

An addendum to this Public Summary Document (PSD) has been included at the end of the document.

5.09 PATISIRAN, Solution concentrate for I.V. infusion 10 mg in 5 mL, Onpattro®, Alnylam Australia Pty Ltd

1 Purpose of submission

- 1.1 The Category 1 submission requested a Section 100 (Highly Specialised Drugs Program) Authority Required (Written) listing for patisiran for the treatment of hereditary transthyretin-mediated (hATTR) amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy.
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus best supportive care (BSC). The PBAC has not previously considered patisiran for any indication.

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

Component	Description
Population	Adult patients with hATTR amyloidosis and stage 1 or 2 polyneuropathy, defined by FAP stage
Intervention	Patisiran 0.3 mg/kg (to a maximum 30 mg for patients ≥ 100 kg) every 3 weeks by IV infusion, in addition to best supportive care (BSC).
Comparator	BSC alone for symptom relief
Outcomes	Change in neurological impairment, polyneuropathy progression, ambulatory ability, health related quality of life.
Clinical claim	Patisiran (added to BSC) has superior efficacy and similar safety to BSC in adult patients with hATTR amyloidosis with stage 1 or 2 polyneuropathy.

Source: Table 1.1, p24 of the submission.

Abbreviations: BSC, best supportive care; FAP, Familial amyloid polyneuropathy; hATTR, hereditary transthyretin-mediated amyloidosis; IV, intravenous

2 Background

Registration status

- 2.1 Patisiran was TGA registered on 18 November 2022 for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with Familial Amyloid Neuropathy (FAP) stage 1 or stage 2 polyneuropathy. Clinical staging systems for patients with hATTR amyloidosis with polyneuropathy are discussed in paragraph 4.7.

3 Requested listing

- 3.1 Secretariat additions are in italic and deletions in strikethrough.

*Public Summary Document – July 2023 PBAC Meeting, September 2023, and December 2023
Addendum*

MEDICINAL PRODUCT medicinal product pack	PBS item code	Dispensed Price for Max. Qty	Max. qty units	No. of Rpts	Available brands
PATISIRAN					
10 mg (5 mL) vial for complex IV infusion, 1	NEW NEW	Public: \$ XXXX published price \$ XXXX effective price	3	8.7 in a 6-month period ^a 7	Onpattro
Category / Program: Section 100 HSD – Public Hospital Section 100 HSD – Private Hospital					
Prescriber type: ☒ Medical Practitioners					
Condition:	Hereditary transthyretin hATTR-amyloidosis with polyneuropathy.				
PBS indication:	Hereditary transthyretin amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy				
Restriction:	☒ Authority Required - In Writing				
Treatment criteria:	Must be treated by a consultant physician with experience in the management of amyloid disorders.				
Treatment phase:	Initiating treatment				
Clinical criteria:	- The condition must be <i>hereditary transthyretin hATTR</i>-amyloidosis confirmed by genetic testing; and - The patient must have a PND score description of I, II, IIIA, or IIIB or the patient must have an FAP stage description of 1 or 2.				
Prescriber Instruction	Clinical staging scales relevant to clinical criteria ¹				
	Familial Amyloid Polyneuropathy (FAP) stage		Polyneuropathy Disability (PND) Score		
	Stage 0	No symptoms	Stage 0	No symptoms	
	Stage 1	Unimpaired ambulation	Stage I	Sensory disturbances but preserved walking capability	
	Stage 2	Assistance with ambulation required	Stage II	Impaired walking capacity but able to walk without stick or crutches	
			Stage IIIA	Walking with help of one stick or crutch	
			Stage IIIB	Walking with help of two sticks or crutches	
	Stage 3	Wheelchair- bound or bedridden	Stage IV	Confined to wheelchair or bedridden	
Treatment phase:	Continuing treatment				
Clinical criteria:	- The patient must have previously received PBS-subsidised treatment with this drug for this condition; and - The patient must continue to demonstrate clinical benefit; and - The patient must not be permanently bedridden or receiving end-of-life care.				
Treatment phase:	Grandfather arrangements				
Clinical criteria:	- The patient must have previously received non-PBS-subsidised treatment with this drug for this condition; and - The patient must continue to demonstrate clinical benefit; and - The patient must not be permanently bedridden or receiving end-of-life care.				

^aAccounts for one repeat every 3 weeks

¹ Adams D. Recent advances in the treatment of familial amyloid polyneuropathy. Ther Adv Neurol Disord. 2013 Mar;6(2):129-39.

- 3.2 The ESC noted that the submission requested a single vial size containing 10 mg of patisiran. The ESC noted that a degree of drug wastage would occur for most patients, i.e. those requiring a dose that does not correspond to a multiple of 10 mg, e.g. a patient weighing 70 kg would require a dose of 21 mg according to the recommended dosing regimen which would require 3 vials. The pre-PBAC response stated that the sponsor manufactures only one vial size of patisiran for global use, and this cannot be altered. The PBAC advised that wastage must be incorporated in the economic model consistent with PBAC guidelines.
- 3.3 The submission requested listing for the Highly Specialised Drug program (S100-HSD) in the public hospital setting only, however the Pre-Sub-Committee Response (PSCR) noted the Secretariat's suggested update to the proposed restriction to reflect public and private hospital settings and accepted this change.
- 3.4 The submission proposed a special pricing arrangement with an effective ex-manufacturer price of \$1 per 10 mg vial.
- 3.5 Patisiran is dosed by weight at 0.3 mg per kg of body weight, but for patients weighing 100 kg or more, the recommended dose is fixed at 30 mg. Patients with a body weight over 66.7 kg will require the maximum quantity of 3 vials per dose (corresponding to approximately 40% of the APOLLO trial population).
- 3.6 The requested restriction is consistent with the TGA indication, hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy (FAP stage 1 or 2, or PND score I, II, IIIA or IIIB), however the requested restriction also requires the hATTR amyloidosis to be confirmed by genetic testing.
- 3.7 The requested restriction is generally consistent with the evidence presented in the submission, with the exception of eligibility for continued treatment with patisiran. While patients in the APOLLO clinical trial were excluded at baseline if bedridden or in a wheelchair (stage 3 polyneuropathy), they were not required to cease treatment if disease progressed to this stage during the trial, or during the open-label extension study. Patients in the patisiran arm transitioning into the PND IV health state were assumed to cease treatment in the economic evaluation presented by the submission (paragraph 6.52).
- 3.8 The submission stated that patients should continue to receive treatment with patisiran until no further clinical benefit from treatment is evident, as assessed by a physician with experience in the management of amyloid disorders. The submission stated that the assessment should include PND or FAP staging systems (measures of ambulatory ability), alongside appraisal of other aspects of the patient's condition, treatment, daily routine and outlook. The continuation criteria exclude patients that are permanently bedridden or are receiving end-of-life care. It is unclear whether a formal definition of clinical benefit from treatment with patisiran, or specific discontinuation criteria should be included. Patients and clinicians may be reluctant to cease treatment with patisiran in FAP Stage 3 or PND IV (confined to wheelchair or

- bedridden) if treatment is still considered to be providing a benefit despite evidence of disease progression.
- 3.9 The submission noted a recently approved MBS listing (Item 73422, which commenced on 1 November 2022) for next-generation sequencing for the diagnosis of early-onset or familial neuromuscular disorders. The genetic panel testing includes TTR, which is the gene that requires sequencing when making a diagnosis of hATTR amyloidosis. The submission noted that the addition of genetic testing for neuromuscular disorders to the MBS is likely to increase the detection rate for hATTR amyloidosis. The availability of MBS-funded genetic testing and the PBS listing of a disease-modifying treatment may lead to an increase in diagnostic testing and may identify greater numbers of patients at early stages of disease.
- 3.10 The ESC noted that the submission proposed a treatment criteria that the patient “Must be treated by a consultant physician with experience in the management of amyloid disorders.” The ESC considered this may require clarification, such as defining the relevant specialist prescriber types. The PBAC considered that initiation by neurologists would be appropriate and should be specified in the restriction.
- 3.11 The submission stated that grandfathered patients (currently enrolled in clinical trials or receiving patisiran via an alternative access scheme) should receive PBS-funded treatment once patisiran is PBS-listed. The pre-PBAC response estimated that up to < 500 patients could be eligible for grandfathering once patisiran is PBS-listed. The PBAC considered that a grandfather restriction was appropriate.
- 3.12 In addition to the subjective continuation criteria, there is potential for use of patisiran outside of the requested restriction due to use in patients with hATTR amyloidosis with cardiomyopathy (in the absence of polyneuropathy). Results were recently published for APOLLO-B, a randomised, double-blind, placebo-controlled trial of patisiran in 360 patients with ATTR amyloidosis (wild-type or hereditary) with cardiomyopathy (Maurer 2022, presented at the XVIII Meeting of the International Society of Amyloidosis). The primary endpoint, change from baseline to Month 12 in 6 minute walk test, showed a statistically significant difference in favour of patisiran. An open-label extension period for the APOLLO-B trial is ongoing. However, the ESC considered that the risk of usage outside the restriction was covered by the written Authority required.
- 3.13 The proposed restriction is generally consistent with the eligibility criteria for the pivotal patisiran study (APOLLO), although the trial also excluded patients with a previous liver transplant, and patients with New York Heart Association (NYHA) heart failure classification of >2. The PBAC considered the proposed restriction should include these criteria for consistency with the trial population.

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

4 Population and disease

- 4.1 ATTR amyloidosis is a rare, rapidly progressive, and fatal disease, caused by misfolded transthyretin (TTR) protein that leads to the accumulation of amyloid deposits in the body. There are two types of ATTR amyloidosis: hereditary (hATTR) amyloidosis (also referred to as variant ATTR amyloidosis, ATTRv), and wild-type (wtATTR) amyloidosis. hATTR amyloidosis is less prevalent than wtATTR amyloidosis, with the submission reporting estimates of approximately 50,000 patients worldwide with hATTR amyloidosis versus 200,000 to 300,000 with wtATTR amyloidosis.
- 4.2 hATTR amyloidosis is an inherited, autosomal dominant, multisystem disease with a heterogenous clinical presentation that includes sensory, motor, and autonomic dysfunction, polyneuropathy and cardiomyopathy, with the potential involvement of other organ systems as well. Symptoms of hATTR amyloidosis will vary depending on the organ systems affected. Over 120 reported TTR genetic variants are associated with hATTR amyloidosis that result in varying clinical presentation, ranging from predominantly neuropathic (e.g., early onset V30M) to predominantly cardiac (V122I, wild-type ATTR), to mixed disease (e.g. late onset V30M, Adams 2021). However, Adams (2021) notes that a mixed phenotype including polyneuropathy and cardiomyopathy can be found in the majority of patients. The V30M variant is the most frequently reported and is responsible for the high prevalence of hATTR amyloidosis in endemic areas, including Portugal, Sweden, and Japan (Carroll 2022). hATTR amyloidosis is often underdiagnosed or misdiagnosed due to disease and symptom heterogeneity. The mean age of onset is 55 years, and 61 years at diagnosis (Waddington Cruz 2017).
- 4.3 hATTR amyloidosis with polyneuropathy is associated with significant morbidity and profound and rapid worsening of health-related quality of life, leading to premature death. Peripheral nerve dysfunction can begin with lower-limb numbness and pain, while autonomic nerve dysfunction may manifest as constipation alternating with diarrhoea, nausea and vomiting, orthostatic hypotension, and sexual dysfunction. Disease progression eventually leads to motor weakness, decreased pain sensation, loss of ambulation and inanition (exhaustion due to prolonged undernutrition).
- 4.4 Median survival after disease onset or diagnosis varies depending on the TTR variant and organ system involvement. In patients with hATTR amyloidosis with polyneuropathy, median survival from disease onset ranges from approximately 12 years in those with early-onset V30M disease (predominantly polyneuropathy symptoms) to approximately 7 years in those with late-onset disease caused by V30M or V107I genetic variant (mixed polyneuropathy and cardiomyopathy symptoms), with death often due to inanition caused by malnutrition due to GI autonomic neuropathy and advanced neuropathy (increased PND/FAP stage, Adams 2021). Given the frequent delay in diagnosing hATTR amyloidosis, median survival time from diagnosis for all hATTR amyloidosis is 4.7 years. For patients with the late-onset V30M variant,

median survival after diagnosis has been reported from 3.5 to 5.7 years (associated with mixed polyneuropathy/cardiomyopathy symptoms. Adams 2021; Carroll 2022). In patients presenting with cardiomyopathy-predominant hATTR amyloidosis, median survival from diagnosis is shorter at approximately 3.4 years, with death usually due to progressive heart failure or life-threatening cardiac arrhythmia (Adams, 2021).

- 4.5 A retrospective analysis of hATTR amyloidosis patients attending Australian Amyloidosis Network (AAN) clinics between 2007-2022 identified 130 prevalent patients with hATTR amyloidosis, of whom 59 patients were reported to have FAP stage 1 or 2 disease. Of all prevalent patients, 40% had neuropathic-predominant disease, 32% cardiac, 25% mixed cardiac and neuropathic symptoms, and 3% other organs. The study authors noted that patient numbers were an underestimate, as hereditary amyloidosis is an under-recognised and underdiagnosed disorder, and diagnosed cases are not necessarily referred to an AAN clinic (Carroll et al, unpublished abstract).
- 4.6 The population targeted in the submission was adult patients with a confirmed diagnosis of hATTR amyloidosis with stage 1 or stage 2 polyneuropathy (symptomatic but not wheelchair-bound or bedridden).
- 4.7 The submission described two clinical staging systems for patients with hATTR amyloidosis with polyneuropathy: the FAP stage system, developed to classify the disease based on the patient's ability to ambulate (Coutinho 1980); and the PND score, based on both sensory and motor impairment and associated impact on ambulation (Suhr 1994; see Table 2). In both scales, a higher stage is indicative of greater disease severity and impact on ambulation. The TGA indication and requested PBS restriction for patisiran limit treatment to patients with Stage 1 or 2 polyneuropathy (i.e. FAP stage 1 or 2, or PND score of I, II, IIIA, or IIIB).

Table 2: Clinical staging in hATTR amyloidosis with polyneuropathy

Familial Amyloid Polyneuropathy (FAP) stage		Polyneuropathy Disability (PND) Score	
Stage 0	No symptoms	Stage 0	No symptoms
Stage 1	Unimpaired ambulation	Stage I	Sensory disturbances but preserved walking capability
Stage 2	Assistance with ambulation required	Stage II	Impaired walking capacity but able to walk without stick or crutches
		Stage IIIA	Walking with help of one stick or crutch
		Stage IIIB	Walking with help of two sticks or crutches
Stage 3	Wheelchair-bound or bedridden	Stage IV	Confined to wheelchair or bedridden

Source: Table 1.2, p30 of the submission.

- 4.8 The submission noted that the 10-metre walk test (10-MWT) is also an outcome for assessment of ambulatory ability in clinical studies of patients with hATTR amyloidosis with polyneuropathy. The modified Neuropathy Impairment Score +7 (mNIS+7) is another measure of polyneuropathy impairment which is used as the primary endpoint in the key clinical trial (APOLLO). The submission noted that the detailed assessment of muscle weakness, muscle stretch reflexes, sensory loss and autonomic impairment required for the mNIS+7 is valuable in clinical studies but requires specific

training and monitoring, and is time consuming to complete, which may limit the usefulness of this measure in clinical practice.

- 4.9 Patisiran is a small interfering ribonucleic acid (siRNA) therapeutic that is specifically engineered to target a sequence in the mRNA that codes for TTR, blocking production of the TTR protein, and thus reducing the accumulation of TTR-derived amyloid deposits in tissues and organs. Patisiran is administered every 3 weeks by intravenous infusion (over approximately 80 minutes). At least 60 minutes prior to each patisiran infusion, patients receive premedication to minimise infusion-related adverse events, including intravenous (IV) corticosteroids (dexamethasone 10 mg, or equivalent), oral paracetamol (500 mg), IV H1 blocker (diphenhydramine 50 mg, or equivalent), and IV H2 blocker (ranitidine 50 mg, or equivalent). Co-administered therapies include best supportive care for symptom management. Treatment with patisiran is expected to be ongoing, subject to the clinical judgment of the treating physician.
- 4.10 By reducing serum TTR protein, patisiran treatment leads to a decrease in serum vitamin A levels. Vitamin A supplementation at approximately 2500 IU per day is advised to reduce the potential risk of ocular toxicity due to vitamin A deficiency.

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

5 Comparator

- 5.1 The submission nominated BSC as the main comparator. The main argument provided in support of this nomination was that patisiran is the only therapy with market authorisation in Australia for patients with hATTR amyloidosis with polyneuropathy and there are no PBS-funded disease modifying treatments available for these patients. In the absence of disease modifying treatments, BSC is provided for relief of neuropathic pain and amelioration of symptoms of autonomic neuropathy. BSC varies based on the symptoms experienced, but may include treatments for early satiety, postural hypotension, diarrhoea/constipation, painful neuropathy, light-headedness, and fainting.
- 5.2 Tafamidis is TGA-approved for the treatment of adult patients with wtATTR or hATTR amyloid cardiomyopathy and is being considered for PBS listing at the July 2023 PBAC meeting² (refer to tafamidis Public Summary Document (PSD), July 2023 PBAC meeting) for the treatment of transthyretin amyloid cardiomyopathy (also referred to as ATTR amyloidosis with cardiomyopathy or ATTR-CM). The submission noted that this patient group does not align with the indicated population and requested restriction for treatment with patisiran and, as such, tafamidis is not a near-market comparator. There may be some overlap in the relevant patient groups for tafamidis and patisiran, as some patients with hATTR amyloidosis will experience mixed

² <https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/agenda/july-2023-pbac-meeting>, accessed 19 April 2023.

neuropathy and cardiac symptoms. Australian data from the AAN (see above) suggests that approximately 25% of prevalent patients have mixed symptoms.

- 5.3 The submission also noted that the PBAC has previously considered that diflunisal, which is not currently listed on the Australian Register of Therapeutic Goods, but used off-label in some patients with ATTR with cardiomyopathy, was not a near-market comparator for tafamidis (para 5.3, tafamidis PSD, July 2020 PBAC meeting), and therefore would not be a near-market comparator for patisiran. While not currently registered for use in Australia, diflunisal may be accessed through the Special Access Scheme (SAS) for treatment of amyloidosis³. Published guidelines proposed by expert consensus (Ando 2022)⁴ reported that diflunisal inhibited progression for patients with familial ATTR amyloidosis, based on an international, placebo-controlled RCT which enrolled 130 patients with hereditary TTR amyloid polyneuropathy. The AAN has reported that diflunisal has efficacy in delaying the prevention of peripheral neuropathy in hATTR amyloidosis and may be useful to delay progression of cardiomyopathy in ATTR amyloidosis as well⁵.
- 5.4 Other disease-modifying treatments for hATTR amyloidosis with polyneuropathy are approved for use in other countries. Vutrisiran (administered by subcutaneous injection every 3 months) and inotersen (once-weekly subcutaneous injection) have a similar mechanism of action to patisiran. Whilst these therapies are not currently TGA-approved or PBS-listed for use in Australian patients, they may be potential future comparators.
- 5.5 Orthotopic liver transplant was not considered a suitable comparator, as it is only an option for a very small number of patients with early-stage hATTR amyloidosis with polyneuropathy, and is associated with high mortality and morbidity, as well as worsening of polyneuropathy within 3 to 5 years post-transplant for some patients. The ESC considered this was reasonable as liver transplant is no longer considered a treatment option in practice, noting that the condition is known to progress after liver transplant.

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

³ <https://www.tga.gov.au/products/unapproved-therapeutic-goods/special-access-scheme-sas-and-authorised-prescriber/prescribe-unapproved-therapeutic-good/list-products-established-history-use/special-access-scheme-sas-category-c-lists>, accessed 16 May 2023.

⁴ Ando et al. (2022) Guidelines and new directions in the therapy and monitoring of ATTRv amyloidosis, *Amyloid*, 29:3, 143-155.

⁵ Australian Amyloidosis Network (2020), Submission to Inquiry into approval processes for new drugs and novel medical technologies in Australia Submission #98: Australian Amyloidosis Network https://www.apph.gov.au/Parliamentary_Business/Committees/House/Health_Aged_Care_and_Sport/Newdrugs/Submissions, accessed 16 May 2023.

Australian Amyloidosis Network (2019) – Diflunisal information for patients. <https://aan.org.au/wp-content/uploads/2019/08/Diflunisal-Patients-Information-AAN-website.pdf>, accessed 16 May 2023.

