

5.02 CIPAGLUCOSIDASE ALFA

Powder for I.V infusion 105 mg,

Pombiliti®

MIGLUSTAT

Capsule 65 mg,

Opfolda®

Amicus Therapeutics Pty Ltd

1 Purpose of submission

- 1.1 The Category 2 submission requested listing for cipaglucoisidase with miglustat (CIPAMIG) on the Pharmaceutical Benefits Scheme (PBS) for the treatment of adults with late-onset Pompe disease (LOPD), with the aim of funding through the Life Saving Drugs Program (LSDP). The Pre-Sub Committee Response (PSCR) affirmed that the submission’s objective was for CIPAMIG to be included on the LSDP.
- 1.2 The listing was requested on the basis of a cost-minimisation approach versus alglucosidase alfa-rcg (ALGLU) and avalglucosidase alfa (AVAL).

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

Component	Description
Population	Adults with late-onset Pompe Disease
Intervention	Cipaglucoisidase alfa with miglustat
Comparator	Alglucosidase alfa and avalglucosidase alfa
Outcomes	6 Minute Walk Distance (6MWD) Sitting Forced Vital Capacity (FVC) Manual Muscle Test (MMT) PROMIS questionnaire Subject’s Global Impression of Change (SGIC) Gait, Stairs, Gowers’ Manoeuvre and Chair (GSGC) Treatment-emergent adverse events (TEAEs) Serious TEAEs Infusion-associated reactions (IARs)
Clinical claim	Cipaglucoisidase alfa plus miglustat (CIPAMIG) has at least non-inferior efficacy and non-inferior safety compared to (i) alglucosidase alfa (ALGLU) and (ii) avalglucosidase alfa (AVAL).

Source: Table 1, p6 of the submission.

2 Background

Registration status

- 2.1 The TGA status at the time of PBAC consideration – from ARTG certificate:
- cipaglucoisidase alfa was TGA registered on 17 February 2025
 - miglustat was TGA registered on 16 December 2024

- 2.2 CIPAMIG was approved for use by the European Medicines Agency (EMA) in March 2023 for the treatment of adults with late-onset Pompe Disease (lysosomal acid α -glucosidase [GAA] deficiency). The approved indication in the US from September 2023 is for the treatment of adult patients with late-onset Pompe Disease (lysosomal acid alpha-glucosidase [GAA] deficiency) weighing \geq 40 kg who are not improving on their current enzyme replacement therapy (ERT).

Previous PBAC consideration

- 2.3 The PBAC has not previously considered a submission for CIPAMIG. The PBAC considered a submission for AVAL for the treatment of LOPD in November 2021 (avalglucosidase alfa Public Summary Document (PSD), November 2021) and rejected it for listing on the PBS based on a high and uncertain incremental cost-effectiveness ratio compared to no treatment. It was subsequently included on the LSDP. ALGLU was first included on the LSDP for infantile-onset Pompe Disease (IOPD) in 2010, after the PBAC rejected listing on the PBS in November 2010 (alglucosidase alfa PSD, November 2010). The LSDP listing was expanded to include juvenile-onset Pompe Disease in February 2015 and late-onset Pompe Disease in September 2015. The classification of Pompe disease is now either infantile-onset or late-onset, late-onset including both juvenile-onset and adult-onset. This change was made following the LSDP Expert Panel Review of Pompe disease in 2020. Recommendations from this review included that the prevalence of Pompe disease be reviewed within 5 years to determine whether it continues to meet the LSDP definition of an ultra-rare disease and that the pricing and listing arrangements for alglucosidase alfa be reassessed with the goal of improving value for money when:
- (i) current deeds of agreements with sponsors expire; and/or
 - (ii) new medicines for Pompe disease are considered for entry onto the LSDP or other subsidy programs; and/or
 - (iii) changes in eligibility criteria are being considered.
- 2.4 Miglustat has been considered by the PBAC previously for use in Gaucher Disease (miglustat PSD, March 2008), and in Niemann-Pick Type C Disease (miglustat PSD, November 2011). It was included on the LSDP for Gaucher Disease between 2009 and 2022 but was subsequently delisted.
- 2.5 The LSDP has commenced a 24-month review of AVAL, which is due to be completed in February 2025. The terms of reference for the review are outlined on the [Department of Health and Aged Care's website](#).

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

3 Requested listing

- 3.1 The submission proposed initial and continuing restrictions which were modelled on the current LSDP criteria for alglucosidase alfa and avalglucosidase alfa for the treatment of Pompe Disease.
- 3.2 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

CipaglucoSIDase alfa (initial restriction)

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No.of Rpts	Available brands
CIPAGLUCOSIDASE ALFA					
CipaglucoSIDase alfa, 105 mg injection , 1 vial	NEW	1	1	445	Pombiliti
Restriction Summary / Treatment of Concept:					
	Category / Program: <input checked="" type="checkbox"/> Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Restriction type: <input checked="" type="checkbox"/> Authority Required (Written Authority) [new/existing code]				
	Authority type: <input checked="" type="checkbox"/> Non-complex Authority Required (non-CAR)				
	Administrative Advice: No increase in the maximum number of repeats may be authorised.				
	Administrative Advice: Special Pricing Arrangements apply.				
	<i>Episodicity:</i> [blank]				
	<i>Severity:</i> [blank]				
	Condition: Late-onset Pompe disease (LOPD)				
	Indication: Late-onset Pompe disease (LOPD)				
	Treatment Phase: Initiation				
	Clinical criteria:				
	The patient must be diagnosed with late-onset Pompe disease				
	AND				
	Clinical criteria:				
	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				
	Clinical criteria:				
	The patient must not have another life threatening or severe disease where prognosis is unlikely to be influenced by ERT				
	AND				
	Clinical criteria:				
	The patient must not have another medical condition that might reasonably be expected to compromise a response to ERT				
	AND				
	Clinical criteria:				
	The patient must not be a current smoker				

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	AND
	Clinical criteria:
	The patient must present with FVC, supine and erect, < 80% of the predicted value
	OR
	The patient must have sleep disordered breathing;
	OR
	The patient must have significant muscular weakness.
	AND
	Treatment criteria:
	Must not be administered concomitantly with alglucosidase alfa or avalglucosidase alfa
	AND
	Treatment criteria:
	Must be used in combination with miglustat
	Population criteria:
	Patient must be at least 18 years of age
	Prescribing Instructions: At the time of authority application, prescribers should request the appropriate number of vials adequate for the duration of a months' treatment, based on the patient's weight. A maximum of 5 repeats may be authorised under this restriction
	Caution: This drug is a Category D drug and must not be given to pregnant women. If this drug is taken during pregnancy, a teratogenic effect in humans cannot be ruled out.

Cipaglucosidase alfa (continuation restriction)

Restriction Summary / Treatment of Concept:	
	Category / Program: <input checked="" type="checkbox"/> Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required (Streamlined) [new/existing code]
	Authority type: <input checked="" type="checkbox"/> Non-complex Authority Required (non-CAR)
	Condition: Pompe disease
	Indication: Late-onset Pompe disease (LOPD)
	Treatment Phase: Continuation
	Clinical criteria:
	The patient must have received prior treatment with this drug for this condition
	AND
	Clinical criteria:
	The patient must demonstrate clinical improvement;
	OR
	The patient must demonstrate stabilisation of the disease condition
	Prescribing Instructions: At the time of authority application, prescribers should request the appropriate number of vials adequate for the duration of a months' treatment, based on the patient's weight. A maximum of 5 repeats may be authorised under this restriction

Miglustat (initial restriction)

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No.of Rpts	Available brands
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MIGLUSTAT						
Miglustat, 65mg capsule, 4	NEW	4 2	4 8	445	Opfoda	
Restriction Summary / Treatment of Concept:						
	Category / Program: <input checked="" type="checkbox"/> Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)					
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
	Restriction type: <input checked="" type="checkbox"/> Authority Required (Written Authority) [new/existing code]					
	Authority type: <input checked="" type="checkbox"/> Non-complex Authority Required (non-CAR)					
	Administrative Advice: No increase in the maximum number of repeats may be authorised.					
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.					
	Administrative Advice: Special Pricing Arrangements apply.					
	Condition: Pompe disease					
	Indication: Late-onset Pompe disease (LOPD)					
	Treatment Phase: Initiation					
	Clinical criteria: The patient must be diagnosed with late-onset Pompe disease					
	AND					
	Clinical criteria: 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					
	Clinical criteria: The patient must not have another life threatening or severe disease where prognosis is unlikely to be influenced by ERT					
	AND					
	Clinical criteria: The patient must not have another medical condition that might reasonably be expected to compromise a response to ERT					
	AND					
	Clinical criteria: The patient must not be a current smoker					
	AND					
	Clinical criteria: 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.					
	AND					
	Treatment criteria: Must not be administered concomitantly with alglucosidase alfa or avalglucosidase alfa					
	AND					
	Treatment criteria:					

	Must be used in combination with cipaglucoisidase alfa
	Population criteria:
	Patient must be at least 18 years of age
	Prescribing Instructions: At the time of authority application, prescribers should request the appropriate number of capsules adequate for the duration of a months' treatment. A maximum of 5 repeats may be authorised under this restriction
	Caution: This drug is a Category D drug and must not be given to pregnant women. If this drug is taken during pregnancy, a teratogenic effect in humans cannot be ruled out.

