) (as a proxy for avalglucosidase alfa (AVAL)) vs placebo

6.62 The submission claimed ALGLU (as a proxy for AVAL) was superior in terms of effectiveness compared with placebo (i.e., no ERT) for treatment of patients with LOPD and IOPD in terms of OS. However, the evaluation considered the following issues need to be considered when examining this claim:

- The PBAC previously expressed concerns about the uncertainty associated with short-term surrogate outcomes (i.e., FVC and 6MWT) being correlated with patient survival (ALGLU PSD, July 2011 PBAC meeting).
- For LOPD, the survival benefit of ALGLU versus placebo (natural history) was based on the KM curves of the pooled analysis of Nagura 2019 and the EMC Pompe Survey February 2011. The Nagura paper noted that Japanese patients diagnosed with LOPD may differ from that of patients in Europe and North America based on the distribution of age at LOPD onset, potentially influenced by the level of disease recognition in that region, but also possibly that the disease itself may have region-specific differences (Nagura et al, 2019).

- There was great intra and inter-study variability with regards to ALGLU dosing (also not reported in 3 of the 5 ALGLU treated LOPD studies). Overall, there was inconsistency in terms of the information provided and lack of reporting within the trials, which made it difficult to compare to the Australian population. Moreover, whilst the dose of AVAL and ALGLU were the same in LOPD (i.e., 20 mg/kg q2w), the dose of AVAL for IOPD is twice that of ALGLU (i.e. 40 vs 20 mg/kg q2w). Thus, the use of ALGLU as a proxy for AVAL in this instance may not be an accurate representation of efficacy.

6.63 The submission did not present any safety data associated with the comparison of ALGLU (as a proxy for AVAL) in comparison to placebo (natural history) for either LOPD or IOPD.

6.64 The ESC considered the claim that ALGLU results in an OS benefit compared to placebo for LOPD was not adequately supported by the clinical evidence provided in the submission. As the claim for AVAL relied on ALGLU as a proxy, the ESC considered the claim that AVAL provided a survival benefit compared to placebo for LOPD was also not adequately supported.

6.65 The ESC considered treatment with ALGLU results in an OS benefit compared to placebo for IOPD but the extent of the benefit in life expectancy beyond early childhood remained unclear. The ESC considered the claim that treatment with AVAL results in an overall survival benefit compared to placebo was uncertain due to the reliance on ALGLU as a proxy and the non-inferiority claim for AVAL with ALGLU not being supported (see paragraph 6.59).

Economic analysis

6.66 The submission presented a cost-minimisation approach (CMA) comparing AVAL with ALGLU and cost-utility analysis (CUA) comparing ALGLU (as a proxy for AVAL) with BSC, for LOPD and IOPD.

CMA – avalglucosidase alfa (AVAL) vs alglucosidase alfa (ALGLU)

6.67 The submission presented separate CMAs comparing AVAL with ALGLU for LOPD and IOPD patients based on the therapeutic conclusions of non-inferior efficacy and safety. The key components and assumptions of the CMA are presented in Table 9.

Table 9: Key components and assumptions of the cost-minimisation analysis

Component	Claim or assumption	
	LOPD (including JOPD and AOPD)	IOPD
Therapeutic claim: effectiveness	AVAL is non-inferior to ALGLU in terms of effectiveness and safety	
Evidence base	Direct comparison from COMET.	Direct comparison from mini-COMET.
Equi-effective doses	AVAL 20 mg/kg q2w equivalent to ALGLU 20 mg/kg q2w	AVAL 40 mg/kg q2w equivalent to ALGLU 20 mg/kg q2w
Direct medicine costs	Equivalent	
Other cost (offset)	No other costs (offsets) considered in the analysis	

Source: Adapted from Table 3(a).1-1, p211 and Table 3(b).1-1, p219 of the submission.
Abbreviations: AOPD = adult-onset Pompe disease; BSC = best supportive care; CMA = cost-minimisation analysis; IOPD = infantile-onset Pompe disease; JOPM = juvenile-onset Pompe disease; LOPD = late-onset Pompe disease; q2w = once every two weeks.

6.68 The CMA for both LOPD and IOPD only considers the cost of medicines over a time horizon of 1-month. The submission noted that there were no differences in medicine-specific monitoring requirements or safety profiles between ALGLU and AVAL that result in costs (offset) that warrant inclusion in the CMA.

6.69 The submission proposed for price parity with ALGLU for both patient populations. The submission presented an effective price per vial for AVAL for IOPD ($[redacted]) but not for LOPD.

LOPD

6.70 The equi-effective doses for the treatment of JOPD and AOPD were derived from COMET and were estimated as AVAL 20 mg/kg equivalent to ALGLU 20 mg/kg, both administered q2w via IV infusion. The submission also presented the average and median dose of ALGLU reported as part of the review of the LSDP medicines in Australian clinical practice which showed that the dose is similar to that employed in COMET.

6.71 Results of the CMA for JOPD and AOPD is presented in Table 10 and Table 11, respectively. The submission did not present an AEMP per vial for JOPD and AOPD; however, the total cost of treatment per month remains fixed at price parity with ALGLU irrespective of the number of vials.

Table 10: Results of the cost-minimisation analysis at the effective price [a] - JOPD

Component	AVAL	ALGLU
Vials per administration		
Dosing regimen	20 mg/kg q2w	20 mg/kg q2w
Patients body weight	57.7 kg	57.7 kg
Dose per administration	1,154 mg [20 mg x 57.7 kg]	1,154 mg [20 mg x 57.7 kg]
mg per vial	100 mg	50 mg
Vials per administration	11.54 vials [1,154 mg / 100 mg]	23.08 vials [1,154 mg / 50 mg]
Round up to next whole number	12 vials	24 vials
Cost of treatment		
AEMP per vial	N/P[b]	N/P[b]
Administration per month	2.17 [(52/12)/2]	2.17 [(52/12)/2]
Vials per administration	12	24
Vials per month	26	52
Total cost of treatment per month	$ [redacted][c]	$ [redacted][c]
Incremental cost of treatment	$0.00	

Source: Table 3(a).4-2, p216 of the submission.

Abbreviations: AEMP = approved ex manufacturer price; ALGLU = alglucosidase alfa; AVAL = avalglucosidase alfa; JOPD = juvenile onset Pompe disease; N/P = not provided; SPA = special pricing arrangement; q2w = once every two weeks.