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician discussed the natural history of the disease and the impact of the condition on patient quality of life. The clinician also discussed the genetic characteristics of hATTR in Australia and presented clinical case studies. The PBAC considered that the hearing was informative as it provided an experienced clinical perspective on managing this uncommon disease.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (57) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with patisiran including improvement in the individual's condition and the slowing of deterioration. The input also described an improvement in quality of life on treatment, but noted the time needed for regular infusions. The input described anticipated improvements in ability to perform daily activities and live a more fulfilling life due to treatment. The input indicated minimal side effects were anticipated. Concerns were raised regarding the unaffordability of the drug without compassionate access.
- 6.3 The PBAC noted the advice received from the Australian Amyloidosis Network (AAN) discussing the effects of the condition and need for effective therapies. It was noted that patients with hATTR are typically younger than their wtATTR counterparts, and they require assistance from multiple specialists to continue to function as best they can. The AAN supported the proposed listing based on clinical experience with patisiran in clinical trials and medicine access programs. The medication was described as well tolerated with minimal and manageable toxicity.
- 6.4 The PBAC noted the advice from the Amyloidosis Research Consortium which reported on an online global survey conducted using the ATTR Quality of Life Questionnaire to measure symptoms and the impact of ATTR on physical functioning, activities of daily living, emotional well-being, and productivity (n=390). Of patients completing the survey, 56 (14%) had PN only and 57 (40%) reported both CM and PN. The input provided a detailed description of physical effects, impacts on QOL (physical and emotional), and concerns about the future reported by patients.

Clinical trials

- 6.5 The submission was based on one randomised placebo-controlled trial (APOLLO) comparing patisiran with placebo in patients with hATTR amyloidosis with polyneuropathy (n=225).
- 6.6 The submission also presented a brief summary of efficacy and safety outcomes from a phase 2 multiple ascending dose study (ALN-TTR02-002) and associated open label extension study (ALN-TTR02-003), as well as interim results from an ongoing global

open label extension study (Global OLE, ALN-TTR02-006). Patients who completed studies ALN-TTR02-003 or the APOLLO trial were eligible to continue into the Global OLE study.

6.7 Details of the trials presented in the submission are provided in Table 3.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
APOLLO (ALN-TTR02-004)	APOLLO: A Phase 3 Multicenter, Multinational, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Patisiran (ALN-TTR02) in Transthyretin (TTR)-Mediated Polyneuropathy (Familial Amyloidotic Polyneuropathy-FAP). Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. Gonzalez-Duarte A, Berk JL, Quan D, et al. Analysis of autonomic outcomes in APOLLO, a phase III trial of the RNAi therapeutic patisiran in patients with hereditary transthyretin-mediated amyloidosis. Minamisawa M, Claggett B, Adams D, et al. Association of patisiran, an RNA interference therapeutic, with regional left ventricular myocardial strain in hereditary transthyretin amyloidosis: the APOLLO study. Obici L, Berk JL, González-Duarte A, et al. Quality of life outcomes in APOLLO, the phase 3 trial of the RNAi therapeutic patisiran in patients with hereditary transthyretin-mediated amyloidosis. Solomon SD, Adams D, Kristen A, et al. Effects of patisiran, an RNA interference therapeutic, on cardiac parameters in patients with hereditary transthyretin-mediated amyloidosis. Yamashita T, Ueda M, Koike H, et al. Patisiran, an RNAi therapeutic for patients with hereditary transthyretin-mediated amyloidosis: sub-analysis in Japanese patients from the APOLLO study.	Clinical Study Report, August 2017 N Engl J Med 2018; 379(1):11-21 J Neurology 2020; 267(3):703-712 JAMA Cardiology 2019; 4(5):466-472 Amyloid 2020; 27(3):153-162 Circulation 2019; 139(4):431-443 Neurol Clin Neurosci 2020; 8(5):251-260
ALN-TTR02-002	Suhr OB, Coelho T, Buades J, et al. Efficacy and safety of patisiran for familial amyloidotic polyneuropathy: A phase II multi-dose study.	Orphanet J Rare Dis. 2015;10:109
ALN-TTR02-003 (Phase 2 OLE study)	A Phase 2, Multicentre, Open-label, Extension Study to Evaluate the Long-Term Safety, Clinical Activity, and Pharmacokinetics of ALN-TTR02 in Patients with Familial Amyloidotic Polyneuropathy Who Have Previously Received ALN-TTR02 Coelho T, Adams D, Conceição I, et al. A phase II, open-label, extension study of long-term patisiran treatment in patients with hereditary transthyretin-mediated (hATTR) amyloidosis.	Clinical Study Report, February 2017 Orphanet J Rare Dis. 2020;15(1):179.
ALN-TTR02-006 (Global OLE study)	A Multicenter, Open-Label, Extension Study to Evaluate the Long-term Safety and Efficacy of Patisiran in Patients with Familial Amyloidotic Polyneuropathy Who Have Completed a Prior Clinical Study with Patisiran Adams D, Polydefkis M, González-Duarte A, et al. Long-term safety and efficacy of patisiran for hereditary transthyretin-mediated amyloidosis with polyneuropathy: 12-month results of an open-label extension study.	Clinical Study Report: Data Update Report 1, 17 March 2022 Lancet Neurol. 2021 Feb 21;20(1):49-59

Source: Table 2.3, p46; Section 2.2.6, pp46-47 of the submission.

Abbreviations: OLE, open-label extension

Note: Abstracts of studies with full publications are not presented.

6.8 The key features of the key randomised APOLLO trial and Global OLE study are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation ^a
Patisiran versus placebo						
APOLLO	225	Randomised, double blind, placebo controlled multicentre trial, 18 months	Low	18-85 years, hATTR amyloidosis with polyneuropathy (NIS of 5-130 and PND of ≤IIIB)	Primary: Neurological impairment (mNIS+7) Secondary: Health-related quality of life (Norfolk QoL-DN), weakness (NIS-W), disability (R-ODS), 10-MWT, mBMI, autonomic symptoms (COMPASS-31) Exploratory: PND score change from baseline, Serum TTR reduction, EQ-5D-5L	EQ-5D-5L Change in PND score Overall survival Time to treatment discontinuation Serious adverse events
Global OLE	211	Open label, single-arm study 5 years (ongoing – 36-month data presented in this submission)	High	Completed a patisiran trial (APOLLO or Phase 2 extension trial) and tolerated trial drug	Primary: AEs leading to study drug discontinuation Secondary: neurological impairment (mNIS+7), health-related quality of life (Norfolk QoL-DN), disability (R-ODS), , mBMI, change in FAP and PND scores	Change in PND score. Overall survival Time to treatment discontinuation

Source: Table 2.6, pp53-54; Table 2.13, p57; Table 2.14, p58 of the submission; Table 2.15, p62 of the submission.

Abbreviations: 10-MWT, 10 metre walk test; AE, adverse events; mBMI, modified body mass index (BMI x serum albumin concentration); NIS, neuropathic impairment scale; Norfolk QoL-DN, Norfolk quality of life diabetic neuropathy; OLE, open label extension; PND, polyneuropathy disability score; R-ODS, Rasch-built Overall Disability Scale; TTR, transthyretin.

^a Individual patient data from the APOLLO trial and Global OLE study were used in the modelled evaluation.

6.9 Overall, the risk of bias in the APOLLO trial was low, although there may be a risk of attrition bias with a larger proportion of patients in the placebo group being withdrawn from the study compared to the patisiran group, and a potential for functional unblinding of treatment groups given the substantial differences in discontinuation rates between treatment arms. A total of 11 (7%) patisiran-treated patients and 29 (38%) placebo-treated patients discontinued their trial regimen, with most (10 and 22 patients, respectively) withdrawn completely from the trial. Of the 11 patisiran patients who discontinued treatment, 3 had an adverse event, 5 died, 1 had progressive disease, 1 had a protocol violation and 1 withdrew consent. In the placebo arm, 12 of the 29 patients withdrew consent (9 of whom stated that they felt their disease had progressed), 7 had an adverse event, 4 died, 4 had progressive disease, and 2 were withdrawn by a physician. The submission noted that the primary population included for efficacy and safety analyses was the modified intention-to-treat (mITT) population, which included all patients who received at least 1 dose of patisiran or placebo. Missing data were handled via the mixed-effects model for

repeated measures (MMRM) method for the primary, secondary and exploratory endpoints involving continuous measures, with sensitivity analyses utilising alternative methods of handling missing data also conducted. The Pattern-Mixture model based on multiple imputation with mixed missing data mechanisms was performed to assess the robustness of the primary MMRM results to the possible violation of the missing at random missingness assumption.

- 6.10 The risk of bias in the Global OLE study was high given the single-arm, open label nature of the study design.
- 6.11 The APOLLO trial included patients with a confirmed diagnosis of hATTR amyloidosis with polyneuropathy (mNIS+7 of 5-130 and PND score of $\leq$ IIIB, i.e. symptomatic but not confined to a wheelchair or bedridden). Some analyses were performed on a pre-specified cardiac subpopulation (56% of all patients) with pre-existing cardiac amyloid involvement, defined as baseline left ventricular (LV) wall thickness $\geq$ 13 mm, and no history of aortic valve disease or hypertension.
- 6.12 Baseline patient characteristics were generally well-balanced between the treatment arms of the APOLLO trial. However, there was a higher proportion of patients in the patisiran arm with a non-V30M genotype (62.2%) compared with the placebo group (48.1%), and a greater proportion of patients in the predefined cardiac subpopulation in the patisiran group (60.8%) compared to the placebo group (48.1%). The APOLLO trial included subgroup analyses of the primary outcome (change from baseline in mNIS+7 scores) by genotype (non-V30M versus V30M) and by cardiac subpopulation/non-cardiac subpopulation. Improvement in mNIS+7 scores appeared to be greater in the V30M genotype and cardiac subpopulations compared to their complements, however no tests for treatment effect interaction were presented.
- 6.13 The Global OLE study is ongoing and assesses the long-term safety and efficacy of patisiran in patients (N=211) with hATTR amyloidosis with polyneuropathy who participated in the phase 2 open-label extension or the phase 3 APOLLO trial. The estimated duration of trial treatment for each patient in the Global OLE study is 5 years. At the most recent data cut provided in the submission (from January 2021, at the 36-month timepoint), there were 148 patients ongoing in the trial, 4 completed, and 59 withdrawn (30 due to patient death). The ESC considered that updated information from the Global OLE study would be informative in helping to assess the long-term benefits of patisiran, whilst recognising that these data would be non-comparative.

Comparative effectiveness

- 6.14 Results for the primary outcome of change from baseline in mNIS+7 and subscales are summarised in Table 5. The mNIS+7 is based on the Neuropathy Impairment Score (originally used to evaluate sensorimotor polyneuropathy in patients with conditions such as diabetic polyneuropathy) and was developed as a more tailored measure of polyneuropathy progression in patients with hATTR amyloidosis with seven additional

nerve tests. The NIS has been shown to correlate with both FAP stage and PND scores (Adams 2015). The mNIS+7 is scored from 0 to 304, with a higher score indicative of greater neurologic deficit, and negative changes in values suggesting neurologic improvement.

Table 5: Mean change from baseline to Month 18 in mNIS+7 and subscales in APOLLO trial

Outcome	Baseline score, mean (SD)		Least Squares mean change from baseline (95%CI) (unless specified)		
	Patisiran (n=148)	Placebo (n=77)	Patisiran (n=148)	Placebo (n=77)	Difference
mNIS+7 Total score	80.93 (41.51)	74.61 (37.04)	-6.03 (-9.46, -2.60)	27.96 (22.83, 33.09)	-33.99 (-39.86, -28.13)
NIS-Weakness score	32.69 (25.23)	29.03 (22.95)	0.05 (-2.52, 2.63)	17.93 (14.07, 21.79)	-17.87 (-22.32, -13.43)
NIS-Reflexes score	12.81 (6.07)	12.75 (5.90)	0.22 (-0.31, 0.74)	0.75 (0.01, 1.49)	-0.54 (-1.39, 0.31)
QST score	27.2 (17.73)	24.8 (15.34)	-6.0 (-8.0, -4.1)	7.0 (4.1, 9.9)	-13.05 (-16.33, -9.77)
Σ5 NCS score	7.58 (2.32)	7.43 (2.24)	-0.03 (-0.21, 0.15)	1.02 (0.75, 1.29)	-1.04 (-1.35, -0.74)
Postural BP score	0.7 (0.79)	0.6 (0.74)	-0.2 (-0.3, -0.1)	0.1 (-0.1, 0.2)	-0.28 (-0.47, -0.10)
mNIS+7, % patients improved	-	-	56.1 (48.1, 64.1)	3.9 (0.0, 8.2)	52.2 (43.1, 61.3) OR 39.9, 95% CI 11.0, 144.4

Source: Table 2.16, pp65-66 of the submission.

Abbreviations: BP, blood pressure; CI, confidence interval; LS, least squares; mNIS+7, modified Neuropathy Impairment Score + 7; OR, odds ratio; QST, quantitative sensory testing; Σ5 NCS, nerve conduction studies;

Note: mNIS+7 scores range from 0 to 304; NIS-Weakness from 0-192; NIS-Reflexes from 0-20; QST from 0-80; NCS from 0-10; Postural BP from 0-2. For the proportion of patients with improvement in mNIS+7, any reduction in the score (<0, where a lower score indicates fewer symptoms) was classed as an improvement.

Statistically significant differences are highlighted in **bold**. Note that significance testing of mNIS+7 subcomponents was only conducted for the Weakness subscale, significance testing for other subcomponents were not reported.

- 6.15 Change from baseline in mNIS+7 was statistically significantly greater in the patisiran group than in the placebo group. The submission noted that the 34 point difference between treatment arms exceeded the 2 point minimum clinically important difference (MCID) from the International Peripheral Nerve Society for the original NIS score, and the 12.2 point MCID for the mNIS+7 scale estimated from a distribution-based approach in the phase 3 clinical trial for inotersen (NEURO-TTR), and represents a clinically meaningful benefit in terms of neurological impairment for patients with hATTR amyloidosis with polyneuropathy. Overall, 56.1% of patisiran-treated patients had an improved mNIS+7 score, compared with 3.9% of the placebo-treated patients (OR 39.9, 95% CI 11.0, 144.4).
- 6.16 The submission stated that additional prespecified analyses involving different statistical models, approaches to data censoring, and methods for handling missing data all resulted in a consistent estimate of treatment effect of patisiran compared to placebo. Differences between treatment groups in mNIS+7 scores were also observed at the 9-month time point (LS mean -15.98 points; 95% CI -20.70, -11.27).

6.17 Results of subgroup analyses (dichotomous categories by age, sex, race, region, neuropathic impairment score, genotype (V30M versus other, and early onset V30M versus all other mutations), previous tafamidis or diflunisal use, FAP stage (1 versus 2 or 3) or cardiac subpopulation versus non-cardiac subpopulation) for the primary outcome were consistent with the overall results, with all subgroups demonstrating statistically significantly greater improvements in mNIS+7 scores at Month 18 for patisiran-treated patients compared to placebo-treated patients.

6.18 Results of key secondary and exploratory outcomes from the APOLLO trial are summarised in Table 6.

Table 6: Secondary and exploratory outcomes at Month 18 in APOLLO trial

Outcome	Patisiran (n=148)	Placebo (n=77)	Patisiran (n=148)	Placebo (n=77)	Difference
	Baseline values, mean (SD)		LS mean change from baseline (95% CI)		
Norfolk QoL-DN score	59.6 (28.18)	55.5 (24.34)	-6.7 (-10.2, -3.3)	14.4 (9.0, 19.8)	-21.1 (-27.2, -15.0)
mBMI, kg/m ² x albumin g/dL	969.7 (210.45)	989.9 (214.19)	-3.7 (-22.6, 15.1)	-119.4 (-148.0, -90.8)	115.7 (82.4, 149.0)
COMPASS-31 score	30.61 (17.58)	30.31 (16.37)	-5.29 (-7.85, -2.72)	2.24 (-1.59, 6.06)	-7.53 (-11.89, -3.16)
10-MWT gait speed, m/s	0.795 (0.4009)	0.790 (0.3188)	0.077 (0.03, 0.12)	-0.235 (-0.31, -0.16)	0.311 (0.230, 0.393)
R-ODS score	29.7 (11.51)	29.8 (10.76)	0.0 (-1.1, 1.2)	-8.9 (-10.7, -7.2)	9.0 (7.0, 10.9)
Serum TTR KD, mean % decrease	196.5 mg/L (range 52-411 mg/L)	198.8 mg/L (range 59 to 320 mg/L)	84.3 (SEM: 1.48)	4.8 (SEM: 3.38)	-79.5 (NR)
			Patients with improved or stable scores from baseline, n (%)		
Norfolk QoL-DN improved ^a	-	-	NR (51.4)	NR (10.4)	NR (41%) OR: 10.0 (95% CI 4.4, 22.5)
Stable PND scores	-	-	96 (65)	23 (30)	-
Improved PND scores	-	-	12 (8)	0 (0)	-

Source: Table 2.16, pp65-66 of the submission, APOLLO Clinical Study Report.

Abbreviations: CI, confidence intervals; COMPASS-31, Composite Autonomic Symptom Score 31; KD, knockdown; LS, least squares; mBMI, modified body mass index; Norfolk QoL-DN, Norfolk quality of life – diabetic neuropathy; NR, not reported; OR, odds ratio; PND, polyneuropathy disability; R-ODS, Rasch-build Overall Disability Scale; SEM, standard error of the mean; TTR, transthyretin

Note: Norfolk QoL-DN scores can range from -4 to 136 points, with a lower score indicative of improvement; COMPASS-31 from 0 to 100 with higher scores indicating greater autonomic symptom burden; R-ODS from 0 to 48, with lower scores indicating increased disability. mBMI is measured as kg/m² x albumin g/dL.

^a For the proportion of patients with improvement in Norfolk QoL-DN scores, any reduction in the score (<0, where a lower score indicates fewer symptoms) was classed as an improvement.

6.19 At 18 months, Norfolk QoL-DN scores (a measure of health-related quality of life) improved from baseline in the patisiran group and worsened in the placebo group, with a statistically significant difference between the groups. The submission noted that the 21.9-point difference in scores at 18 months was greater than the MCID of 8.8 points specified for the Norfolk QoL-DN (based on an anchor-based approach used in the phase 3 clinical trial of inotersen in hATTR amyloidosis with polyneuropathy), and indicative of clinically meaningful change in health-related quality of life.