Miglustat (continuation restriction)

Restriction Summary/ Treatment of Concept:	
	Category / Program: <input checked="" type="checkbox"/> Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required (Written Authority) [new/existing code]
	Authority type: <input checked="" type="checkbox"/> Non-complex Authority Required (non-CAR)
	Condition: Pompe disease
	Indication: Late-onset Pompe disease (LOPD)
	Treatment Phase: Continuation
	Clinical criteria:
	The patient must have received prior treatment with this drug
	AND
	Clinical criteria:
	The patient must demonstrate clinical improvement
	OR
	The patient must demonstrate stabilisation of the disease condition
	Prescribing Instructions: At the time of authority application, prescribers should request the appropriate number of capsules adequate for the duration of a months' treatment. A maximum of 5 repeats may be authorised under this restriction

- 3.3 The restrictions as proposed in the submission are largely identical to the LSDP eligibility requirements for Pompe disease to which the submission referred. However, the LSDP eligibility criteria require FVC and 6 Minute Walk Test for patients over 18 only while the proposed PBS restrictions would allow access based on measurements made prior to the patient being 18 years old. Further, the wording "supine or erect" makes the proposed restrictions meaningfully less strict than the LSDP eligibility criteria which uses the wording "supine and erect", because even in healthy adults measured supine vital capacity is usually lower than erect vital capacity, and the difference is greater if there is weakness of the diaphragm. The PSCR stated that the wording "supine or erect" used in the submission was based on the previous version of the treatment guidelines for LOPD which were updated in September 2024 and considered that the wording should be changed to "supine and erect" to align with the current the LSDP eligibility criteria.
- 3.4 Patients in the PROPEL trial were required to have FVC > 30% predicted, without an upper limit. The upper quartile of patients in the trial had FVC = 84% predicted. The

PSCR stated that the discrepancy between the LSDP criteria requiring FVC < 80% and the PROPEL trial FVC criteria is explained by that patients in the PROPEL trial were largely treatment experienced with ERTs, and the relatively high FVC values in the study population reflect the fact that patients were responding to therapy while LSDP criteria are supposed to apply to patients who are initiating ERTs and are therefore more likely to have severely compromised respiratory function.

- 3.5 The ESC advised the clinical criteria on disordered sleeping should be consistent with the current LSDP criteria.
- 3.6 Although the clinical criteria requirement for being under the care of / in conjunction with a clinician experienced in managing inborn errors of metabolism is not a requirement within the LSDP criteria, the ESC considered it would be appropriate to include in the PBS restriction.
- 3.7 The proposal by the submission was for Authority Required (STREAMLINED); this would not be appropriate as the current LSDP Guidelines require applications in writing with supporting information. The ESC agreed with the evaluation that streamlined authority was not appropriate and advised that a PBS listing should be written authority for consistency with the LSDP Guidelines. The PSCR considered that the PBS authority level was not relevant given the submission's intention to list CIPAMIG on the LSDP.
- 3.8 The submission did not explicitly propose a grandfather restriction; however, the submission identified < 500 patients who are currently enrolled in a compassionate access program from the PROPEL trial.
- 3.9 It was not clear whether the submission proposed a Special Pricing Arrangement based on equivalent published prices of the comparator. The PSCR confirmed that Special Pricing Arrangements are not applicable as it is expected that any agreement to fund CIPAMIG on the LSDP would be subject to confidentiality.

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

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 one year.
 - LOPD for presentations in early childhood, adolescence and adulthood.

- 4.2 IOPD presents with cardiac failure and muscle weakness. Without enzyme replacement therapy (ERT), only about one quarter of patients survive to one year of age, but ERT dramatically reduces the risk of death and ventilator dependence.
- 4.3 Patients with LOPD rarely develop cardiomyopathy; most patients have progressive proximal limb-girdle weakness leading to difficulty walking and diaphragmatic weakness leading to respiratory failure. Overall survival without ERT is about 95% at five years after diagnosis and 40% at 30 years after diagnosis. Cohort studies suggest that ERT roughly halves the chance of dying at any time point after it is started¹². Many patients will, nevertheless, require non-invasive and in some cases invasive ventilatory support and will have significant limitations of mobility.
- 4.4 CIPAMIG is a combination therapy for the treatment of LOPD. CIPA is a recombinant human GAA enzyme naturally expressed with high levels of bis-M6P (Mannose 6-Phosphate), designed to increase uptake into muscle cells. Once in the cell, CIPA can be processed into its most active form to break down glycogen. MIG is a small molecule chaperone which has a stabilising effect on recombinant enzymes such as CIPA, leading to improved pharmacokinetics and pharmacodynamics. It prolongs the distribution half-life of CIPA and increases levels of active enzyme.
- 4.5 The recommended dose of CIPA is 20 mg/kg bodyweight every second week as an intravenous infusion. MIG capsules should be taken 1 hour before starting the infusion. The dose of MIG is 260 mg (4 capsules of 65 mg) for patients weighing ≥ 50 kg and 195 mg (3 capsules) for patients weighing ≥ 40 kg to < 50 kg. The current and proposed treatment algorithm is shown in ATTACHMENT ES.3.

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

5 Comparator

- 5.1 The submission nominated ALGLU and AVAL as the main comparators. The argument provided in support of these nominations was that both products are currently listed on the LSDP for the treatment of LOPD. The submission stated it is unknown which of the currently listed ERTs would most likely be replaced by CIPAMIG if it were to be listed on the LSDP. Therefore, both products were nominated as comparators.

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

¹ van der Meijden JC, Güngör D, Kruijshaar ME, Muir AD, Broekgaarden HA, van der Ploeg AT. Ten years of the international Pompe survey: patient reported outcomes as a reliable tool for studying treated and untreated children and adults with non-classic Pompe disease. *J Inherit Metab Dis* 2015; 38:495-503.

² Schoser B, Stewart A, Kanters S *et al*. 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.

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician provided an overview of Pompe disease and the heterogeneous presentation of late-onset Pompe disease. The clinician noted that results from a longer term study have shown that some patients with late-onset Pompe disease may experience worsening of symptoms after being on ERT for several years. The clinician noted there are challenges with existing ERTs for Pompe disease which may impact delivery of enzyme into tissues and that cipaglifosidase alfa has been engineered to have high levels of bis-M6P (Mannose 6-Phosphate) to increase uptake into muscle cells. The clinician also presented an overview of the pivotal trial comparing CIPAMIG to ALGLU.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (16), and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with CIPAMIG including increased quality of life, improvements in respiratory function and muscle strength. Comments also indicated that the ability to receive infusions at home was desirable for patients noting the long travel times experienced to access treatment at health services. Some contributors note the long travel times experienced to access treatment at health services.
- 6.3 The Australian Pompe Association (APA) expressed its support for making CIPAMIG available to patients with Pompe disease. The APA highlighted that CIPAMIG may provide an alternative treatment for patients who have or may experience sensitivity to existing treatments. The APA noted that since the availability of the first subsidised treatment for Pompe disease in 2015, there has been an increase in patient numbers which is likely due to increased awareness of the disease, improved diagnostic techniques and patients living longer from receiving ERT.

Clinical Trials

- 6.4 The submission was based on one head-to-head trial comparing CIPAMIG to ALGLU in mostly treatment-experienced (i.e., already receiving ALGLU) patients (PROPEL, n=123). The submission presented a second head-to-head trial comparing ALGLU to AVAL in treatment-naïve patients (COMET, n=100) which was used in an indirect comparison. The submission also presented a network meta-analysis. The COMET trial was previously considered by the PBAC in its November 2021 consideration of AVAL.
- 6.5 Details of the publications and reports for the trials presented in the submission are provided in Table 2.

Table 2: Publications and reports for the submitted trials

Trial ID	Protocol title/ Publication title	Publication citation
PROPEL NCT03729362.	A phase 3 double-blind randomized study to assess the efficacy and safety of intravenous atb200 co-administered with oral at2221 in adult subjects with late-onset Pompe disease compared with alglucosidase alfa/placebo.	CSR Amicus Therapeutics 2021.
	Byrne BJ, Schoser B, Kishnani PS, Bratkovic D, Clemens PR, Goker-Alpan O, et al. Long-term safety and efficacy of cipaglucosidase alfa plus miglustat in individuals living with Pompe disease: an open-label phase I/II study (ATB200-02).	<i>Journal of Neurology</i> . 2024;271(4):1787-801. http://dx.doi.org/10.1007/s00415-023-12096-0
	Claeys KG, Kushlaf H, Raza S, Hummel N, Shohet S, Keyzor I, et al. Minimal clinically important differences in six-minute walking distance in late-onset Pompe disease.	<i>Orphanet Journal of Rare Diseases</i> . 2024;19(1). http://dx.doi.org/10.1186/s13023-024-03156-3
	MacCulloch A, Griffiths A, Johnson N, Shohet S. Health-Related Quality-of-Life Utility Values in Adults Living With Late-Onset Pompe Disease: Analyses of EQ-5D Data from the PROPEL Clinical Trial.	<i>Journal of Health Economics and Outcomes Research</i> . 2024;11(2):80-5. http://dx.doi.org/10.36469/001c.121928
	Schoser, B., Roberts, M., Byrne, B. J., Sitaraman, S., Jiang, H., Laforêt, P., Toscano, A., Castelli, J., Diaz-Manera, J., Goldman, M., van der Ploeg, A. T., Bratkovic, D., Kuchipudi, S., Mozaffar, T., Kishnani, P. S., & PROPEL Study Group (2021). Safety and efficacy of cipaglucosidase alfa plus miglustat versus alglucosidase alfa plus placebo in late-onset Pompe disease (PROPEL): an international, randomised, double-blind, parallel-group, phase 3 trial.	<i>The Lancet. Neurology</i> , 20(12), 1027–1037. https://doi.org/10.1016/S1474-4422(21)00331-8
COMET NCT02782741.	Boentert M, Campana ES, Attarian S, Diaz-Manera J, Dimachkie MM, Periquet M, et al. Post-hoc Nonparametric Analysis of Forced Vital Capacity in the COMET Trial Demonstrates Superiority of Avalglucosidase Alfa vs Alglucosidase Alfa.	<i>Journal of neuromuscular diseases</i> . 2023. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02650692/full
	Diaz-Manera J, Dimachkie MM, Salort-Campana E, Attarian S, Berger KI, Periquet M, et al. Nonparametric analysis of forced vital capacity in the COMET trial demonstrates superiority of avalglucosidase alfa vs alglucosidase alfa.	<i>Molecular genetics and metabolism</i> . 2023a;138(2). https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02545275/full