Note: [a] The total cost of treatment per patient per month for AVAL for JOPD and AOPD is irrespective of the number of vials that are required per administration; identical to that of ALGLU for JOPD and AOPD.

[b] Not provided by the submission.

[c] This price corresponds to the confidential special pricing arrangement, not the price per vial times the number of vials required.

Table 11: Results of the cost-minimisation analysis at the effective price - AOPD

Component	AVAL	ALGLU
Vials per administration		
Dosing regimen	20 mg/kg q2w	20 mg/kg q2w
Patients body weight	76.8 kg	76.8 kg
Dose per administration	1,536 mg [20 mg x 76.8 kg]	1,536 mg [20 mg x 76.8 kg]
mg per vial	100 mg	50 mg
Vials per administration	15.36 vials [1,536 mg/100 mg]	30.72 vials [1,536 mg/50 mg]
Round up to next whole number	16 vials	31 vials
Cost of treatment		
AEMP per vial	N/P[a]	N/P[a]
Administration per month	2.17 [(52/12)/2]	2.17 [(52/12)/2]
Vials per administration	16	31
Vials per month	34.7	67.2
Total cost of treatment per month	$ [redacted][b]	$ [redacted][b]
Incremental cost of treatment	$0.00	

Source: Table 3(a).4-2, p216 of the submission.

Abbreviations: AEMP = approved ex manufacturer price; ALGLU = alglucosidase alfa; AOPD = adult onset Pompe disease; AVAL = avalglucosidase alfa; N/P = not provided; SPA = Special pricing arrangement; q2w = once every two weeks.

Notes: [a] Not provided by the submission.

[b] This price corresponds to the confidential special pricing arrangement, not the price per vial times the number of vials required.

IOPD

6.72 The equi-effective doses for the treatment of IOPD were derived from the pooled analysis of the AVAL treatment arms (Cohorts 1 to 3) and ALGLU treatment arm (Cohort 3) of mini-COMET. The equi-effective doses were estimated as AVAL 40 mg/kg is equivalent to ALGLU 20 mg/kg, both administered q2w by IV infusion. The equi-effective dose was consistent with the dose recommended in the approved TGA PI for ALGLU and the proposed draft PI for avalglucosidase alfa provided with the submission; and the dose used in the economic model presented in the submission. However, the proposed equi-effective dose of 20 mg/kg q2w for ALGLU was lower than the average dose reported in mini-COMET. In mini-COMET, only one of the six patients receiving ALGLU received the TGA approved dose of 20 mg/kg q2w, all other patients received a higher dose. The PBAC noted the recommended dose in the revised draft PI provided with the pre-PBAC response was 20 mg/kg every other week with dose escalation to 40 mg/ kg every other week considered for patients with IOPD who experience insufficient control or declining response at the lower dose.

6.73 Results of the CMA for IOPD is presented in Table 12.

Table 12: Results of the cost-minimisation analysis at effective AEMP - IOPD

Component	AVAL	ALGLU
Vials per administration		
Dosing regimen	40 mg/kg q2w	20 mg/kg q2w
Patients body weight	15.53 kg	15.53 kg
Dose per administration	621.2 mg [40 mg x 15.53 kg]	310.6 mg [20 mg x 15.53 kg]
mg per vial	100 mg	50 mg
Vials per administration	6.21 vials [621.20 mg / 100 mg]	6.21 vials [310.60 mg / 50 mg]
Round up to next whole number	7.00 vials	7.00 vials
Cost of treatment		
AEMP per vial	$ [redacted][a]	$ [redacted]
Vials per administration	7.00[b]	7.00
Administrations per month	2.17 [(52/12)/2]	2.17 [(52/12)/2]
Total cost of treatment per month	$ [redacted]	$ [redacted]
Incremental cost of treatment	$0.00	

Source: Table 3(b).4-2, p224 of the submission.

Abbreviations: ALGLU = alglucosidase alfa; AEMP = approved ex manufacturer price; AVAL = avalglucosidase alfa; IOPD = infantile onset Pompe disease; q2w = once every two weeks.

Notes: [a.] Total cost of treatment per month remains at price parity with ALGLU.

[b.] Sanofi commits to price parity with ALGLU in terms of total cost of treatment per month. AVAL is being reviewed by the TGA. The final approved dose will range from 20 mg/kg to 40 mg/kg.

[c.] This price corresponds to the confidential special pricing arrangement.

6.74 The average body weight used in the CMA (15.53 kg based on draft report of the review of LSDP medicines) was different to that reported in mini-COMET (28.5 kg in Cohort 1 and 32.5 kg in Cohort 2).

CUA – ALGLU (as a proxy for AVAL) vs placebo

6.75 The submission presented a modelled economic evaluation for LOPD and IOPD. The key components and assumptions of the CUA are presented in Table 13.

Table 13: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	ALGLU (as a proxy for AVAL) versus BSC
Time horizon	LOPD: 30 years in the base case. IOPD: 20 years in the base case.
Outcomes	Life years and quality adjusted life years gained.
Methods used to generate results	Survival model
Health states	Alive and dead
Cycle length	2 weeks
Allocation to health states	LOPD OS were derived directly from the pooled analysis of the KM estimates from the July 2011 ALGLU submission and Nagura 2019.
	IOPD OS were derived from the pooled analysis of the ALGLU (4 studies[a] plus the LSDP population) and natural history studies (2 studies[b]).
Extrapolation method	LOPD Independent Weibull distributions were used to extrapolate to the time horizon of the economic evaluation. An assumption of declining benefit was implemented for ALGLU where the ln(hazard) starts converging to that of BSC from month 90 and reaches full convergence at 25 years.
	IOPD A dependent generalised gamma distribution was used to extrapolate beyond the available clinical evidence. The effect of ALGLU was extrapolated to 83 months beyond this point the ln(hazard) converged to that of BSC before reaching full convergence at (20 years).
Health related quality of life	Source: Simon 2019. Base case (moderate symptoms): 8 years = 0.414; ≥ 18 years = 0.683.

Source: Table 3(c).1-1, pp228-229, Table 3(d).1-1, pp263-264, Table 3(c).5-2, p249 and Table 3(d).5-2, p288 of the submission.
Abbreviations: ALGLU = alglucosidase alfa; AVAL = avalglucosidase alfa; BSC = best supportive care; IOPD = infantile onset Pompe disease; KM = Kaplan Meier; LOPD = late onset Pompe disease; OS = overall survival.
Notes: [a] Broomfield et al (2016); Kishnani et al (2009); Parini et al (2018); and Chien et al (2015).
[b] van den Hout et al (2003) and Kishnani et al (2006).