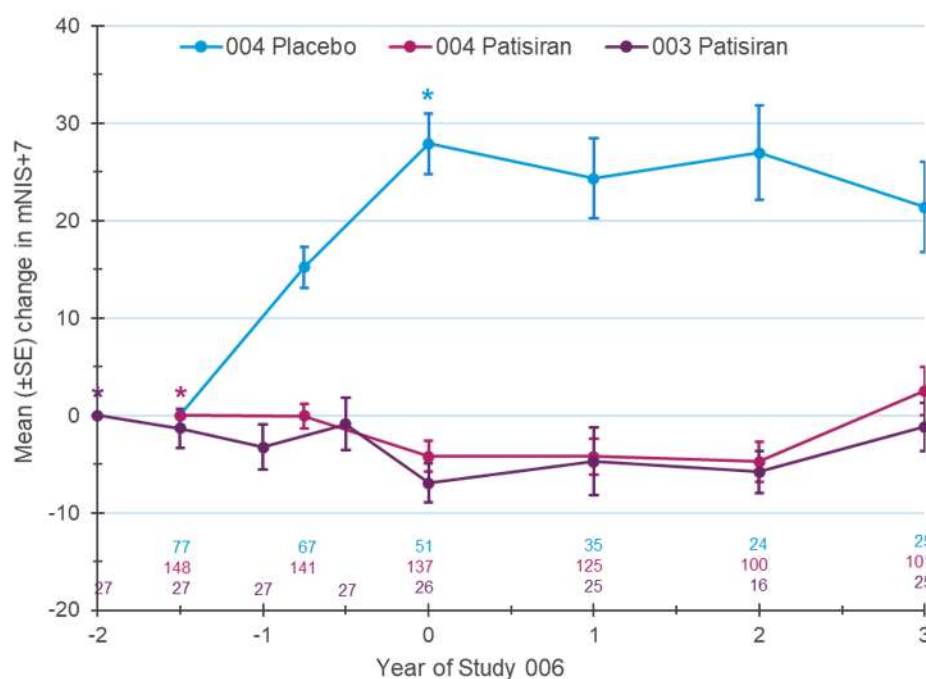
- 6.20 Results of the subgroup analyses for change from baseline in Norfolk QoL-DN scores were generally consistent with the overall results.
- 6.21 All other secondary outcomes showed significant between-group differences in favour of patisiran at 18 months, including motor strength (measured on NIS-Weakness scale), daily and social activities such as holding a book, eating, dancing, standing and running (measured with R-ODS scale), nutritional status (measured with mBMI), and autonomic neuropathy symptoms (including diarrhoea, male erectile dysfunction and fainting, measured with COMPASS-31).
- 6.22 Patients treated with patisiran showed similar gait speed at 18 months compared to baseline, as measured on the 10 metre walk test, compared to a decline in the placebo group, with a similar difference observed at the 9-month time point. The submission noted that for older adults, a change of 0.10 m/s has been suggested to represent a clinically meaningful change in gait speed based on a publication by Perera et al. (2006)⁶. There was a 0.31 m/s mean improvement in gait speed in patients receiving patisiran relative to those receiving placebo, which the submission argued was a clinically meaningful benefit in ambulation.
- 6.23 Change from baseline in serum TTR was measured in the APOLLO trial as an exploratory outcome. Mean TTR levels at baseline were similar between treatment arms, with rapid and sustained reduction (knockdown) in serum TTR levels observed over the 18-month study period in the patisiran arm.
- 6.24 Change from baseline in PND score was measured as an exploratory outcome. More patients in the patisiran group (73%) had stable or improved PND scores compared to the placebo group (30%). In the patisiran group, 8% of patients improved their PND score from baseline, most from PND IIIA/IIIB (requiring a walking aid) to PND I (walking unassisted), while no patients in the placebo arm improved. The submission argued that 'no change' in PND score reflects a preservation of ambulatory function and therefore a halting of disease impairment, a highly clinically meaningful outcome in hATTR amyloidosis with polyneuropathy, and claimed the benefit observed with patisiran over placebo on the outcome of PND score is inherently clinically meaningful.
- 6.25 Hospitalisation and all-cause mortality were assessed in a post hoc analysis as a composite outcome (Solomon 2019). There were 7 (4.7%) deaths and 50 (33.8%) all-cause hospitalisations for patients in the patisiran arm and 6 (7.8%) deaths and 30 (39.0%) all-cause hospitalisations in the placebo arm. Occurrence of the composite outcome of patients with any hospitalisation and/or death was lower in the patisiran arm (51 patients (34.5%)) than the placebo arm (31 (40.3%)). Rates of hospitalisation and/or death per 100 patient years were also reported (patisiran: 34.7 per

⁶ Perera S, Mody SH, Woodman RC, Studenski SA. Meaningful change and responsiveness in common physical performance measures in older adults. *J Am Geriatr Soc.* 2006;54(5):743-749.

100 patient-years, placebo: 71.8 per 100 patient-years). The submission noted that this corresponded to a risk reduction of approximately 50% for patisiran.

- 6.26 The change from baseline (of the parent trial) to Year 3 of the Global OLE study in mNIS+7 scores is summarised in Figure 1. At this timepoint patients in the Phase 2 extension study (003) had received patisiran for 60 months, while patients in the APOLLO trial (004) had received patisiran for 54 months (if originally randomised to patisiran) or 36 months (if originally randomised to placebo).

Figure 1: Change from baseline (of parent trial) to Year 3 in mNIS+7 scores, Global OLE study



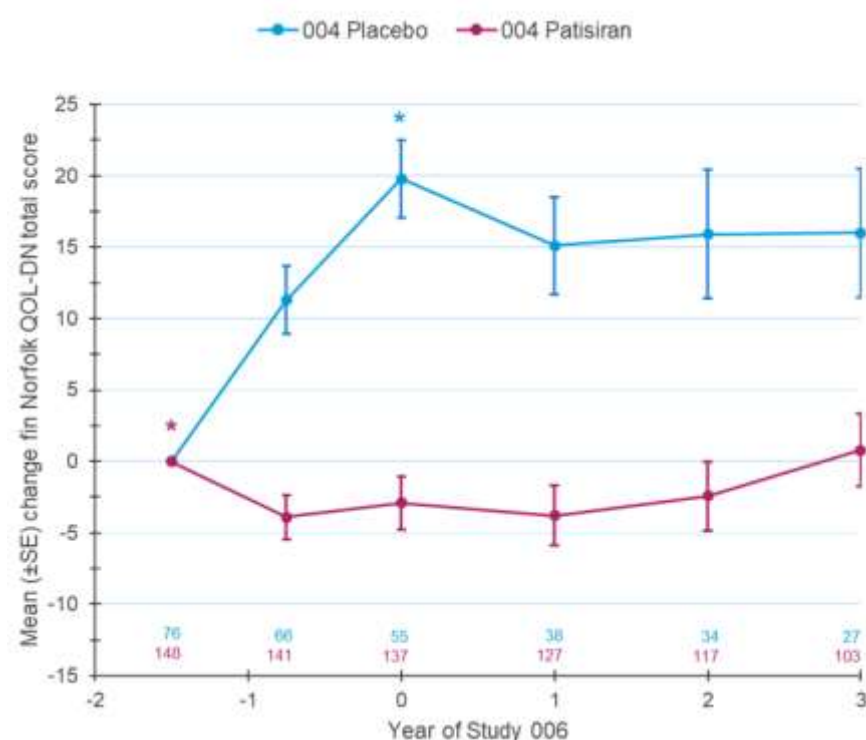
Source: Figure 2.16, p76 of the submission.

Abbreviations: SE, standard error

Note: Negative years refer to time on parent trial. APOLLO is trial 004 and phase 2 open label extension trial is 003. * denotes start of treatment with patisiran for each group.

- 6.27 Results demonstrated sustained stabilisation of polyneuropathy (measured with mNIS+7) in patients originally treated with patisiran and ceased progression (and stabilisation) of polyneuropathy in patients who switched from placebo to patisiran at the start of the Global OLE study.
- 6.28 Change from baseline to Year 3 of the Global OLE study in Norfolk QoL-DN scores is presented in Figure 2.

Figure 2: Change from baseline (of parent trial) to Year 3 in Norfolk QoL-DN scores, Global OLE study



Source: Figure 2.17, p77 of the submission.

Abbreviations: SE, standard error

Note: Negative years refer to time on parent trial. Trial 004 is the APOLLO trial. * denotes start of treatment with patisiran for each group.

6.29 Results demonstrated maintenance of health-related quality of life (HRQoL, measured with Norfolk QoL-DN) in patients originally treated with patisiran and halting of decline in patients who switched from placebo to patisiran at the start of the Global OLE study.

6.30 The proportion of patients with PND score worsening, staying the same or improving from baseline to Year 3 of the Global OLE study is summarised in Table 7.

Table 7: Change in PND status from baseline to Year 3 in Global OLE study

	Parent study group		
	Phase 2 OLE (N=25)	APOLLO patisiran group (N=137)	APOLLO placebo group (N=49)
Worsened	5 (20.0)	29 (27.6)	6 (22.2)
No change	17 (68.0)	67 (63.8)	19 (70.4)
Improved	3 (12.0)	9 (8.6)	2 (7.4)

Source: APOLLO Global OLE Clinical Study Report.

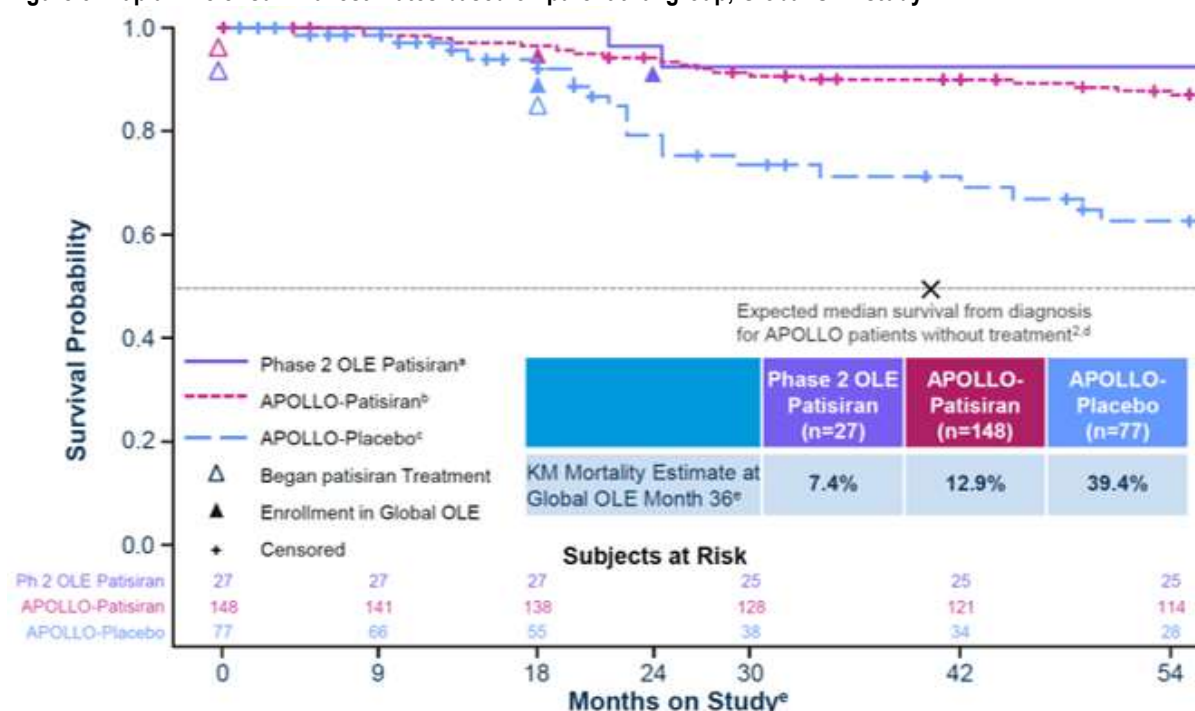
6.31 Improvement or stability in PND score from baseline to Year 3 in the Global OLE study were observed in the majority of patients in all patient groups.

6.32 Kaplan-Meier survival estimates for patients in the Global OLE study based on parent trial group (Wixner, 2022⁷) are presented in Figure 3. The ESC noted that the Global

⁷ Wixner J, Ueda M, Marques Junior, W, et al. Patisiran global open-label extension study at 36 months: Effect of long-term treatment on mortality and ambulatory function in patients with hATTR amyloidosis with

OLE study provided some evidence which suggested that there may be a mortality benefit for patisiran compared to that expected with placebo (Figure 3).

Figure 3: Kaplan-Meier survival estimates based on parent trial group, Global OLE study



Source: Wixner 2022 conference presentation.

Abbreviations: OLE, open label extension

^a The Phase 2 OLE patisiran group received patisiran in the Phase 2 OLE for 24 months and continued patisiran in the Global OLE. ^b APOLLO-patisiran received patisiran in APOLLO for 18 months and started patisiran in the Global OLE.

^c APOLLO-placebo received placebo in APOLLO for 18 months and continued patisiran in the Global OLE.

^d APOLLO patients were diagnosed 16.8 months prior to study baseline. Median survival from diagnosis of 4.7 years from hATTR amyloidosis diagnosis based on a natural history study of 266 patients.

^e Until censored or died. Patients were censored at the study withdrawal, 90 days past the last dose of patisiran, or at the last known alive date on or prior to data cut-off (January 27, 2021). Counting deaths within 90 days of last dose of study drug continues an established convention for patisiran mortality rates.

6.33 Patients in the APOLLO trial and Phase 2 OLE study who received patisiran in their parent studies had the lowest disease burden at Global OLE study baseline and the lowest mortality rates. Patients in the APOLLO placebo group had the highest disease burden at baseline and the highest mortality rate, however the mortality rate appeared to slow 6 months after commencing patisiran treatment. Wixner (2022) noted results of a multivariate Cox proportional hazards analysis which showed that parent study treatment (patisiran versus placebo), N-terminal pro brain-type natriuretic peptide level (>3000 ng/L versus ≤3000 ng/L), and NYHA Classification (II/III/IV versus I) were independent factors for mortality in the Global OLE.

polyneuropathy. XVIII Meeting of the International Society of Amyloidosis (ISA) 2022, Oral Presentation OP044. Available from: <https://capella.alnylam.com/2022/09/08/pati-isa-2022>, accessed 10 May 2023.

Comparative harms

- 6.34 Key adverse events occurring in the APOLLO trial are summarised in Table 8. All safety analyses were performed with the safety population (patients who received at least one dose of the study drug).

Table 8: Summary of key adverse events in the APOLLO trial

Adverse event	Patisiran (N=148) Number of patients (%)	Placebo (N=77) Number of patients (%)
Any adverse event	143 (96.6)	75 (97.4)
Severe adverse event	42 (28.4)	28 (36.4)
Serious adverse event	54 (36.5)	31 (40.3)
AE leading to discontinuation	7 (4.7)	11 (14.3)
AE leading to study withdrawal	7 (4.7)	9 (11.7)
AE related to study drug	73 (49.3)	30 (39.0)
Severe study drug-related AE	3 (2.0)	2 (2.6)
Deaths	7 (4.7)	6 (7.8)

Source: Table 2.18, p82 of the submission; Section 2.5.2, pp79-80 of the submission; APOLLO Clinical Study Report

Abbreviations: AE, adverse event

- 6.35 Similar proportions of patients in each treatment arm experienced an adverse event or serious adverse event. Diarrhoea was the only serious adverse event reported in more patients in the patisiran group (5.4%) than in the placebo group (1.3%).
- 6.36 A greater proportion of patients in the placebo group experienced an adverse event leading to treatment discontinuation (14.3%) or study withdrawal (11.7%) than the patisiran group (4.7% and 4.7%, respectively). Adverse events leading to treatment discontinuation reported in 2 or more patients included cardiac failure (2 patients, 1.4%) in the patisiran group and acute kidney injury (2 patients, 2.6%) in the placebo group. These events also led to withdrawal from the study. One patient in the patisiran group discontinued treatment due to an infusion related reaction that was moderate in severity.
- 6.37 There were more treatment-related adverse events in the patisiran group (49.3%) compared to the placebo group (39.0%). The only treatment-related adverse event reported in 5% or more of the patisiran group was infusion related reactions, with at least one event reported for 28 (18.9%) patisiran treated patients, a total of 145 infusion related reaction events over the course of the trial. The submission noted that the majority of infusion related reactions were mild in severity and decreased over time while on treatment with patisiran. There were no severe infusion related reactions and none were reported as serious adverse events. Treatment-related events experienced by 5% or more patients in the placebo group included diarrhoea (6.5%), nausea (6.5%), peripheral oedema (6.5%) and fatigue (5.2%).
- 6.38 As patisiran is directed to the liver, and because non-clinical studies revealed changes in serum liver marker and liver histopathology, the frequency of hepatic events was evaluated. There were more hepatic adverse events in the placebo group (9.1%) than in the patisiran group (5.4%). Most events were mild or moderate in severity and

- considered not or unlikely to be related to the study drug. Two events were considered to be related to patisiran treatment (hepatic enzyme increase, and alkaline phosphatase increase in one patient (0.7%) each), both mild in severity.
- 6.39 Cardiac adverse events and serious adverse events occurred at similar frequencies in both treatment groups in the overall trial mITT population.
- 6.40 There were 7 deaths (4.7%) in patisiran-treated patients, and 6 deaths (7.8%) in placebo-treated patients. All deaths were considered unlikely or not related to the study drug, with the submission noting that the causes of death were primarily cardiovascular in nature and were consistent with the natural history of hATTR amyloidosis.
- 6.41 The safety profile of the cardiac subpopulation was similar to the overall trial safety population. The proportion of patients experiencing cardiac disorders and serious cardiac disorders was similar between treatment arms. In the cardiac subpopulation there were 5 deaths (5.6%) in the patisiran group and 4 (11.1%) in the placebo group; no deaths were considered to be related to the study drug.
- 6.42 The duration of treatment with patisiran for Global OLE study participants differed depending on their previous trial enrolment: a maximum 36 months for patients previously treated with placebo in the APOLLO trial, 54 months for patients previously treated with patisiran in the APOLLO trial, and 60 months for patients in the Phase 2 OLE study (all previously treated with patisiran). All patients had at least one adverse event during the Global OLE study, with adverse events considered to be related to the study drug reported in 35.1% of patients overall. Specific adverse events were similar to those experienced in the APOLLO trial, with 27.0% of all patients experiencing diarrhoea, 25.1% peripheral oedema, 22.3% urinary tract infection, 21.3% nasopharyngitis, and 20.9% falls. 15.6% of patients experienced an infusion-related reaction. Most adverse events were mild or moderate in severity. Severe adverse events were reported for 44.1% of patients, and treatment-related severe adverse events were reported for 2.4% of patients. Serious adverse events were reported in 57.3% of patients and most were considered unlikely or not related to patisiran, with study drug related serious adverse events reported in 1.9% of patients. There were 35 (16.6%) deaths during the reporting period, just over half of whom (18 patients) were originally treated with placebo in the APOLLO trial. No deaths were considered to be related to the study drug.

Benefits/harms

- 6.43 On the basis of direct evidence presented in the submission, for every 100 patients treated for 18 months with patisiran in comparison with placebo:
- Approximately 52 additional patients will show improvement in neurological impairment (Table 5).

- Approximately 30 additional patients would have stable PND scores and approximately 8 people would have improved PND scores (Table 6).
- Approximately 41 additional patients will show improvement in health-related quality of life measured by the Norfolk QoL-DN scale (Table 6).
- Approximately 19 patients will experience an infusion related reaction (Table 8).
- Approximately 8 fewer patients will experience a severe adverse event (Table 8).
- There will be no difference in the number of deaths (Table 8).

Clinical claim

- 6.44 The submission described patisiran as superior in terms of delaying disease progression, reducing neuropathy symptoms, and improving health-related quality of life compared to placebo. The claim was supported by the primary outcome of change from baseline in mNIS+7, and secondary outcomes including Norfolk QoL-DN scores (a measure of health-related quality of life), motor strength (measured on NIS-Weakness scale), daily and social activities (measured with R-ODS scale), nutritional status (measured with mBMI), and autonomic neuropathy symptoms (measured with COMPASS-31). The claim was adequately supported over the randomised trial period but the magnitude of benefit in the long term is uncertain. The APOLLO trial did not demonstrate a significant difference in mortality. There was a lack of comparative efficacy and safety data beyond the 18-month APOLLO randomised trial. The applicability of the results to the Australian patient population was uncertain. It is unclear whether the distribution of PND scores from the APOLLO trial will be applicable to the proposed Australian population given potential differences in the distribution of patients across PND scores and proportion of patients with cardiac involvement. The availability of MBS-funded genetic testing and the PBS listing of a disease-modifying treatment may lead to an increase in diagnostic testing and may identify greater numbers of patients at early stages of disease.
- 6.45 The submission described patisiran as comparable in terms of safety compared to placebo. This claim was not adequately supported. While overall safety was comparable between treatment arms in the APOLLO trial, patisiran treated patients experienced more infusion-related reactions. The ESC also noted that mRNA interference therapies are relatively new and that there is limited long term experience with these types of therapies. Whilst the ESC considered that safety, as demonstrated in the APOLLO trial, was similar to placebo, overall there was inadequate longer-term evidence to support a conclusion of comparable safety.
- 6.46 The PSCR provided additional discussion in regard to concerns raised in the commentary about the lack of comparative efficacy and safety data beyond the 18-month APOLLO randomised trial. The PSCR stated that the APOLLO trial design was based on guidance from the European Medicines Agency (EMA) and the US Food and

Drug Administration (FDA) which suggested that the 18-month duration of placebo-controlled follow-up was reasonable, balancing between the need to clearly demonstrate separation between drug and placebo (which would favour longer follow-up) and the need to limit dropout rates (which would favour shorter trial durations). The PSCR noted that the trial duration for APOLLO was consistent with trials of other therapies in this indication. The PSCR also discussed ethical concerns associated with requiring patients to receive placebo treatment in the context of a disease that causes irreversible morbidity. The PSCR also noted that the Global OLE study provided evidence of long-term stabilisation with patisiran that was unlikely to be attributable to open-label bias in view of the known natural history of hATTR amyloidosis. The PSCR stated there was no biological rationale to anticipate reduced efficacy after repeated patisiran administration, as the silencing of TTR mRNA with patisiran inhibits the main source of TTR (the disease-causing protein) in the body, and antidrug antibodies to patisiran are rare (occurring in 3.4% of patients in APOLLO) and do not appear to impact treatment efficacy.

