

7.05 NUSINERSEN

Solution for injection 12 mg in 5 mL, Spinraza[®], Biogen Australia Pty Ltd

1 Purpose of submission

- 1.1 The standard re-entry resubmission requested a Section 100 (Highly Specialised Drug Program) Authority Required (Written) listing for treatment of individuals with pre-symptomatic spinal muscular atrophy (SMA) with 3 copies of the survival of motor neuron 2 (*SMN2*) gene, aged less than 18 years.
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus the standard of care (SoC), which was the symptomatic treatment of patients with SMA with 3 copies of *SMN2* with nusinersen. Table 1 provides a summary of the key components of the resubmission.

Table 1: Key components of the clinical issue addressed by the resubmission

Component	Description
Population	Treatment of individuals with pre-symptomatic SMA (<i>SMN1</i> deletion or mutation) with a <i>SMN2</i> copy number of 3 aged under 18 years. ^a
Intervention	Nusinersen administered at a dose of 12 mg via intrathecal injection with four loading doses and two maintenance doses in year 1 and three doses per year thereafter.
Comparator	Nusinersen (administered as above) upon symptom onset.
Outcomes	<ul style="list-style-type: none"> • Time to death or respiratory intervention (primary endpoint) • Survival and Motor function as assessed by HINE-2, CHOP INTEND, and WHO instruments • Safety
Clinical claim	In individuals with pre-symptomatic SMA with 3 <i>SMN2</i> copies, nusinersen is clinically superior in terms of comparative effectiveness and no worse in terms of comparative safety, compared to treatment with nusinersen upon symptom onset in the same population.

Source: Table 1.1, p32 of the resubmission

CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE = Hammersmith Infant Neurological Examination; SMA = spinal muscular atrophy; *SMN* = survival of motor neuron; WHO = World Health Organization

Underlined text indicates the proposed additional patient population compared current nusinersen PBS listing.

^a The resubmission also proposed a change in the current pre-symptomatic PBS listing to allow initiation of nusinersen treatment in patients aged less than 18 years, instead of the current 36 months.

2 Background

Registration status

- 2.1 Nusinersen was TGA registered “for the treatment of 5q spinal muscular atrophy (SMA)” on 2 November 2017. The TGA indication would include the patient population in the proposed restriction.

Previous PBAC consideration

- 2.2 This was a resubmission for the pre-symptomatic initiation of nusinersen for the treatment of SMA. The PBAC has considered several submissions for this population. Nusinersen for the pre-symptomatic treatment of SMA in individuals with 1, 2 or 3 copies of *SMN2* was considered at the July 2019 and November 2019 PBAC meetings. Subsequently, pre-symptomatic treatment of SMA in individuals with 1 or 2 copies of *SMN2* was considered at the July 2020 PBAC meeting.
- 2.3 Table 2 provides a summary of the outstanding matters of concern relating to the SMA population with 3 *SMN2* copies identified in the November 2019 submission, as provided by the resubmission.

Table 2: Summary of outstanding matters of concern from previous submission

Matter of concern	How this resubmission addressed it
<p>PBS restriction</p> <p>The PBAC considered that in the absence of further information to better predict the progression of pre-symptomatic patients with SMA, it may be appropriate to restrict any future listing of nusinersen for the pre-symptomatic initiation of treatment to those with 2 or less copies of <i>SMN2</i> (paragraph 11.4, nusinersen PSD, July 2019 PBAC meeting).</p>	<p>Nusinersen treatment for individuals with 1 or 2 <i>SMN2</i> copies in the pre-symptomatic setting was PBS-listed in December 2020. Concern regarding the appropriateness of listing nusinersen for the pre-symptomatic treatment of SMA with 3 copies of <i>SMN2</i> still remains as no additional data was provided to allow the progression of pre-symptomatic patients with SMA to be better predicted.</p>
<p>Clinical</p> <p>PBAC considered there was likely an incremental benefit from pre-symptomatic treatment with nusinersen compared with symptomatic treatment. However, the magnitude of incremental benefit could not be ascertained without appropriate comparative data (paragraph 11.3, nusinersen PSD, July 2019 PBAC meeting).</p>	<p>Not addressed. No data was provided in the resubmission to allow the magnitude of incremental benefit for pre-symptomatic nusinersen treatment compared to symptomatic treatment to be ascertained.</p>
<p>Economic</p> <p>The PBAC considered the economic model was unsuitable for decision making based on issues around extrapolation of treatment effect, estimated incremental duration of treatment, estimated utility gain and assumption of no difference in adverse events between pre-symptomatic initiation of treatment and symptomatic treatment (paragraph 11.6, nusinersen PSD, July 2019 PBAC meeting).</p>	<p>The resubmission claimed that these issues were previously addressed in the July 2020 submission, resulting in a positive recommendation in individuals with 1-2 <i>SMN2</i> copies. An updated cost-utility analysis was provided in the current resubmission, using the same methodology as the July 2020 submission, updated to reflect the proposed population (i.e., 3 <i>SMN2</i> copies) and recent changes to clinical practice (i.e., nusinersen listing in Type IIIb/c SMA). The PBAC previously noted it was uncertain whether the model structure accurately reflected the progression of SMA and that a rebate to reduce uncertainty was required (paragraph 7.6, nusinersen PSD, July 2020 PBAC meeting). Efficacy benefit for pre-symptomatic treatment was still not based on clinical data and the economic model continued to rely on assumptions (e.g., benefit based on assumed difference in utility, 20-year duration of treatment effect, no SMA-related mortality).</p>

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Matter of concern	How this resubmission addressed it
Estimated cost to PBS	
The PBAC noted that the sponsor had not confirmed whether the rebate for [REDACTED] [REDACTED] [REDACTED] [REDACTED] which currently applies for patients diagnosed with SMA Type II or IIIa is intended to be extended to patients who initiate treatment prior to the onset of symptoms and requested that any future resubmission confirm this matter (paragraph 11.7, nusinersen PSD, July 2019 PBAC meeting).	Addressed. The resubmission proposed a rebate for [REDACTED] [REDACTED] for individuals with pre-symptomatic SMA with 3 SMN2 copies.
The PBAC advised that any resubmission should include revised financial estimates to account for underestimate in treatment duration, potential increase in SMA screening and for patients enrolled in any ongoing clinical trials for investigating treatments for pre-symptomatic patients genetically diagnosed with SMA (paragraph 11.8, nusinersen PSD, July 2019 PBAC meeting).	Addressed. The resubmission included updated financial estimates with a revised treatment duration (as used in the updated economic model) and the impact of an increase in SMA screening. The net increase in financial implications was a result of the earlier treatment of the population who would have received nusinersen following the onset of symptoms (i.e., costs were brought forward).

Source: Table 1.2, p33 of the resubmission

PSD = public summary document; SMA = spinal muscular atrophy; SMN = survival of motor neuron

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

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed price for maximum quantity	Maximum quantity	Number of repeats	Available brands
INITIAL LOADING DOSE				
Nusinersen 12 mg/5 ml injection, 5 mL vial, 1	DPMQ (public): \$110,000 DPMQ (private): \$110,047.82 AEMP: \$110,000 ^a effective price: \$1	1	3	Spinraza
MAINTENANCE TREATMENT				
Nusinersen 12 mg/5 ml injection, 5 mL vial, 1	DPMQ (public): \$110,000 DPMQ (private): \$110,047.82 AEMP: \$110,000 ^a effective price: \$1	1	0	Spinraza

^a Published approved ex-manufacturer price.

Category/Program	Section 100 – Highly Specialised Drugs Program
Restriction	<input checked="" type="checkbox"/> Authority Required (in writing only via post/HPOS upload)
Condition	Pre-symptomatic spinal muscular atrophy (SMA)
PBS Indication	Initial treatment of pre-symptomatic spinal muscular atrophy (SMA) - Loading doses
Treatment phase	Initial – New patients
Treatment criteria	Must be treated by a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA; or in consultation with a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA.
Clinical criteria	The condition must have genetic confirmation of 5q homozygous deletion of the survival motor neuron 1 (SMN1) gene; OR The condition must have genetic confirmation of deletion of one copy of the SMN1 gene in addition to a pathogenic/likely pathogenic variant in the remaining single copy of the SMN1 gene, AND

	<p>The condition must have genetic confirmation that there are 1 to 2 3 copies of the survival motor neuron 2 (<i>SMN2</i>) gene, AND The condition must be pre-symptomatic, AND The treatment must be given concomitantly with best supportive care for this condition, AND The treatment must not exceed four loading doses (at days 0, 14, 28 and 63) under this restriction, AND Patient must be untreated with gene therapy.</p>
Population criteria	Patient must be aged under 36 months 18 years prior to commencing treatment.

Source: Table 1.9, p46 of the resubmission
Bold text reflects change from the current listing.