	Diaz- Diaz-Manera J, Kishnani P, Ladha S, Miossec P, Armstrong N, Thibault N, et al. COMET: safety of avalglucosidase alfa in patients with late-onset Pompe disease who switched treatment from alglucosidase alfa.	<i>Neuromuscular disorders</i> . 2023b;33:S149. https://doi.org/10.1016/j.nmd.2023.07.339
	Manera, J., Kishnani, P. S., Kushlaf, H., Ladha, S., Mozaffar, T., Straub, V., Toscano, A., van der Ploeg, A. T., Berger, K. I., Clemens, P. R., Chien, Y. H., Day, J. W., Illarioshkin, S., Roberts, M., Attarian, S., Borges, J. L., Bouhour, F., Choi, Y. C., Erdem-Ozdamar, S., Goker-Alpan, O., ... COMET Investigator Group (2021). Safety and efficacy of avalglucosidase alfa versus alglucosidase alfa in patients with late-onset Pompe disease (COMET): a phase 3, randomised, multicentre trial.	<i>The Lancet. Neurology</i> , 20(12), 1012–1026. https://doi.org/10.1016/S1474-4422(21)00241-6
	Dimachkie MM, Kishnani PS, Ivanescu C, Flore G, Gwaltney C, Van Der Beek NAME, et al. Measurement Properties of 2 Novel PROs, the Pompe Disease Symptom Scale and Pompe Disease Impact Scale, in the COMET Study.	<i>Neurology: Clinical Practice</i> . 2023;13(5). http://dx.doi.org/10.1212/CPJ.0000000000200181
	Kishnani P, van der Beek N, Haack KA, Armstrong N, Periquet M, Thibault N, et al. COMET: effects of avalglucosidase alfa and treatment switch from alglucosidase alfa on week 145 QMFT individual item responses.	<i>Neuromuscular disorders</i> . 2023a;33:S148-S9. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02623943/full
	Kishnani PS, Diaz-Manera J, Toscano A, Clemens PR, Ladha S, Berger KI, et al. Efficacy and Safety of Avalglucosidase Alfa in Patients with Late-Onset Pompe Disease after 97 Weeks: A Phase 3 Randomized Clinical Trial.	<i>JAMA Neurology</i> . 2023b;80(6):558-67. http://dx.doi.org/10.1001/jamaneurol.2023.0552
	Kushlaf H, Attarian S, Borges JL, Bouhour F, Chien YH, Choi YC, et al. Efficacy and Safety Results of the Avalglucosidase alfa Phase 3 COMET Trial in Late-Onset Pompe Disease Patients.	<i>Neurology</i> . 2021;96(15 SUPPL 1). https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02368996/full
	Toscano A, Pollissard L, Mshid J, van der Beek N, Kishnani PS, Dimachkie MM, et al. Effect of avalglucosidase alfa on disease-specific and general patient-reported outcomes in treatment-naïve adults with late-onset Pompe disease compared with alglucosidase alfa: Meaningful change analyses from the Phase 3 COMET trial.	<i>Molecular Genetics and Metabolism</i> . 2024;141(2). http://dx.doi.org/10.1016/j.ymgme.2023.108121

Source: Table 16, pp33-35 of the submission.

6.6 The key features of the trials are summarised in Table 3.

Table 3: Key features of the included trials

	PROPEL NCT03729362 N = 123	COMET NCT02782741 N = 100
Design/ duration	R, DB, MC, 52 wk; completers eligible for OLE.	R, DB, MC, 49 wk; completers eligible for OLE.
Randomisation	CIPAMIG vs ALGLU, 2:1, stratified by prior ERT or not; 6MWD 75 to <150 m, 150 to <400 m or ≥400 m.	AVAL vs ALGLU, 1:1, stratified by %FVC <55 or ≥55; sex; age <18 or ≥18.
Patient population	LOPD age ≥ 18 yrs, weight ≥ 40 kg; previous ERT allowed, 95/123 (77.2%) receiving ALGLU at baseline; sitting FVC ≥ 30% predicted; 6MWD ≥ 75 m and ≤ 90% predicted; no ventilatory support (including NIV) > 6 h/day when awake.	Age ≥ 3 yrs; no previous ERT allowed; upright FVC 30-85% predicted; 6MWD ≥ 40 m without stopping; no cardiac hypertrophy, invasive ventilation (NIV allowed), wheelchair dependence.
Primary Outcome	Change in 6MWD from baseline to 52 wk.	Change in % predicted upright FVC from baseline to 49 wk.
Key Secondary Outcome	Change in % predicted FVC from baseline to 52 wk.	Change in 6MWD from baseline to 49 wk.
Overall Risk of Bias	Low	Low

Source: Table 17, p39 of the submission; PROPEL CSR, pp29-30, p33; Diaz-Manera, 2021.

6MWD = six-minute walking distance; ALGLU = alglucosidase; AVAL= avalglucosidase; CIPAMIG = cipaglucosidase + miglustat; DB = double blind; ERT = enzyme replacement therapy; FVC = forced vital capacity; LOPD = late onset Pompe Disease; MC = multi-centre; NIV = non-invasive ventilation; OLE = open label extension; R = randomised.

6.7 Measured forced vital capacity (FVC) and six-minute walking distance (6MWD) are highly dependent on effort and motivation. Therefore, blinding of patients, clinicians and technical staff performing spirometry and 6MWD tests to treatment allocation is important in these studies (see paragraphs 6.6-6.7 below).

6.8 A complete assessment of the risk of bias in the trials is in Attachment ES.4 Table ES.4.1. Although the overall risk of bias in the studies was low, because of the nature of the outcome measures, the studies were highly vulnerable to unblinding. Several features of the treatments being compared make effective blinding unusually difficult:

- cipaglucosidase, avalglucosidase and alglucosidase require reconstitution immediately before administration, the procedures are different, and the pharmacists who do the reconstitution must, therefore, be unblinded;
- the un-reconstituted vials of cipaglucosidase and alglucosidase and the cartons containing the vials supplied for each patient are distinguishable, so access to the un-reconstituted vials has to be restricted to avoid unblinding;
- the reconstituted solutions of avalglucosidase are easily distinguishable (reconstituted avalglucosidase is added to 5% dextrose for infusion and reconstituted cipaglucosidase and alglucosidase to 0.9% NaCl, and these solutions were provided by study sites), and the reconstituted solutions of cipaglucosidase and alglucosidase are not identical (PROPEL Protocol, p51).

6.9 Data from one patient in PROPEL (allocated to alglucosidase) were excluded because, after data-base lock, the patient confessed to deliberately restricting his performance on screening FVC and 6MWD in order to meet the inclusion criteria for the trial and

gain access to ERT (PROPEL CSR, pp91-92). The effect of restricting this performance at screening was implausibly large improvements on treatment, which had a substantial effect on overall trial outcomes: if this patient's data are included, the least squares mean (95% CI) difference in 6MWD between CIPAMIG-treated and ALGLU-treated patients was 5.3 (-15.3, 25.9); if this patient's data are excluded, the result becomes 14.2 (-2.6, 31.0) (Table 27 of the submission).

6.10 This patient's data were excluded from the published account of the trial (Schoser, 2021). The data were also excluded from most of the efficacy results reported in the CSR, including for % predicted FVC, and, for consistency, data excluding this patient have been used in the evaluation (safety data in the CSR included this patient).

6.11 Doses and treatment exposure in the trials are shown in Table 4.

Table 4: Doses and treatment exposure in PROPEL and COMET

	Treatment	Dosing Regimen	Treatment Duration, months, Mean (SD)	Number of Doses Mean (SD) Median (range)
PROPEL	CIPAMIG	CIPA 20 mg/kg 2nd weekly; MIG 3 x 65 mg 2nd weekly if 40-50 kg, 4 x 65 mg 2nd weekly if ≥ 50 kg	11.8 (1.8)	25.7 (3.8) 27.0 (25.0, 27.0)
	ALGLU + placebo	ALGLU 20 mg/kg 2nd weekly; placebo matched for weight.	12.0 (0.7)	26.2 (2.0) 27.0 (26.0, 27.0)
COMET	AVAL	20 mg/kg 2nd weekly	49 weeks protocol	NR
	ALGLU	20 mg/kg 2nd weekly	49 weeks protocol	NR

Source: Table 22, p62 of the submission.

ALGLU = alglucosidase; AVAL = avalglucosidase; CIPA = cipaglucoisidase; CIPAMIG = cipaglucoisidase + miglustat; MIG = miglustat; NR = not reported; SD = standard deviation.

6.12 Inclusion and exclusion criteria in the trials are shown in ATTACHMENT ES.4, Table ES.4.1. Baseline characteristics of patients in the trials are shown in Table 5. The ESC noted that only one patient treated with AVAL in COMET was aged less than 18 years.