6.76 The submission presented a survival model comprising of two health states, alive and dead to compare ALGLU (as a proxy for AVAL) with BSC. The same model structure was used for LOPD and IOPD. Previous PBAC submissions for Pompe disease were trial-based evaluations (with time horizon ranging from 52 to 78 weeks) based on short-term surrogate outcomes such as 6MWT and FVC (March 2009, November 2009, and November 2010 ALGLU submissions). The EMC Pompe Survey February 2011 was previously used to construct various survival models to support the OS outcome, but no economic evaluation was presented (ALGLU PSD, July 2011 PBAC meeting).

6.77 The pooled analysis to derive the KM curves to compare ALGLU and no treatment (based on natural history studies) that formed the basis of economic evaluation may be subject to transitivity and applicability issues, therefore, may not have been appropriate.

6.78 The submission indicated that there are insufficient data to capture Pompe disease symptoms (such as loss of mobility, pain, shortness of breath, fatigue, drowsiness, etc.) as separate health states. The submission stated that given the sparsity of data, the model structure was aligned as close as possible to the goals of treatment, which include slowing disease progression and improving OS while maintaining QoL. The presented model structure captured the survival benefits only, while the impact of slowing disease progression on quality of life was not considered. As acknowledged by the submission, the differences in health gain were only due to differences in life expectancy. Moreover, the model structure did not account for the potential of disease progression and use of supportive care (such as ventilator dependence and early wheelchair) in either arm. The PSCR stated that although it would have been preferable to capture costs and outcomes associated with disease progression in the economic model, Pompe disease affects multiple body systems, including respiratory, musculoskeletal, cardiac, and gastrointestinal, it is not possible to define a single health state 'progressive disease'. The PSCR stated that while impacts on the musculoskeletal and respiratory systems could perhaps be captured by the 6MWT or FVC % predicted, respectively, the clinical outcomes are less clear for the cardiac and gastrointestinal systems. The ESC noted the model structure only accounts for survival benefit for which there is no direct evidence and does not capture other potential benefits of treatment such as slowing progression. The ESC considered the explanation provided in the PSCR for not including a progressive health state in the economic model was not reasonable.

6.79 The time horizon of the economic evaluation when assessing LOPD patients was 30 years. The evaluation considered a 30-year time horizon may be reasonable and sufficient to capture the incremental differences in costs and health outcomes between ALGLU and BSC.

6.80 The time horizon proposed for the economic evaluation for patients with IOPD was 20 years. Based on the pooled KM OS curve, only 5 patients who had received ALGLU were at risk at 132 months (11 years), while no patients were at risk at 36 months (3 years) in the placebo arm. Furthermore, the mean age of death of patients with IOPD receiving ALGLU in Australia as reported in the LSDP was 42 months (3.5 years). The ESC considered a 20 year time horizon is too long for this population and noted the ICER with a 10 year time horizon decreased from $455,000 to < $555,000/QALY to $455,000 to < $555,000/QALY.

6.81 The LOPD and IOPD models implemented a decline in the ALGLU effect from a pre-specified time-point to the corresponding time horizon. In the LOPD model, convergence occurred from 84 months to 25 years, while in the IOPD model, convergence occurred from 24 months to 20 years. This was reasonable as the intent of ERT is not curative and it is expected that patients will deteriorate overtime.

6.82 For LOPD, the ALGLU arm was derived from the pooled KM estimates from the EMC Pompe survey February 2011 and the combined JOPD and AOPD arms of Nagura 2019 up to 89 months given that no further changes in the KM estimates were observed

beyond this time. For BSC, the proportion of patients in the health state alive was obtained from the KM estimates from the EMC Pompe survey February 2011 up to 91 months.

6.83 The ALGLU arm for IOPD was derived from the KM estimates from a pooled analysis of the studies by Broomfield et al (2016), Kishnani et al (2009), Parini et al (2018), Chien et al (2015) and the LSDP population up to 48 months.

6.84 Health utilities were based on a study (Simon 2019) that reported utility values by disease severity and age categories. In the model, health state utilities for patients with Pompe disease (LOPD or IOPD) were constant over time, and did not differ between patients receiving ALGLU and BSC and were assumed to correspond to patients experiencing moderate symptoms. For LOPD, the submission assumed that the age category 8 years and ≥ 18 years corresponded to JOPD and AOPD, respectively. In addition, the model assumed that 19% and 81% of the patients had JOPD and AOPD, respectively. This was reasonable and consistent with data from the LSDP that reported that [redacted]% had JOPD and [redacted]% had AOPD in Australia. Similarly, for IOPD patients, the utility reported for the age categories 8 years and ≥18 years was assumed for patients <18 years and ≥18 years, respectively.

6.85 The approach to estimating QALYs was the same for ALGLU and BSC. QALYs associated with the health state "Alive" were estimated by applying the cycle length adjusted health state utility to the proportion of patients in the health state "Alive" in each cycle and were half cycle corrected. Thus, the health benefit is derived from the "Alive" health state only. The ESC noted the incremental health benefits of ALGLU were entirely driven by OS.

6.86 The utility values used in the economic model were obtained from an online survey to a community sample who valued health states for patients with Pompe disease based on symptom severity and age of onset using a modified time trade off (mTTO) approach (Simon et al 2019). The key limitations of this study as acknowledged by the authors were:

- The possibility that parental spillover effects are incorporated in child health state valuations, which would result in double counting the loss in quality-of-life among parents. It may be hardest for parents to separate the effect of a disease on themselves versus their child.
- Wide confidence intervals on many of the estimates reported may indicate substantial variability and uncertainty in the measurements.
- The study could not select patients as respondents due to the rare nature of Pompe disease.
- Moreover, some inconsistencies were noted from the utility values reported on Simon 2019 among 8-year-old patients, where a lower utility value was reported for moderate symptoms (0.414) compared to severe symptoms (0.466).

6.87 The economic evaluation included all TEAEs graded as severe due to the limited safety data from COMET and mini-COMET. The proportion of patients who experience these events while receiving treatment with AVAL was applied to all patients upon commencing therapy. The latter assumes that the costs associated to the AEs were incurred in the first cycle. This approach was considered conservative in terms of the ICER. No disutility was attached to the events. The PBAC previously noted that treatment with ALGLU is associated with significant toxicities. (ALGLU PSD, July 2011 PBAC meeting).