- 3.1 This request could have been more clearly expressed as two separate requests for expansion of the current listing:
- The addition of treatment in the pre-symptomatic SMA setting for patients with 3 *SMN2* copies who are aged less than 18 years when commencing treatment; and
 - Modification of the existing pre-symptomatic SMA listing to increase the age at which patients with 1 to 2 copies of *SMN2* can commence treatment with nusinersen from under 36 months to under 18 years.
- 3.2 The resubmission stated that the continuation criteria for the current PBS restriction for nusinersen would also be applicable under the proposed initiation restriction, therefore no specific continuation criteria was proposed.
- 3.3 No grandfathering restriction was proposed in the resubmission. However, the request to extend listing of pre-symptomatic treatment to patients under 18 years of age was functionally a grandfathering restriction as it would only affect prevalent patients, with all incident patients likely to be identified via newborn bloodspot screening (NBS), which would allow them to be treated under the current restriction (i.e., aged < 36 months). The Pre-Sub-Committee Response (PSCR) and the pre-PBAC response stated that this request was made to avoid creating a treatment gap and noted that it would not affect the current listing for pre-symptomatic treatment of patients with 1 or 2 *SMN2* copies as symptom onset would occur before 3 years of age. The ESC and the PBAC noted that there was no clinical evidence presented in support of the proposed increased age for commencement of pre-symptomatic treatment.
- 3.4 An effective price of \$ [redacted] per dose with [redacted] [redacted] [redacted] [redacted] was proposed. This was the same as the special pricing arrangement (SPA) that is currently applied in the symptomatic setting for SMA Type II/IIIa and in the pre-symptomatic setting for individuals with SMA with 1 to 2 *SMN2* copies. The current SPA for symptomatic treatment includes an effective nusinersen price of \$ [redacted] but no [redacted] for patients with SMA Type I and an effective price of \$ [redacted] with [redacted] for SMA Type IIIb/c. That is, in symptomatic treatment, the effective price is higher for patients likely to have more severe disease and lower for patients likely to have less severe disease. However, the proposed price

for pre-symptomatic treatment in patients with 3 copies of *SMN2* was the same as for patients with 1 to 2 copies of *SMN2*.

- 3.5 In its consideration of onasemnogene abeparvovec for the pre-symptomatic treatment of SMA in patients with 3 copies of *SMN2*, the PBAC previously considered that the incremental benefit of pre-symptomatic treatment with onasemnogene abeparvovec compared to symptomatic treatment with disease modifying therapies (DMT) for patients with 3 *SMN2* copies would be less than that for patients with 1 to 2 *SMN2* copies due to patients with 3 *SMN2* copies likely having better outcomes in the absence of pre-symptomatic treatment (i.e., the baseline for patients would be higher therefore the potential incremental benefit would be lower) (paragraph 7.6, onasemnogene abeparvovec Public Summary Document (PSD), November 2022 PBAC meeting) and that to be considered similarly cost-effective, the price of onasemnogene abeparvovec in individuals with 3 *SMN2* copies would need to be lower than for those with 1-2 *SMN2* copies (paragraph 7.10 onasemnogene abeparvovec PSD, November 2022 PBAC meeting). The PBAC considered the same applied for nusinersen: i.e., that the price of nusinersen for pre-symptomatic treatment in patients with 3 copies of *SMN2* should be lower than for patients with 1 to 2 copies of *SMN2*. The PSCR disagreed that the incremental benefit was lower for patients with 3 copies *SMN2*. The PSCR argued that the proposed ICER was lower than the accepted ICER for symptomatic treatment of SMA and that “aligning cost-effectiveness and price directly to severity assumes nusinersen treatment effect is linear across the 1-2 and 3 *SMN2* copies populations”.
- 3.6 The requested maximum quantity and number of repeats remained unchanged from the current nusinersen listing.

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

4 Population and disease

- 4.1 SMA is an autosomal recessive progressive neuromuscular disease caused by mutations or deletions in the *SMN1* gene on chromosome 5q. Alterations to this gene result in deficiency of SMN protein, which in turn results in loss of motor function and respiratory failure, which is a major cause of morbidity and mortality. The *SMN2* gene also produces SMN protein, albeit at low levels which are not sufficient to sustain survival of spinal motor neuron function. As *SMN2* copy number varies from patient to patient, there is a clinical spectrum of the disease where fewer *SMN2* gene copies may correlate to earlier age of onset and increased disease severity. SMA is classified based on age of onset and maximal motor function achieved, into types (0, I, II, III and IV) with Type III SMA further classified into subtypes (a, b, c), see Table 3.

Table 3: Classification of SMA based on age of onset and maximal motor function achieved

Terminology	SMA type	SMN2 copies ^{a, b}	Age at symptom onset	Highest motor function achieved without treatment	Average life expectancy without treatment
Pre-natal	0	1	Prenatal	None – unable to sit or roll	Death within weeks
Infantile-onset	I	1, 2, 3	< 6 months	None – unable to sit or roll	Death within two years
Childhood-onset	II	2, 3, 4	6 - 18 months	Sitting – unable to walk independently	Survival into adulthood
	III	2, 3, 4	< 3 years (IIIa) > 3 years (IIIb) > 12 to ≤ 18 years (IIIc)	Independently stand and walk, may lose ability to walk over time	Normal lifespan
Adult-onset	IV	4, 5	> 18 years	Normal – mild motor impairment	Normal lifespan

Source: Tables 1.3 and 1.4, pp 34 and 35 of the resubmission

SMA = spinal muscular atrophy; SMN = survival of motor neuron

^a In SMA the majority of infants (>90%) with two SMN2 copies develop SMA Type I and the majority of infants (>80%) with 3 copies of SMN2 develop SMA Type II. The resubmission sourced this statement from Sampaio 2018, however this data was inconsistent with the assumptions used in Sections 3 and 4 of the resubmission where data from 11 studies was used to calculate the distribution of SMN2 copy number by SMA type.

^b Figures in bold letters represent the most common copy numbers.

- 4.2 Under the proposed restriction, patients with confirmed *SMN1* deletion or mutation and an *SMN2* copy number of 3 will be treated with nusinersen in the absence of any SMA symptoms. Currently, nusinersen is PBS subsidised for patients with confirmed *SMN1* deletion or mutation and an *SMN2* copy number of 1 or 2, as well as for symptomatic SMA populations.
- 4.3 The resubmission reported that in clinical practice, healthcare providers currently offer NBS to all babies born in Australia and that NBS for the detection of SMA in Australian infants is expected to roll out nationally. It is therefore likely that, once NBS for the detection of SMA is implemented across Australia, all patients with SMA will be detected soon after birth and eligibility for the proposed nusinersen listing will be able to be determined.

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

5 Comparator

- 5.1 The resubmission nominated nusinersen in the symptomatic setting as the main comparator (SoC) to the proposed use of nusinersen in the pre-symptomatic setting. This was based on the absence of a DMT being listed on the PBS for the treatment of SMA in patients with 3 copies of *SMN2* (as of March 2023). The nominated comparator was previously accepted by the PBAC (July 2019 PBAC meeting) and was appropriate.
- 5.2 The resubmission additionally nominated risdiplam and onasemnogene abeparvovec as near market comparators for the treatment of individuals with pre-symptomatic SMA with 3 copies of *SMN2*. Expansion of the onasemnogene abeparvovec indication was sought at the November 2022 PBAC meeting to include individuals with pre-symptomatic SMA with 3 *SMN2* copies but was not recommended, with another resubmission considered at the July 2023 PBAC meeting. Reimbursement was sought

for risdiplam for the same population (as listed in the PBAC meeting agenda for March 2023). The submission to expand the PBS listing for risdiplam to include the pre-symptomatic treatment of patients with 3 copies of *SMN2* was withdrawn by the sponsor.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician discussed the heterogenous spectrum of disease severity that can develop when a patient with 3 copies of *SMN2* is not treated pre-symptomatically and the significant need for pre-symptomatic treatment to prevent irreversible residual motor deficit. The clinician noted all types of SMA represent a severe disease, but the disease is less severe on average in patients with 3 copies of *SMN2* compared with patients with fewer copies. The clinician discussed that SoC for patients who have not developed symptoms includes education on how to monitor for symptoms at home and regular assessment by neuromuscular specialists to minimise treatment delay. The clinician noted that this places a particularly high burden on families in rural and remote areas. The clinician also addressed other matters in response to the Committee's questions. The PBAC considered that the hearing was informative.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (1), health care professionals (1) and The National Paediatric Medicines Forum via the Consumer Comments facility on the PBS website. The comments emphasised the importance of early diagnosis and treatment of SMA, including the potential for improved motor function in children with SMA who undergo early intervention.
- 6.3 The PBAC noted the advice received from the National Paediatric Medicines Forum (NPMF) in support of PBS listing of nusinersen for patients with SMA who have 3 copies of *SMN2*. The NPMF considered that this expanded listing would improve equitable access and best outcomes for all stakeholders, while reducing anguish for families of recently diagnosed babies. The NPMF noted that currently approximately 30% of newborns with a SMA diagnosis and 3 *SMN2* copies are not eligible for genetic therapy. By the time signs of irreversible motor neuron degeneration manifest and they become eligible for genetic therapy, it can be too late to save the death of many more motor neurons, leading to the potential for a lifetime of neurodisability. The range of presentations are intermediate in half (onset in first three years and ability to sit but not walk), severe for 15% (inability to sit), and 'mild' for one third (falls and mobility problems in childhood). The NPMF also referred to Australian data (Kariyawasam et al, 2023) demonstrating significant functional differences from pre-symptomatic treatment, with all children with 3 *SMN2* copies achieving walking status when treated pre-symptomatically, whereas walking was rarely achieved in those treated after symptom onset.