Table 5: Baseline characteristics of patients in the trials

	PROPEL		COMET	
	CIPAMIG N = 85	ALGU N = 38	AVAL N = 51	ALGLU N = 49
Age, years				
Mean (SD)	47.6 (13.2)	45.1 (13.3)	46.0 (14.5)	50.3 (13.7)
Median (IQR)	48.0 (38.0, 57.0)	46.0 (34.0, 55.0)	NR	NR
Range	19, 74	22, 66	16, 78	20, 78
Female, n (%)	49 (57.6%)	18 (47.4%)	24 (47%)	24 (49%)
Prior ERT, n (%)	65 (76.5%)	30 (78.9%)	NA	NA
ERT duration, years			NA	NA
Mean (SD)	7.5 (3.4)	7.1 (3.6)		
Median (IQR)	7.6 (4.3, 10.2)	7.1 (3.8, 10.4)		
Range	2.0, 13.7	2.1, 13.2		
Using any assistive device, n (%) ¹	17 (20.0%)	11 (28.9%)	NR	
History of falls, n (%) ²	44 (51.8%)	17 (44.7%)	NR	
6MWD, m				
Mean (SD)	357.9 (111.8)	350.1 (119.8)	399.3 (110.9)	378.1 (116.2)
Median (IQR)	359.5 (298.9, 418.5)	358.4 (285.5, 420.0)	NR	NR
Range	79.0, 575.0	112.5, 623.0	118, 630.0	138.0, 592.0
6MWD, % predicted				
Mean (SD)	57.8 (15.8)	55.7 (17.2)	57.3 (15.0)	55.3 (16.6)
Median (IQR)	59.2 (48.2, 69.4)	55.8 (46.6, 69.4)	NR	NR
Range	11.1, 91.0	17.1, 83.2	18.5, 85.9	22.6, 101.9
6MWD category, n (%)			NR	NR
≥75 to <150m	4 (4.7%)	4 (10.5%)		
≥150 to <400m	55 (64.7%)	22 (57.9%)		
≥400m	26 (30.6%)	12 (31.6%)		
% predicted FVC				
Mean (SD)	70.7 (19.6)	70.0 (21.3)	62.5 (14.4)	61.6 (12.4)
Median (IQR)	70.0 (56.0, 84.0)	71.2 (50.0, 89.0)	NR	NR
Range	30.5, 132.5	31.5, 122.0	32.1, 84.8	39.3, 84.5
PROMIS PF score			NA	NA
Mean (SD)	66.9 (12.3)	68.0 (13.1)		
Median (IQR)	67.0 (60.0, 75.5)	67.0 (59.0, 74.0)		
Range	37.0, 96.0	44.0, 97.0		
SF-12 PCS				
Mean (SD)	NA	NA	35.6 (7.8)	36.8 (9.4)
Range			17.8, 55.8	16.3, 57.3
SF-12 MCS				
Mean (SD)	NA	NA	48.3 (10.1)	50.6 (8.7)
Range			24.2, 70.8	30.4, 65.0

Source: PROPEL CSR, Table 9, pp74-75; Table 10, pp75-76, Table 11, p77. Diaz-Manera, 2021.

¹ Walking stick, walking frame or chair walker; if used for 6MWD at baseline required for all later tests. ² Falls were not defined in the PROPEL or COMET Protocols.

6MWD = six-minute walking distance; ALGLU = alglucosidase; AVAL = avalglucosidase; CIPAMIG = Cipaglucosidase + miglustat; ERT = enzyme replacement therapy; FVC = forced vital capacity; IQR = inter-quartile range; m = metres; PROMIS PF = Patient-Reported Outcomes Measurement Information System Physical Function; SD = standard deviation; SF-12 MCS = Short Form 12 item, Mental Component Summary; SF-12 PCS = Short Form 12 item, Physical Component Summary.

6.13 In PROPEL, ALGLU therapy before the trial was permitted while it was not in COMET. This is an important difference in design, because most patients with LOPD starting

ERT for the first time demonstrate improved respiratory muscle strength and exercise capacity, but many experience a secondary decline in FVC and 6MWD despite continued ERT.³ It is unknown whether patients benefit from switching from one ERT to another, or how long such an effect might last, but if there is a short-term benefit from switching, the effect of CIPAMIG relative to ALGLU may be exaggerated in a relatively short duration trial by comparison with ongoing ALGLU rather than with first-time treatment as in COMET.

- 6.14 Baseline characteristics other than prior ERT use were similar in the PROPEL and COMET trials, and in all cases similar for intervention and comparison groups, except that FVC was slightly lower in COMET than in PROPEL, consistent with the inclusion criteria for % predicted FVC in COMET having an upper limit and not in PROPEL.
- 6.15 It should be noted, however, that sleep studies were not performed as part of either PROPEL or COMET, so whether patients in the trials were comparable with regard to sleep-disordered breathing is unknown. This is important because sleep-disordered breathing is an independent criterion for access to the LSDP for Pompe Disease.

Trial outcomes - Minimum Clinically Important Differences

- 6.16 Minimum clinically important differences (MCID) for 6MWD and % predicted FVC in Pompe Disease have not been defined.
- 6.17 Studies in other conditions suggest that for Patient-Reported Outcomes Measurement Information System Physical Function (PROMIS PF) scores, a change of 2-6 is a reasonable MCID. An analysis of the PROPEL data suggested that for patients with baseline 6MWD over 150 m, a change in PROMIS PF score of at least 4 was associated with a change in 6MWD of about 7%, or 20-30 m for most patients in PROPEL (Claeys, 2024). For patients with baseline 6MWD less than 150 m the analysis failed: improvements in PROMIS PF corresponded to falls in 6MWD (see Figure 1 of Claeys, 2024); however, there were only 8 patients with baseline 6MWD less than 150 m.
- 6.18 Premature mortality in Pompe Disease is mostly related to respiratory failure, due to respiratory muscle weakness, and % predicted FVC is the most widely used measure of respiratory muscle strength (maximum inspiratory and expiratory pressures are very difficult to measure reliably in untrained subjects; inspiratory pressures during a sniff and gastric pressure during a cough are more reliable but require insertion of an oesophageal or gastric balloon).
- 6.19 Cohort studies suggest that ERT has a substantial effect on survival; in a cohort of 283 patients initiated before ERT was available, the hazard ratio (95% CI) for death in

³ Harlaar L, Hogrel J-Y, Perniconi B, et al. Large variation in effects during 10 years of enzyme therapy in adults with Pompe disease. *Neurology* 2019; <https://doi.org/10.1212/WNL.0000000000008441>

patients treated with ERT at any time was 0.41 (0.19, 0.87).⁴ A systematic review and meta-analysis of 19 studies with 438 patients found that the rate ratio (95% credible interval) for mortality over average follow-up of 45 months among treated vs untreated patients was 0.21 (0.11, 0.41) while the difference between treated and untreated patients in % predicted FVC over the same period was 6 percentage points.⁵ The difference (95% CI) between ALGLU-treated and placebo-treated patients in % predicted FVC was 3.40 (1.03, 5.77).⁶ Assuming that the observed mortality benefit is explained by the observed improvement in % predicted FVC, and that a much smaller mortality benefit would be clinically important, the MCID for % predicted FVC is very small.

- 6.20 For patients aged over 6 years, the maximum acceptable variation in FVC with consecutive forced expiratory efforts is 150 mL, which for an adult aged 47 years with 50th percentile height and % predicted FVC of 70, corresponds to a difference in % predicted FVC of 4. For patients with lower predicted FVC, the effect on % predicted FVC of the same absolute difference in FVC is greater. Because in Pompe Disease the FVC tends to fall over time, while in patients who are still growing predicted FVC will be rising and in patients who are not growing it will fall with age, the effect on % predicted FVC of the constant effort-to-effort variability is very complex. For this reason, it is difficult to interpret small mean or median changes when most individual patient values correspond to changes in FVC no larger than is expected with consecutive manoeuvres (see e.g., the median and inter-quartile range data for % predicted FVC in Table 6). For this reason also, the MCID for % predicted FVC may be less than the difference that can be measured reliably.

Comparative effectiveness

- 6.21 6MWD and % predicted FVC results in the trials are shown in Table 6.
- 6.22 Changes in 6MWD with CIPAMIG and AVAL were near or below the MCID defined by Claeys, 2024 (see 6.14).
- 6.23 Differences in % predicted FVC between CIPAMIG and AVAL were similar to the differences between ALGLU and placebo seen in the placebo-controlled trial,⁴ and, based on the mortality benefits associated with ERT, clinically significant. However, these represent changes for many individual patients below the smallest change in % predicted FVC that can be accurately measured.

⁴ Gungor D, Kruijshaar ME, Plug I, et al. Impact of enzyme replacement therapy on survival in adults with Pompe Disease: results from a prospective international observational study. *Orphanet J Rare Dis* 2013, doi: [10.1186/1750-1172-8-49](https://doi.org/10.1186/1750-1172-8-49)

⁵ Schoer B, Stewart A, Kanters S, et al. Survival and long-term outcomes in late-onset Pompe Disease following alglucosidase alfa treatment: a systematic review and meta-analysis. *J Neurology*, 2017; 264:621-630.

⁶ van der Ploeg AT, Clemens PR, Corzo D, et al. A randomized study of alglucosidase alfa in late-onset Pompe's Disease. *New Engl J Med* 2010; 362:1396-1406.

- 6.24 In PROPEL, patients allocated to ALGLU recorded clinically and statistically significant falls in % predicted FVC, the mean fall being greater than that seen in placebo-treated patients over 78 weeks in the placebo-controlled trial of ALGLU.⁴ This is not easily explained and would exaggerate the effect of CIPAMIG vs AVAL in the indirect treatment comparison.
- 6.25 PROPEL patients receiving ALGLU before the trial may have had less improvement in 6MWD during the trial than the population as a whole, but the difference was neither statistically nor clinically significant, reflecting the fact that these were 75% of the patients and dominated the results of the population as a whole.