6.88 Health care resource utilisation and their associated costs included costs of medicines, disease monitoring and routine follow up, and management of adverse events. As mentioned previously the model did not take into account the potential of disease progression and use of supportive care, therefore, all potential costs expected to be associated with these events were not considered by the submission.

6.89 The submission noted that AVAL is expected to be administered to paediatric patients in the hospital inpatient setting while managed in the hospital outpatient setting for those aged ≥18 years, which is consistent with Australian clinical practice. The submission assumed that the cost of administration of ERT in the hospital outpatient setting corresponded to that of the MBS item 13950, which refers to the parenteral administration of antineoplastic agents or monoclonal antibody therapy. The cost of administering AVAL in the hospital inpatient setting corresponded to AR DRG K63B, which is for admissions related to inborn errors of metabolisms. The proposed PBS restriction for IOPD patients in limits the use of AVAL to the hospital outpatient setting only.

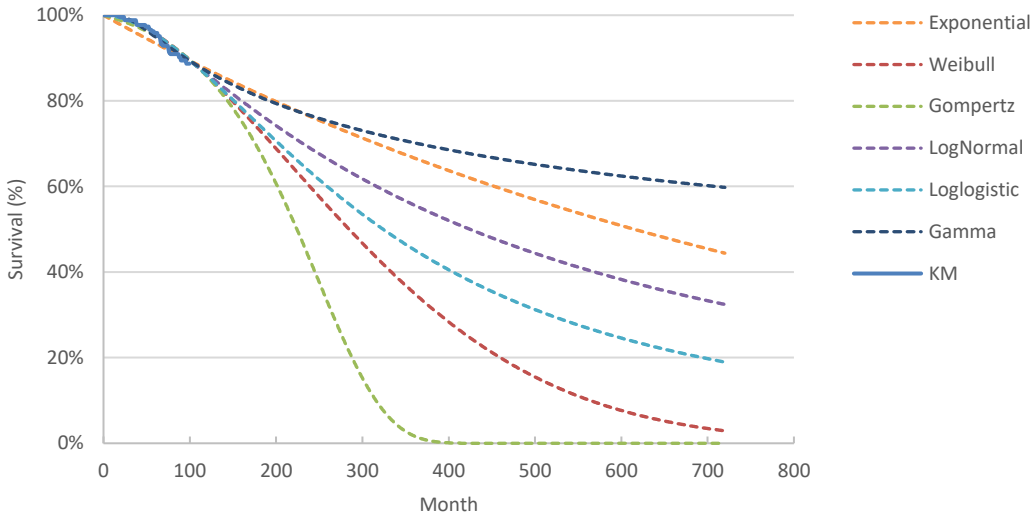
Extrapolation

LOPD

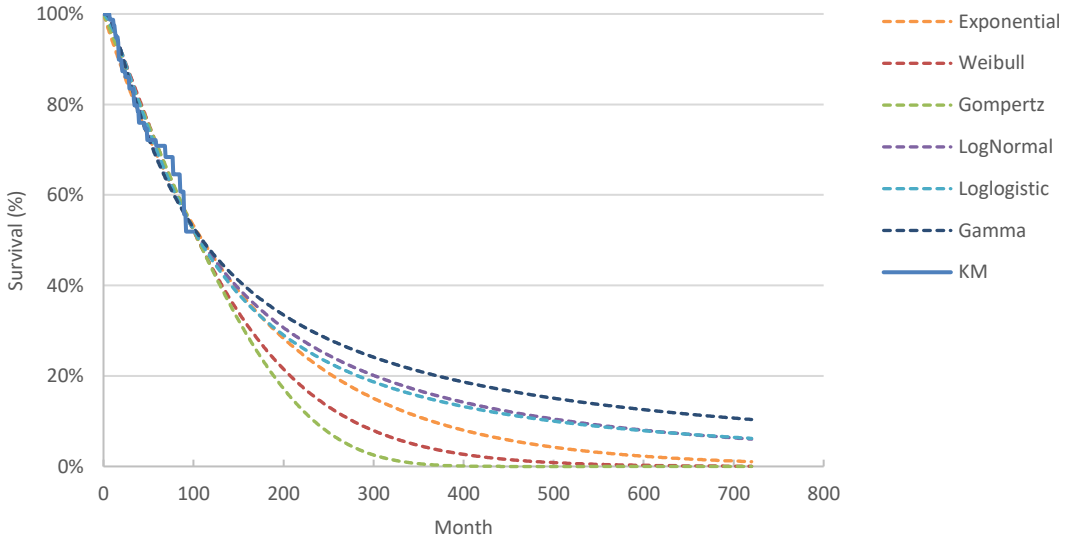
6.90 The KM curves and independent survival model for ALGLU and BSC is presented in Figure 8. The submission extrapolated OS data for LOPD using the Weibull distribution based on clinical plausibility and that it provided the second most conservative estimates of the long-term survival for ALGLU and BSC.

Figure 8: Kaplan Meier OS and dependent survival models for (a) ALGLU and (b) BSC

(A)



(B)



Source: Figure 3(c).4-4, p247 of the submission.
Abbreviations: ALGLU = alglucosidase alfa; KM = Kaplan-Meier.

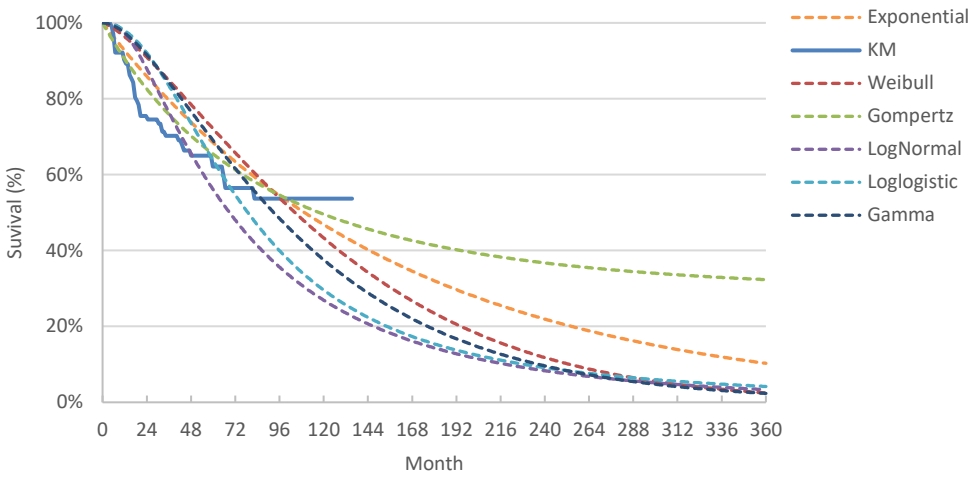
IOPD

6.91 The KM curves and dependent survival model for ALGLU and BSC is presented in Figure 9. The submission extrapolated OS data for IOPD using the generalised gamma distribution as the second best fit to the observed data given that it provided