Clinical studies

- 6.4 The resubmission was primarily based on an updated interim analysis of NURTURE, an ongoing phase 2 study of nusinersen in infants with confirmed homozygous or compound heterozygous *SMN1* deletion and either 2 or 3 copies of *SMN2*. NURTURE was included in previous nusinersen submissions that were considered at the November 2017, July 2019 and July 2020 PBAC meetings when interim analyses from the February 2017 (median follow up unknown), May 2018 (median follow up = 27.1 months; interim analysis 4) and March 2019 (median follow-up = 33.8 months) data cut-offs were presented. The data from the most recent NURTURE interim analysis (data cut off February 2020, interim analysis 5: median follow up 48.3 months for all patients and 44.44 months for the 10 patients with 3 copies of *SMN2*) formed the evidence base of the current resubmission. A conference presentation including data from a subsequent interim analysis (Crawford 2022; data cut-off February 2021, median follow-up 4.9 years for all patients) was also presented.
- 6.5 In addition to NURTURE, four studies (Alves 2021, Boemer 2022, Kariyawasam 2023 and Vill 2021) were identified in the resubmission that investigated individuals with SMA treated with nusinersen prior to the onset of symptoms. These studies were included as supportive data to inform the effectiveness of nusinersen used in a pre-symptomatic SMA population with 3 *SMN2* copies.
- 6.6 Additionally, a naïve, numerical comparison of results of pre-symptomatic treatment with nusinersen and treatment upon symptom onset was presented in the resubmission. No formal statistical comparisons were provided. The data presented to represent treatment upon symptom onset was comprised of six studies (Alves 2021, Aragon-Gawinska 2018, Chen 2021, CS3A, EMBRACE and Kariyawasam 2023). CS3A was previously used in the naïve informal indirect comparison with NURTURE presented in the nusinersen July 2020 and July 2019 PBAC (re)submissions.
- 6.7 While the resubmission also proposed an increase in age cut off for pre-symptomatic patients with SMA and 1 or 2 copies of *SMN2* (from 36 months to 18 years), no data was provided to support the use of nusinersen in this population.
- 6.8 Details of the studies presented in the resubmission to support the pre-symptomatic treatment of patients with SMA with 3 copies of *SMN2* are provided in Table 4.

Table 4: Studies and associated reports presented in the resubmission

Study ID	Study design	Publication citation
Clinical trial		
SM201/NURTURE ^a	Phase 2	Clinical study report, Interim 5. 05 November 2020 Crawford (2022). Nusinersen Effect in Infants in the Presymptomatic Stage of SMA: 4.9-Year Interim of the NURTURE trial. MDA (2022) Muscular Dystrophy Association – 4th Clinical and Scientific Conference
Observational studies to support pre-symptomatic treatment		
Alves 2021	Prospective case series	Alves, C. R. R., et al. (2021). "Implications of circulating neurofilaments for spinal muscular atrophy treatment early in life: A case series." <i>Molecular Therapy - Methods and Clinical Development</i> 23: 524-538.
Boemer 2022	Prospective cohort study	Boemer, et al. (2022). Three years pilot of spinal muscular atrophy newborn screening turned into official program in Southern Belgium. <i>Sci Rep.</i> 2021 Oct 7;11(1):19922.
Kariyawasam 2023	Observational non-randomised cohort study	Kariyawasam, S., et al (2023). Newborn screening for spinal muscular atrophy in Australia: a non-randomised cohort study. <i>Lancet Child and Adolescent health.</i> S2352-4642(22)00342-X
Vill 2021, 2022	Prospective cohort study	Vill, K., et al. (2019). "One year of newborn screening for SMA – Results of a German pilot project." <i>Journal of Neuromuscular Diseases</i> 6(4): 503-515.
		Vill, K., et al. (2021). "Newborn screening for spinal muscular atrophy in Germany: clinical results after 2 years." <i>Orphanet Journal of Rare Diseases</i> 16(1).
		Mueller-Felber, W., et al. (2019). "P.211Pilot study of genetic newborn screening for spinal muscular atrophy in Germany: clinical results after more than a year." <i>Neuromuscular Disorders</i> 29: S128.

Source: Table 2.4, p60 of the resubmission

Blue shaded cells indicate studies that PBAC has previously considered, though with an earlier data cut-off.

^a In addition to earlier data cuts for NURTURE, the PBAC has previously considered some outcomes data from the February 2-20 interim analysis in the pre-PBAC response to the July 2020 resubmission (Figure 2, nusinersen PSD, July 2020).

6.9 The key features of the studies are summarised in Table 5.

Table 5: Key features of the included evidence

Study	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
NURTURE	25	OL, NC, 5 years Interim analysis 5 follow-up 44.44 months	High ^a	Age <6 weeks with SMA and no symptoms; 2 or 3 <i>SMN2</i> copies	EFS, OS, WHO milestones, HINE- 2, CHOP Intend, HFMSE, 6MWT	Not used
Alves 2021	22	Longitudinal cohort study ^b , NC; follow-up was up to 1,095 days	High ^a	Aged 0 to 3 years, with pre- symptomatic or symptomatic SMA; 2, 3 or 4 <i>SMN2</i> copies	WHO milestones, HINE-2, CHOP Intend, HFMSE	
Boemer 2022	9	3-year pilot screening study of neonates for SMA	High ^a	Newborns with pre- symptomatic SMA; 2, 3 or 4 <i>SMN2</i> copies	HINE-2, CHOP Intend	
Kariyawasam 2023	33	Prospective cohort study; follow-up 2 years	High ^a	Patients aged <16 years ^c ; pre-symptomatic or symptomatic SMA with 2, 3 or 4 <i>SMN2</i> copies	WHO milestones, HINE-2	
Vill 2021, 2022	43	2-year pilot screening study of neonates for SMA	High ^a	Newborns with pre- symptomatic SMA with 2, 3 or 4 <i>SMN2</i> copies	HINE-2, CHOP Intend	

Source: Table 9, p11 nusinersen PSD November 2020, Alves 2021, Boemer 2022, Kariyawasam 2023, Vill 2022

6MWT = six-minute walking test; OL = open label; OS = overall survival; CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; EFS = event-free survival; NC = non-comparative; SMA = spinal muscular atrophy; HINE = Hammersmith Infant Neurological Examination; HFMSE = Hammersmith Functional Motor Scale-Expanded; SMA = spinal muscular atrophy; SMN = survival of motor neuron

^a Considered during the evaluation to have a high risk of bias due to being an open-label or non-randomised study.

^b Patients could receive either nusinersen or onasemnogene abeparvovec or both.

^c Median age at SMA diagnosis of screening group = 2.1 weeks. Median age at SMA diagnosis of comparator group = 47.8 weeks.

Blue shaded cells indicate studies that PBAC has previously considered, though with an earlier data cut-off.

6.10 The resubmission included six studies to represent the use of nusinersen in patients with symptomatic SMA with 3 copies of *SMN2* (i.e., SoC). Details of these studies are presented in Table 6.

Table 6: Studies and associated reports presented in the resubmission describing nusinersen treatment of symptomatic patients with 3 SMN2 copies

Author year/ Study ID	Study design	Citation	Relevant data
Acsadi 2021/ EMBRACE	P2 trial	Safety and efficacy of nusinersen in spinal muscular atrophy: The EMBRACE study. <i>Muscle & nerve</i> , 63(5), 668–677.	Subgroups with SMN2 copy number of 3 presented (N=10)
Alves 2021	Prospective case series	Alves, C. R. R., et al. (2021). "Implications of circulating neurofilaments for spinal muscular atrophy treatment early in life: A case series." <i>Molecular Therapy - Methods and Clinical Development</i> 23: 524-538.	IPD available for those with 3 SMN2 copies
Aragon-Gawinska 2018	Report of EAP results	Nusinersen in patients older than 7 months with spinal muscular atrophy type 1. <i>Neurology</i> 91(14): E1312-E1318.	Data for patients with 3 SMN2 copies available
Chen 2021	Observational cohort study	Real-world respiratory and bulbar comorbidities of SMA type 1 children treated with nusinersen: 2-Year single centre Australian experience. <i>Paediatric respiratory reviews</i> , 39, 54–60.	3 'newly diagnosed' patients described with 3 SMN2 copies
Finkel 2016/2021 CS3A	P2 trial	Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study." <i>The Lancet</i> 388(10063): 3017-3026. Finkel, R. S., et al. (2021). "Treatment of infantile-onset spinal muscular atrophy with nusinersen: final report of a phase 2, open-label, multicentre, dose-escalation study." <i>The Lancet Child and Adolescent Health</i> 5(7): 491-500.	2 patients with SMN2 copy number of 3
Kariyawasam 2023	Observational cohort study	Kariyawasam, S., et al (2023). Newborn screening for spinal muscular atrophy in Australia: a non-randomised cohort study. <i>Lancet Child and Adolescent health</i> . S2352-4642(22)00342-X	IPD available for those with 3 SMN2 copies

Source: Table 2.5, p67 of the resubmission.

IPD = individual patient data; SMA = spinal muscular atrophy; SMN = survival of motor neuron

Blue shaded cells indicate studies that PBAC has previously considered, but not data specific for the 3 copies SMN2 population.

Comparative effectiveness

6.11 The proportion of patients with 3 copies of SMN2 who experienced symptoms of SMA in NURTURE at 13 and 24 months is detailed in Table 7.