Table 6: 6MWD and % predicted FVC outcomes in the trials

PROPEL				
	6MWD, meters		% predicted FVC	
	CIPAMIG, N= 85	ALGLU, N = 37	CIPAMIG, N = 85	ALGLU, N = 37
Change from Baseline to 52 wk Median (IQR)	12.5 (-3.8, 43.5)	3.2 (-21.8, 22.8)	-1.0 (-5.0, 4.0)	-3.0 (-6.5, 0.0)
LS Mean Change (95 % CI) to 52 wk	21.3 (12.1, 30.5)	7.1 (-6.9, 21.1)	-1.0 (-2.3, 0.2)	-3.7 (-5.6, -1.8)
LS Mean Difference (95% CI) CIPAMIG - ALGLU	14.2 (-2.6, 31.0)		2.7 (0.4, 4.9)	
	Patients with prior alglucosidase, n = 65	Patients with prior alglucosidase, n = 30	Patients with prior alglucosidase, n = 65	Patients with prior alglucosidase, n = 30
LS Mean Change (95 % CI) to 52 wk	17.0 (6.8, 27.3)	0.6 (-14.5, 15.6)	-0.1 (-1.5, 1.2)	-3.6 (-5.7, -1.6)
LS Mean Difference (95% CI) CIPAMIG - ALGLU	16.4 (-1.9, 34.8)		3.5 (1.0, 6.0)	
COMET				
	6MWD, meters		% predicted FVC	
	AVAL, N=51	ALGLU, N = 49	AVAL, N=51	ALGLU, N = 49
LS Mean Change (95% CI) to 49 wk	32.2 (12.7, 51.7)	2.2 (-18.2, 22.6)	2.9 (-0.8, 4.6)	0.5 (-0.9, 2.3)
LS Mean Difference (95% CI) AVAL - ALGLU	30.0 (1.3, 58.7)		2.4 (-0.1, 5.0)	

Source: PROPEL CSR, Table 20, p94; Table 22, p98; Diaz-Manera, 2021.

Note that one patient was excluded because performance at baseline was deliberately restricted. All patients in COMET were treatment naive. Statistically significant results are in **bold**.

6MWD = six-minute walking distance; ALGLU = alglucosidase; AVAL = Avalglucosidase; CI = confidence interval; CIPAMIG = cipaglusosidase + miglustat; FVC = forced vital capacity; LS = least squares.

- 6.26 In ALGLU-treated patients in the COMET trial, the results for 6MWD were clearly inferior, and the results for % predicted FVC were probably inferior compared to those in ALGLU-treated patients in the placebo-controlled trial of ALGLU in LOPD.⁴ In that trial the mean (95% CI) change in 6MWD to 78 weeks was 25.1 (10.1, 40.2) in the ALGLU-treated group and -3.0 (-24.2, 18.2) in the placebo-treated group, with a mean (95% CI) between-group difference of 28.1 (2.1, 54.2). The mean (95% CI) change in % predicted FVC was 1.2 (-0.16, 2.6) in the ALGLU-treated group and -2.2 (-4.1, -0.3) in the placebo-treated group, with a mean (95% CI) between-group difference of 3.4 (1.0, 5.8).⁴ Given that patients in both trials were treatment-naive, it is difficult to explain the lesser effect of ALGLU in COMET than in the placebo-controlled trial.

- 6.27 Data for changes in quality-of-life measures in the trials are shown in Table 7.
- 6.28 The PROPEL trial used the PROMIS PF scale (PF = physical function), this scale has a mean score in a reference population of 50, with a standard deviation of 10; higher scores indicate better function. A change in score of 2-6 has been proposed as an MCID (Claeys, 2024). Most patients had baseline scores in the normal range (see Table 5).
- 6.29 The COMET trial used the SF-12, with physical component summary (PCS) and mental component summary (MCS) scores. These scores have a mean value in a reference population of 50 with standard deviation of 10. Most patients had PCS scores low in the normal range and MCS scores in the normal range. The MCID for SF-12 MCS and PCS have been estimated for a range of conditions, and most are about 5, but values for Pompe Disease have not been defined.

Table 7: Changes in QoL scores in the trials

	PROPEL PROMIS PF Score	
	CIPAMIG, N= 85	ALGLU, N = 37
LS Mean Change (95 %CI) to 52 wk	1.98 (0.15, 3.80)	0.11 (-2.7, 2.9)
LS Mean Difference (95% CI) CIPAMIG - ALGLU	1.87 (-1.5, 5.2))	
COMET SF-12 Scores		
	AVAL, N=51	ALGLU, N = 49
SF-12 PCS LS Mean Change (95 %CI) to 49 wk	2.4 (0.4, 4.3)	1.6 (-1.0, 3.7)
SF-12 PCS LS Mean Difference (95% CI) AVAL - ALGLU	0.77 (-2.13, 3.67)	
SF-12 MCS LS Mean Change (95 %CI) to 49 wk	2.9 (-1.2, 5.3)	0.76 (-0.73, 2.25)
SF-12 MCS LS Mean Difference (95% CI) AVAL - ALGLU	2.12 (-1.46, 5.69)	

Source: PROPEL CSR, Table 26, p111; Diaz-Manera, 2021.

CI = confidence interval; LS = least squares; PROMIS PF = Patient-Reported Outcomes Measurement Information System Physical Function; QoL = quality of life; SD = standard deviation; SF-12 MCS = Short Form 12 item, Mental Component Summary; SF-12 PCS = Short Form 12 item, Physical Component Summary.

- 6.30 There were no clinically important changes in quality-of-life scores in either trial. This is not surprising given most patients' pre-treatment scores were within or only slightly below the normal range.

Indirect Treatment Comparison comparing CIPAMIG and AVAL

- 6.31 The indirect treatment comparison was a Bucher-method comparison using PROPEL and COMET with alglucosidase as the common treatment. Analyses were presented for the whole PROPEL population (76.5% ERT experienced and 23.5% ERT naive) versus the COMET population (100% ERT naive), and for the ERT naive patients in PROPEL vs COMET.
- 6.32 Because nearly all LOPD patients in Australia are receiving ERT, neither the treatment comparison for the populations as a whole nor that for the ERT naive PROPEL population vs COMET was informative.

- 6.33 A network meta-analysis was presented (a) using data from PROPEL and COMET, and (b) including not only PROPEL and COMET but also the open label extension phases of PROPEL and COMET.
- 6.34 The network meta-analysis was funded by Amicus Therapeutics and five of ten authors of the published paper were employees or stockholders of Amicus, including the corresponding author. The authors declared that they had no other competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript.
- 6.35 The study proposed a non-inferiority margin for the Bucher indirect treatment comparison % predicted FVC of -1.1 (CIPAMIG - AVAL). This was the margin used in the COMET trial, which PBAC considered in relation to the proposed listing of AVAL. That margin was in turn based on the placebo-controlled trial of ALGLU,⁴ being "approximately 50% of the lower bound of the 80% confidence interval for the alglucosidase alfa versus placebo treatment effect" (COMET Protocol, p112).
- 6.36 This proposed non-inferiority margin is approximately 40% of the treatment effects in the PROPEL (2.7) and COMET (2.4) trials. The 95% CI for the effects in PROPEL and COMET were, approximately, zero to 5. It is difficult for the non-inferiority criterion for CIPAMIG vs AVAL not to be met, which would mean meeting the non-inferiority criterion would be consistent with CIPAMIG being inferior to placebo.
- 6.37 Further, effect sizes for % predicted FVC of around 3 appear to be associated with large mortality benefits, and a treatment with 30-40% less effect on mortality could not reasonably be considered clinically equivalent.
- 6.38 The submission suggested a non-inferiority margin for 6MWD of 57.2 m, based on the analysis of the PROPEL data by Claeys, 2024. This is too large, as it is 2 to 3 times the best supported MCID from the same analysis.
- 6.39 Results of the indirect treatment comparison are shown in Table 8.

Table 8: Results of the indirect treatment comparison for 6MWD and % predicted FVC

	PROPEL			COMET			Indirect Comparison (95% CI), CIPAMIG - AVAL
	6MWD, meters, mean change from baseline to 52 wk (SD)		Difference (95% CI)	6MWD, meters, mean change from baseline to 49 wk (SEM)		Difference (95% CI)	
	CIPAMIG	ALGLU	14.2 (-2.6, 31.0)	AVAL	ALGLU	30.0 (1.3, 58.7)	-15.8 (-49.0, 17.5)
All patients	21.3 (4.7)	7.1 (7.0)		32.2 (9.9)	2.2 (10.4)		
ERT Naive	33.4 (48.7)	38.3 (29.3)	-6.6 (-48.2, 35.1)	32.2 (9.9)	2.2 (10.4)	30.0 (1.3, 59.8)	-36.8 (-87.1, 14.0)
	% Predicted FVC, mean change from baseline to 52 wk (SD)		Difference (95% CI)	% Predicted FVC, mean change from baseline to 49 wk (SEM)		Difference (95% CI)	Indirect Comparison (95% CI), CIPAMIG - AVAL
All patients	-0.9 (6.2)	-4.0 (4.9)	2.7 (0.4, 5.0)	2.9 (0.9)	0.5 (0.9)	2.4 (-0.1, 5.0)	0.2 (-3.2, 3.7)
ERT Naive	-4.5 (1.5)	-2.5 (2.8)	-1.95 (-8.9, 5.0)	2.9 (0.9)	0.5 (0.9)	2.4 (-0.1, 5.0)	-4.4 (-11.8, 3.1)

Source: Table 49, p119 of the submission; Diaz-Manera (2021, does not report SD for 6MWD or % predicted FVC but does report SEM, and the SEM has been used where Table 49 gives NR. **Bold** indicates statistical significance.

6MWD = six-minute walking distance; ALGLU = alglucosidase; AVAL = avalglucosidase; CI = confidence interval; CIPAMIG = cipaglugosidase + miglustat; ERT = enzyme replacement therapy; FVC = forced vital capacity; SD = standard deviation; SEM = standard error of the mean.