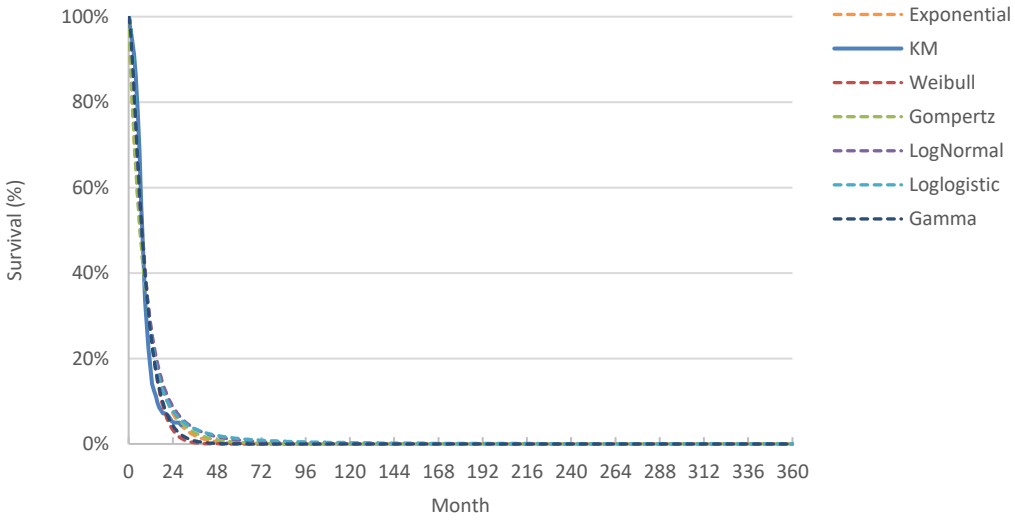
a more conservative estimate of the long term survival with ALGLU and does not result in an overextended tail compared with the loglogistic distribution.

Figure 9: Kaplan Meier OS and dependent survival models for (a) ALGLU and (b) BSC

(A)



(B)



Source: Figure 3(d).4-4, p282 of the submission.
Abbreviations: ALGLU = alglucosidase alfa; KM = Kaplan-Meier.

Results

LOPD

6.92 The estimated annual cost of treatment with ALGLU (as a proxy for AVAL) was $[redacted] and $[redacted], excluding the costs of the IV infusion, for JOPD and AOPD, respectively. The cost of ALGLU cost per patient for JOPD and AOPD was consistent with cost per patient reported by the LSDP review report. The LSDP review reported

the cost per JOPD and LOPD patient to be $[redacted] ($[redacted] per month) and $[redacted] ($[redacted] per month), respectively.

6.93 The result of the stepped economic evaluation for LOPD is presented in Table 14.

Table 14: Results of the stepped economic evaluation - LOPD

Step and component	ALGLU (as a proxy for AVAL)	BSC	Increment
Step 1: Clinical evidence with time horizon of 8 years			
Costs ($)	[redacted]	$0	[redacted]
LYG	6.55	5.32	1.23
Incremental cost/extra LYG gained			[redacted][1]
Step 2: Step 1 including extrapolation to 30 years, declining benefit, and population mortality			
Costs ($)	[redacted]	$0	[redacted]
LYG	12.13	7.59	4.54
Incremental cost/extra LYG gained			[redacted][2]
Step 3: Step 2 including all resource use			
Costs ($)	[redacted]	$4,639	[redacted]
LYG	12.13	7.59	4.54
Incremental cost/extra LYG gained			[redacted][2]
Step 4: Step 3 including transformation to QALYs			
Costs ($)	[redacted]	$4,639	[redacted]
QALYs	7.65	4.79	2.87
Incremental cost/extra QALY gained			[redacted][1]

Source: Table 3(c).8-1, p256 of the submission.

Abbreviations: ALGLU = alglucosidase alfa; AVAL = avalglucosidase alfa; BSC = best supportive care; LOPD = late onset Pompe disease; LYG = Life year gained; QALY = quality adjusted life year.

The redacted values correspond to the following ranges:

[1] *> $1,055,000*

[2] *$755,000 to < $855,000*

6.94 The model estimated an overall difference in survival of 4.54 years (and 2.97 QALYs) when comparing ALGLU to BSC considering a 30 year time horizon (including declining benefit and population mortality). The estimated gain in survival was 1.23 years when considering a time horizon of 8 years (as per the clinical evidence).

6.95 The model resulted in an incremental cost of $[redacted] which was driven by the cost of ALGLU accounting for 98.9% of the incremental cost.

6.96 A summary of the key drivers of the model is presented in Table 15.

Table 15: Key drivers of the model

Description	Method/Value	Impact Base case: [redacted][1]/QALY gained.
Distribution of patients with JOPD	JOPD: 19% in the base case	High, favours ALGLU. Use of 100% JOPD increased the ICER to [redacted][1]/QALY gained.
Distribution of patients with AOPD	AOPD: 81% in the base case	Moderate, favours BSC. Use of 100% AOPD decreased the ICER to [redacted][2]/QALY gained.
Utilities	Base case moderate symptoms utilities obtained from Simon 2019: 8 years: 0.414 ≥ 18 years: 0.683	Use of severe symptoms utilities increased the ICER to [redacted][1]/QALY gained. Use of mild symptoms utilities decreased the ICER to [redacted][2]/QALY gained.
OS data	Pooled analysis of the Kaplan Meier estimates from the EMC Pompe Survey February 2011 (ALGLU, July 2011 submission) and the pooled JOPD and AOPD arms of Nagura 2019.	High, favours ALGLU. Use of OS from Gungor 2011 increased the ICER to [redacted][1]/QALY gained.