Table 7: NURTURE - SMA symptoms in patients with 3 copies of SMN2

	Interim analysis 4	Interim analysis 4	Interim analysis 5	Interim analysis 5
	At 13 months	At 24 months	At 13 months	At 24 months
Number of patients (N)	10	5	10	10
No. patients with percutaneous gastric tube inserted, n (%)	0	0	0	0
No. patients with weight below the 5th percentile, n (%)	0	0	0	0
No. patients with weight dropping 2 or more major percentiles over 6 months, n (%)	0	0	0	0
No. patients who lose a WHO milestone or fail to demonstrate all expected WHO milestones, n (%)	2 (20)	0	2 (20)	0
No. patients with manifestation of SMA symptoms, n (%)	2 (20)	0	2 (20)	0
Proportion, (95% CI)	0.20 (0.04-0.56)	0 (0.00-0.54)	0.20 (0.04-0.56)	0 (0.00-0.34)

Source: Nusinersen commentary July 2019 6.05.COM.51 Table 2.5.1, p43; Nusinersen CSR Interim 5 Tables 23, 24 and Table 2.23, p98 of the resubmission

SMA = spinal muscular atrophy; SMN = survival of motor neuron

Blue shaded data previously considered by the PBAC in the nusinersen submission, July 2019 PBAC meeting.

- 6.12 Despite a median follow-up time of 3.7 years for NURTURE Interim analysis 5, results were not provided for SMA symptoms observed beyond 24 months. The increase in follow up time for interim analysis 5 provided limited additional data regarding the onset of SMA symptoms in patients with 3 copies of *SMN2*. Although the number of patients was increased from five to 10 for the 24-month analysis, data for longer time durations was not provided. For both analyses, the number of patients with 3 copies of *SMN2* who reported any of the pre-defined SMA symptoms was small: at each interim analysis only two patients were reported to have manifestation of SMA symptoms (failed to achieve WHO milestones at that age) following 13 months of treatment and no patients who had received 24 months of treatment had manifestation of SMA symptoms (i.e., patients who failed to meet milestones at 13 months of treatment subsequently achieved all six WHO milestones and had no other predefined signs of symptoms of SMA).
- 6.13 An overview of symptom onset for patients in the supportive studies is provided in Table 8.

Table 8: Supportive studies – Summary of symptom onset in patients with SMA with 3 copies of SMN2^a

Study	Details of symptom onset
Vill 2021	The six patients treated with nusinersen with 3 SMN2 copies all remained without onset of symptoms over the observation period (median follow-up = 13 months). All treated patients with 3 SMN2 copies remained asymptomatic. All untreated patients with 3 SMN2 copies (n=4) developed proximal weakness during their first year.
Alves 2021	Of the five patients treated with nusinersen who had 3 SMN2 copies, two were pre-symptomatic at treatment initiation and three were symptomatic. The two pre-symptomatic participants remained symptom-free and achieved all motor milestones within a range of that expected in healthy children at 36 months of age. Only one of the three children symptomatic at treatment initiation achieved independent walking at 31.0 months, considerably later than expected
Boemer 2022	The two patients identified as having 3 SMN2 copies and were treated prior to the onset of symptoms were reported to have developed normally with no symptoms of SMA (aged 33 and 12 months at last assessment).

Source: Constructed during evaluation using p102-104 of the resubmission, Vill 2021

SMA = spinal muscular atrophy; SMN = survival of motor neuron

^a While Kariyawasam 2023 was listed as a supportive study, it was not clear which DMTs were received by the five participants enrolled with 3 SMN2 copies who received pre symptomatic treatment (either nusinersen or onasemnogene abeparvovec). Consequently, the data for pre-symptomatically treated patients from Kariyawasam 2023 was of limited value and has not been reported in the commentary.

6.14 No participants enrolled in NURTURE had died at the latest data cut-off. None of the participants with 3 SMN2 copies had met the primary endpoint of death or respiratory intervention, defined as either invasive or non-invasive ventilation for ≥ 6 hours/day continuously for ≥ 7 consecutive days or tracheostomy with median follow-up of 4.9 years (range 3.9 to 5.7 years) as reported by Crawford 2022. In the supportive studies, no deaths were reported in patients with SMA and 3 copies of SMN2.

6.15 The milestones of sitting without support, standing with assistance, hands-and-knees crawling, walking with assistance, standing alone, and walking alone are the motor milestones that the WHO expects healthy children to attain by 24 months of age. For NURTURE, the mean WHO total motor milestones over time are shown in Table 9.

Table 9: NURTURE - Shifts in milestones in patients with SMA with 3 copies of SMN2

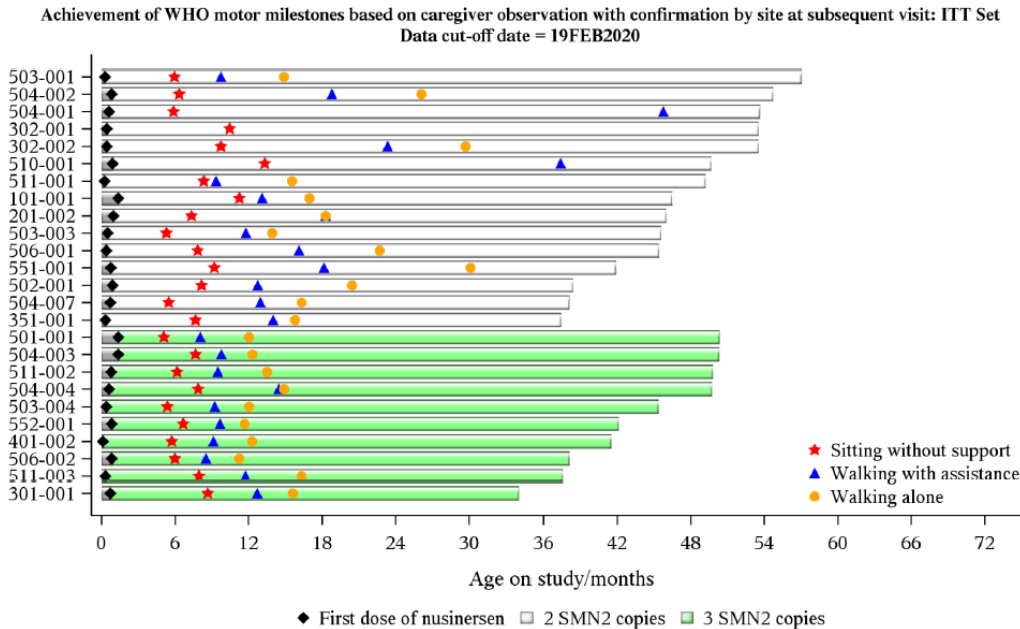
Motor milestones or Assessments	n (%)														
	Base-line	Day 64	Day 183	Day 302	Day 365	Day 421	Day 540	Day 659	Day 700	Day 778	Day 897	Day 1135	Day 1374	Day 1611	Last visit
N	7	10	10	10	10	10	10	9	9	10	10	8	5	0	10
Sitting without support	0	0	6 (60)	10 (100)	10 (100)	10 (100)	10 (100)	8 (89)	9 (100)	9 (90)	10 (100)	8 (100)	5 (100)	0	10 (100)
Hands-and-knees crawling	0	0	1 (10)	1 (10)	8 (80)	9 (90)	8 (80)	9 (100)	9 (100)	9 (90)	8 (80)	8 (100)	5 (100)	0	10 (100)
Standing with assistance	0	1 (10)	2 (20)	10 (100)	10 (100)	9 (90)	10 (100)	9 (100)	9 (100)	10 (100)	10 (100)	8 (100)	5 (100)	0	10 (100)
Walking with assistance	0	0	0	6 (60)	9 (90)	9 (90)	10 (100)	9 (100)	9 (100)	9 (90)	10 (100)	8 (100)	5 (100)	0	10 (100)
Standing alone	0	0	0	1 (10)	6 (60)	7 (70)	10 (100)	9 (100)	9 (100)	10 (100)	10 (100)	8 (100)	5 (100)	0	10 (100)
Walking alone	0	0	0	0	5 (50)	7 (70)	10 (100)	9 (100)	9 (100)	9 (90)	10 (100)	8 (100)	5 (100)	0	10 (100)

Source: Constructed during evaluation using NURTURE CSR Interim 5 Table 47

SMA = spinal muscular atrophy; SMN = survival of motor neuron

- 6.16 Individual patient results for WHO milestones are presented in Figure 1, with patients with 3 copies of *SMN2* shown in green. The ESC noted that this analysis showed that patients with 3 copies of *SMN2* treated pre-symptomatically with nusinersen generally achieved motor milestones at earlier timepoints than those with 1-2 copies of *SMN2*.

Figure 1: NUTURE - WHO motor milestones achieved by age on study



The horizontal bars show the age of the subject at the last visit a subject attended.

ITT = intention to treat; SMN = survival of motor neuron; WHO = World Health Organisation

- 6.17 Results for WHO milestones were not reported for patients with SMA with 3 copies of *SMN2* in the supportive studies.
- 6.18 The proportion of patients who achieved various motor milestones defined by the HINE motor milestones (Section 2) in NUTURE is detailed in Table 10. The median age for achieving standing independently was 13.0 months and for achieving walking independently was 13.7 months for participants with 3 *SMN2* copies. The resubmission claimed that patients treated prior to the onset of symptoms achieved milestones at ages similar to those expected in healthy infants without SMA.