- 6.40 Although none reached statistical significance, in both patient groups, comparisons of 6MWD favoured AVAL over CIPAMIG, and for the ERT naïve, the difference was clinically significant. In the ERT naïve, the comparison of % predicted FVC favoured AVAL and the difference was clinically significant.
- 6.41 The network meta-analysis using PROPEL and COMET data was consistent with the Bucher indirect treatment comparison, finding that for both 6MWD and % predicted FVC, AVAL was probably superior to CIPAMIG. For 6MWD the relative effect (95% CI) CIPAMIG - AVAL for change from baseline was -10.0 m (-23.6, 4.0) and the Bayesian probability of AVAL being superior was 91.8%. For % predicted FVC the relative effect (95% CI) CIPAMIG - AVAL for change from baseline was -1.45 (-3.01, 0.07) and the Bayesian probability of AVAL being superior was 96.8%. The difference in 6MWD would be below the threshold of clinical significance; the difference in % predicted FVC would be clinically significant.
- 6.42 When the open-label extension data from PROPEL and COMET were included in the network meta-analysis these effects were reversed. CIPAMIG was found certainly superior to AVAL for 6MWD, with relative effect (95% CI) 28.9 m (8.3, 50.1), and for % predicted FVC, with relative effect (95% CI) 2.9 (1.1, 4.7); the Bayesian probability that CIPAMIG was superior was > 99% in both cases. Both differences would be clinically significant. Because of the dependence of 6MWD and % predicted FVC on motivation and effort, results from the open label phases of the studies are less reliable than those from the double-blind phases.

- 6.43 The submission presented data from a number of pre-specified subgroups. Apart from ERT experienced vs ERT naive patients (see Tables 6 and 8) these showed no clinically or statistically significant effects.
- 6.44 The submission also included data for 17 patients in PROPEL treated in Australian centres. The point estimates of effect on 6MWD and % predicted FVC were similar to those of the population as a whole.

Comparative harms

- 6.45 Adverse events in the trials are shown in Table 9.
- 6.46 The frequency of adverse events was generally lower in PROPEL than in COMET, but this difference was accounted for mostly by differences in the respective ALGLU-treated arms. Infusion-associated reactions were similar in all groups in the two trials.
- 6.47 Antibodies to recombinant human acid alpha-glucosidase (rh-GAA) appeared in nearly all patients receiving ERT; there was no clear difference between ALGLU, AVAL and CIPAMIG. Severe immune reactions were infrequent in the PROPEL trial; there was one anaphylactoid reaction in a CIPAMIG-treated patient.
- 6.48 Comparative harms were not assessed in the indirect treatment comparison or network meta-analysis.
- 6.49 The need for patients to receive miglustat one hour before the infusion of cipaglucosidase begins, and to fast for two hours before taking miglustat, may increase the treatment burden of CIPAMIG compared to ALGLU and AVAL. No data relevant to this issue were collected in the trials.

Extended Assessment of Harms

- 6.50 Data from the open-label extension (OLE) of PROPEL were presented. The frequency of adverse events was similar to that seen in the double-blind phase, and no new adverse events were identified in the OLE data set.
- 6.51 Infusion-associated reactions occurred in 27 (31.8%) patients continuing CIPAMIG, in 19 (27.0%) patients switching to CIPAMIG from ALGLU, and in 21 (24.7%) in CIPAMIG-treated patients in the double-blind phase.
- 6.52 CIPAMIG was discontinued because of an infusion-associated reaction in 5 (4.1%) patients.
- 6.53 No new adverse events were reported in post-marketing surveillance of CIPAMIG was presented, but exposure was modest (total 51.2 patient years).

Table 9: Adverse events in the trials

	PROPEL			COMET		
	CIPAMIG N = 85	ALGLU N = 38	Total N = 123	AVAL N = 51	ALGLU N = 49	Total N = 100
Any TEAE, n (%)	81 (95.3%)	37 (97.4%)	118 (95.9%)	44 (86%)	45 (92%)	89 (89%)
Any Study Drug-Related TEAE, n (%)	26 (30.6%)	14 (36.8%)	40 (32.5%)	23 (45%)	24 (49%)	47 (47%)
Any TESAE, n (%)	8 (9.4%)	1 (2.6%)	9 (7.3%)	8 (16%)	12 (25%)	20 (20%)
Any TEAE leading to study drug discontinuation, n (%)	2 (2.4%)	0	2 (1.6%)	0	4 (8%)	4 (4%)
TEAE Leading to Death, n (%)	0	0	0	0	1 (2%)	1 (1%)
Any Severe TEAE, n (%)	8 (9.4%)	2 (5.3%)	10 (8.1%)	6 (12%)	7 (14%)	13 (13%)
Infusion Associated Reactions, n (%)	21 (24.7%)	10 (26.3%)	31 (25.2%)	13 (26%)	16 (33%)	29 (29%)
IAR Reported as TESAE, n (%)	1 (1.2%)	0	1 (0.8%)	NR	NR	NR
IAR leading to Study Drug Discontinuation, n (%)	2 (2.4%)	0	2 (1.6%)	NR	NR	NR
Anaphylactoid Reaction, n (%)	1 (1.2%)	0	1 (0.8%)	NR	NR	NR
Headache, n (%)	20 (23.5%)	9 (23.7%)	29 (23.6%)	NR	NR	NR
Diarrhoea, n (%)	11 (12.9%)	4 (10.5%)	15 (12.2%)	NR	NR	NR
Positive anti-rhGAA Antibodies, ERT Experienced, n/N (%)				NA	NA	NA
Baseline	55/65 (84.6%)	22/30 (73.3%)	77/95 (81.0%)			
52 wk	45/58 (77.8%)	22/27 (81.5%)	67/85 (78.8%)			
Positive anti-rhGAA Antibodies, ERT Naive, n/N (%)						
Baseline	3/20 (15.0%)	0/8 (0%)	3/28 (10.7%)	2 (3.9%)	2 (4%)	4 (4%)
Positive at 52 wk (PROPEL) or Positive Any Time (COMET), n/N (%)	15/16 (93.8%)	6/6 (100%)	21/22 (95.4%)	47 (92%)	44 (92%)	91 (91%)

Source: PROPEL CSR, Table 58, pp229-230; Table 60, pp233-234; Table 62, p239, Table 63, pp240-242; Diaz-Manera, 2021. Antibody data was available for all patients in COMET. ALGLU = alglucosidase; AVAL = avalglucosidase; CIPA = cipaglucosidase; CIPAMIG = cipaglucosidase + miglustat; ERT = enzyme replacement therapy; IAR = infusion-associated reaction; MIG = miglustat; rh-GAA = recombinant human acid alpha-glucosidase; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

Benefits/harms

6.54 A benefits and harms table was not presented as the submission made a claim of non-inferiority.

Clinical claim

- 6.55 The clinical claims were that in adults with LOPD, CIPAMIG was "at least non-inferior" in efficacy and non-inferior in safety to ALGLU and AVAL.
- 6.56 With regard to efficacy, the evaluation noted this claim was not adequately supported for the comparison with either ALGLU or AVAL. In relation to ALGLU, the observed changes in % predicted FVC and 6MWD in PROPEL were highly variable, with some patients improving significantly and others deteriorating significantly, so that small differences in mean change were difficult to interpret, and, if there is a short-term treatment-switching effect, may not reflect long-term efficacy. In relation to AVAL, the submitted non-inferiority intervals were too wide, and the indirect treatment comparison was consistent with clinically meaningful superiority of AVAL over CIPAMIG.
- 6.57 With regard to safety, the evaluation noted the claim was adequately supported.
- 6.58 The PBAC noted the uncertainties with respect to the clinical data raised by the evaluation. However, the PBAC considered that on balance, the claim of non-inferior effectiveness of CIPAMIG compared to ALGLU and AVAL was reasonable.
- 6.59 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

- 6.60 The submission presented a cost-minimisation approach (CMA), on the basis that CIPAMIG is non-inferior to ALGLU and AVAL. The submission stated that 'in November 2021 AVAL was recommended on a cost-minimisation basis vs ALGLU and the resulting AVAL price was a cost-minimised price in adults with LOPD', based on Table 20 in the November 2021 AVAL PSD. This is not correct; AVAL was not recommended for PBS listing as it was not found to be cost-effective by the PBAC. Table 20 in the AVAL PSD was the estimated cost per patient per year for AVAL, not a cost-minimisation analysis. The submission presented an analysis of CIPAMIG vs AVAL in adults with the assumption that the cost of ALGLU is the same or higher. The key components of the analysis are shown in Table 10. The submission's approach may not be sufficient given there is no basis to establish cost-effectiveness for the PBS since the comparators were not recommended by the PBAC and are currently listed on LSDP. The submission may have presented a CMA to an LSDP listed drug as a proxy to establish that CIPAMIG would not be cost-effective for PBS listing. The PSCR confirmed that the submission's intent was to present a cost-minimisation analysis to AVAL as a proxy to establish that CIPAMIG would not meet cost-effectiveness criteria for PBS listing.

Table 10: Key components and assumptions of the cost-minimisation approach

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on evidence presented in Section 2, CIPA MIG is assumed to be non-inferior in terms of effectiveness relative to AVAL (and ALGLU)
Therapeutic claim: safety	Based on evidence presented in Section 2, CIPA MIG is assumed to be non-inferior in terms of safety relative to AVAL (and ALGLU)
Evidence base	CIPA 20 mg/kg MIG 260 mg vs ALGLU: PROPEL AVAL 20 mg/kg vs ALGLU: COMET
Equi-effective doses	CIPA 20 mg/kg by IV infusion every 2 weeks plus MIG 260 mg oral capsule every 2 weeks is equi-effective to AVAL 20 mg/kg by IV infusion every 2 weeks OR ALGLU 20 mg/kg by IV infusion every 2 weeks
Direct medicine costs	The annual cost of CIPA MIG at the prices proposed is identical to that of the comparator AVAL, at the published price
Other costs or cost offsets	None considered (consistent with the AVAL versus ALGLU cost-minimisation analysis, November 2021)

Source: Table 59, p138 of the submission. ALGLU= alglucosidase alfa; AVAL = avalglucosidase alfa, CIPA MIG, = cipaglucoisidase alfa plus miglustat; IV = Intravenous; kg= kilogram; mg = milligram

6.61 The equi-effective doses were estimated as:

- CIPA 20 mg/kg every 2 weeks plus 260 mg MIG every 2 weeks
- AVAL 20 mg/kg by IV infusion every 2 weeks
- ALGLU 20 mg/kg by IV infusion every 2 weeks.