- 6.47 The PBAC considered that the evidence supported a claim of superior efficacy for patisiran compared with BSC, however the magnitude and duration of benefit remained uncertain. The PBAC considered that the long-term safety of patisiran was uncertain due to the limited duration of follow-up to date, which was particularly relevant in the context of the new mechanism of action of patisiran. The PBAC considered there was inadequate long-term evidence to support a conclusion of comparable safety and considered that patisiran was inferior to BSC in terms of safety, noting that patisiran-treated patients experienced more infusion-related reactions than the comparator group.

Economic analysis

- 6.48 The submission presented a modelled economic evaluation comparing patisiran with BSC, for the treatment of patients with hATTR amyloidosis with polyneuropathy. The economic evaluation was presented as a cost-utility analysis.

Table 9: Summary of model structure, key inputs and rationale

Component	Description
Treatments	Patisiran versus best supportive care (BSC)
Time horizon	40 years versus up to 18 months for the placebo arm in the APOLLO trial and up to 54 months (4.5 years) for the patisiran arm in the APOLLO trial and the Global OLE study.
Outcomes	Quality-adjusted life years
Methods used to generate results	Markov model
Health states	Seven health states: PND 0, PND I, PND II, PND IIIA, PND IIIB, PND IV, and death. Patients in the patisiran arm could be on or off treatment with patisiran.
Cycle length	6 months
Transition probabilities	Health state transitions: - Patisiran arm transitions during initial 18 months derived from APOLLO trial individual patient data for the patisiran arm (baseline to Month 18). Transitions from 18 months to 54 months derived from the Global OLE study individual patient data (Months 18 to 54). Transitions

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Addendum*

Component	Description
	beyond 54 months derived from individual patient data from the Global OLE study (Months 42 to 54). - BSC arm transitions during initial 18 months derived from APOLLO trial individual patient data for the placebo arm (baseline to Month 18). Transitions beyond 18 months derived from APOLLO trial individual patient data for the placebo arm (baseline to 18 months). Treatment persistence: - Derived from time to treatment discontinuation data for patisiran in the APOLLO trial and the Global OLE stud. The trial data was extrapolated to 40 years using an exponential function, selected on the basis of goodness-of-fit statistics and visual inspection. - Patients transitioning to PND IV are assumed to discontinue treatment. Health state mortality: - Mortality rate for patients in PND 0, I and II assumed to be the same as for the Australian general population. - Mortality rate for patients in PND IIIA/IIIB (1.90 x general population) and PND IV (9.42 x general population) estimated from a multivariate regression model of data from ALN-TTR02-003, the APOLLO trial and the Global OLE study. General population mortality based on Australian Bureau of Statistics life tables.
Utility values	Average health state utilities based on PND score estimated from an analysis of EQ-5D data from the APOLLO trial (PND 0: 0.6840; PND I: 0.6460; PND II: 0.4780; PND IIIA 0.3531; PND IIIB: 0.1746; PND IV: -0.0038). Cumulative monthly utility increment (0.0029) applied to patients on treatment with patisiran and cumulative monthly utility decrement (0.0092) applied to patients not on treatment with patisiran derived from an analysis EQ-5D data from the APOLLO trial. Additional disutility to reflect autonomic dysfunction applied to patients not receiving patisiran treatment (disutility of 0.0727 applied to patients in PND II and disutility of 0.1243 applied to patients in PND IIIA, PND IIIB, and PND IV). Overall utilities limited by set minima and maxima for each PND health state.
Costs	Patisiran drug cost based on the proposed effective price^a; administration cost based on MBS Item 13950 (for parenteral administration of antineoplastic agents); and premedication costs estimated based on PBS/RPBS items. Adverse event costs based on serious adverse events occurring in ≥2% of patients in the APOLLO trial. Healthcare resource utilisation estimated by a Delphi panel consisting of seven clinical experts in the UK. Resource utilisation adapted to the Australian setting by mapping medicines and procedures to PBS and MBS items. End of life costs based on estimates reported by Reeve et al. (2017).

Source: Table 3.1, p98 of the submission.

Abbreviations: BSC, best supportive care; OLE, open label extension; PND, polyneuropathy disability.

^a The submission base case included anniversary price reductions for patisiran. These were removed from the base case presented in the commentary and ESC Advice.

6.49 Health states in the model were defined based on PND scores. The submission argued that the results of the APOLLO trial suggest that PND scores are strongly associated with neuropathy impairment (as measured by mNIS+7) and health-related quality of

life (as measured by the Norfolk QoL-DN). PND scores are solely based on mobility status and may not adequately capture all aspects of the condition, including sensory issues (e.g., numbness, tingling and pain), autonomic neuropathy symptoms (e.g., dizziness or fainting, impotence, constipation, diarrhoea, faecal/urinary incontinence), or symptoms associated with cardiomyopathy (e.g., shortness of breath, fatigue). The degree of correlation between the PND score, other aspects of the disease, and quality of life is unclear. The PSCR acknowledged that PND score may not capture all aspects of hATTR amyloidosis disease but argued that alternative measures such as the Neuropathic Impairment Scale (NIS) and the Norfolk Quality of Life - Diabetic Neuropathy (Norfolk QoL-DN) questionnaire are unsuitable for modelling due to the lack of established cut-off scores with known clinical importance. The PSCR claimed that the NIS and Norfolk QoL-DN questionnaire scores are correlated with the PND score. However, the ESC considered that the degree of correlation between advancing PND score, and other aspects of the disease (e.g., sensory issues, autonomic dysfunction, cardiomyopathy) is unclear. On balance the ESC agreed with the sponsor that PND score would likely produce the best health states to base the economic model on.

- 6.50 In the model, patients begin in either the PND I, PND II, PND IIIA or PND IIIB health states based on the distribution of patients at baseline in the APOLLO trial. Each cycle, patients can remain in the same health state, transition to an improved PND health state, transition to a worse PND health state, or die. All patients in the patisiran arm start on treatment and can discontinue treatment. Patients who discontinue treatment remain off treatment for the duration of the model.
- 6.51 Transitions between health states were derived from individual patient data from the APOLLO trial and the Global OLE study. Transitions beyond 54 months in the patisiran arm were assumed to be the same as for Months 42 to 54 in the Global OLE study. Transitions beyond 18 months in the BSC arm of the APOLLO trial were assumed to be the same as the transitions over the initial 18 months in the APOLLO trial. Due to the relatively small number of patients in the APOLLO trial, there was sparse data informing many of the transitions. A substantial amount of extrapolation of the transition probabilities was required in the model (from 18 months for the placebo arm in the APOLLO trial and 54 months for the patisiran arm in the APOLLO trial/Global OLE study to 40 years in the model). While treatment with patisiran may provide long-term benefits, current evidence on the duration and magnitude of benefit is lacking. Due to differences in mortality risk associated with the different PND scores in the model, treatment with patisiran in the model was associated with a survival benefit, as disease progression among patients in the patisiran arm was slower than for patients in the BSC arm.
- 6.52 Patients in the patisiran arm transitioning into the PND IV health state were assumed to cease treatment. While this assumption matched the proposed PBS restriction, it differed from the protocols for the APOLLO trial and the Global OLE study, which did

- not require patients with a PND score of IV to cease treatment. Patients and clinicians may be reluctant to cease treatment with patisiran in PND IV if treatment is still considered to be providing a benefit, e.g. by slowing the rate of disease progression.
- 6.53 A multivariate regression analysis of mortality data from ALN-TTR02-003, the APOLLO trial, and the Global OLE study was used to estimate a hazard ratio for mortality by PND health state, using PND I/II as a reference group. The submission assumed that patients with a PND score of 0, I or II would experience the same mortality risk as patients in the general population. This assumption was not adequately justified and lacked face validity. Additionally, the assumption that mortality risk was related to PND score only may not be reasonable, as other aspects of the condition including the presence of cardiomyopathy would also impact the mortality risk. The ESC noted that the NICE submission model included additional mortality multipliers for patients with cardiomyopathy, however, these multipliers were not included in the submission model.
- 6.54 Health state utilities in the model were estimated from a mixed model for repeated measures (MMRM) regression analysis of EQ-5D data from the APOLLO trial. The estimated mean utility value for patients in PND IV was negative (-0.0038), indicating quality of life worse than death. No published estimates of utility values based on PND health states were presented in the submission to validate the derived health state utilities. The ESC considered that the estimated utility for PND IV (-0.0038) may be considered appropriate in the context of a disease that has profound effects on QOL, as observed in patients with hATTR amyloidosis with polyneuropathy due to symptoms such as progressive muscle failure, loss of ambulation and inanition.
- 6.55 The submission argued that the quality of life of patients with hATTR amyloidosis with polyneuropathy can vary while remaining in the same PND health state and presented a series of post hoc analyses of the APOLLO trial in which the mean change from baseline in health-related quality of life outcomes for patients who maintained the same PND score were compared between patisiran and placebo. The submission noted that the results of the analysis suggest that for patients who did not change PND score during the APOLLO trial, the mean EQ-5D utility increased for those treated with patisiran and decreased for those treated with placebo.
- 6.56 Interaction coefficients between time and treatments in the MMRM regression analysis were used to estimate the trend in utilities over time observed for patisiran and BSC. Based on the results of the regression analysis, the submission applied a utility increment of 0.0029 each month for patients remaining on treatment with patisiran, and a utility decrement of 0.0092 each month for patients not receiving treatment with patisiran. In the model, the impact of the cumulative utility increments and decrements was constrained by applying maximum and minimum utility values, respectively, for each PND score.

- 6.57 Health state utilities did not reset to the average health state utility when a patient transitioned into a new health state. This did not appear to be reasonable, as this assumption appeared to disregard the results of the regression analysis. Instead, the applied utility for transitioning patients was the starting health state utility plus the treatment-related utility increment/decrement multiplied by the number of months since model initiation.
- 6.58 Table 10 presents the maximum and minimum utilities by PND score included in the economic model.

Table 10: Maximum and minimum health state utility values included in the economic model

Health state	Average utility value ^a	Minimum utility value	Maximum utility value ^b
PND 0	0.6840	0.625	1.000
PND I	0.6460	0.375	0.921
PND II	0.4780	0.126	0.733
PND IIIA	0.3531	-0.075	0.642
PND IIIB	0.1746	-0.254	0.441
PND IV	-0.0038	-0.593	0.297

Source: Table 3.18, p115 of the submission.

Abbreviations: PND, polyneuropathy disability.

^a Average health state utilities derived from the APOLLO trial.

^b An additional cap was applied to ensure that the utilities did not exceed the Australian general population utility (0.89 for patients aged 55-65 years and 0.87 for patients aged 65-74 years).

- 6.59 Application of the treatment-related utility increments and decrements resulted in health state utilities for each PND score that differed substantially from the estimated average health state utilities. While the minimum and maximum utility caps limited the time dependent utility, the range of permitted values was wide, and the adjusted health state utilities were able to exceed the average health state utilities of adjacent PND health states.
- 6.60 In the BSC arm, patients in the PND I state reached the minimum utility of 0.375 after 3.0 years, patients in the PND II state reached the minimum utility of 0.126 after 4.0 years, patients in the PND IIIA state reached the minimum utility of -0.075 after 4.5 years, patients in the PND IIIB state reached the minimum utility of -0.254 after 4.5 years, and patients in the PND IV state reached the minimum utility of -0.593 after 6.0 years. The ESC considered that the approach to the modelling produced utilities values that were not plausible.
- 6.61 The minimum utility values for patients in the patisiran arm who discontinued treatment were adjusted based on the cycle in which treatment discontinuation occurred. This appeared to introduce a bias in favour of the patisiran arm, as the adjustment resulted in higher minimum utilities for patients discontinuing treatment in the patisiran arm, compared to the minimum utilities that could be achieved in the best supportive care arm.
- 6.62 An additional disutility to reflect autonomic dysfunction was applied each cycle for patients in PND II to PND IV who were not receiving treatment with patisiran (i.e., patients in the BSC arm and patients in the patisiran arm who had ceased treatment).

Disutilities were sourced from a published catalogue of UK EQ-5D disutilities (Sullivan et al., 2011). For patients not receiving patisiran, a disutility of 0.0727 was assumed each cycle for patients in PND II, and a disutility of 0.1243 was assumed each cycle for patients in PND IIIA, PND IIIB or PND IV. The inclusion of a separate disutility to reflect autonomic dysfunction was poorly supported, given that autonomic dysfunction would already be captured by the average health state utility scores, and by the additional health state increments/decrements applied for being on/off treatment with patisiran. The PSCR stated that the inclusion of disutility for autonomic dysfunction was consistent with patient input which described the significant personal impacts of the condition, such as loss of dignity associated with gastrointestinal symptoms and inability to attend family gatherings, and stated this approach was validated by clinical experts in the UK. It was also noted that APOLLO had demonstrated significant improvements in favour of patisiran over BSC for autonomic neuropathy symptoms (including diarrhoea, male erectile dysfunction and fainting, measured with COMPASS-31).

- 6.63 The PSCR stated that additional utilities/disutilities were included in the model to better capture the effects of treatment with patisiran, and autonomic symptoms experienced by patients.
- 6.64 The submission base case included anniversary price reductions applied to the patisiran drug costs. Anniversary price reductions were excluded from the base case presented in these PSD. The PBAC agreed with the ESC that anniversary price reductions should not be included in the model.
- 6.65 Key drivers of the economic model are summarised in Table 11.

Table 11: Key drivers of the model

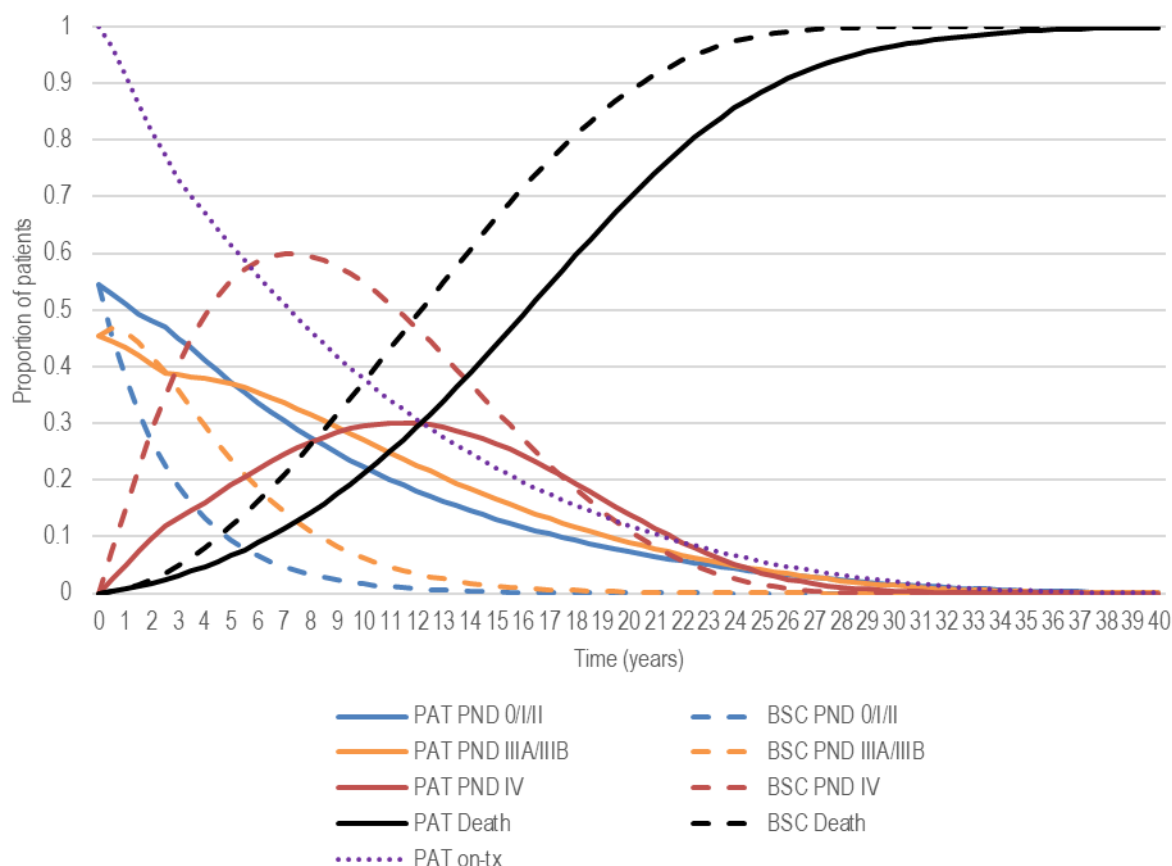
Description	Method/Value	Impact
Time horizon	The submission base case incorporated a 40-year time horizon. There was substantial uncertainty associated with the extrapolation of the transition probabilities. Due to differences in mortality risk associated with the different PND scores in the model, treatment with patisiran in the model was associated with a survival benefit, as disease progression among patients in the patisiran arm (informed by the extrapolated transition probabilities) was slower than for patients in the BSC arm. While treatment with patisiran may provide long-term benefits, current evidence on the duration and magnitude of benefit is lacking.	Moderate, favours patisiran
Disease-related mortality	The submission assumed that patients with a PND score of 0, I, and II would experience the same mortality risk as patients in the general population. Mortality for patients in PND IIIA/IIIB was assumed to be 1.90 x the general population mortality and mortality for patients in PND IV was assumed to be 9.42 x the general population mortality. The modelled survival for the BSC arm (12 years) was substantially longer than the median survival from diagnosis of 4.7 years reported by Swiecicki et al. (2015) for patients with hATTR amyloidosis.	High, favours patisiran
Treatment-related utility increments/decrements	The submission applied a utility increment of 0.0029 each month for patients remaining on treatment with patisiran, and a utility decrement of 0.0092 each month for patients not receiving treatment with patisiran. Application of the treatment-related utility increments and decrements resulted in health state utilities for each PND score that differed substantially from the estimated average health state utilities. While the minimum and maximum utility caps limited the time dependent utility, the range of permitted values was wide and the adjusted health state utilities were able to exceed the average health state utilities of adjacent PND health states.	High, favours patisiran
Autonomic dysfunction disutilities	A disutility was applied to reflect autonomic dysfunction occurring in patients receiving BSC and in patients who discontinue patisiran. The inclusion of a separate disutility to reflect autonomic dysfunction was poorly supported, given that autonomic dysfunction would already be captured by the health state utility scores, and by the additional health state increments/decrements applied for being on/off treatment with patisiran.	Moderate, favours patisiran

Source: Constructed during the evaluation.

Abbreviations: BSC, best supportive care; PND, polyneuropathy disability.

6.66 Model traces for the patisiran and BSC arms are presented in Figure 4.

Figure 4: Model traces for the patisiran and BSC arms



Source: Constructed during the evaluation using the Section 3 economic model Excel workbook.
Abbreviations: BSC, best supportive care; PAT, patisiran; PND, polyneuropathy disability.

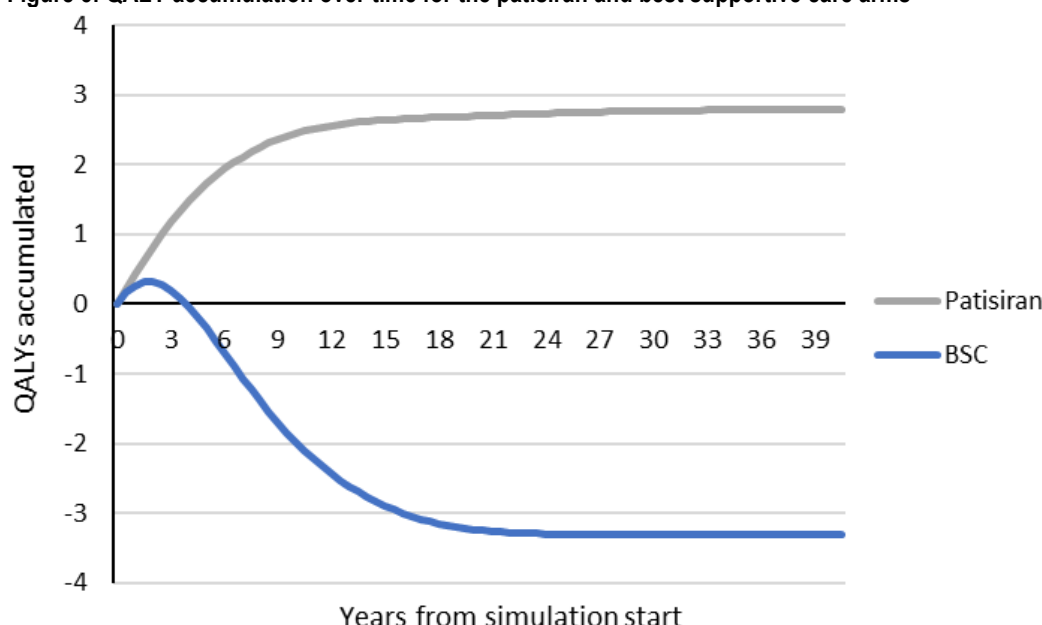
- 6.67 Median survival for patients in the patisiran arm was longer than for patients in the BSC arm (approximately 16 years for the patisiran arm versus approximately 12 years for the BSC arm). The modelled survival for the BSC arm was substantially longer than the median survival from diagnosis of 4.7 years reported by Swiecicki et al. (2015) for patients with hATTR amyloidosis (noting that patients in the APOLLO trial were diagnosed, on average, 2.5 years prior to the commencement of the trial).
- 6.68 The PSCR noted that the estimate of 4.7 years from diagnosis reported by Swiecicki et al., was based on a retrospective assessment of 266 patients with hATTR amyloidosis who presented to the Mayo Clinic in Rochester, USA over a 43-year period. The PSCR suggested that the discrepancy in median survival reported in this study versus modelled median survival in the submission is likely due to two reasons. Firstly, an improvement in diagnostics and family screening leading to earlier diagnosis. Secondly, the presence of patients with more advanced heart failure (including patients with NYHA Class III-IV HF) in the Mayo Clinic cohort compared to the model cohort (based on the APOLLO trial, which explicitly excluded patients with NYHA Class III-IV HF). While it is acknowledged that survival outcomes would be expected to be

impacted by NYHA Class, the proposed PBS restriction did not exclude patients with NYHA Class III and IV heart failure (see paragraph 3.13).