Table 10: NUTURE - Improvement in HINE motor milestones (Section 2) in patients with SMA with 3 copies of SMN2

Improvement in HINE Section 2, N (%)	Baseline	Day 64	Day 183	Day 302	Day 365	Day 421	Day 540	Day 700	Day 778	Last visit
N	10	10	10	10	10	10	10	10	6	10
Head control: all time upright	2 (20)	5 (50)	10 (100)	10 (100)	10 (100)	10 (100)	10 (100)	10 (100)	6 (100)	10 (100)
Ability to kick, touch toes	0	0	7 (70)	9 (90)	9 (90)	7 (70)	9 (90)	10 (100)	6 (100)	10 (100)
Rolling, Prone to supine or supine to prone	0	1 (10)	9 (90)	10 (100)	9 (90)	10 (100)	10 (100)	10 (100)	6 (100)	10 (100)
Sitting, stable	0	0	5 (50)	10 (100)	10 (100)	10 (100)	10 (100)	10 (100)	6 (100)	10 (100)
Crawling, on hands and knees	0	0	1 (10)	8 (80)	9 (90)	10 (100)	10 (100)	10 (100)	6 (100)	10 (100)
Stands unaided	0	0	0	1 (10)	7 (70)	8 (80)	10 (100)	10 (100)	6 (100)	10 (100)
Cruising (walk holding on)	0	0	1 (10)	7 (70)	10 (100)	10 (100)	10 (100)	10 (100)	6 (100)	10 (100)
Walking independently	0	0	0	0	5 (50)	7 (70)	10 (100)	10 (100)	6 (100)	10 (100)
Achievement of all of the above	0	0	0	0	5 (50)	7 (70)	10 (100)	10 (100)	10 (100)	10 (100)

Source: Table 2.22, p94 of the resubmission

SMA = spinal muscular atrophy; SMN = survival of motor neuron

Blue shading indicates data previously considered by the PBAC.

For some motor milestones, different sub-characteristics of the HINE motor milestones were previously presented (e.g., walking – bouncing was presented in July 2019 for patients aged up to 6 months but not in the resubmission) and hence not all earlier data has previously been reviewed. Also, not all data points shown above were in the previous submission.

Naïve indirect comparison

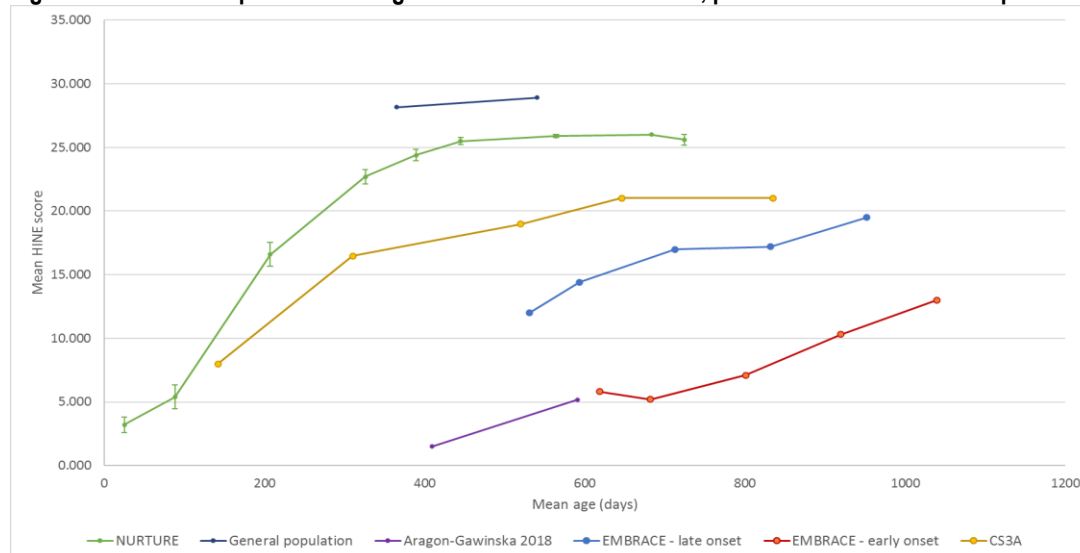
- 6.19 The resubmission presented a naïve numerical comparison of the results reported in the studies investigating pre-symptomatic treatment compared to the results of the symptomatic studies in patients with SMA with 3 SMN2 copies. No formal statistical comparisons were provided. The resubmission stated that the sponsor acknowledged the limitations of these naïve comparisons; however, these were presented in the resubmission to be informative to the PBAC.
- 6.20 For the previous submission in July 2019, the PBAC noted that the comparison of pre-symptomatic treatment to symptomatic treatment was informed by a naïve indirect comparison with multiple transitivity issues and was considered unlikely to be meaningful or reliable (paragraph 6.26, nusinersen PSD, July 2019 PBAC meeting). Even though a new set of comparator studies were used in the naïve comparison in the resubmission (instead of CHERISH and ENDEAR, which were excluded in the resubmission), substantial transitivity and applicability issues remain, and the results were likely biased in favour of pre-symptomatic treatment. As such, the evaluation considered the indirect analysis should be interpreted with caution and overall, was unlikely to provide meaningful or accurate information on the magnitude of the incremental benefit of early treatment with nusinersen versus the treatment following symptom onset in the proposed population. The resubmission did not

provide any quantitative estimates of the incremental benefit (potentially) associated with pre-symptomatic treatment compared to symptomatic treatment.

- 6.21 The evaluation considered that the use of studies that included symptomatic treatment of SMA with nusinersen to inform SoC was likely unreasonable. Given the introduction of NBS, patients who have SMA and 3 copies of *SMN2* but have not developed symptoms will likely be much more closely monitored for symptoms (as this would allow patients to begin active treatment) than in the symptomatic treatment studies. This means that in the proposed PBS population, the delay in treatment will likely be shorter (and therefore associated with better outcomes) than in the included symptomatic studies. Therefore, using results from the symptomatic treatment studies to represent current SoC would likely bias the results against the current SoC in the proposed PBS population and favour pre-symptomatic treatment. The PBAC has previously noted this issue in the consideration of onasemnogene abeparvovec for pre-symptomatic treatment of SMA (paragraph 7.5, onasemnogene abeparvovec PSD, November 2022). The ESC noted this potential source of bias and agreed with the evaluation that this likely biased the results against the current SoC.
- 6.22 Additionally, there may be difference in the likely phenotype of patients enrolled in the pre-symptomatic studies with the symptomatic studies. The clinical course of patients with 3 copies of *SMN2* enrolled in pre-symptomatic studies was unknown and could include a wide spectrum of phenotypes, owing to the 3 copies of *SMN2* being an imperfect prognostic factor as discussed by the MSAC (i.e., it was unclear whether the patients would have otherwise developed any of the SMA types I-IV without pre-symptomatic treatment). Comparatively, patients enrolled in the symptomatic studies have a known SMA phenotype, which was likely more severe (i.e., primarily SMA types I-IIIa) than patients enrolled the pre-symptomatic studies, leading to a bias in favour of the pre-symptomatic studies.
- 6.23 None of the patients with an *SMN2* copy number of 3 died in any of the included studies reporting pre-symptomatic treatment. Similarly, none of the symptomatic treatment studies reported any death or permanent ventilation among patients with 3 *SMN2* copies who were treated after symptom onset.
- 6.24 The resubmission presented a comparison of the HINE-2 data in NURTURE with the corresponding HINE-2 scores derived from EMBRACE, CS3A and Aragon-Gawinska 2018. The resubmission claimed that whilst limited to a numerical comparison, the graph demonstrates that early treatment with nusinersen prior to the onset of symptoms yields favourable outcomes. Overall, irrespective of whether patients were treated pre-symptomatically or after symptom development, it appears that treatment with nusinersen will improve HINE-2 (Figure 2). The ESC noted that these results indicated that studies where treatment initiation was close to symptom onset (e.g., CS3A) had a trajectory of disease progression closer to that seen with pre-symptomatic treatment compared to where there was a longer delay (e.g., EMBRACE). This supports the hypothesis that with NBS, which is likely to result in very early

initiation of treatment once symptoms are identified, a small difference compared with pre-symptomatic treatment is likely.

Figure 2: Indirect comparison - Change in HINE-2 scores over time, patients with SMA with 3 copies of SMN2



Source: Figure 2.14, p112 of the resubmission

Notes: (1) NURTURE data represents pre-symptomatic treatment; general population represent unaffected children; all other studies represent symptomatic treatment; (2) Data for general population from Haatja 1999.

HINE = Hammersmith Infant Neurological Examination; SMA = spinal muscular atrophy; SMN = survival of motor neuron

6.25 A summary of the motor milestones achieved across all studies included in the indirect treatment comparison was provided in the resubmission. The resubmission acknowledged that the instruments and definitions of motor milestone attainment varied between studies and therefore may not be comparable and that variation exists between the studies with regard to the duration of disease prior to initiation of treatment. Due to the differences in motor milestone attainment methods and the variation in patient age and duration of disease prior to treatment, it was difficult to draw conclusions from the data.

Comparative harms

6.26 Of the included studies for pre-symptomatic treatment with nusinersen, NURTURE was the only study that reported safety of pre-symptomatic treatment with nusinersen. Safety data for NURTURE is presented in Table 11.