6.62 These doses were based on the trials of CIPAMIG vs ALGLU and AVAL vs ALGLU. As noted in Table 4, the PROPEL trial reported treatment duration and mean and median dose for both treatment groups, but the COMET trial did not.

6.63 As all drugs have weight-based doses, the submission used a standard patient weight of 76.8 kg, as was used in the AVAL November 2021 submission (Table 11, Avalglucosidase PSD, PBAC meeting November 2021). The submission used the proposed published AEMP of AVAL of \$| per mg (Table 20, Avalglucosidase PSD, PBAC meeting November 2021) and calculated a total annual drug cost for AVAL of \$| as the basis of the cost-minimisation.

6.64 As miglustat is not currently listed on the PBS, the submission proposed that its price should be approximately the same as that currently in the UK of \$| per 65 mg capsule. No justification for this approach was presented. The price of CIPA was calculated by subtracting the cost of MIG from the total annual cost of AVAL.

6.65 No other costs were included in the analysis. The results as presented in the submission are shown in Table 11.

Table 11: Results of the CMA - One year cost of CIPAMIG

Row	Parameter	CIPA 20 mg/kg and MIG 240 mg	Reference
A	Total cost-minimising treatment cost (based on proposed published AVAL price)	\$ [REDACTED]	Table 61 of the submission
B	Total CIPA MIG treatment cost per patient per year	\$ [REDACTED]	Equating cost per patient per year
C	Number of MIG capsules per year	104	4 capsules per 2-weekly infusion
D	MIG costs per year	\$ [REDACTED]	C x \$ [REDACTED] per capsule
E	CIPA costs per year	\$ [REDACTED]	B – D
F	Number of CIPA doses per year	26.0	2-weekly infusions
G	CIPA mg per patient per year*	39,936	20 mg/kg x 76.8 kg x 26 doses/yr
H	CIPA cost per mg	\$ [REDACTED]	E / G
I	CIPA cost per 105 mg vial	\$ [REDACTED]	H x 105 mg

Source: Table 62, p141 of the submission. AEMP = approved ex-manufacturer price; AVAL = avalglucosidase alfa; CIPA MIG, cipaglucoisidase alfa plus miglustat; mg = milligram.

* The analysis assumes patients weigh 76.8kg, consistent with the AVAL November 2021 PSD (which refers to the LSDP review [October 2020] as the original source of data).

6.66 Results using the effective price of AVAL are presented in the Committee-in-Confidence section of the commentary.

Drug/ cost/patient/ year

6.67 As noted above, the submission calculated an annual treatment cost per patient of \$ [REDACTED] based on the proposed published price of AVAL from the November 2021 AVAL PSD. The annual treatment cost based on the effective price of AVAL is shown in the Committee-in-Confidence section of the commentary.

Estimated PBS usage & financial implications

6.68 This submission was not considered by DUSC.

6.69 The submission stated that a market share approach to estimating utilisation and costs of CIPAMIG would be optimal but that data from the current utilisation of AVAL and ALGLU on the LSDP were not available for confidentiality reasons. The submission therefore presented an epidemiological approach to estimate the utilisation and financial impacts associated with listing CIPAMIG. The key inputs used for the estimates are shown in Table 12.

6.70 After undertaking a literature review, the submission selected a Belgian study (Vanherpe, 2020) as the basis for estimating the prevalence of Pompe Disease. This study stated that ‘we identified 52 patients with LOPD, belonging to 48 families. The calculated prevalence of LOPD in Belgium is 3.9 cases per million, on a current population of 11,431,406.’ It is not clear from the paper how this estimate was derived, since, based on the figure of 52 patients in a population of 11,431,406, the prevalence would be 4.5 cases per million. In addition, the study was done in referral centres and there was a diagnostic delay of almost 13 years. This would suggest that the prevalence estimate maybe an underestimate.

- 6.71 The current threshold for prevalence in the LSDP guidelines specifies a prevalence of less than 1 in 50,000.⁷ The 2020 review of LSDP Medicines for Pompe Disease found that the prevalence in Australia was best estimated to be 0.18 cases per 50,000. The PSCR highlighted that the estimate of 105 LOPD patients in Australia in Year 1 aligns closely with the 2020 review of LSDP Medicines for Pompe Disease which found the prevalence in Australia was best estimated to be 0.18 cases per 50,000. Based on current population estimates this equates to 96 patients.
- 6.72 UpToDate⁸ currently states that Pompe Disease may be as prevalent as 1 in 40,000 based on the Netherlands Newborn Study (1999) and that the prevalence is almost certainly higher as the screening study only included three alleles. Other newborn screening programs suggest prevalences that are higher still: Austria 1 in 8,686; Illinois 1 in 21,979, although these combine infantile and late-onset forms of Pompe Disease. Chin and Fuller⁹ reported a prevalence of 2.19 cases per 100,000 for the period 2009-2020, based on a retrospective study of data from the national referral laboratory for lysosomal storage disorders. The PSCR noted that the Chin (2022) study purported to report the incidence and prevalence of lysosomal storage disorders, including Pompe disease, in Australia; however, as noted in the March 2024 PSD for migalastat, the definition of prevalence used in this study was actually an alternative method of estimating incidence. Specifically, “prevalence” was calculated by dividing the total number of postnatal and prenatal diagnoses during the study period by the number of live births during the same period. The PSCR therefore considered the study’s estimated prevalence of 2.19/100,000 to be a significant overestimate.

⁷ <https://www.health.gov.au/sites/default/files/documents/2021/11/procedure-guidance-for-medicines-funded-through-the-life-saving-drugs-program-lsdp.pdf>, accessed December 4 2024.

⁸ Kaplan S. Lysosomal acid alpha-glucosidase deficiency (Pompe disease, glycogen storage disease II, acid maltase deficiency). UpToDate. 2025.

⁹ Chin SJ, Fuller M. Prevalence of lysosomal storage disorders in Australia from 2009 to 2020. *The Lancet Regional Health - Western Pacific* 2022;19: 100344 <https://doi.org/10.1016/j.lanwpc.2021.100344>.

Table 12: Key inputs for financial estimates

Parameter	Value applied and source	Comment																		
Prevalent population of symptomatic LOPD patients, adult	Prevalence of 3.9 cases per million population based on Vanherpe 2020; applied to ABS Australian population estimates 2025-2030 <table border="1"> <tr><td>Year 1</td><td></td><td>†</td></tr> <tr><td>Year 2</td><td></td><td>†</td></tr> <tr><td>Year 3</td><td></td><td>†</td></tr> <tr><td>Year 4</td><td></td><td>†</td></tr> <tr><td>Year 5</td><td></td><td>†</td></tr> <tr><td>Year 6</td><td></td><td>†</td></tr> </table>	Year 1		†	Year 2		†	Year 3		†	Year 4		†	Year 5		†	Year 6		†	Based on study from Belgium; submission acknowledged possible difference in genetic and environmental factors but stated that this was the most rigorous recent study. See paragraph 6.65.
Year 1		†																		
Year 2		†																		
Year 3		†																		
Year 4		†																		
Year 5		†																		
Year 6		†																		
Proportion who are symptomatic	97.7%, Vanherpe, 2020, calculated to be 105 patients in Australia in year 1 <table border="1"> <tr><td>Year 1</td><td></td><td>†</td></tr> <tr><td>Year 2</td><td></td><td>†</td></tr> <tr><td>Year 3</td><td></td><td>†</td></tr> <tr><td>Year 4</td><td></td><td>†</td></tr> <tr><td>Year 5</td><td></td><td>†</td></tr> <tr><td>Year 6</td><td></td><td>†</td></tr> </table>	Year 1		†	Year 2		†	Year 3		†	Year 4		†	Year 5		†	Year 6		†	Assumes that adult prevalence estimates in Vanherpe (42/43) can be applied to the Australian population – see comments in paragraph 6.65
Year 1		†																		
Year 2		†																		
Year 3		†																		
Year 4		†																		
Year 5		†																		
Year 6		†																		
Uptake rate	█% in Year 1 increasing to █% in Year 6. Based on clinical opinion. <table border="1"> <tr><td>Year 1</td><td></td><td>█%</td></tr> <tr><td>Year 2</td><td></td><td>█%</td></tr> <tr><td>Year 3</td><td></td><td>█%</td></tr> <tr><td>Year 4</td><td></td><td>█%</td></tr> <tr><td>Year 5</td><td></td><td>█%</td></tr> <tr><td>Year 6</td><td></td><td>█%</td></tr> </table>	Year 1		█%	Year 2		█%	Year 3		█%	Year 4		█%	Year 5		█%	Year 6		█%	Sponsor assumption –could not be verified.
Year 1		█%																		
Year 2		█%																		
Year 3		█%																		
Year 4		█%																		
Year 5		█%																		
Year 6		█%																		
Grandfathered patients	16 from PROPEL trial	No breakdown of how these patients were included was provided.																		
Dose/duration	CIPA 20 mg/kg every second week: \$█/105 mg vial MIG 4 x 65 mg capsules immediately prior to infusion: \$█ Uses standardised weight as per economic evaluation	Consistent with CMA																		
MBS item	None included	Appropriate																		

Source: constructed from Section 4.1, pp 142-150 of the submission.