6.69 Patients in the patisiran arm spent a higher proportion of time in less severe PND health states (i.e., PND I-IIIb) compared to the BSC arm, whereas patients in the BSC arm spent a substantially higher proportion of time in PND IV. The time spent in PND IV by patients in the BSC arm (8.1 years) lacked face validity, as survival among patients with a PND score of IV is likely to be poor.

6.70 Figure 5 presents a plot of the QALY accumulation over time by treatment arm.

Figure 5: QALY accumulation over time for the patisiran and best supportive care arms



Source: Figure 3.11, p137 of the submission.
Abbreviations: BSC, best supportive care.

6.71 The results of the modelled economic evaluation, excluding anniversary price reductions for patisiran, are summarised in Table 12.

Table 12: Results of the economic evaluation

Component	Patisiran	BSC	Increment
Costs	\$1	\$415,534	\$1
LYs	10.863	9.033	1.830
QALYs	2.786	-3.310	6.095
Incremental cost QALY gained			\$1 [†]

Source: Section 3 economic evaluation Excel workbook.

Note: The submission's base case included anniversary price reductions at 5 years (5%), 10 years (5%) and 15 years (30%). These reductions were removed during the evaluation. Results inclusive of anniversary price reductions are presented as a sensitivity analysis.

The redacted values correspond to the following ranges:

[†]\$255,000 to < \$355,000

6.72 Based on the economic model, treatment with patisiran was associated with an incremental cost per QALY gained of \$255,000 to < \$355,000 compared to BSC. The submission estimated an incremental cost per QALY gained of \$255,000 to < \$355,000

compared to BSC (inclusive of anniversary price reductions for patisiran). Due to the accrual of negative QALYs in the best supportive care arm (total QALYs of -3.310), the incremental difference in QALYs (6.095 QALYs) was larger than the incremental difference in life years (1.830 life years).

- 6.73 The difference in total cost between treatment arms was primarily driven by the patisiran drug costs. The difference in health outcomes was primarily driven by the time spent in the PND IV versus other PND health states (patients in the BSC arm spent a higher proportion of time in the PND IV state, resulting in accrual of a large number of negative QALYs).
- 6.74 In the model, 70% of incremental QALYs, 50% of patisiran drug costs (drug costs, administration costs, premedication costs), and 42% of incremental disease management costs (health care resource use, adverse event costs, end of life care costs) were accrued in the extrapolated period beyond 4.5 years (corresponding to the duration of follow-up for the patisiran arm in the APOLLO trial and Global OLE).
- 6.75 For every 10 patients treated with patisiran versus BSC and followed up for 40 years, the economic evaluation (without discounting) estimated that there would be:
- Additional patisiran drug costs of \$20 million to < \$30 million (drug costs, administration costs, premedication costs) and a reduction in disease management costs of \$0 to < \$10 million (health care resource use, adverse event costs, end of life care costs).
 - An additional 38.4 years of life lived and an additional 89.9 quality-adjusted life years lived.
 - An additional 3 serious occurrences of diarrhoea, 2 fewer serious occurrences of acute kidney injury, and 2 fewer serious occurrences of urinary tract infection.
- 6.76 The results of key sensitivity analyses presented in the submission and conducted during the evaluation are summarised in Table 13.

Table 13: Results of sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER	% change
Base case^a	\$	6.095	\$ ¹	-
Discount rate (base case: 5% costs and outcomes)				
0% costs and outcomes	\$	8.988	\$ ¹	-5%
3.5% costs and outcomes	\$	6.785	\$ ¹	-2%
Time horizon (base case: 40 years)				
10 years	\$	4.427	\$ ¹	7%
20 years	\$	5.935	\$ ¹	-1%
30 years	\$	6.084	\$ ¹	0%
Patisiran anniversary price reductions (base case: excluded¹)				
Included (5% at 5 years, 5% at 10 years, 30% at 15 years)	\$	6.095	\$ ¹	-6%
Baseline PND score distribution (base case: PND 0: 0%, PND I: 25.0%, PND II: 29.5%, PND IIIA: 28.1%, PND IIIB: 17.4%, PND IV: 0%).				
AAN distribution population (PND 0: 0%, PND I: 54.7%, PND II: 24.5%, PND IIIA: 7.5%, PND IIIB: 13.2%, PND IV: 0%).	\$	6.505	\$ ¹	0%
Patisiran treatment duration (base case: exponential extrapolation; treatment ceased in PND IV)				
Log-normal	\$	6.723	\$ ¹	3%
Mortality (base case: PND 0/II: same as general population; PND IIIA/IIIB: 1.90 x PND 0/II; PND IV: 9.42 x PND 0/II)				
PND 0/II: 2.00 x general population; PND IIIA/IIIB: 1.90 x PND 0/II; PND IV: 9.42 x PND 0/II	\$	5.047	\$ ¹	14%
PND 0/II: 3.00 x general population; PND IIIA/IIIB: 1.90 x PND 0/II; PND IV: 9.42 x PND 0/II	\$	4.422	\$ ²	24%
PND 0/II: 4.00 x general population; PND IIIA/IIIB: 1.90 x PND 0/II; PND IV: 9.42 x PND 0/II	\$	3.980	\$ ²	31%
PND 0/II: 5.00 x general population; PND IIIA/IIIB: 1.90 x PND 0/II; PND IV: 9.42 x PND 0/II	\$	3.641	\$ ²	36%
Starting health state utilities (base case: PND 0: 0.684; PND I: 0.646; PND II: 0.478; PND IIIA: 0.353; PND IIIB: 0.175; PND IV: -0.004)				
All states increased by 0.1	\$	6.097	\$ ¹	0%
All states decreased by 0.1	\$	5.925	\$ ¹	3%
Treatment-related utility increment/decrement (base case: on treatment: 0.003; BSC/off treatment: -0.009)				
Treatment-related utility increment/decrement removed	\$	2.339	\$ ³	161%
Treatment-related utility increment/decrement halved	\$	4.906	\$ ²	24%
Minimum/maximum utilities (base case: PND 0: 0.625/1.000; PND I: 0.375/0.921; PND II: 0.126/0.733; PND IIIA: -0.075/0.642; PND IIIB: -0.254/0.441; PND IV: -0.593/0.297)				
Minimum and maximum based on average health state utility +/- 0.15	\$	4.650	\$ ²	31%
Minimum and maximum based on average health state utility +/- 0.10	\$	4.205	\$ ²	45%
Minimum and maximum based on average health state utility +/- 0.05	\$	3.665	\$ ⁴	66%
Limit utilities to 0 for each PND health state (i.e., no negative utilities for PND health states)	\$	4.712	\$ ²	29%
Limit utilities to 0 (i.e., no negative utilities after disutilities applied)	\$	3.857	\$ ⁴	58%
Carer disutilities (base case: not included)				

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Analyses	Incremental cost	Incremental QALY	ICER	% change
Included (PND I: -0.003; PND II, IIIA, IIIB: -0.028; PND IV: -0.250)	\$ ¹	6.639	\$ ¹	-8%
Autonomic dysfunction disutility (base case: PND II: -0.0727; PND IIIA, IIIB, IV: -0.1243)				
Removed	\$ ²	5.163	\$ ¹	18%
Patisiran treatment in PND IV (base case: treatment discontinued in PND IV)				
Treatment continued in PND IV	\$ ³	6.601	\$ ¹	5%

Source: Constructed during the evaluation using the Section 3 economic model Excel workbook.

Abbreviations: AAN, Australian Amyloidosis Network; PND, polyneuropathy disability.

^a Anniversary price reductions include in the submission's base case removed.

The redacted values correspond to the following ranges:

¹\$255,000 to < \$355,000

²\$355,000 to < \$455,000

³\$755,000 to < \$855,000

⁴\$455,000 to < \$555,000

- 6.77 The modelled results were most sensitive to changes in the mortality risk, the application of treatment-related utility increments/decrements for being on/off treatment with patisiran, and the assumed minimum and maximum health state utilities.
- 6.78 The ESC noted that the submission provided a sensitivity analysis incorporating the impact of carer disutilities. The submission stated that caring for patients with hATTR amyloidosis with polyneuropathy is challenging and is understood to impact caregiver health-related quality of life, by negatively affecting their physical and mental health, and by requiring vast amounts of time, reducing their ability to be productive and function socially. The submission noted that inclusion of caregiver disutilities that were accepted by NICE in the appraisal of patisiran reduced the ICER by 8% from the base-case analysis (Table 13).
- 6.79 The ESC noted that numerous concerns about the economic model had been identified during the evaluation. The ESC considered that the main concerns were:
- Model health states were defined by PND scores which are solely based on mobility status and may not adequately capture all aspects of the condition, including sensory issues (e.g., numbness, tingling and pain), autonomic symptoms (e.g., dizziness or fainting, impotence, constipation, diarrhoea, faecal/urinary incontinence), or symptoms associated with cardiomyopathy (e.g., shortness of breath, fatigue). The ESC considered that a model structure based on PND scores was appropriate, despite the limitations described, however considered that the submission's approach which applied additional monthly decrements/increments based on treatment category (paragraphs 6.54 to 6.61), as well as an additional disutility for autonomic dysfunction (paragraph 6.62), was not appropriate.
 - The model time horizon was 40 years in the base case, which was associated with considerable uncertainty given the limited clinical evidence available to inform the model, which included a relatively short period of trial evidence (up to 18

months for placebo and up to 54 months for patisiran) and a relatively limited clinical trial population size (n=225 in APOLLO).

- The ESC noted that while the model was relatively insensitive to the time horizon because the impact was overshadowed by other assumptions of the model (see Figure 5), a shorter time horizon in the order of 10-15 years was likely to have been more appropriate, given the uncertainty in the data. In the model, 70% of incremental QALYs, 50% of patisiran drug costs (drug costs, administration costs, premedication costs), and 42% of incremental disease management costs were accrued in the extrapolated period beyond 4.5 years (corresponding to the duration of follow-up for the patisiran arm in the APOLLO trial and Global OLE). The ESC noted that the model traces for the patisiran and BSC arms prepared during evaluation, showed the impact of the 40 year time horizon, and that convergence of the survival curves did not occur until approximately 35 years of the modelled period (Figure 4).
 - Patients transitioning to PND IV are assumed to discontinue treatment, which may not be adhered to in clinical practice.
 - The mortality benefit incorporated in the economic model was uncertain. The ESC noted that a significant improvement in overall survival had not been demonstrated by the clinical evidence, whilst recognising that there was a trend suggestive of improvement (see paragraph 6.32). The ESC considered that the submission's approach to modelling survival relied on key assumptions that had not been validated. The model assumed PND categories 0/I/II had mortality equal to general population. The ESC considered there was no evidence provided to support this, and it may overestimate the survival benefits for patisiran. Mortality multipliers were applied for PND IIIA/IIIB and PND IV in the model, which assumes that mortality risk only applies to patients with substantial mobility impairment requiring at least one stick or crutch (where PND IIIA refers to a patient able to walk but requiring at least one stick or crutch) or patient is confined to wheelchair or bedridden (PND IV). The ESC noted that alternative inputs were tested in sensitivity analyses (Table 13), however these did not address the uncertainty associated with the model structure, which inherently assumed that progression to worse PND health states increased mortality risk compared with PND categories 0/I/II (which did not account for potential increases in mortality risk within those categories). The ESC considered that data from the trial could be used to inform mortality estimates for all PND states compared with the general population.
- 6.80 The pre-PBAC response defended the use of a regression analysis for utilities and autonomic dysfunction-related disutilities as applied in the submission. The response stated that PND score does not accurately capture autonomic dysfunction or other changes in patients' clinical status that may impact their HRQoL and that patients'

HRQoL can change substantially without a change in PND score. For example, a patient in PND IIIA (defined by the need for one stick or crutch to walk) may experience improvement in pain, numbness, or tingling in their arms and hands (associated with neuropathy) within a certain timeframe, thereby improving their HRQoL, even if they are not able to stop using a walking stick during the same period and therefore maintain the same PND score. It was noted that patisiran-treated patients showed improvement across multiple outcomes relating to HRQoL (EQ-5D, Norfolk QoL-DN, Composite Autonomic Symptom Score [COMPASS-31], and R-ODS) compared to placebo even in patients whose PND score remained constant over the course of APOLLO. The response also reiterated the debilitating effects of autonomic dysfunction and the need to apply a disutility for autonomic dysfunction as an additional modelling step due to the limitations of EQ-5D in capturing these effects, and given that the previously described regression model for estimating utility values as a function of PND score and the interaction of treatment with time was informed solely by EQ-5D utility.

Drug cost/patient/year

6.81 Table 14 presents the drug costs for patisiran included in the economic model and financial estimates. The cost of BSC in the economic model and the financial estimates was assumed to be nil.

Table 14: Drug cost per patient for patisiran

	APOLLO trial	Economic model	Financial estimates
Treatment regimen	0.3 mg/kg to a maximum of 30 mg every 3 weeks	0.3 mg/kg to a maximum of 30 mg every 3 weeks	0.3 mg/kg to a maximum of 30 mg every 3 weeks
Cost per dose	-	\$ ^a	\$ ^a
Adherence	Relative dose intensity: 0.969	96.9%	96.9%
Cost per year	-	\$ ^b	\$ ^b
Proportion of patients on treatment (persistence)	92.6% of patients remained on treatment at 18 months	Year 1: 94% ^c Year 2: 84% ^c Year 3: 75% ^c Year 4: 69% ^c Year 5: 63% ^c Year 6: 57% ^c	Year 1: 100% ^d Year 2: 100% ^d Year 3: 100% ^d Year 4: 100% ^d Year 5: 100% ^d Year 6: 100% ^d

Source: Table 10, p80 of the APOLLO trial clinical study report; 'Costs' and 'Markov Patisiran' tabs of the economic model Excel workbook; '3a. Scripts – proposed' tab of the financial implications Excel Workbook.

^a Based on the proposed AEMP of \$[REDACTED] per 10 mg vial, assuming 2.38 vials per treatment.

^b Based on the proposed patisiran AEMP of \$[REDACTED] per 10 mg vial, assuming 2.38 vials per treatment, 17.39 treatments per year (365.25 ÷ 21), and treatment adherence of 96.9%.

^c Inclusive of half-cycle correction.

^d A treatment duration of 72.27 months was assumed in the financial implications Excel workbook, which resulted in 100% treatment persistence over the initial 6 years of listing. The source of the estimated treatment duration was unclear.

Estimated PBS usage & financial implications

6.82 This submission was considered by DUSC.

6.83 The submission used an epidemiological approach to estimate the utilisation and financial impacts associated with listing patisiran for the treatment of patients with hATTR amyloidosis with polyneuropathy.

6.84 Key sources of data used to derive the financial estimates are presented in Table 15.

Table 15: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Number of prevalent hATTR amyloidosis patients by PND score	PND 0: 59; PND I: 29; PND II: 13; PND IIIA: 4; PND IIIB: 7; PND IV: 1; PND unknown: 17. Based on data obtained from the AAN, comprising 4 treatment centres and 3 affiliate services, collected from clinic databases spanning 2007-2022.	Correspondence from the AAN indicated that: - The centres included in the network do not see every case of hATTR amyloidosis in Australia, as even if a case is diagnosed, they are not necessarily referred to an AAN service. - The numbers are an underestimate due to hereditary amyloidosis being an under-recognised and under-diagnosed disorder. The PSCR acknowledged that there is underdiagnosis of hATTR amyloidosis, recognising that detection may increase with clinical trial activity and introduction of MBS item (73422). DUSC agreed with the commentary that the prevalent patient data from the AAN is underestimated. It was noted that the sponsor had not used prevalence rates from available literature, and this may have been more appropriate. DUSC agreed with the commentary that the availability of MBS-funded genetic testing and the PBS listing of a disease-modifying treatment may lead to an increase in diagnostic testing and may identify greater numbers of patients at early stages of disease. DUSC suggested using prevalent rates from available literature to make changes to prevalent population numbers. Noting that when taking a prevalent patient approach there is no need to include incident population, as they are already captured in the prevalence estimates.
Distribution of patients by PND score	PND 0: 52% PND I: 26% PND II: 12% PND IIIA: 4% PND IIIB: 6% PND IV: 1% Derived by dividing the number of prevalent hATTR amyloidosis patients in each PND score category by the total number of prevalent patients with a known PND score (113 patients).	DUSC considered that despite only capturing one dimension of disease, the use of PND as the marker was reasonable.
Distribution of patients with unknown PND	Derived by assuming that the PND score distribution among patients with an unknown PND score is the same as for patients with a known PND score.	This appeared reasonable.