Source: Constructed during the evaluation.
Abbreviations: ALGLU = alglucosidase alfa; AOPD = adult onset Pompe disease; ICER = incremental cost effectiveness ratio; JOPD = juvenile onset Pompe disease; OS = overall survival; QALY = quality adjusted life years.
The redacted values correspond to the following ranges:
[1] *> $1,055,000*
[2] *$855,000 to < $955,000*

6.97 The submission stated that the main drivers of the economic evaluation were the distribution across JOPD and AOPD patients, and the health state utility values. It was noted that the benefit in OS of ALGLU compared to BSC (derived from the KM curves) was likely a key driver of the model, however, this was difficult to test in a sensitivity analysis and its impact could not be fully quantified.

6.98 The submission conducted a scenario analysis based on OS data of adult patients with Pompe disease prior to treatment with ERT using the KM data from Gungor 2011 and the ICER increased from > $1,055,000/QALY to > $1,055,000/QALY (247% increase from the base case).

6.99 The results of key univariate sensitivity analyses are summarised in Table 16.

Table 16: Results of sensitivity analyses presented by the submission with an impact >10% on the base case ICER

	Incremental outcomes	Incremental cost ($)	ICER ($/QALY)	Change in ICER from base case[a]
Base case	2.87	[redacted]	[redacted][1]	N/A
Costs and population				
JOPD: 100%	1.88	[redacted]	[redacted][1]	154%
AOPD: 100%	3.10	[redacted]	[redacted][2]	-22%
Health states utilities				
Simon 2019 – Mild symptoms	3.83	[redacted]	[redacted][2]	-25%
Simon 2019 – Severe symptoms	2.37	[redacted]	[redacted][1]	21%
Kanters 2011	3.27	[redacted]	[redacted][1]	-12%
Scenario analysis based on KM data from Gungor 2011[b]				
Base case	0.92	[redacted]	[redacted][1]	247%

Source: Table 3(c).9-1, p259 of the submission.
Abbreviations: admin. = administration; BSC = best supportive care; N/A = not applicable; OS = overall survival; QALY = quality adjusted life year gained.

Notes: [a] Estimated during the evaluation.
[b] OS data of adult patients with Pompe disease prior to treatment with ERT obtained from Gungor 2011.
The redacted values correspond to the following ranges:
[1] > $1,055,000
[2] $855,000 to < $955,000

IOPD

6.100 The result of the stepped economic evaluation for IOPD is presented in Table 17.

Table 17: Results of the stepped economic evaluation - IOPD

Step and component	ALGLU	BSC	Increment
Step 1: clinical evidence with time horizon of 28 months			
Costs ($)	[redacted]	$0	[redacted]
LYG	0.54	0.48	0.06
Incremental cost/extra LYG gained			[redacted][1]
Step 2: Step 1 including extrapolation to 20 years, declining benefit, and population mortality			
Costs ($)	[redacted]	$0	[redacted]
LYG	5.58	0.77	4.80
Incremental cost/extra LYG gained			[redacted][2]
Step 3: Step 2 including all resource use			
Costs ($)	[redacted]	$1,545	[redacted]
LYG	5.58	0.77	4.80
Incremental cost/extra LYG gained			[redacted][2]
Step 4: Step 3 including transformation to QALYs			
Costs ($)	[redacted]	$1,545	[redacted]
QALYs	2.31	0.32	1.99
Incremental cost/extra QALY gained			[redacted][3]

Source: Table 3(d).8-1, p294 of the submission.
Abbreviations: ALGLU = alglucosidase alfa; BSC = best supportive care; IOPD = infantile onset Pompe disease; LYG = Life year gained; QALY = quality adjusted life year gained.
The redacted values correspond to the following ranges:
[1] $755,000 to < $855,000
[2] $155,000 to < $255,000
[3] $455,000 to < $555,000

6.101 The model estimated an overall difference in survival between ALGLU and BSC equivalent to 4.80 years when considering a 20 year time horizon (including declining benefit and population mortality). When a time horizon of approximately 2.3 years (28 months as per the clinical evidence) the incremental gain was 0.06 years.

6.102 The model resulted in an incremental cost of $[redacted] which was driven by the cost of ALGLU and the associated IV infusion administration costs which accounted for 75.5% and 23.4% of the incremental costs, respectively.

6.103 A summary of the key drivers of the model is presented in Table 18.

Table 18: Key drivers of the IOPD model

Description	Method/Value	Impact Base case: [redacted][1]/QALY gained
Utilities	Base case moderate symptoms utilities obtained from Simon 2019: 8 years: 0.414 ≥ 18 years: 0.683	High, favours ALGLU. Use of mild symptoms utilities from Simon 2019 and utility values from Kanters 2014 decreased the ICER to [redacted][2]/QALY and [redacted][3]/QALY gained, respectively.
Time horizon	20 years in the base case	Moderate, favours ALGLU. Use of 10-year time horizon decreased the ICER to [redacted][4]/QALY gained.
Extrapolation	OS was extrapolated using the generalised gamma distribution as the second best fit to the observed data in the base case.	Moderate, favours ALGLU Use of different parametric functions increased the ICER at varying rates based on the selected parametric model. The highest impact was observed with the use of independent Gompertz and Gamma models, which increased the ICER to [redacted][5]/QALY and [redacted][5]/QALY gained, respectively.

Source: Constructed during the evaluation.
Abbreviations: ALGLU = alglucosidase alfa; IOPD = infantile onset Pompe disease; ICER = incremental cost effectiveness ratio; OS = overall survival; QALY = quality adjusted life years.
The redacted values correspond to the following ranges:
[1] *$455,000 to < $555,000*
[2] *$255,000 to < $355,000*
[3] *$255,000 to < $355,000*
[4] *$455,000 to < $555,000*
[5] *$555,000 to < $655,000*

6.104 The key drivers of the economic model were the health state utility and the assumptions for the extrapolation of OS.

6.105 The results of key univariate sensitivity analyses are summarised in Table 19.

Table 19: Results of sensitivity analyses presented by the submission -IOPD

	Incremental QALY	Incremental cost	ICER ($/QALY)	Change in ICER from base case[a]
Base case	1.99	[redacted]	[redacted][1]	-
Costs[a]				
IV admin. in outpatient setting - MBS item 13950	1.99	[redacted]	[redacted][2]	-22%
Health state utilities				
Simon 2019 – Mild symptoms	3.84	[redacted]	[redacted][3]	-48%
Kanters 2014	2.98	[redacted]	[redacted][3]	-33%
Parametric functions – ALGLU [BSC Indep.: Loglogistic]				
OS Indep. – Exponential	2.49	[redacted]	[redacted][4]	17%
OS Indep. – Weibull	2.63	[redacted]	[redacted][4]	19%
OS Indep. – Gompertz	2.86	[redacted]	[redacted][4]	24%
OS Indep. – LogNormal	2.64	[redacted]	[redacted][4]	20%
OS Indep. – LogLogistic	2.62	[redacted]	[redacted][4]	19%
OS Indep. - Gamma	2.94	[redacted]	[redacted][4]	25%
OS Dep. – Gompertz	2.51	[redacted]	[redacted][4]	16%
Time horizon				
Time horizon 10 years	1.80	[redacted]	[redacted][1]	-7%

Source: Table 3(d).9-1, p297 of the submission.