Table 11: Summary of adverse events in NURTURE – ITT Set^a

	2 SMN2 copies	3 SMN2 copies	N (%)
Number of patients dosed	15 (100)	10 (100)	25 (100)
Number of patients with AE	15 (100)	10 (100)	25 (100)
Number of patients with a moderate or severe event	13 (87)	6 (60)	19 (76)
Number of participants with a severe event	6 (40)	0	5 (20)
Number of participants with an event, possibly related or related to:			
Study treatment	5 (33)	6 (60)	11 (44)
Lumbar puncture	7 (47)	3 (30)	10 (40)
Number of participants with an event related to:			
Study treatment	0	0	0
Lumbar puncture	5 (33)	1 (10)	6 (24)
Number of participants with a serious event	9 (60)	3 (30)	12 (48)
Number of participants with a serious event related to study treatment	0	0	0
Number of participants discontinuing treatment due to an event	0	0	0
Number of participants withdrawing from study due to an event	0	0	0

Source: Table 2.28, p106 of the resubmission

^a As NURTURE safety data is available only for a small number of patients with 3 copies of *SMN2*, data is also presented for patients with 2 copies of *SMN2*.

AE = adverse event; ITT = intention to treat

6.27 The PBAC previously noted that the majority of adverse events in NURTURE were respiratory in nature and appeared to be related to the SMA disease process. However, the PBAC noted that the long-term safety of repeated lumbar puncture in the context of a lifelong disease was unknown (paragraph 7.5, nusinersen PSD, July 2019 PBAC meeting and paragraph 6.28, nusinersen PSD, July 2020 PBAC meeting). The ESC considered that since patients treated pre-symptomatically would receive a greater number of lumbar punctures compared to SoC, the resubmission’s claim that safety would be no worse than SoC was not supported.

Benefits/harms

6.28 The naïve indirect comparison presented in the resubmission did not allow for a quantitative comparison of the benefits and harms for the use of nusinersen for the treatment of SMA with 3 copies of *SMN2* in the pre-symptomatic versus symptomatic settings. Accordingly, a benefits/harms table has not been presented.

Clinical claim

6.29 The resubmission concluded that in individuals with pre-symptomatic SMA with 3 *SMN2* copies, nusinersen is clinically superior in terms of comparative effectiveness and no worse in terms of comparative safety, compared to treatment with nusinersen upon symptom onset in the same population.

6.30 The therapeutic conclusion was plausible but was not clearly supported by the evidence presented in the resubmission because:

- As in the previous submission, the clinical data available did not allow for an estimation of the incremental benefit of early nusinersen treatment compared to nusinersen treatment under the current PBS restriction. The PBAC previously noted

that without a control group, the relative effect of pre-symptomatic initiation of treatment with nusinersen cannot be accurately determined for those with 2 or 3 *SMN2* copies (paragraph 6.11, nusinersen PSD, July 2019 PBAC meeting).

- There remained substantial transitivity and applicability issues with the available data. The additional studies included did not allow the magnitude of incremental benefit (if any) of pre-symptomatic treatment compared to symptomatic treatment initiation to be estimated robustly since:
 - The underlying phenotype of patients enrolled in the pre-symptomatic studies was likely to be more favourable than those enrolled in the symptomatic studies;
 - There were differences in patient age between the two sets of studies which affects the interpretation of achievement of motor milestones (which are correlated with patient age);
 - Patients enrolled in the symptomatic studies likely experienced a longer time between symptom onset and treatment initiation than the proposed PBS population, who would be identified as having genetic SMA due to NBS.
- 6.31 Previously, the PBAC considered there was likely an incremental benefit from pre-symptomatic treatment with nusinersen compared with symptomatic treatment. However, the magnitude of incremental benefit could not be ascertained without appropriate comparative data (paragraph 11.3, nusinersen PSD, November 2019 PBAC meeting). The ESC considered that this conclusion still applied for the current resubmission, noting that the comparison of change in HINE-2 scores (Figure 2) indicated that the incremental benefit of pre-symptomatic treatment with nusinersen compared with symptomatic initiation decreased with earlier symptomatic initiation of nusinersen treatment.
- 6.32 The ESC noted that no clinical data was provided to inform the efficacy of pre-symptomatic initiation of nusinersen in patients with 1-3 *SMN2* copies aged under 3 to under 18 years, and as such, the ESC did not make any comments in relation to this patient population.
- 6.33 The ESC noted that it had previously considered the claim of non-inferior comparative safety was not adequately supported, and that the PBAC had previously noted that the long-term safety of repeated lumbar puncture associated with nusinersen in the context of a lifelong disease was unknown (paragraphs 6.27 and 6.28, nusinersen PSD, July 2020 PBAC meeting). The ESC considered that the same comments were applicable for this resubmission.
- 6.34 The PBAC considered that the claim of superior comparative effectiveness was plausible, with the magnitude of the benefit being difficult to estimate.
- 6.35 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data.

Economic analysis

6.36 The resubmission presented a modelled cost-utility analysis that was largely based on assumptions made by the sponsor. No data from the clinical evaluation was included in the model.

6.37 Table 12 provides a summary of the key components of the economic evaluation.

Table 12: Summary of model structure, key inputs and rationale

Component	Description	Justification/comments
Type of analysis	Cost-utility analysis	This was appropriate.
Outcomes	QALYs	This was appropriate.
Time horizon	20 years	The model applied mortality rates of the general population to both treatment arms irrespective of SMA type or treatment status; the assumption that all patients have a normal life expectancy may be optimistic. Additionally, a 20-year time horizon may also be optimistic given the NURTURE (Interim analysis 5) median follow-up time was 3.7 years for patients with 3 copies of SMN2.
Methods used to generate results	Cohort-based state transition (Markov) model	Reasonable, although the ESC noted the crudeness of the assumptions around transitions within the model.
Health states	15 health states corresponding to individuals with underlying SMA Type (I, II, IIIa, IIIb/c and IV), and treatment status (pre-symptomatic treated, pre-symptomatic untreated, and symptomatic treated), plus death.	The health states were modified to split Type IIIb/IV into two distinct health states, due to changes in the availability of nusinersen in individuals with Type IIIb/c SMA since the March 2020 submission. SMA Type IV pre-symptomatically treated and symptomatically treated health states were assumed to not occur for any patients under the proposed restriction in the base case.
Cycle length	6 months	Six monthly cycles may be too long and not sensitive enough to capture the likely rapid progression and deterioration of Type I SMA, which formed 25% of the estimated cohort.
Transition probabilities	Transition probabilities are not included in the model. Individuals in the SoC arm remain in their baseline health until symptom onset, when they transition to the corresponding (SMA type) symptomatic health state.	As for the model from the July 2020 submission, it is possibly unrealistic to have all patients of the same type becoming symptomatic at the same time. This does not model the degenerative and progressive nature of SMA in the model.
Duration of incremental effect for pre-symptomatic treatment	The benefit and cost savings decrease over 20 years to align with the utility and health care resource costs applied in the symptomatic SoC arm.	Assumption, and the ESC noted the sensitivity of the ICER to the assumption about the reduced rate of regression in the intervention arm of the model.
Discount rate	5% annually	Reasonable.
Proportion of each SMA type in cohort	Type I: 25.41%; Type II: 44.40%; Type IIIa: 22.40%; Type IIIb: 7.79%; Type IV: 0.00%	This was different to the July 2020 submission with a different source for data (Sarv 2021) used to inform the distribution. The ESC considered that the Sarv 2021 data appeared potentially useful but noted the relatively small sample size (n=57) introduced uncertainty into this distribution.

Source: Table 3.2, p124 of the resubmission

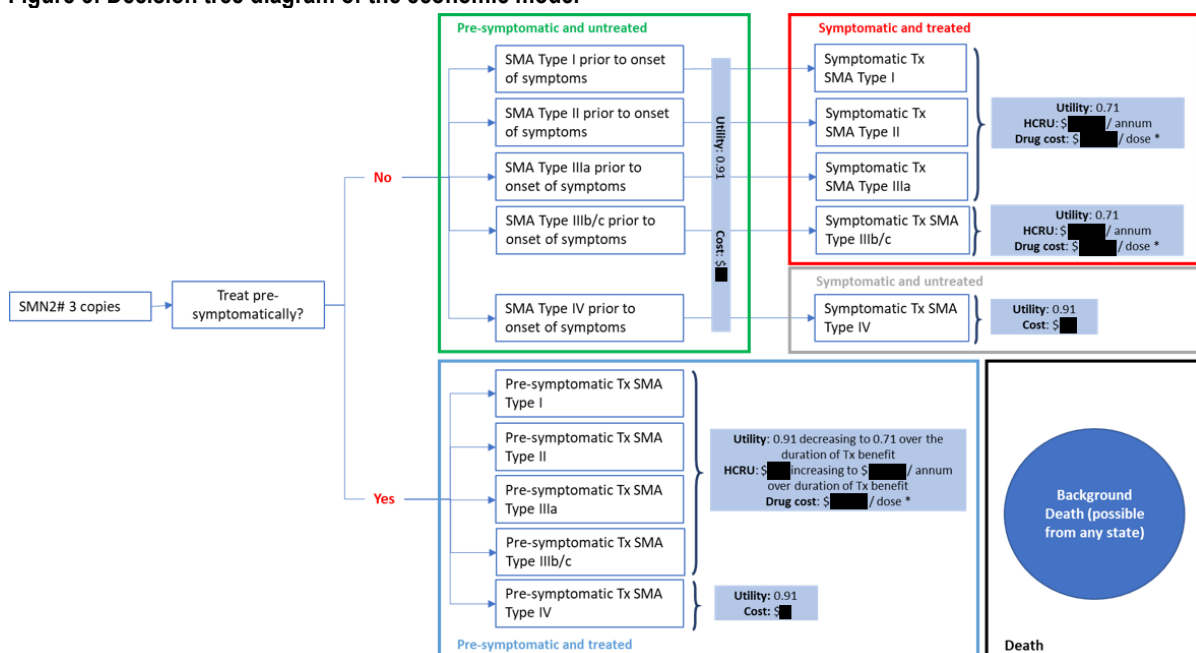
QALY=quality adjusted life year; SMA=spinal muscular atrophy; SMN = survival of motor neuron; SoC = standard of care

6.38 The resubmission model applied the same underlying structure and assumptions as the July 2020 submission, adjusted to reflect the proposed population. The

resubmission argued that given nusinersen was recommended by the PBAC for use in patients with ≤ 2 SMN2 copies in July 2020, it was reasonable to assume the economic model used in the resubmission was considered suitable for decision making. The evaluation considered that this may not be a reasonable assumption. The PSCR argued that the resubmission’s approach was taken to help maintain consistency of PBAC decision making across similar patient groups. The PBAC previously noted that it was uncertain whether the model structure accurately reflected the progression of SMA and that a rebate for III was required to reduce uncertainty (paragraph 7.6, nusinersen PSD, July 2020 PBAC meeting).