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Parameter	Value applied and source	Comment
Patients currently treated with patisiran	11 patients Data provided by the sponsor.	The submission stated that patients in Australia currently enrolled in clinical trials or receiving patisiran via an alternative access scheme should receive PBS-funded treatment once patisiran is PBS-listed.
Number of patients requiring treatment (patients who are not currently on treatment)	PND I/II: 23; PND IIIA/IIIB: 11; Unknown: 8. PND I/II patients not currently treated estimated based on data from the AAN. In the absence of data, the submission assumed that all patients with PND IIIA/IIIB, and all unknown patients assumed to have a PND score of I/II/IIIA/IIIB are not on treatment.	There may be additional patients currently receiving treatment with alternative hATTR treatments who will switch to patisiran if it is listed on the PBS. DUSC noted that use outside of the indication is likely, which would further add to the numbers of patients seeking treatment.
Prevalent PND 0 patients requiring treatment within 5 years	16 patients. Assumption. Out of 56 patients with PND 0 who are not currently on treatment, 16 are assumed to require treatment in the next 5 years.	The submission assumed that these patients would progress to PND I or higher at a constant annual rate over the next 5 years (i.e., 3.2 patients annually). DUSC considered that PND and FAP are both subjective and availability of the medicine could affect assessment with more patients graded as PND 1 rather than 0.
Incident patients	10 per year. Assumption based on data provided by the Australian Amyloidosis Network which indicated 10 newly diagnosed patients in 2021 and 2022.	There may be additional incident patients managed outside of the AAN. The submission noted that the addition of genetic testing for neuromuscular disorders to the MBS (Item 73422) is likely to increase the detection rate of hATTR amyloidosis. The PSCR commented that the possibility of enrolment into clinical trials over the last few years has likely increased diagnosis rates. However, the sponsor agreed that underdiagnosis of hATTR amyloidosis could occur in Australia, which may be addressed by the introduction of MBS item 73422. The utilisation estimates thus represent a lower bound of plausible incidence estimates for patients diagnosed over the coming years. DUSC commented that the estimated number of incident patients is likely underestimated.
Incident patient PND score	PND 0: 67.05%; PND I: 32.95%. Assumption based on the proportion of patients with PND 0 and PND I disease, the submission assumed that 6.7 of the 10 incident patients each year are in PND 0 and 3.3 patients are in PND I.	Incident patients who are initially diagnosed in PND 0 are also likely to require treatment in subsequent years (i.e., following progression to a worse PND score). Treatment of these patients in subsequent years was not included in the submission estimates.
Uptake rate (prevalent patients)	Yr 1: 11%; Yr 2: 11%; Yr 3: 11%; Yrs 4-6: 11%. Assumption.	Uptake may be higher than estimated given the lack of other available treatment options. A resubmission for tafamidis, for the treatment of patients with cardiomyopathy associated with hATTR or wtATTR was considered at the July 2023 PBAC meeting. There is potential for overlap between the two submissions, as patients with hATTR amyloidosis may experience symptoms of polyneuropathy, cardiomyopathy, or both. DUSC agreed with the commentary that the uptake rates are underestimated. DUSC commented that the uptake

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Parameter	Value applied and source	Comment
		rate should start at █% and increase progressively to █% by Year 6 of listing
Uptake rate (incident patients)	Yrs 1-6: █%. Assumption.	Uptake may be higher than estimated given the lack of other available treatment options. DUSC commented that the uptake rate of incident patients is not required when a prevalence-based approach is used.
Treatment duration	72.27 months. Assumption.	The source of the treatment duration estimate was unclear. DUSC commented this parameter is not required in applying a prevalence-based only approach to estimate the utilisation.
Treatment adherence	96.9%. Based on the relative dose intensity for patisiran reported in the APOLLO trial, calculated as the ratio of the cumulative number of doses received divided by the total number of doses.	Treatment adherence is likely to be lower in clinical practice compared to the clinical trial. DUSC commented that the high treatment adherence rate was reasonable. Noting that it is likely high due to the treatment being an infusion.
Vials per administration	2.38 vials per administration per patient. An average of 2.38 vials per administration was assumed, based on a patisiran dose of 0.3 mg/kg (to a maximum of 30 mg) and a body weight distribution among patients who did not have a Val30Met mutation (34-66kg: 62%; ≥67 kg: 38%).	While the method used to calculate the dose appropriately accounted for wastage, there may be differences in the body weight distribution between patients in the APOLLO trial and the Australian PBS population which may impact the average number of vials used.
Patisiran costs	\$█. Requested effective DPMQ for Section 100 public hospital listing.	The submission estimated costs assuming a public hospitals listing only. The dispensed cost would be higher for a private hospital listing, due to additional fees and mark-ups associated with private hospital supply of PBS items.
Administration costs	\$89.92. MBS Item 13950 (parenteral administration of one or more antineoplastic agents), 80% of Schedule fee.	The assumed cost was not reasonable given that patisiran is not an antineoplastic agent. DUSC considered that the administration costs were unclear, noting that in some rural areas MBS costs might be incurred.
Genetic test	MBS Item 73422 (genetic testing for neuromuscular disorders) was described in submission but no increase in utilisation was assumed	This may not be reasonable as the availability of an effective treatment may contribute to higher rates of testing for hATTR amyloidosis.

Source: Section 4, pp150-160 of the submission; Section 4 financial implications Excel workbook.

Abbreviations: AAN, Australian Amyloidosis Network; DPMQ, dispensed price for maximum quantity; hATTR, hereditary transthyretin-mediated amyloidosis; IV, intravenous; PBAC, Pharmaceutical Benefits Advisory Committee; PND, polyneuropathy disability; wtATTR, wild-type transthyretin-mediated amyloidosis; Yr, Year.

The redacted values correspond to the following ranges:

¹ < 500

6.85 The estimated net cost to the PBS/RPBS of listing patisiran based on the proposed effective price is presented in Table 16. Sensitivity analyses prepared by the DUSC Secretariat are also provided.

Table 16: Estimated utilisation and net cost of listing patisiran

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Total treated patients	¹	¹	¹	¹	¹	¹
Total scripts (16.85 per year)	¹	²	²	²	²	²
Net cost to PBS/RPBS (\$)	³	³	⁴	⁴	⁴	⁴
Net cost to the MBS	³	³	³	³	³	³
Net cost to the PBS/RPBS/MBS (\$)	³	³	⁴	⁴	⁴	⁴
Sensitivity analyses						
Removing incident patients (\$)	³	³	³	³	³	³
Assuming 30% of patients are not recorded on the registry (\$)	³	³	⁴	⁴	⁴	⁴
Uptake rate (base case assumed Yr 1: ¹ %; Yr 2: ¹ %; Yr 3: ¹ %; Yrs 4-6: ¹ %; Incident ¹ %)	³	³	⁴	⁴	⁴	⁴
Yr 1: ¹ %; Yr 2: ¹ %; Yr 3: ¹ %; Yrs 4-6: ¹ %						
Two-way sensitivity analysis: 30% of patients not recorded; Yr 1: ¹ %; Yr 2: ¹ %; Yr 3: ¹ %; Yrs 4-6: ¹ %	³	⁴	⁴	⁴	⁴	⁴

Source: Table 4.5, p155; Table 4.6, p155; Table 4.10, p157 of the submission; Section 4 financial implications Excel workbook.

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

6.86 The submission estimated a net cost to the PBS/RPBS/MBS of \$0 to < \$10 million in Year 1, increasing to \$10 million to < \$20 million in Year 6, an estimated net cost of \$60 million to < \$70 million over the first six years of listing. The sensitivity analyses resulted in higher estimates, up to \$80 million to < \$90 million over the first six years of listing (Table 16).

6.87 The estimated utilisation and financial impact to the PBS/RPBS appeared to be underestimated due to the following reasons:

- The number of prevalent and incident patients were derived from data supplied by the Australian Amyloidosis Network (AAN). Correspondence from the AAN indicated that the numbers were underestimates, as not all patients in Australia diagnosed with hATTR amyloidosis are referred to an AAN service.
- The addition of Item 73422 to the MBS (genetic testing for neuromuscular disorders), which includes identification of gene mutations in the transthyretin gene, is likely to increase the detection rate of hATTR amyloidosis. The availability of an effective treatment may also contribute to higher rates of testing for hATTR amyloidosis.

- There is potential for use outside of the proposed restriction among patients with earlier stage disease (i.e., PND 0) or among patients who have progressed to PND IV (i.e., patients and clinicians may be reluctant to cease treatment with patisiran in PND IV if treatment is still considered to be providing a benefit).
 - There may be additional patients currently receiving treatment with alternative hATTR treatments who will switch to patisiran if it is listed on the PBS.
 - Uptake rates may be higher than assumed in the submission due to the lack of alternative treatments available for hATTR amyloidosis.
 - The submission did not account for disease progression in the future among patients in the incident patient population with a PND score of 0 at diagnosis.
- 6.88 The pre-PBAC response provided revised estimates of the treatment-eligible population based on literature as suggested by DUSC. The response proposed estimates based on published prevalence data by Schmidt et al. (2018). Based on the Australian population (N=25,688,079 lives)⁸ and the high-end prevalence estimate from Schmidt et al. (7.52 per million), a total of 193 patients with hATTR amyloidosis with polyneuropathy in Australia was estimated. Applying the same proportion of patisiran-eligible patients from the prevalent pool of patients as demonstrated in the submitted AAN data (30.75%; see Table 17) and the incidence of 3.3 incident PND I patients per year, in addition to the < 500 patients who are currently receiving patisiran, resulted in totals of < 500, < 500, < 500, < 500, < 500, and < 500 treatment-eligible patients in Years 1, 2, 3, 4, 5, and 6 (compared to < 500, < 500, < 500, < 500, < 500 and < 500 patients in the original submission). Note, these figures refer to treatment-eligible patients, and not treated patients, with the difference being due to uptake rates.
- 6.89 Regarding uptake rates, the pre-PBAC response noted the higher rates of uptake proposed by DUSC in sensitivity analyses (Table 16). The pre-PBAC response stated that while the DUSC proposed higher rates of uptake in the prevalent population based on assumption, the rates of uptake in the original submission were based on observations from countries where patisiran has been reimbursed. The sponsor also stated it was open to a budget cap. The pre-PBAC response did not revise the uptake rates assumed in the submission.
- 6.90 The PBAC noted that several concerns about the financial estimates had been raised by the commentary and DUSC advice. The PBAC agreed with the DUSC that uptake rates appeared to be inappropriately low in the submission. The PBAC noted the DUSC sensitivity analyses proposed uptake rates of |% to |%, which appeared more likely.

⁸ The World Bank. Australia. <https://data.worldbank.org/country/AU>. Accessed 22 June 2023.

Table 17: Revised patient estimates based on data from the Australian Amyloidosis Network

Table 11: Revised patient estimates based on data from the Australian Amyotrophic Lateral Sclerosis Network						
Prevalent patient population						
PND score	Number of patients	Estimated patients*	Treated	Untreated	Distribution	Incident distribution
0	59	68	4	64	52.21%	67.05%
1	29	33	19	29	25.66%	32.95%
2	13	15			11.50%	
3A	4	5	2	3	3.54%	Incident distribution is calculated as the proportion of PND 0 or I patients divided by the sum of PND 0 and I patients.
3B	7	8	0	8	6.19%	
4	1	1	0	1	0.88%	
Unknown PND score	17	NA	NA	NA		
Total	130	130	25	105		
Total patisiran-eligible patients	40	Sum of untreated patients in PND I, II, IIIA, and IIIB (bolded in untreated column)				
Incident patient population						
Known PND 0 progressors in next 5 years	16					
Current PND 0 annual progressors	3.2 (16 patients over 5 years = 3.2 per year)					
Estimated annual new incident patients	10					
Incident patients at PND 0**	6.7					
Incident patients at PND 1**	3.3					

PND, polyneuropathy disability.

*Including redistributed patients with unknown PND score based on current distribution.

**Based on incident distribution column of table.

Source: Pre-PBAC response.

Quality Use of Medicines

- 6.91 No quality use of medicines issues were raised in the submission, and no activities to support the quality use of medicines were proposed. The DUSC considered that as patisiran was a first-in-class treatment, additional surveillance and education should be provided, and that current management guidelines should be revised.

Financial Management – Risk Sharing Arrangements

- 6.92 No risk-sharing arrangements were proposed.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend patisiran for treatment of patients with hATTR with polyneuropathy. The PBAC considered there was a high unmet need in the requested patient population, and that efficacy and safety of patisiran compared with BSC had been demonstrated by the clinical evidence, although there was a limited duration of randomised evidence. The PBAC considered that the submission had not demonstrated patisiran is cost-effective.

- 7.2 The primary reason for this outcome was due to the economic evaluation presented.
- 7.3 The PBAC noted the input from individuals and organisations and acknowledged there was a high unmet need for PBS subsidised treatment for this condition.
- 7.4 The PBAC considered the submission's nomination of BSC as the main comparator was appropriate.
- 7.5 The PBAC noted that the primary clinical evidence supporting the submission was APOLLO, a randomised, double blind, placebo controlled multicentre trial in patients with hATTR amyloidosis with polyneuropathy (n=225). The submission also presented supportive evidence from a phase 2 multiple ascending dose study (ALN-TTR02-002) and associated open label extension study (ALN-TTR02-003), as well as interim results from an ongoing global open label extension study (Global OLE, ALN-TTR02-006). Patients who completed studies ALN-TTR02-003 or the APOLLO trial were eligible to continue into the Global OLE study. The PBAC noted the APOLLO trial had demonstrated clinically meaningful improvements for patisiran compared with placebo, including the primary endpoint (neurological impairment, mNIS+7); and secondary endpoints (Health-related quality of life (Norfolk QoL-DN), weakness (NIS-W), disability (R-ODS), 10-MWT, mBMI, autonomic symptoms (COMPASS-31)). The PBAC noted that a significant improvement in overall survival had not been demonstrated in APOLLO, however considered there was a trend suggestive of improvement.
- 7.6 The PBAC considered that the claim of superior comparative efficacy of patisiran compared with BSC was reasonable based on the primary and secondary outcomes in APOLLO over the 18 month trial period (Table 5, Table 6), however the magnitude and duration of benefit remained uncertain. The PBAC considered that the global OLE study was supportive of ongoing benefit on efficacy endpoints (Figure 1, Figure 2, Figure 3). The PBAC considered that the long-term safety of patisiran was uncertain due to the limited duration of follow-up to date and the claim of non-inferior comparative safety of patisiran compared with BSC was not adequately supported by the data.
- 7.7 The PBAC considered the ICER estimated in the submission was high and uncertain. The PBAC noted ESC's concerns regarding robustness of the survival data, extrapolation methods, and application of treatment-related utility increments and decrements.
- 7.8 The PBAC noted that the submission applied a utility increment of 0.0029 each month for patients remaining on treatment with patisiran, and a utility decrement of 0.0092 each month for patients not receiving treatment with patisiran. The application of the treatment-related utility increments and decrements resulted in health state utilities for each PND score that differed substantially from the estimated average health state utilities derived in the MMRM regression analysis. Furthermore, the adjusted health state utilities were able to exceed the average health state utilities of adjacent PND

- health states and were able to fall below -0.5 (see Table 10). Removal of this increment/decrement resulted in an ICER of \$755,000 to < \$855,000 per QALY gained compared with \$255,000 to < \$355,000 per QALY gained in the base case (excluding anniversary price reductions).
- 7.9 The PBAC considered that the incremental QALY gain estimated by the submission was highly uncertain, however accepted the arguments in the pre-PBAC response that the definition of health states based on PND score did not adequately capture the full impact of the condition (paragraph 6.80). The PBAC considered that the submission's approach resulted in an overly optimistic estimate of incremental QALY gain, but in the context of a rare disease and significant unmet need, the submission's approach would be acceptable if the treatment-related utility increment/decrements were halved as proposed during the evaluation and the other matters discussed in paragraph 7.11 were addressed. The PBAC noted that halving these increments/decrements resulted in an ICER of \$355,000 to < \$455,000 per QALY gained (Table 13; excluding anniversary price reductions).
- 7.10 The PBAC noted that the submission provided a sensitivity analysis incorporating the impact of carer disutilities as discussed in paragraph 6.78. The PBAC noted that disease progression has a significant impact on caregivers and considered the sensitivity analysis was informative (Table 13).
- 7.11 Notwithstanding the remaining uncertainties with the economic model, but noting the high unmet clinical need in this rare disease, the PBAC foreshadowed that use of a respecified model would be appropriate in a resubmission if (i) the anniversary price reductions were removed (see paragraph 6.64); (ii) the treatment-related utility increments and decrements were halved (see paragraph 7.9); and (iii) the ICER was in the range \$220,000-\$250,000/QALY.
- 7.12 With regard to the utilisation estimates, the PBAC considered that the patient population was underestimated by the submission as discussed in 6.92 and Table 15. The PBAC considered that the revised estimates provided by the pre-PBAC response addressed these concerns, and that additional uncertainty could be addressed by a risk sharing arrangement which assumed % rebate for expenditure above agreed caps. The PBAC noted that the financial estimates would need to be updated to account for the additional fees and mark-ups associated with private hospital supply (see paragraph 3.3) of patisiran for a proportion of patients treated under the proposed listing (proportion to be estimated and justified by the resubmission).
- 7.13 The PBAC considered the Early Resolution resubmission should include a proposal to address the uncertain cost-effectiveness of patisiran including consideration of how patisiran is likely to be used in clinical practice. The resubmission should include a Risk Sharing Arrangement that includes a rebate above the financial expenditure caps (which the submission proposed), and also includes a Managed Access Program (MAP) which addresses key uncertainties in the economic model including the longer-term

clinical outcomes. The PBAC advised that the sponsor's proposal should define how the additional data could be incorporated in the economic model in the future to better assess the cost-effectiveness of patisiran. The PBAC considered that the proposal should focus on clinical outcomes that have a significant effect on cost effectiveness in the submission's economic model, such as survival and PND score. The PBAC considered this reassessment of cost-effectiveness should occur within 3 to 5 years after PBS listing.

- 7.14 The PBAC considered it would be valuable to seek input from the AAN regarding the data that could feasibly be collected as part of a MAP.
- 7.15 The PBAC considered that updated information from ongoing global clinical trials may be informative regarding long term effects of patisiran and could be proposed for consideration in a MAP. It was noted that for the Global OLE study (N=211), the most recent data cut provided in the submission was from January 2021 at which time 70% of patients were ongoing in the trial (148 of 211).
- 7.16 The PBAC considered the outstanding issues could be resolved in a simple resubmission for patisiran. The PBAC also considered patisiran addresses a high and urgent unmet clinical need and was expected to provide a substantial and clinically relevant improvement in efficacy/reduction of toxicity, over any alternative therapies. Therefore, the PBAC considered an early resolution pathway would be acceptable. If the sponsor accepts this pathway, the following changes may address these outstanding issues without requiring further re-evaluation.
- Revision of inputs in the economic model outlined in paragraph 7.11.
 - Revision of the financial estimates as discussed in paragraph 7.12 and recalculation of the financial implications using the revised patisiran price.
 - Submit a proposal for a managed access program (MAP) to address PBAC's concern regarding the uncertain cost-effectiveness as discussed in paragraphs 7.13 to 7.15).
- 7.17 The early resolution resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If the issues cannot be addressed by the sponsor in a simple resubmission and the early resolution timing is not acceptable, a standard re-entry pathway is available.
- 7.18 The PBAC gave the following advice with regard to the restriction:
- The proposed restriction is generally consistent with the eligibility criteria for the pivotal patisiran study (APOLLO), although the trial also excluded patients with a previous liver transplant, and patients with New York Heart Association (NYHA) heart failure classification of >2. The PBAC considered the proposed restriction should include these criteria for consistency with the trial population (see paragraph 3.13).

- Treatment with patisiran should be initiated by neurologists or by clinicians experienced in the treatment of amyloid with neurologist input to ensure correct diagnosis.
- It is unclear whether access to patisiran should be limited to clinical centres that are affiliated with the AAN. The sponsor is asked to address this matter as part of the proposed MAP proposal and add this information to the proposed restriction if applicable.
- The restriction should specify relevant information in the prescriber instructions concerning the clinical staging scales relevant to determining eligibility and ongoing treatment benefit.
- A grandfather restriction will be required (see paragraph 3.11)

7.19 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.

Addendum to the July 2023 PBAC PSD:

**7.01 PATISIRAN,
Solution concentrate for I.V. infusion 10 mg in 5 mL,
Onpattro®,
Alnylam Australia Pty Ltd**

10 Background

- 10.1 The early resolution resubmission requested a Section 100 (Highly Specialised Drugs Program) Authority Required (Written) listing for patisiran for the treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy. Patisiran was considered by the PBAC and not recommended for PBS listing at the July 2023 meeting. The PBAC considered there was a high unmet need in the requested patient population, and that efficacy and safety of patisiran compared with BSC had been demonstrated by the clinical evidence, although there was a limited duration of randomised evidence. The PBAC considered that the submission had not demonstrated patisiran was cost-effective. The PBAC considered that the outstanding issues could be addressed using the early resolution pathway if the matters were addressed as outlined in Table 18. A summary of the resubmission's approach to these matters is also provided in Table 18.

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Table 18: Issues to be addressed (July 2023 PBAC PSD)

Matter of Concern		Resubmission
Matters Raised by PBAC (PSD, para 7.16)		
1	Revision of inputs in the economic model outlined in paragraph 7.11. (i) Remove anniversary price reductions. (ii) Halve the treatment-related utility increments and decrements. (iii) ICER in the range \$220,000-\$250,000/QALY.	The resubmission proposed a revised base case which removed the anniversary price reductions but did not amend the utility increments/decrements. The ICER in the resubmission base case was \$¹/QALY. The resubmission proposed an effective price for patisiran (AEMP=\$¹ per 10 mg vial) that was ²% lower than the July 2023 price (AEMP= \$¹ per 10 mg vial). The resubmission did not accept the rationale for halving of the treatment-related utility increments and decrements but provided a sensitivity analysis which assumed a 20% reduction in utility increments/decrements, see Table 19.
2	Revision of the financial estimates as discussed in paragraph 7.12 and recalculation using the revised patisiran price. (i) PBAC considered the submission estimates were underestimated but these concerns were addressed by the pre-PBAC response. (ii) Additional uncertainty could be addressed by a risk sharing arrangement which assumed ³% rebate for expenditure above caps.	The resubmission provided revised estimates (Table 20). The resubmission estimated up to ² eligible patients, which was similar to the pre-PBAC response (up to ² patients). The resubmission stated the difference was due to updated ABS data, rounding and an adjustment to incident patients in Year 1. The resubmission estimated up to ² patients treated (in year 6), and between ³ and ³ vials per year. The resubmission proposed a cap threshold based on a vial consumption of ³ vials per calendar year (corresponding to ² patients treated, with 40.11 vials per patient). Above this volume, the proposed post-rebate price was \$¹ per vial (reflects approx. ³% rebate above the cap).
3	Submit a proposal for a managed access program (MAP) to address PBAC's concern regarding the uncertain cost-effectiveness as discussed in paragraphs 7.13 to 7.15.	The resubmission noted the request for a MAP and proposed that a future reassessment of patisiran could incorporate data from the patisiran Global open-label extension (OLE) study and from the ConTTRIBUTE Global observational study.
4	Update restriction, as outlined in paragraph 7.18	The resubmission provided updated restriction criteria, however some of the PBAC's concerns were not addressed.