The redacted values correspond to the following ranges:

1 < 500

6.73 The estimated use and financial implications of listing CIPAMIG, based on the price calculated from the proposed published price of AVAL and as presented in the submission are shown in Table 13. The submission only provided estimates of the financial impact of listing CIPAMIG on the LSDP and did not provide estimates of the financial impact of listing on the PBS. The sponsor’s utilisation and cost model are not suitable for PBS decision-making purposes. The sponsor was asked to use the utilisation and cost model template to build the ABS population and incorporate the appropriate eligibilities to build the proposed population. The methods and assumptions should be clearly presented in the revised utilisation cost model together with detailed derivation and clear references to the data. Further information is available in the utilisation and cost model User Manual. The PSCR considered that the financial impact to the PBS was not relevant for this submission given the intended

listing of CIPAMIG is for the LSDP and on this basis did not provide a completed PBAC Utilisation and Cost Model Workbook.

- 6.74 Estimates based on the effective price of AVAL are provided in the Committee-in-Confidence section of the commentary. It is not clear whether the grandfathered patients noted in the submission were included in this patient population.

Table 13: Estimated use and financial implications for the LSDP

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	1	1	1	1	1	1
Number of CIPA scripts dispensed ^a	2	2	2	2	2	3
Number of MIG scripts dispensed ^a	4	4	4	4	4	4
Estimated financial implications of CIPAMIG						
Cost to LSDP	5	5	6	6	7	7
Estimated financial implications for AVAL and ALGL on the LSDP						
Cost to LSDP	8	8	8	8	8	8
Net financial implications to Government						
Net cost to Government	8	8	8	8	8	8

Source: Table 69, Table 70,; of the submission.

^a Assuming 380.34 vials of CIPA per patient per year and 26 MIG scripts per patient per year as estimated by the submission. There appeared to be rounding errors in the number of scripts dispensed, the number of CIPA scripts dispensed per year does not match the number of patients per year multiplied by the estimated number of CIPA vials per patient per year.

The redacted values correspond to the following ranges:

¹ < 500

² 10,000 to < 20,000

³ 20,000 to < 30,000

⁴ 500 to < 5,000

⁵ \$20 million to < \$30 million

⁶ \$30 million to < \$40 million

⁷ \$40 million to < \$50 million

⁸ net cost saving

- 6.75 The net cost to the LSDP using the effective price of AVAL to calculate the effective price of CIPA MIG and actual LSDP utilisation data is presented in the Committee-in-Confidence section.

- 6.76 The submission did not present any sensitivity analyses for these estimates.

Quality Use of Medicines

- 6.77 The submission did not provide any information about the quality use of medicines with respect to CIPAMIG.

Financial Management – Risk Sharing Arrangements

- 6.78 The submission did not propose a risk share or any other financial arrangement for the PBS as the sponsor intended to list on the LSDP. As noted in Section 3, the submission did not propose a Special Pricing Arrangement.

- 6.79 The submission also provided information about the price of CIPAMIG in overseas markets (Table 73 of the submission).

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 cipaglucosidase alfa and miglustat (CIPAMIG) for the treatment of adults with late-onset Pompe disease (LOPD). The PBAC considered treatment with CIPAMIG for LOPD was likely non-inferior to alglucosidase alfa (ALGLU) and avalglucosidase alfa (AVAL). The PBAC considered CIPAMIG was not adequately cost-effective to list on the PBS based on the submission's cost-minimisation approach versus AVAL noting it had previously considered the nominated comparators AVAL and ALGLU, not adequately cost-effective for listing on the PBS.
- 7.2 The PBAC noted that the submission had stated its objective was to seek listing CIPAMIG on the Life Saving Drugs Program (LSDP) alongside the existing enzyme replacement therapies (ERTs) for the treatment of LOPD.
- 7.3 The PBAC noted the consumer comments describing the benefits of treatment with CIPAMIG including improved respiratory and muscle function. The PBAC noted the comments indicated that having the option to receive infusions at home was desirable. The PBAC noted that home infusion administered by a health care professional following the establishment of safety and tolerability in a clinical setting, is an available option for both CIPAMIG and AVAL.
- 7.4 The submission nominated ALGU and AVAL as the main comparators. The PBAC noted ALGU and AVAL are currently available on the LSDP for LOPD and considered both these ERTs were appropriate comparators given they are most likely to be replaced by CIPAMIG.
- 7.5 The PBAC noted the submission was based on results from PROPEL (N=123), a head-to-head randomised trial comparing the efficacy and safety of CIPAMIG (N=85) to ALGLU (N=35) in mostly treatment-experienced (i.e., already receiving ALGLU) patients. The PBAC noted the submission also presented results from COMET (N=100), a head-to-head randomised non-inferiority trial comparing the efficacy and safety of ALGLU (N=49) and AVAL (N=51) in treatment-naïve patients, in an indirect comparison using COMET and PROPEL to compare CIPAMIG and AVAL with ALGLU as the common treatment. The PBAC also noted the submission presented a network meta-analysis using data from PROPEL and COMET and their open label extensions. The PBAC recalled it had previously considered COMET in its November 2021 consideration of AVAL.
- 7.6 The PBAC recognised the limitation of the clinical data in this rare disease. The PBAC recalled it had previously considered the surrogate outcome measures forced vital capacity (FVC) and 6 Minute Walk Distance (6MWD) to be reasonable in determining comparative effectiveness between AVAL and ALGLU. The PBAC considered that on balance, the results from PROPEL and the indirect comparison supported a conclusion of non-inferior effectiveness for CIPAMIG compared to ALGLU and AVAL.
- 7.7 The PBAC considered that based on the available evidence, it was reasonable to accept

the claim of non-inferior comparative safety compared to ALGLU and AVAL.

- 7.8 The PBAC considered that in the context of seeking listing on the PBS, the cost-minimisation analysis versus AVAL was not an appropriate approach given it had previously considered the nominated comparators to not be adequately cost-effective for listing on the PBS. However, the PBAC acknowledged that the sponsor had taken this approach intentionally as a drug must first be considered by the PBAC as clinically effective but rejected for PBS listing because it fails to meet the required cost-effectiveness criteria, before it can be considered for inclusion on the LSDP. The PBAC considered that CIPAMIG was not adequately cost-effective for PBS listing on the basis that it had previously considered the nominated comparators to not be adequately cost-effective for PBS listing.
- 7.9 The PBAC noted that the submission did not provide estimates of financial impact for listing CIPAMIG on the PBS and instead provided estimated financial impact for listing on the LSDP. The PBAC noted that the financial implications for the LSDP would be a matter for the LSDP Expert Panel (LSDP EP) should the sponsor submit a future application for LSDP listing. The PBAC noted that the submission took an epidemiological approach to estimate the utilisation of CIPAMIG and used a Belgian study (Vanherpe, 2020). The PBAC considered that the estimated number of patients was uncertain as it was unclear how Vanherpe, 2020 calculated the prevalence of 3.9 cases per million population for LOPD.
- 7.10 The PBAC noted that the LSDP EP is currently undertaking a 24-month review of AVAL for the treatment of Pompe disease (AVAL review) which is expected to be finalised later in the year, with recommendations to be agreed at the LSDP EP's July 2025 meeting.
- 7.11 The PBAC noted that the PBAC Chair had received a letter from the LSDP EP Chair, on behalf of the LSDP EP, which provided a preliminary view on Pompe disease eligibility for noting. The PBAC noted the AVAL review is considering recent literature to inform a position on whether the current prevalence of Pompe disease now exceeds the definition of an ultra-rare disease, of one case per 50,000 people or fewer in the Australian population. The PBAC noted that findings on prevalence include the following:
- The traditional estimated global incidence of Pompe disease is 1 per 40,000 (Stevens et al, 2022).¹⁰
 - Newborn screening of Pompe disease indicates a global birth prevalence rate of 1 per 18,771 (Colburn and Lapidus, 2024).¹¹

¹⁰ Stevens S, Milani-Nejad S & Mozaffar T. Pompe Disease: a Clinical, Diagnostic, and Therapeutic Overview. *Current Treatment Options in Neurology* 2022; 24:573-588: 10.1007/s11940-022-00736-1

¹¹ Colburn R & Lapidus D. An analysis of Pompe newborn screening data: a new prevalence at birth, insight and discussion. *Frontiers in Pediatrics* 2024; 11:1221140: 10.3389/fped.2023.1221140

- the reported Australian birth prevalence of Pompe disease is 1 per 46,000 (Chin and Fuller, 2022).⁹

The PBAC noted the following observations from the LSDP EP:

- Colburn and Lapidus, 2024 report that there was no difference between the birth prevalence rates across populations of European, Latin American, or Asian ancestry.
- In the sponsor's submission to the European Medicines Agency for consideration of CIPAMIG, the provided point prevalence rate was 0.37 per 10,000 (or 1.85 per 50,000) which would not meet the LSDP's criterion of an ultra-rare disease.

The PBAC noted that the LSDP EP considered that 'point' prevalence is more suitable in guiding its consideration on LSDP eligibility than birth prevalence. The PBAC noted that the LSDP EP highlighted that while much of the literature considers birth prevalence, there could be some residual uncertainty about whether Pompe disease prevalence continues to meet the LSDP threshold.

7.12 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

Amicus welcomes the PBAC's determination that Pombiliti/Opfolda are effective treatment for Pompe disease and, on balance, non-inferior to the existing Enzyme replacement therapies currently funded through the Life Saving Drugs Program. We look forward to working with the LSDP executive to make this new treatment available to patients with Pompe disease in Australia.