6.39 As per the July 2020 submission, the economic model in the resubmission compared quality of life and reductions in the costs of patient health care of nusinersen (in conjunction with best supportive care) for the treatment of individuals with pre-symptomatic SMA with 3 SMN2 copies versus SoC, consisting of treatment with nusinersen upon symptom onset for individuals with Type I, II, and III SMA (in conjunction with best supportive care). A Markov approach was employed to model the costs and QALYs in the two treatment arms separately in six-month cycles. An overview of the economic model is provided in Figure 3.

Figure 3: Decision tree diagram of the economic model



Source: Figure 3.4, p130 of the resubmission

HCRU = healthcare resource utilisation; SMA = spinal muscular atrophy; Tx = treatment; SPA = Special pricing arrangement

* Note: the current nusinersen SPA includes the rebate of █ █ █ for individuals with symptomatic Type II, IIIa and IIIb/c. The SPA proposed for nusinersen in the resubmission includes the rebate of █ █ █ for pre-symptomatic patients with 3 SMN2 copies.

1 HCRU costs derived from Dangouloff (2022).

2 Utilities derived from Lloyd (2019).

3 Patients assumed to be Type I, II, IIIa and IIIb/c assumed to transition to symptomatic and treated at 6 months, 12 months, 27 months and 10.5 years, respectively, in SoC (pre-symptomatic and untreated) arm.

6.40 The main differences between the current model and the July 2020 model were:

- The number of health states were changed to reflect the current nusinersen PBS-listing;
 - AE unit costs, health care costs and nusinersen price were updated; and
 - The proportion of each SMA type in the modelled cohort was changed from the previous model (Type I: 89.56%; Type II: 7.63%; Type IIIa: 0.80%; Type IIIb/IV: 2.01%) to the current model (Type I: 25.41%; Type II: 44.40%; Type IIIa: 22.40%; Type IIIb: 7.79%; Type IV: 0.00%).
- 6.41 In each cycle, independent of treatment or SMA type, patients may die from background mortality based on ABS life tables for Australians aged 0-20 years. No SMA-related mortality was incorporated into the model as the resubmission claimed that there was no evidence that patients with Type I SMA and 3 copies of *SMN2* had increased mortality. While it was accurate that no deaths were reported in these patents in the identified studies, this may not be a reasonable conclusion as there was a paucity of data in mortality of patients with Type I SMA and 3 copies of *SMN2*. Only two of the identified studies (EMBRACE and CS3A) were likely to have reported mortality data that was informative, and only from seven patients with Type I SMA and 3 copies of *SMN2*.
- 6.42 For the model in the July 2020 submission, it was noted that given that the life expectancy of patients with Type I SMA is around 2 years, the omission of mortality from SMA was inappropriate and may overestimate the duration of assumed benefit in pre-symptomatic initiation of treatment compared to SoC in Type I SMA (paragraph 6.36, nusinersen PSD, July 2020 PBAC meeting). While the current model included a lower proportion of patients with Type I SMA (25.4% compared to 89.7% in the July 2020 model), the lack of additional mortality in SMA Type I patients remains relevant for the resubmission.
- 6.43 The resubmission adapted the methodology used in the July 2019 and the July 2020 (re)submissions to incorporate a distribution of *SMN2* copy number by SMA type using data from published studies into the economic model. For the July 2020 model, the distribution of *SMN2* copy numbers as a function of SMA type was based on data of 901 individuals extracted from ten studies. The resubmission stated that while no additional studies were identified that met the specified inclusion criteria, one additional study (Sarv 2021) was identified as assessing the birth prevalence of SMA by type which was used in the resubmission's base case to inform the distribution of expected SMA type at birth among all individuals with SMA.
- 6.44 Sarv 2021 retrospectively reviewed the clinical and laboratory data of all individuals with genetically diagnosed SMA in Estonia to estimate the birth prevalence of SMA by type. A total of 57 individuals with SMA were identified, of which one had Type 0 SMA and was thus not relevant to the pre-symptomatic treatment setting. Of the remaining 56 individuals, 25 (44.6%) were Type I, 13 (23.2%) Type II, 17 (30.3%) Type III and one (1.8%) Type IV.

- 6.45 The resubmission provided no rationale as to why data from Sarv 2021 should be relied upon in the resubmission despite it not meeting the inclusion criteria (did not separately report patients with SMA Type IIIa and IIIb). Additionally, the resubmission inappropriately did not combine the results of patients from Sarv 2021 into the data of the 901 individuals previously considered. During the evaluation, data from the 50 patients in Sarv 2021 in whom *SMN2* copy number and SMA type was known (excluding the 1 patient who was SMA type 0) were added to the existing information and these results were used to present a revised base case in the commentary. The ESC considered this revised base case was an appropriate adjustment to the model and recommended the PBAC consider the ICERs using this approach as a respecified base case.
- 6.46 Transition probabilities were not explicitly included in the model. Patients moved from being pre-symptomatic and not receiving nusinersen to being symptomatic and receiving nusinersen at a fixed time point in the model based on the average expected symptom onset time, which was entirely dependent on the assumed SMA type (Type I - 0.5 years, Type II - 1 year, Type IIIa – 2.25 years, Type IIIb/c – 10.5 years, Type IV 50.5 years). The PBAC previously considered there to be uncertainty associated with applying a uniform fixed age of symptom onset for each SMA type, noting that it was possibly unrealistic to have all patients of the same type being symptomatic at the same time and that this approach does not account for the degenerative and progressive nature of SMA in the model (paragraph 6.29, nusinersen PSD, July 2020 PBAC meeting). The resubmission provided a sensitivity analysis that applied a distribution to the expected age of symptom onset for each SMA type, resulting in an ICER of \$155,000 to < \$255,000 per QALY, which suggests that the submission's assumption of a fixed age of onset may favour pre symptomatic treatment.
- 6.47 The current model used data from Dangouloff 2022 to determine health state costs, as this paper reported health care costs by *SMN2* copy number and symptom onset in an SMA cohort. The resubmission considered these costs to be more applicable to the pre-symptomatic treatment setting than the costs and assumptions previously applied in the July 2020 model (Klug 2016). An annual cost of \$429.76 was applied in the pre-symptomatic arm until the projected time of symptom onset for each SMA type, after which a linearly increasing cost to \$26,107.92 per year was applied over 20 years. It was unreasonable to assume that the health care costs in symptomatic patients with 3 *SMN2* copies (\$26,107.92 per year) will be substantially greater than what was previously accepted for patients with 2 *SMN2* copies (\$14,380 per year) given that patients with 3 *SMN2* copies are likely to have less severe disease. It was also unreasonable to assume patients in the pre-symptomatic arm would slowly accrue additional health care costs once symptomatic but patients in the SoC arm would incur the full cost as soon as they were symptomatic. The ESC considered the resubmission's derivation of health care costs to be optimistic, and uncertain given the data do not come from Australian sources.

- 6.48 As in the July 2020 submission the base case assumed utility benefit of 0.2 between treatment arms, based on a utility of 0.91 for pre-symptomatic treatment versus 0.71 for symptomatic treatment. The utility benefit was not supported by any evidence and is purely an assumption. The PSCR argued that the clinical evidence from NURTURE supported the economic model's proposition that patients with 3 *SMN2* copies treated with nusinersen reach functional milestones consistent with normal development and can therefore be expected to have normal quality of life. The PSCR also noted that the incremental utility benefit was consistent with previous PBAC decision making regarding SMA quality of life outcomes for patients treated when symptomatic and the clinical evidence supporting the normal development of children treated pre-symptomatically. The ESC questioned the pre-symptomatic utility value of 0.91, given it was based on adult norms, and the symptomatic utility value of 0.71, given the relevance/applicability of the vignettes used to derive the utility value to patients with 3 copies of *SMN2*, and as such, considered the incremental utility benefit to be highly uncertain, and likely overestimated.
- 6.49 The ESC had previously considered a time horizon of 20 years to be optimistic in the context of the available clinical data. For patients with 3 copies of *SMN2*, the ESC considered that a time horizon of 20 years was reasonable given the better prognosis.
- 6.50 The base case assumed no patients with 3 copies of *SMN2* will have Type IV SMA. This was based on published literature, however it differed compared with the July 2020 submission and patients with Type IV SMA may be underrepresented in the literature. The ESC considered this assumption was potentially optimistic and noted that a small change in this parameter resulted in a substantial increase in the ICER.
- 6.51 The key drivers of the model are highlighted in Table 13.