The redacted values correspond to the following ranges:

¹ 155,000 to < \$255,000

² < 500

³ 500 to < 5,000

11 Requested listing

11.1 Secretariat additions are in italic and deletions in strikethrough.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Dispensed Price for Max. Qty	Max. qty units	No.of Rpts	Available brands
PATISIRAN					
10 mg (5 mL) vial for complex IV infusion, 1	NEW NEW	Public: \$ published price \$ effective price Private: \$ published price \$ effective price	3	7	Onpattro
Category / Program: Section 100 HSD – Public Hospital Section 100 HSD – Private Hospital					
Prescriber type: ☒ Medical Practitioners					
Condition:	Hereditary transthyretin amyloidosis with polyneuropathy.				
PBS indication:	Hereditary transthyretin amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy				
Restriction:	☒ Authority Required - In Writing				
Treatment criteria:	Must be treated by a consultant physician with experience in the management of amyloid disorders.				
Treatment phase:	Initiating treatment				
Clinical criteria:	• The condition must be hereditary transthyretin amyloidosis confirmed by genetic testing; and • The patient must have a PND score description of I, II, IIIA, or IIIB or the patient must have an FAP stage description of 1 or 2. • Patient must not have previously undergone a liver transplant. • Patient must not exhibit heart failure symptoms (defined as New York Heart Association [NYHA] class III or IV).				
Prescriber Instruction	Clinical staging scales relevant to clinical criteria ⁹				
	Familial Amyloid Polyneuropathy (FAP) stage		Polyneuropathy Disability (PND) Score		
	Stage 0	No symptoms	Stage 0	No symptoms	
	Stage 1	Unimpaired ambulation	Stage I	Sensory disturbances but preserved walking capability	
	Stage 2	Assistance with ambulation required	Stage II	Impaired walking capacity but able to walk without stick or crutches	
			Stage IIIA	Walking with help of one stick or crutch	
			Stage IIIB	Walking with help of two sticks or crutches	
	Stage 3	Wheelchair- bound or bedridden	Stage IV	Confined to wheelchair or bedridden	
	Clinical staging of heart failure¹⁰				
	New York Heart Association (NYHA) functional classification				

⁹ Adams D. Recent advances in the treatment of familial amyloid polyneuropathy. Ther Adv Neurol Disord. 2013 Mar;6(2):129-39.

¹⁰ American Heart Association. Classes and Stages of Heart Failure. 2023; <https://www.heart.org/en/health-topics/heart-failure/what-is-heart-failure/classes-of-heart-failure>.

	Class I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or shortness of breath.
	Class II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, shortness of breath or chest pain.
	Class III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, shortness of breath or chest pain. No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or shortness of breath.
	Class IV	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, shortness of breath or chest pain. Symptoms of heart failure at rest. Any physical activity causes further discomfort.
Treatment phase:	Continuing treatment	
Clinical criteria:	- The patient must have previously received PBS-subsidised treatment with this drug for this condition; and - The patient must continue to demonstrate clinical benefit; and - The patient must not be permanently bedridden or receiving end-of-life care.	
Treatment phase:	Grandfather arrangements	
Clinical criteria:	- The patient must have previously received non-PBS-subsidised treatment with this drug for this condition; and - The patient must continue to demonstrate clinical benefit; and - The patient must not be permanently bedridden or receiving end-of-life care.	

- 11.2 The PBAC noted that the changes made to the proposed restrictions in the resubmission were consistent with its July 2023 advice. However, the PBAC considered that further refinement of the restrictions was required (see paragraph 11.9).
- 11.3 The resubmission added NYHA classification to the proposed restriction consistent with PBAC advice, however some of the details included within the prescriber instructions were incorrect. These have been amended above.

12 Consideration of the evidence

Economic analysis

- 12.1 The resubmission provided a revised base case, in which anniversary price reductions were removed and the resubmission's proposed price was applied (AEMP = \$1 per 10 mg vial). The ICER for the resubmission base case was \$155,000 to < \$255,000/QALY, which was consistent with the ICER range specified by the PBAC in July 2023, however the resubmission did not follow the PBAC's advice concerning amendment of the utility increments/decrements (see paragraph 7.11). In July 2023, the PBAC considered that the submission's approach resulted in an overly optimistic estimate of incremental QALY gain, but in the context of a rare disease and significant unmet need, the submission's approach would be acceptable if the treatment-related utility increment/decrements were halved as proposed during the evaluation and the other matters discussed in paragraph 7.11 were addressed. The resubmission provided a sensitivity analysis which assumed a 20% reduction in utility

increments/decrement, see Table 19. The resubmission also provided a sensitivity analysis which included caregiver disutilities, see Table 19.

Table 19: Economic evaluation – July 2023 submission and September 2023 resubmission

Analyses	Incremental cost	Incremental QALY	ICER (\$/QALY)
July 2023 submission			
Submission base case (anniversary price reductions removed by evaluator)	\$ [REDACTED]	6.10	[REDACTED] ¹
September 2023 resubmission			
Resubmission base case (anniversary price reductions removed and proposed price)	\$ [REDACTED]	6.10	[REDACTED] ²
Sensitivity Analysis: Utility increments and decrements for being on/off treatment with patisiran at 80% of base-case values	\$ [REDACTED]	5.75	[REDACTED] ¹
Sensitivity Analysis: Inclusion of caregiver disutilities	\$ [REDACTED]	6.64	[REDACTED] ²

The redacted values correspond to the following ranges:

¹ \$255,000 to < \$355,000

² \$155,000 to < \$255,000

- 12.2 The average number of vials required per patient per administration was calculated to be 2.38, based on the reported weight distribution for the non-V30M population in the APOLLO trial (34-66 kg: 62.0%; 67-99 kg: 34.1%; 100-132 kg: 3.9%), 62% of patients would require 2 vials, and 38% of patients would require 3 vials. Wastage was accounted for in the economic model, however, there may be differences in body weight distribution between the modelled population and the proposed PBS population that may affect the number of vials required.

Estimated PBS usage and financial implications

- 12.3 The resubmission provided revised financial estimates as presented in Table 20. The resubmission estimated up to < 500 eligible patients, which was similar to the pre-PBAC response (up to < 500 patients, see paragraph 6.88). The resubmission stated the difference was due to updated ABS data, rounding and an adjustment to incident patients in Year 1.
- 12.4 The resubmission estimated up to < 500 patients treated (in year 6), and between 500 to < 5,000 and 500 to < 5,000 vials per year. The resubmission estimated a net cost to the PBS/RPBS of \$100 million to < \$200 million over the first six years of listing.

Table 20: Estimated utilisation and net cost of listing patisiran (effective price)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
July 2023 Submission						
Total eligible patients	1	1	1	1	1	1
Total treated patients	1	1	1	1	1	1
Total scripts	1	2	2	2	2	2
Net cost to PBS/RPBS	5	5	3	3	3	3
Net cost to the MBS	5	5	5	5	5	5
Net cost to the PBS/RPBS/MBS	5	5	3	3	3	3
July 2023 Pre-PBAC response						
Total eligible patients	1	1	1	1	1	1
Total treated patients (did not specify uptake)	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
September 2023 Resubmission						
Total eligible patients ^a	1	1	1	1	1	1
Total treated patients	1	1	1	1	1	1
Total scripts	2	2	2	2	2	2
Total vials	6	6	6	6	6	6
Net cost to PBS/RPBS	3	3	3	3	4	4
Net cost to the MBS ^b	5	5	5	5	5	5
Net cost to the PBS/RPBS/MBS	3	3	3	3	4	4

n.r. = not reported.

a. The resubmission noted this estimate differed from pre-PBAC response, and stated this was due to correcting for the use of Australian population estimates for 2023 from the Australian Bureau of Statistics, rounding and previously only partially capturing new incident patients in Year 1.

b. MBS Item 116 - Professional attendance by consultant physician.

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ \$10 million to < \$20 million

⁴ \$20 million to < \$30 million

⁵ \$0 to < \$10 million

⁶ 500 to < 5,000

Financial Management – Risk Sharing Arrangements

12.5 The resubmission proposed a cap threshold based on a vial consumption of 500 to < 5,000 vials per calendar year (corresponding to < 500 patients treated, with an average 40.11 vials per patient¹¹). Above this volume, the proposed post-rebate price was \$| per vial (reflects approx. |% rebate above the cap). This cap would not be exceeded within the first six years of listing based on the utilisation estimates proposed in the resubmission (Table 20) and would also allow a higher number of patients treated in the early years without breaching the cap.

¹¹ The submission estimated 40.11 vials per patient per year, based on assumptions used in the utilisation estimates, including compliance (96.9%), vials per 3-week period (2.38), and doses per year (17.39, i.e. 52/3).

Managed Access Program (MAP)

- 12.6 The resubmission noted the PBAC's request for a MAP and proposed that the most robust approach to a future reassessment of patisiran would be to incorporate data from the patisiran Global open-label extension (OLE) study¹² and from the ConTTRIBUTE Global observational study of patients with transthyretin-mediated amyloidosis¹³.
- 12.7 The resubmission noted that the ongoing patisiran Global OLE is collecting outcomes of relevance to the economic model including PND score transitions and survival, and numerous other outcomes as presented in the July 2023 submission, such as mNIS+7, and Norfolk QoL-DN score. The resubmission stated that a 5-year update from the Global OLE will be available by year-end 2024.
- 12.8 The resubmission stated that the ConTTRIBUTE Global observational study would also be a relevant data source for future reassessment of patisiran, and that its objectives were to describe clinical characteristics, natural history, and real-world clinical management of transthyretin amyloidosis. The resubmission stated that data from the ConTTRIBUTE Global observational study, including data on treatment outcomes for patients receiving patisiran in real-world practice, will be available in 2025 and beyond.
- 12.9 The resubmission reported that the sponsor is open to performing a reassessment that incorporates longer-term clinical data for patisiran and BSC, with inputs derived from the patisiran Global OLE and ConTTRIBUTE Global observational study. It was noted that the sponsor is not planning additional local data-collection in Australia for patisiran (beyond Australian patients included in the patisiran Global OLE) that would address uncertainties expressed by the PBAC with regard to the economic model. The resubmission proposed that data from the patisiran Global OLE and the ConTTRIBUTE Global observational study will be more robust than local Australian data collection.
- 12.10 The resubmission proposed that if reassessment is considered necessary, the timing of this reassessment should coincide with renewal of the expected 5-year deed of agreement, i.e. 2029.

13 PBAC Outcome

- 13.1 The PBAC deferred making a recommendation for patisiran for the treatment of patients with hATTR with polyneuropathy to allow for further consultation with the sponsor. In deciding to defer making a recommendation, the PBAC reaffirmed its view that there was a high clinical need for effective treatments for this patient population,

¹² Alnylam Pharmaceuticals. Data on File. Data Update Report 1. Open Label Extension Study (Patisiran). Cambridge, MA: 2021.

¹³ Clinicaltrials.gov. ConTTRIBUTE: A Global Observational Study of Patients With Transthyretin (TTR)-Mediated Amyloidosis (ATTR Amyloidosis) (ConTTRIBUTE) (NCT04561518). <https://classic.clinicaltrials.gov/ct2/show/NCT04561518>.

however the PBAC considered that further consultation with the sponsor was required regarding a cost-effective price for patisiran and addressing the uncertainty with the cost-effectiveness estimates (through a MAP) and the financial estimates (through a Risk Sharing Arrangement).

- 13.2 The PBAC recalled it had considered the ICER estimated in the July 2023 submission to be high and uncertain. The main concerns were regarding robustness of the survival data, extrapolation methods, and application of treatment-related utility increments and decrements. The PBAC noted that the resubmission had provided a new base case economic analysis, which did not follow the PBAC's advice concerning amendment of the utility increments/decrements (paragraph 10.1), and considered that the resubmission had not demonstrated cost-effectiveness for patisiran.
- 13.3 Consistent with its earlier advice, the PBAC considered that the resubmission's economic model resulted in an overly optimistic estimate of incremental QALY gain. The PBAC recalled that the application of treatment-related utility increments and decrements resulted in health state utilities that differed substantially from the estimated average health state utilities derived in the MMRM regression analysis (paragraph 7.8). The PBAC noted its previous advice that halving the treatment-related utility increments/decrements would be appropriate (paragraph 7.9). The PBAC noted that reducing these increments/decrements to 80% of base-case values, as proposed in the resubmission, resulted in an ICER of \$255,000 to < \$355,000 per QALY gained (Table 19). The PBAC considered that the previously specified requirement for an ICER of no more than \$155,000 to < \$255,000/QALY remained appropriate for patisiran, and that the concerns about treatment-related utility increments/decrements remained.
- 13.4 The PBAC noted the revised financial estimates presented in the resubmission, which resulted in an estimated net cost to the PBS/RPBS of \$100 million to < \$200 million over the first six years of listing (Table 20).
- 13.5 The PBAC considered that amendments were required to the proposed RSA, because the resubmission did not sufficiently address the uncertainties described in paragraph 7.12. The PBAC recalled that in July 2023, it had advised that a 10% rebate for expenditure above agreed caps would be appropriate, and noted the resubmission did not incorporate this advice. The PBAC noted that the resubmission had proposed a cap threshold based on a vial consumption of 500 to < 5,000 vials per calendar year (corresponding to < 500 patients treated, with 40.11 vials per patient), rather than the financial estimates which assumed < 500 patients treated in Year 1 increasing to < 500 patients in Year 6 (Table 20). The PBAC advised that RSA expenditure caps should be based on estimated utilisation and maintained that 10% rebate for expenditure above agreed caps would be appropriate.
- 13.6 The PBAC considered that the resubmission's proposal for a MAP did not sufficiently address its concern regarding the uncertain cost-effectiveness of the proposed listing. The resubmission proposed that a future reassessment of patisiran could incorporate

data from the patisiran Global open-label extension (OLE) study and from the ConTTRIBUTE Global observational study of patients with transthyretin-mediated amyloidosis, however, did not provide a workable plan for the reassessment. The PBAC considered it was not appropriate to delay reassessment of patisiran until five years after listing, when new data were expected for the two proposed studies within the next two years. The PBAC advised that reassessment of patisiran should occur at a maximum of three years after PBS listing, noting that data from the global OLE and ConTTRIBUTE would be available to enable this. The PBAC advised that if patisiran is recommended for listing, the sponsor should be required to provide a submission to PBAC to support reassessment of the cost-effectiveness of patisiran consistent with this timeframe. The PBAC considered that its future reassessment should consider: 1) whether the data were supportive of long term benefits of patisiran (based on QOL and PND score); 2) whether updated survival data supported the modelled survival benefit; 3) whether updated safety data were consistent with the safety data in the submission and that no new clinically significant safety signals were evident; and 4) whether patisiran was cost-effective based on the updated evidence base.

- 13.7 The PBAC noted that the resubmission requested a single vial size containing 10 mg of patisiran, which would be associated with a degree of drug wastage for most patients. Consistent with its previous advice, the PBAC advised that wastage must be incorporated in the economic model consistent with PBAC guidelines (see paragraph 3.2). The PBAC noted that wastage was accounted for in the economic model (see paragraph 10.2), however the PBAC considered that uncertainty about the number of vials required for each patient (between 1 to 3, depending on patient weight), was an area of uncertainty that should be considered in the economic model and financial estimates.
- 13.8 The PBAC considered that the following changes may address the outstanding concerns:
- Revision of inputs in the economic model as outlined in paragraph 11.3.
 - Recalculation of the financial estimates using the revised patisiran price.
 - A risk sharing arrangement, which includes 1% rebate above agreed financial estimates (< 500 patients in Year 1 increasing to < 500 patients in Year 6; see paragraph 11.5).
 - A commitment from the sponsor with respect to reassessment of the data three years after PBS listing to address PBAC's concern regarding uncertain cost-effectiveness (paragraph 11.6).
 - A new criterion added to the proposed restriction to prevent concomitant use with any other disease modifying medicine for TTR amyloidosis, in the event that such medicines are PBS listed in the future (paragraph 11.9).

13.9 The PBAC noted that the resubmission provided updated restriction criteria, however some of the PBAC's earlier concerns had not been addressed. The PBAC gave the following advice with regard to the restriction:

- It is not necessary to limit prescribing to neurologists, in the context that genotyping is a requirement of the listing. The proposed treatment criterion appears appropriate: "Must be treated by a consultant physician with experience in the management of amyloid disorders." The sponsor is asked to comment whether limiting treatment initiation to neurologists would benefit patients and add this information to the proposed restriction if applicable.
- It remains unclear whether access to patisiran should be limited to clinical centres that are affiliated with the AAN. The sponsor is asked to clarify if this approach would improve patient care or enhance the monitoring of outcomes of patisiran treatment of relevance to a future reassessment of patisiran, and to add this information to the proposed restriction if applicable.
- Concomitant use of patisiran with any other approved disease modifying medicine for TTR amyloidosis should be disallowed in the PBS restrictions if any such medicines are PBS listed in the future. A new criterion should be added to the proposed restriction to reflect this advice. It may be appropriate to allow a patient to change from one PBS-therapy to another, if all restriction criteria are met.

Outcome:

Deferred

14 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.

15 Sponsor's Comment

The sponsor had no comment.

Addendum to the September 2023 PBAC PSD:

7.02 PATISIRAN, Solution concentrate for I.V. infusion 10 mg in 5 mL, Onpattro®, Alnylam Australia Pty Ltd

16 Background

16.6 At the September 2023 intracycle meeting, the PBAC deferred making a recommendation to allow further consultation with the sponsor (see paragraph 13.1). A revised proposal was submitted to address the deferral as outlined in Table 21.

Table 21: Summary of issues

Topic	Revised proposal	Comment	PBAC Advice
Revision of inputs in the economic model	The treatment-related utility increment/decrements were halved as requested. The proposed AEMP was \$[REDACTED] per 10 mg vial. The base case ICER was \$[REDACTED]/QALY.	The revisions were consistent with PBAC advice as outlined in paragraph 13.3.	The revised inputs were accepted, see paragraph 19.3.
Financial estimates and RSA	The proposed RSA was based on estimated utilisation and assumed [REDACTED]% rebate above the caps and were calculated with the revised patisiran price.	The estimated patient numbers were consistent with previous PBAC advice, however the estimates did not take account of patient discontinuations which was inconsistent with the economic model which assumed 57% persistence at Year 6 (Table 14).	The revised price and rebate were accepted, however a discontinuation rate should be applied in the financial estimates, see paragraph 19.4.
Commitment from the sponsor with respect to reassessment of the data 3 years after PBS listing	The sponsor proposed review of data at 3 years and provided a summary of ongoing trials and endpoints in these trials.	The sponsor's proposal appeared consistent with PBAC's request for review of the data 3 years after PBS listing to address PBAC's concern regarding uncertain cost-effectiveness (paragraph 13.6).	The commitment from the sponsor with respect to reassessment of the data 3 years after PBS listing must be documented in the deed of agreement, see paragraph 19.6.
Restriction	Proposed revised restriction	The sponsor's proposal appeared consistent with PBAC's advice (paragraphs 13.8 to 13.9)	The revisions were accepted, see paragraph 19.11.