Abbreviations: admin. = administration; BSC = best supportive care; Dep. = dependent; Indep. = independent; IOPD = infantile onset Pompe disease; IV = intravenous; OS = overall survival; QALY = quality adjusted life year gained.

Notes: [a.] Estimated during the evaluation.

The redacted values correspond to the following ranges:

[1] $455,000 to < $555,000

[2] $355,000 to < $455,000

[3] $255,000 to < $355,000

[4] $555,000 to < $655,000

6.106 Results from a sensitivity analysis conducted during evaluation, which assumed administration of ALGLU in the outpatient setting only (MBS item 13950), showed that the ICER decreased from $455,000 to < $555,000 (base case) to $355,000 to < $455,000/QALY (approximately 22% reduction).

Drug cost/patient/year

6.107 The drug cost per patient per year for JOPD, AOPD, and IOPD is presented in Table 20.

Table 20: Drug cost per patient for AVAL

		Economic model and financial estimates		
		JOPD	**AOPD**	**IOPD**
A	Mean dose (q2w)	20 mg/kg	20 mg/kg	40 mg/kg
B	Cost/pack, 100 mg per 10 mL vial (published AEMP) ($)	[redacted]	[redacted]	[redacted]
C	Cost/mg (published AEMP)	$20.18	$20.18	$20.18
D	Treatment compliance	100%	100%	100%
E	Cost/patient/month (effective AEMP) ($)	[redacted][a]	[redacted][a]	[redacted][b]
F	Cost/patient/year (chronic) (= E*12) ($)	[redacted]	[redacted]	[redacted]

Source: Compiled during the evaluation from Table 1.4-1, p17, Table 3(a).4-2, p216 Table 3(b).4-2, p224, and Table 4.1-1, pp299-300 of the submission. Italicised values have been calculated during evaluation.

Abbreviations: ALGLU = alglucosidase alfa; AEMP = approved ex-manufacturer price; AOPD = adult onset Pompe disease; AVAL = avalglucosidase alfa; JOPD = juvenile onset Pompe disease; LOPD = late onset Pompe disease; N/A = not applicable; q2w = once every 2 weeks.

Notes: [a] Total cost of treatment per month is irrespective of the number of vials that are required per administration; identical to that of ALGLU for JOPD and AOPD.

[b] Total cost of treatment per month remains at price parity with ALGLU.

Estimated PBS usage & financial implications

6.108 This submission was not considered by DUSC. The submission used a market approach to estimate the expected used and associated financial implications of AVAL. The key inputs to inform the financial estimated are summarised in Table 21.

Table 21: Key inputs for financial estimates

Data	Value	Source	Comment
Eligible population			
Patients treated with alglucosidase alfa:	IOPD JOPD AOPD Yr 1: [1] [1] [1] Yr 2: [1] [1] [1] Yr 3: [1] [1] [1] Yr 4 [1] [1] [1] Yr 5: [1] [1] [1] Yr 6: [1] [1] [1]	Historical: Review of LSDP medicines for Pompe disease (2020) Predicted: expected trend of newly initiations and losses (i.e. death or stop treatment)	Use of LSDP review was appropriate given that its relevance to the target population. It was unclear how the predicted number of patients was estimated.
Body weight	IOPD: 15.53 kg JOPD: 57.7 kg AOPD: 76.8 kg	Review of LSDP medicines for Pompe disease (2020) ToR 5	This was appropriate.
Treatment utilisation			
Dosing regimen	AVAL: IOPD: 40 mg/kg q2w JOPD: 20 mg/kg q2w AOPD: 20 mg/kg q2w ALGLU All: 20 mg/kg q2w	AVAL draft PI ALGLU PI	This was appropriate.
Uptake of AVAL (%)	IOPD JOPD AOPD Yr 1: 50 58 56 Yr 2: 100 100 100 Yr 3: 100 100 100 Yr 4: 100 100 100 Yr 5: 100 100 100 Yr 6: 100 100 100	Proposed by sponsor	The assumption used to estimate the uptake rates was not justified by the submission. The submission assumed a 100% uptake from Year 2.
Costs			
AVAL	Effective AEMP/SPA IOPD: $[redacted] per 100 mg/ 10 mL vial [b] JOPD: $[redacted] per month AOPD: $[redacted] per month	Proposed by sponsor	
ALGLU	Effective AEMP/SPA IOPD: $[redacted] per 50 mg/ 10 mL vial JOPD: $[redacted] per month AOPD: $[redacted] per month	Confidential agreement between sponsor and the LSDP	

Source: Table 4.1-1, pp299-300 of the submission.

Abbreviations: ALGLU = alglucosidase alfa; AOPD = Adult Onset Pompe Disease; AVAL = avalglucosidase alfa; IOPD = Infantile Onset Pompe Disease; JOPD = Juvenile Onset Pompe Disease; LSDP = Life Saving Drug Program PBS = Pharmaceutical Benefits Scheme; q2w = once every two weeks; RPBS = Repatriation Pharmaceutical Benefits Scheme; SMA = spinal muscular atrophy.

The redacted values correspond to the following range:

[1] < 500

6.109 The submission estimated the total number of patients who would be expected to receive treatment with AVAL in the years 2022 to 2027 based on the expected patterns of gains and losses observed from patients receiving ALGLU through the LSDP.

6.110 The submission expected a total of < 500 patients to commence treatment with AVAL in Year 1, increasing to < 500patients in Year 6. The submission assumed an uptake rate of 100% in Year 2.

6.111 The submission estimated that each patient who receives treatment with AVAL requires 26 prescriptions per year, with a total of 500 to < 5,000 and 500 to < 5,000 prescriptions expected to be dispensed on the PBS/ RPBS in Year 1 and Year 6 respectively.

6.112 The estimated use and financial implications of AVAL are presented in Table 22. The total cost to the PBS/RPBS of listing AVAL was estimated to be $0 to < $10 million in the first year of listing and $20 million to < $30 million in Year 6. The ESC noted the financial implications appear to be based on AEMP rather than DPMQ.

Table 22: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Estimated financial implications of AVAL						
Cost to PBS/RPBS less co-payments	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][5]	[redacted][5]	[redacted][5]
Net financial implications						
Net cost to PBS/RPBS	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][5]	[redacted][5]	[redacted][5]
Net cost to LSDP	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][5]	[redacted][5]	[redacted][5]
Net cost to the health budget	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]

Source: Table 4.2-1, p305, Table 4.2-3, p306, Table 4.2-6, p308, Table 4.2-8, p309, Table 4.4-1, p309, Table 4.5-4, p311, and Table 4.5-2, p310 of the submission.

Abbreviations: AVAL = avalglucosidase alfa; LSDP = Life Saving Drug Program; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

The redacted values correspond to the following ranges:

[1] *< 500*

[2] *500 to < 5,000*

[3] *$0 to < $10 million*

[4] *$10 million to < $20 million*

[5] *$20 million to < $30 million*

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC did not recommend the requested Section 100 (Highly Specialised Drugs Program) listing of avalglucosidase alfa (AVAL) for the treatment of infantile-onset Pompe disease (IOPD), juvenile-onset Pompe disease (JOPD) or adult-onset Pompe disease (AOPD). The PBAC considered AVAL treatment for late onset Pompe disease (LOPD), including the AOPD and JOPD populations, was likely non-inferior to alglucosidase alfa (ALGLU). The PBAC considered the lack of evidence for the IOPD population made the clinical claim of non-inferiority for that population highly uncertain but that, overall, AVAL was likely to provide similar health outcomes to

ALGLU. The PBAC considered AVAL was an effective treatment for IOPD and LOPD (compared to no treatment) but the extent of benefit was uncertain. The PBAC considered the incremental cost effectiveness ratio (ICER) for AVAL compared to no treatment was very high and uncertain.

7.2 The PBAC noted the Life Saving Drugs Program (LSDP) Expert Panel suggested nomenclature and considered it would be appropriate to consolidate IOPD and LOPD.

7.3 The submission nominated ALGLU as the primary comparator and placebo (representing standard of care) as a supplementary comparator. The PBAC noted ALGLU is currently available on the LSDP for IOPD, JOPD and AOPD and considered it was an appropriate comparator. The PBAC considered that, in the absence of a PBS listed treatment for Pompe disease, placebo was also an appropriate comparator.

7.4 The PBAC noted the consumer comments were strongly supportive of home infusions for the treatment of IOPD and LOPD. The PBAC acknowledged the benefits of home infusion but did not believe the sponsor had adequately justified why this should be unique to treatment with AVAL and not be extended to ALGLU. The PBAC noted AVAL may have a reduction in preparation complexity compared to ALGLU.

7.5 The PBAC noted the limitation of the clinical data in this rare disease. The PBAC noted for LOPD the submission presented the results from COMET (N = 100), a head-to-head randomised non-inferiority trial comparing the efficacy and safety of AVAL (N=51) and ALGLU (N=49) in treatment naïve patients. The PBAC considered the claim AVAL is non-inferior to ALGLU in terms of effectiveness based on surrogate outcome measures (FVC and 6MWT) for the LOPD population was reasonable. The PBAC noted no comparative data on overall survival was available.

7.6 The PBAC noted for IOPD the submission presented the results from mini-COMET (N = 22), a phase 2, open-label, multi-stage ascending dose, cohort trial where children with IOPD were treated with repeated infusions of AVAL. The PBAC noted this trial was a complicated design, in treatment experienced patients, in an older age range than requested for IOPD, with limited data and no formal statistical analyses. The PBAC considered the claim AVAL is non-inferior to ALGLU in terms of effectiveness for the IOPD population was not adequately supported by the data presented. However, the PBAC considered that, overall, AVAL was likely to provide similar health outcomes to ALGLU for the treatment of IOPD.

7.7 The PBAC considered the safety of AVAL appeared comparable to ALGLU but the available evidence was inadequate to support a non-inferiority claim.

7.8 For the comparison with placebo, ALGLU (as a proxy for AVAL) was claimed to be superior to placebo for the outcome of overall survival. For LOPD, the PBAC noted the reliance on surrogate outcomes of FVC and 6MWT translating to overall survival and the recalled the Committee's previous concerns about the uncertainty of the short-term surrogate outcomes being correlated with patient survival. The PBAC considered

there was no new data presented in this submission that could reliably inform a change to its previous view when considering ALGLU.

7.9 For IOPD, the PBAC had previously considered that the results of Study 1602 and Study 2403 in ALGLU suggest that ALGLU prolongs survival in infants but does not appear to extend the lifespan beyond early childhood (ALGLU PSD, July 2008 PBAC meeting). The PBAC noted the limited additional data provided in the submission but considered it did not substantially change its previous view.

7.10 In terms of the economic evaluations, for the comparison of AVAL with ALGLU in LOPD, the PBAC accepted that the equi-effective doses were AVAL 20 mg/kg every other week and ALGLU 20 mg/kg every other week, as proposed in the submission. For the comparison of AVAL with ALGLU in IOPD, the PBAC accepted the equi-effective doses were AVAL 40 mg/kg every other week and ALGLU 20 mg/kg every other week, as proposed in the submission.

7.11 For the comparison of AVAL to placebo, the PBAC noted the simple economic model structure meant that the only health gain modelled was survival, and the quality of life gains from slower disease progression were not captured. For both the LOPD and IOPD models the PBAC considered the ICERs were very high and uncertain. The PBAC noted the base case ICER for LOPD was > $1,055,000/ QALY (with sensitivity analyses ranging from $855,000 to < $955,000/QALY to > $1,055,000/QALY) and for IOPD was $455,000 to < $555,000/ QALY (with sensitivity analyses ranging from $255,000 to < $355,000/ QALY to $555,000 to < $655,000/ QALY). The PBAC considered the extent of the modelled incremental survival benefits (4.5 years for LOPD and 4.8 years for IOPD) were not supported by the clinical data.

7.12 The submission expected a total of < 500 patients to commence treatment with AVAL in Year 1, increasing to < 500 patients in Year 6. The PBAC noted that, accounting for cost offsets to the LSDP, there would be no net cost to the Commonwealth of listing AVAL on the PBS.

7.13 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Not recommended

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available

through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

The sponsor had no comment.