The redacted values correspond to the following ranges:

¹ \$155,000 to < \$255,000

17 Requested listing

17.6 Secretariat additions are in italic and deletions in strikethrough.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Dispensed Price for Max. Qty	Max. qty units	No. of Rpts	Available brands
PATISIRAN					
10 mg (5 mL) vial for complex IV infusion, 1	NEW	Public: \$ published price \$ effective price (based on AEMP of \$ per vial)	3	7	Onpattro
<i>Patisiran 10 mg/5 mL injection, 5 mL vial</i>	NEW	Private \$ published price \$ effective price (based on AEMP of \$ per vial)			
Category / Program: Section 100 HSD – Public Hospital Section 100 HSD – Private Hospital					
Prescriber type: ☒ Medical Practitioners					
Condition:	Hereditary transthyretin amyloidosis with polyneuropathy.				
PBS indication:	Hereditary transthyretin amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy				
Restriction:	☒ Authority Required - In Writing				
Treatment criteria:	- Must be treated by a consultant with experience in the management of amyloid disorders or in consultation with a consultant with experience in the management of amyloid disorders. - Patisiran is to be used as a monotherapy (i.e. not in combination with any other disease modifying medicines for amyloidosis disorders).				
Treatment phase:	Initiating treatment				
Clinical criteria:	- The condition must be hereditary transthyretin amyloidosis confirmed by genetic testing; and - The patient must have a PND score description of I, II, IIIA, or IIIB or the patient must have an FAP stage description of 1 or 2. - Patient must not have previously undergone a liver transplant. - Patient must not exhibit heart failure symptoms (defined as New York Heart Association [NYHA] class III or IV).				
Prescriber Instruction	Clinical staging scales relevant to clinical criteria ¹⁴				
	Familial Amyloid Polyneuropathy (FAP) stage		Polyneuropathy Disability (PND) Score		
	Stage 0	No symptoms	Stage 0	No symptoms	
	Stage 1	Unimpaired ambulation	Stage I	Sensory disturbances but preserved walking capability	
	Stage 2	Assistance with ambulation required	Stage II	Impaired walking capacity but able to walk without stick or crutches	
			Stage IIIA	Walking with help of one stick or crutch	
			Stage IIIB	Walking with help of two sticks or crutches	
	Stage 3	Wheelchair- bound or bedridden	Stage IV	Confined to wheelchair or bedridden	

¹⁴ Adams D. Recent advances in the treatment of familial amyloid polyneuropathy. Ther Adv Neurol Disord. 2013 Mar;6(2):129-39.

	Clinical staging of heart failure¹⁵	
	New York Heart Association (NYHA) functional classification	
	Class I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or shortness of breath.
	Class II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, shortness of breath or chest pain.
	Class III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, shortness of breath or chest pain. No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or shortness of breath.
	Class IV	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, shortness of breath or chest pain. <i>Symptoms of heart failure at rest. Any physical activity causes further discomfort.</i>
Treatment phase:	Continuing treatment	
Clinical criteria:	- The patient must have previously received PBS-subsidised treatment with this drug for this condition; and - The patient must continue to demonstrate clinical benefit; and - The patient must not be permanently bedridden or receiving end-of-life care.	
Treatment phase:	Grandfather arrangements	
Clinical criteria:	- The patient must have previously received non-PBS-subsidised treatment with this drug for this condition; and - The patient must continue to demonstrate clinical benefit; and - The patient must not be permanently bedridden or receiving end-of-life care.	

- 17.7 The proposed restriction incorporated the PBAC's advice concerning concomitant therapy (paragraph 13.8). The sponsor noted the PBAC's request for clarification of two further aspects of the proposed restriction in paragraph 13.9, and proposed that no further changes were required as outlined below (paragraphs 17.3 and 17.4).
- 17.8 The sponsor noted there is an established history of clinical practice in Australia involving haematologists as the main specialists in the management of hATTR amyloidosis with polyneuropathy and stated that limiting treatment initiation to neurologists would be disadvantageous to patients and may result in treatment delays or inequity in access.
- 17.9 The sponsor stated that access to patisiran should not be limited to clinical centres that are affiliated with the AAN. Infusions should take place at the patient's local place of care. It was noted that AAN are available to support patient case reviews, as per their current practice, whereby the majority of patients are either seen by an AAN centre, an AAN affiliate centre, or the patient case is reviewed in consultation. Noting the geographical size of Australia, the sponsor stated that limiting access to patisiran to AAN or affiliated clinical centres may cause inequity of access and will not lead to optimal patient outcomes.

¹⁵ American Heart Association. Classes and Stages of Heart Failure. 2023; <https://www.heart.org/en/health-topics/heart-failure/what-is-heart-failure/classes-of-heart-failure>.

18 Consideration of the evidence

Economic analysis

- 18.1 A revised base case was presented in which the treatment related utility increment/decrements were halved consistent with PBAC advice and resulted in a base case ICER of \$155,000 to < \$255,000/QALY when the proposed price was applied. The revisions to the economic model were consistent with PBAC advice as outlined in paragraph 13.3. Sensitivity analyses were also presented, see Table 22.

Table 22: Economic evaluation

Analyses	Incremental cost (\$)	Incremental QALY	ICER (\$/QALY)
Base case			
December 2023 base case (Utility increments/decrements are 50% of base-case values)		4.91	¹
Sensitivity analyses			
SA.1 Inclusion of care giver utilities		5.45	¹
SA.2 Utility increments/decrements are 80% of July 2023 base-case values		5.75	¹

The redacted values correspond to the following ranges:

¹ \$155,000 to < \$255,000

- 18.2 The assumed utilisation of patisiran per patient in the economic model was unchanged from the previous consideration. The average number of vials required per patient per administration was calculated to be 2.38, based on the reported weight distribution for the non-V30M population in the APOLLO trial (34-66 kg: 62.0%; 67-99 kg: 34.1%; 100-132 kg: 3.9%), 62% of patients would require 2 vials, and 38% of patients would require 3 vials. The submission stated that the Sydney site of the AAN have confirmed the weight distribution is reflective of the Australian symptomatic patient population.

Estimated PBS usage and financial implications

- 18.3 Revised financial estimates were provided as shown in Table 23. The estimated numbers of treated patients were consistent with the September resubmission, see paragraph 13.5).
- 18.4 The estimates assumed an average of 40.11 vials per patient per year, which reflected an assumption of 100% treatment persistence over the first 6 years of listing. The PBAC considered this was not appropriate, noting that the proportion of patients on treatment (persistence) in the economic model ranged from 94% in Year 1 to 57% in Year 6 (inclusive of half cycle correction, see Table 14). The PBAC advised that the financial estimates should be revised to reflect a discontinuation rate as shown in Table 23.

Table 23: Estimated utilisation and net cost of listing patisiran (effective price)^a

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Submitted estimates						
Total treated patients	1	1	1	1	1	1
Discontinuation	0%	0%	0%	0%	0%	0%
Scripts per patient per year	13.37	13.37	13.37	13.37	13.37	13.37
Total scripts	2	2	2	2	2	2
Total vials	N ²	2	2	2	2	2
Net cost to PBS/RPBS	3	4	4	4	4	4
Net cost to the MBS ^b	3	3	3	3	3	3
Net cost to the PBS/RPBS/MBS	3	4	4	4	4	4
Estimates corresponding to PBAC advice						
Total treated patients	1	1	1	1	1	1
Persistence	94%	84%	75%	69%	63%	57%
Discontinuation	6%	16%	25%	31%	37%	43%
Scripts per patient per year ^c	12.57	11.23	10.03	9.22	8.42	7.62
Total scripts	2	2	2	2	2	2
Total vials	2	2	2	2	2	2
Net cost to PBS/RPBS	3	3	4	4	4	4
Net cost to the MBS ^b	3	3	3	3	3	3
Net cost to the PBS/RPBS/MBS	3	3	4	4	4	4

a. Assuming a weighted DPMQ of \$█, based on an anticipated 80% use in public hospitals.

b. MBS Item 116 - Professional attendance by consultant physician.

c. Scripts per patient per year reduced to reflect persistence rate from economic model (rates from Table 14).

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

Financial Management – Risk Sharing Arrangements

18.5 The sponsor proposed capped expenditure of patisiran set at the net cost to PBS/RPBS using the proposed effective price, with █% rebate above the cap of the proposed Risk Share Arrangement.

Reassessment of data after 3 years

18.6 The revised proposal indicated that the sponsor would perform a reassessment of the cost-effectiveness of patisiran three years after PBS listing using data from the patisiran global OLE study¹⁶ and the ConTTRIBUTE Global observational study¹⁷.

18.7 A summary of the proposal is presented in Table 24. It was stated that the reassessment will provide further data to inform mortality hazard ratios for PND health states, as both the Global OLE and ConTTRIBUTE are monitoring PND scores.

¹⁶ Alnylam Pharmaceuticals. Data on File. Data Update Report 1. Open Label Extension Study (Patisiran). Cambridge, MA: 2021.

¹⁷ Clinicaltrials.gov. ConTTRIBUTE: A Global Observational Study of Patients With Transthyretin (TTR)-Mediated Amyloidosis (ATTR Amyloidosis) (ConTTRIBUTE) (NCT04561518). <https://classic.clinicaltrials.gov/ct2/show/NCT04561518>.

Additionally, an updated survival estimate in patients treated long term with patisiran will be available from the Global OLE, and this can be compared with modelled survival in the patisiran arm. The Global OLE will provide long term data to further inform PND health state transitions in the patisiran arm, and data from ConTTRIBUTE could also potentially inform these transitions in the BSC arm. In addition to PND scores, EQ-5D data from the Global OLE could potentially be used to inform HRQoL in the patisiran arm in the 3-year reassessment. Patisiran discontinuation will be updated based on findings from the Global OLE. Regarding safety, serious adverse events from the Global OLE will be used to inform their frequency in the patisiran arm, and it is possible that data from ConTTRIBUTE can be used to inform the frequency of serious adverse events in the BSC arm.

Table 24: Trials used to inform parameters in the original submission and proposed reassessment at 3 years

Modelled parameter	Proposed reassessment				
	Original submission			Global OLE*	ConTTRIBUTE
	APOLLO	Phase 2 OLE	Global OLE		
Mortality HRs for PND health states	Yes	Yes	Yes	Yes	Possibly
Survival estimate in patients treated long term with patisiran a	–	–	–	Yes	–
Transition matrices between PND health states (patisiran)	Yes	–	Yes	Yes	–
Transition matrices between PND health states (BSC)	Yes	–	–	–	Possibly
MMRM analysis for PND health-state utilities (patisiran)	Yes	–	–	Possibly	–
MMRM analysis for PND health-state utilities (BSC)	Yes	–	–	–	–
Maximum and minimum utilities for PND health states	Yes	–	–	Possibly	–
Treatment discontinuation (patisiran)	Yes	–	Yes	Yes	–
SAEs (patisiran)	Yes	–	–	Yes	–
SAEs (BSC)	Yes	–	–	–	Possibly

a. Added to table based on description provided in text form in the submission.

Abbreviations: BSC, best supportive care; HR, hazard ratio; MAP, managed access program; MMRM, mixed-effects model for repeated measures; OLE, open-label extension; PND, polyneuropathy disability; SAE, serious adverse event. *The Global OLE was used to inform the original submission and updated data from the Global OLE will inform the MAP reassessment.

19 PBAC Outcome

- 19.1 The PBAC recommended patisiran for the treatment of patients with hATTR with polyneuropathy. The PBAC noted there was a high clinical need for effective treatment in this population. The PBAC noted the clinical benefits of patisiran in terms of delaying disease progression, reducing neuropathy symptoms, and improving health-related quality of life compared to placebo, based on the primary and secondary outcomes in the APOLLO trial over its 18-month trial period. The PBAC recalled that in September 2023 it had advised that revisions were required to the economic model and that concerns remained regarding uncertainty of the cost-effectiveness estimates and the

financial estimates. The PBAC considered that the outstanding issues regarding the economic model had been satisfactorily resolved by the revised proposal provided by the sponsor, which included a commitment for reassessment of the data after three years. The PBAC advised that further amendments to the financial estimates were necessary to reflect the anticipated discontinuation rate.

- 19.2 The PBAC was satisfied that patisiran provides, for some patients, a significant improvement in efficacy over BSC.
- 19.3 The PBAC noted that the revised inputs in the economic model were consistent with its previous advice as outlined in paragraph 13.3. The PBAC accepted that its concerns about the economic evaluation had been sufficiently addressed to support a recommendation for listing patisiran at this time, however as outlined previously uncertainty remained in regard to long term cost-effectiveness given the limitations of the trial data currently available. The PBAC noted the economic model incorporated an improvement in overall survival however only a trend, and not a statistically significant improvement, was demonstrated in APOLLO.
- 19.4 The PBAC noted the revised financial estimates presented in the submission, which resulted in an estimated net cost to the PBS/RPBS of \$80 million to < \$90 million over the first six years of listing (Table 23). After revision to reflect the anticipated discontinuation rate, the estimates corresponding to PBAC advice correspond to an estimated net cost to the PBS/RPBS of \$50 million to < \$60 million over the first six years of listing (Table 23).
- 19.5 The PBAC noted that the revised proposal agreed to a RSA with a [REDACTED] % rebate above the caps as previously advised. The PBAC confirmed this was appropriate, and that caps should be based on the updated financial estimates as outlined above (paragraph 19.4).

- 19.6 The PBAC noted that a commitment had been provided by the sponsor with respect to reassessment of the data three years after PBS listing to address the PBAC's concern regarding uncertain cost-effectiveness. The PBAC advised that reassessment of patisiran should occur at a maximum of three years after PBS listing, noting that data from the global OLE and ConTTriBute should be available to enable this. Consistent with its previous advice, the PBAC considered that its future reassessment should consider: 1) whether the data were supportive of long term benefits of patisiran (based on QOL and PND score); 2) whether updated survival data supported the modelled survival benefit; 3) whether updated safety data were consistent with the safety data in the submission and that no new clinically significant safety signals were evident; and 4) whether patisiran was cost-effective based on the updated evidence base. The PBAC noted that the sponsor would be required to submit an updated cost-effectiveness analysis for patisiran using an updated economic model with any changes from the current model clearly identified and referenced.
- 19.7 The PBAC noted the summary provided in Table 24, and considered there remains some uncertainty whether the data that will be obtained will meet all of PBAC's expectations regarding resolution of uncertainty. The PBAC discussed the limitations that will be inherent in interpreting the observational data but accepted that relevant signals may emerge from the real-world data that warrant review. The PBAC considered that the proposed updated body of evidence would allow the proposed reassessment to occur. The PBAC advised that the review of cost-effectiveness three years after PBS listing may impact the future PBS price of patisiran, noting that a price reduction would be needed if the review found that patisiran was less cost-effective based on updated data informing the review as set out in Table 24. The PBAC noted there would be no basis for a price increase given the high ICER accepted and inherent uncertainty in the estimated ICER due to the type of clinical evidence available to inform it.
- 19.8 The PBAC considered that the studies listed in Table 24 would provide the basis for the reassessment as discussed above. In addition, the PBAC advised that the sponsor should be required to provide a systematic literature review, to ensure that any relevant clinical evidence is presented for consideration in a manner consistent with the PBAC guidelines. If the literature review identifies any relevant studies beyond those listed in Table 24, these should also be presented within the submission for PBAC consideration.
- 19.9 The PBAC advised that the requirement for a review at three years post the date of listing should be documented in a Deed of Agreement with the sponsor, including an expectation that the sponsor will provide a submission to the PBAC to inform a review of the cost-effectiveness of patisiran as described in paragraphs 19.6 to 19.8.
- 19.10 The PBAC noted that a new criterion had appropriately been added to the proposed restriction to prevent concomitant use with any other disease modifying medicine for TTR amyloidosis, in the event that such medicines are PBS listed in the future.

- 19.11 The PBAC noted the revised restriction and considered this was appropriate, with minor amendments as shown in the recommended listing in Section 16. The PBAC noted that additional discussion was provided by the sponsor as requested (see paragraphs 17.2 to 17.4).
- 19.12 The PBAC advised that patisiran is not suitable for prescribing by nurse practitioners.
- 19.13 The PBAC recommended that the Early Supply Rule should not apply.
- 19.14 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were met. Specifically the PBAC found that in the circumstances of its recommendation for patisiran:
- The treatment is expected to provide a substantial and clinically relevant improvement in efficacy, over alternative therapies, on the basis of the APOLLO study;
 - The treatment is expected to address a high and urgent unmet clinical need due to the lack of treatment options currently;
 - It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings.
- 19.15 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

20 Recommended listing

Add new item:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No.of Rpts	Available brands
PATISIRAN					
patisiran 10 mg/5 mL injection, 5 mL vial	NEW (pub) NEW (priv)	1	3	7	Onpattro
Restriction Summary					
Category / Program: Section 100 – (Highly Specialised Drugs Program) Public Hospital/Private Hospital (Code HB / HS)					
Prescriber type: Medical Practitioners					
Restriction type: Authority Required (in writing only via post/electronic)					
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					

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Administrative Advice: Special Pricing Arrangements apply.
Episodicity: [blank]
Severity: [blank]
Condition: Hereditary transthyretin amyloidosis
Indication: Hereditary transthyretin amyloidosis
Treatment Phase: Initial Treatment
Population criteria:
Patient must have either (i) stage 1 polyneuropathy, (ii) stage 2 polyneuropathy
Clinical criteria:
Patient must not have previously received PBS-subsidised treatment with this drug for this PBS indication
AND
Clinical criteria:
Patient must be at least 18 years of age
AND
Clinical criteria
The condition must be hereditary transthyretin amyloidosis confirmed by genetic testing.
AND
Clinical criteria:
Patient must have a Polyneuropathy Disability (PND) score description of either I, II, IIIA, IIIB, OR
Patient must have a Familial Amyloid Polyneuropathy (FAP) stage description of 1 or 2
AND
Clinical criteria:
Patient must not have previously undergone a liver transplant
AND
Clinical Criteria
Patient must not exhibit heart failure symptoms (defined as New York Heart Association [NYHA] class III or IV).
Treatment criteria:
Must be treated by a consultant physician with experience in the management of amyloid disorders.
Must be treated by a consultant with experience in the management of amyloid disorders or in consultation with a consultant with experience in the management of amyloid disorders.
Patisiran is to be used as a monotherapy (i.e. not in combination with any other disease modifying medicines for amyloidosis disorders).
Prescribing Instructions:
PND scores in the context of this PBS restriction are: Stage 0 - No symptoms Stage I - Sensory disturbances but preserved walking capability Stage II - Impaired walking capacity but able to walk without stick or crutches Stage IIIA - Walking with help of one stick or crutch Stage IIIB - Walking with help of two sticks or crutches Stage IV - Confined to wheelchair or bedridden
FAP stage in the context of this PBS restriction are:

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Stage 0 - no symptoms Stage 1 - unimpaired ambulation Stage 2 - assistance with ambulation required Stage 3 - wheelchair-bound or bedridden
Prescribing Instructions: Applications for authorisation under this treatment phase must be made via the Online PBS Authorities System (real time assessment) or in writing via HPOS form upload or mail. If the application is submitted through HPOS form upload or mail, it must include: (a) a completed authority prescription form; and (b) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).
Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos) Alternatively, applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
Category / Program: Category / Program: Section 100 – (Highly Specialised Drugs Program) Public Hospital/Private Hospital (Code HB / HS)
Prescriber type: Medical Practitioners
Restriction: Authority Required (in writing only via post/electronic)
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.
Episodicity: [blank]
Severity: [blank]
Condition: Hereditary transthyretin amyloidosis
Indication: Hereditary transthyretin amyloidosis
Treatment Phase: Continuing Treatment
Population criteria: Patient must have previously received PBS-subsidised treatment with this drug for this condition.
Clinical criteria: Patient must continue to demonstrate clinical benefit.
AND
Clinical criteria: Patient must not be permanently bedridden, OR

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Patient must not be receiving end-of-life care
Prescribing Instructions: Applications for authorisation under this treatment phase must be made via the Online PBS Authorities System (real time assessment) or in writing via HPOS form upload or mail. If the application is submitted through HPOS form upload or mail, it must include: (a) a completed authority prescription form; and (b) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).
Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos) Alternatively, applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
Category / Program: Category / Program: Section 100 – (Highly Specialised Drugs Program) Public Hospital/Private Hospital (Code HB / HS)
Prescriber type: Medical Practitioners
Restriction: Authority Required (in writing only via post/electronic)
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.
Episodicity: [blank]
Severity: [blank]
Condition: Hereditary transthyretin amyloidosis
Indication: Hereditary transthyretin amyloidosis
Treatment Phase: Grandfather arrangements
Population criteria:
Patient must have received treatment with this drug for this condition prior to [PBS listing date]
Clinical criteria:
The patient must have previously received non-PBS subsidised treatment with this drug for this condition
Patient must continue to demonstrate clinical benefit.
AND
Clinical criteria:
Patient must not be permanently bedridden, OR
Patient must not be receiving end-of-life care
Prescribing Instructions:

Applications for authorisation under this treatment phase must be made via the Online PBS Authorities System (real time assessment) or in writing via HPOS form upload or mail.

If the application is submitted through HPOS form upload or mail, it must include:

(a) a completed authority prescription form; and

(b) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).

Administrative Advice:

Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).

Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au

Applications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos)

Alternatively, applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos

Or mailed to:

Services Australia

Complex Drugs

Reply Paid 9826

HOBART TAS 7001

This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

21 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.

22 Sponsor's Comment

The sponsor had no comment.