Table 13: Key drivers of the model

Description	Method/Value	Impact
Duration of treatment effect	A waning of treatment effect was assumed to occur over 20 years in the model. The ESC noted that there was no basis for this assumption.	High, favoured pre-symptomatic treatment. Base case (20 years): \$█ ¹ 5 years: \$█ ² (+323%) 10 years: \$█ ³ (+110%)
Utility benefit assumed	Base case assumed utility benefit of 0.2 between treatment arms, based on a utility of 0.91 for pre-symptomatic treatment versus 0.71 for symptomatic treatment.	High, uncertain which arm was favoured. Base case (0.2 benefit): \$█ ¹ 0.1: \$█ ⁴ (+102%) 0.4: \$█ ⁵ (-50%)
Time horizon	20 years in base case.	High, favoured pre-symptomatic treatment. Base case (20 years): \$█ ¹ 10 years: \$█ ³ (+41%)
Health state costs	Health state costs were increased from the July 2020 submission (\$14,380 for symptomatic and \$0 for pre-symptomatic health states) using data from Dangouloff 2022 (\$26,108 for symptomatic and \$430 for pre-symptomatic health states).	Moderate, favoured pre-symptomatic treatment. Base case (Dangouloff 2022): \$█ ¹ Klug 2016: \$█ ³ (+27%)
Type IV patients	Base case assumed no patients with 3 copies of <i>SMN2</i> will have Type IV SMA.	Moderate, possibly high, favoured pre-symptomatic treatment. Base case (0%) \$█ ¹ 1% SMA Type IV: \$█ ¹ (+12%)

Source: Table 3.32, p162 of the resubmission; Cost utility analysis (CUA) workbook (Section 3).xlsx

The redacted values correspond to the following ranges:

¹ \$155,000 to < \$255,000 / QALY

² \$855,000 to < \$955,000 / QALY

³ \$255,000 to < \$355,000 / QALY

⁴ \$355,000 to < \$455,000 / QALY

⁵ \$95,000 to < \$115,000 / QALY

6.52 The resubmission estimated an ICER of \$155,000 to < \$255,000 /QALY (Table 14).

Table 14: Results of the economic evaluation (as presented in the resubmission)

Model outcome	Pre-symptomatic treatment	Standard of care	Incremental
Nusinersen costs	\$█	\$█	\$█
Administration costs	\$17,631	\$15,319	\$2,312
Adverse event costs	\$1,504	\$935	\$568
Healthcare resource costs	\$117,999	\$297,413	-\$179,414
Total costs health care perspective	\$█	\$█	\$█
QALYs	10.8436	9.4462	1.3974
Disutility of adverse events	-0.0298	-0.0185	-0.0113
Total QALYs	10.8138	9.4277	1.3861
Incremental cost per QALY gained			\$█¹

Source: Table 3.31, p160 of the resubmission

QALY = quality adjusted life year

The redacted values correspond to the following ranges:

¹ \$155,000 to < \$255,000 / QALY

6.53 As discussed in paragraph 6.51, the distribution of SMA type by *SMN2* was updated during the evaluation to include 50 patients from Sarv 2021 and a revised base case was estimated (Table 15), with the ICER increasing by 5.8% compared to the resubmission's base case. The increase was due to a decrease in SMA Type I (25.41% to 24.36%) and an increase in SMA Type IIIb (7.79% to 8.34%).

Table 15: Incremental cost per QALY of pre-symptomatic treatment with nusinersen versus current practice of treatment upon onset of symptoms (revised base case)

Model outcome	Pre-symptomatic treatment	Standard of care	Incremental
Nusinersen costs	\$█	\$█	\$█
Administration costs	\$17,631	\$15,258	\$2,373
Adverse event costs	\$1,504	\$928	\$576
Healthcare resource costs	\$117,381	\$296,232	-\$178,851
Total costs health care perspective	\$█	\$█	\$█
QALYs	10.8484	9.4554	1.3930
Disutility of adverse events	-0.0298	-0.0184	-0.0114
Total QALYs	10.8186	9.4370	1.3816
Incremental cost per QALY gained			\$█¹

Source: Constructed during evaluation using Cost utility analysis (CUA) workbook (Section 3).xlsx. Details of distribution presented in Table 3.3.5, 3.3.6 and 3.3.7 of the commentary.

QALY = quality adjusted life year

The redacted values correspond to the following ranges:

¹ \$155,000 to < \$255,000 / QALY

6.54 The resubmission presented additional analyses individually investigating each SMA type (Table 16). The resubmission claimed that this illustrates the implicit cost-effectiveness of pre-symptomatic nusinersen versus symptomatic nusinersen as a function of expected SMA type.

Table 16: Economic evaluation: Treatment benefits by SMA type

Description of sensitivity analysis (base case)	Incr. costs	Incr. QALYs	ICER
Base case	\$█	1.3861	\$█ ¹
Results by SMA type			
Type I	-\$█	1.5041	DOMINANT
Type II	\$█	1.4597	\$█ ²
Type IIIa	\$█	1.3373	\$█ ³
Type IIIb	\$█	0.7225	\$█ ⁴
Type IV	\$█	-0.0298	DOMINATED

Source: Table 3.33, p163 of the resubmission

ICER = incremental cost effectiveness ratio; Incr. = incremental; QALY = quality adjusted life year; SMA = spinal muscular atrophy

The redacted values correspond to the following ranges:

¹ \$155,000 to < \$255,000 / QALY

² \$45,000 to < \$55,000 / QALY

³ \$255,000 to < \$355,000 / QALY

⁴ > \$1,055,000 / QALY

6.55 The results of key univariate sensitivity analyses presented by the resubmission and conducted during the evaluation, are summarised in Table 17.

Table 17: Univariate sensitivity analysis

Description of sensitivity analysis (base case)	Incremental costs	Incremental QALYs	ICER	%Δ
Base case	\$█	1.3861	\$█ ¹	0%
Annual health care costs (Dangouloff 2022; pre-symptomatic = \$429.76, symptomatic = \$26,107.92)				
Klug 2016 as for July 2020 (pre-symptomatic = \$0, symptomatic = \$14,379.72)	\$█	1.3861	\$█ ²	+27.34%
Costs applied in July 2020 submission	\$█	1.3861	\$█ ²	+55.2%
Utility values (pre-symptomatic = 0.91; symptomatic = 0.71, 0.2 difference)				
pre-symptomatic = 0.91, symptomatic = 0.81 (0.1 difference)	\$█	0.6874	\$█ ³	+101.6%
pre-symptomatic = 0.91, symptomatic = 0.61 (0.3 difference)	\$█	2.7835	\$█ ⁴	-50.2%
Duration of treatment effects, i.e., healthcare costs and utilities (20 years)				
5 years	\$█	0.4619	\$█ ⁵	+323.4%
10 years	\$█	0.8254	\$█ ³	+109.8%
Mortality (no SMA-specific mortality)				
16% per annum for Type 1 SMA (for 12 months)	\$█	1.3306	\$█ ¹	+7.0%
16% per annum for Type 1 SMA (for life)	\$█	1.1904	\$█ ²	+26.9%
Time horizon (20 years in base case)				
10 years	\$█	1.0284	\$█ ²	+41.1%
40 years	\$█	1.4035	\$█ ¹	+9.4%
Type IV SMA (base case assumes no patients with 3 SMN2 copies develop type IV SMA)				
Assume 1% of patients with 3 copies SMN2 will develop Type IV SMA	\$█	1.3720	\$█ ¹	+12.0%

Source: Table 3.32, p162 of the resubmission; Cost utility analysis (CUA) workbook (Section 3).xlsx

AE = adverse events ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life year; SMN = survival of motor neuron.

a SoC arm: pre-symptomatic = \$0, symptomatic = \$14,379.72. Treatment arm: pre-symptomatic = \$0, symptomatic = \$11,503.78 (linearly increasing to \$14,379.72 over 20 years).

The redacted values correspond to the following ranges:

¹ \$155,000 to < \$255,000

² \$255,000 to < \$355,000

³ \$355,000 to < \$455,000

⁴ \$95,000 to < \$115,000

⁵ \$855,000 to < \$955,000

6.56 During the evaluation, additional sensitivity analyses were conducted around the revised base case in which the data from Sarv 2021 was incorporated in the distribution of SMA type and SMN2 copy number. This is presented in Table 18.

Table 18: Sensitivity analyses results for revised base case

Description of sensitivity analysis (base case)	Incremental costs	Incremental QALYs	ICER	%Δ ^a
Base case (as presented in the resubmission)	\$█	1.3861	\$█ ¹	0%
Data from Sarv 2021 incorporated into the SMA type and SMN2 copy number distribution (revised base case)	\$█	1.3816	\$█ ¹	+5.8%
Annual health care costs for patients as used in July 2020 model (pre-symptomatic = \$0, symptomatic = \$14,379.72) based on Klug 2016 (base: pre-symptomatic = \$429.76, symptomatic = \$26,107.92)	\$█	1.3816	\$█ ²	+33.1%
Incremental difference in utility = 0.1 (-50%)	\$█	0.6851	\$█ ³	+113.4%
Incremental difference in utility = 0.4 (+50%)	\$█	2.7746	\$█ ⁴	-47.32%
Assumed duration of treatment effect = 5 years	\$█	0.4606	\$█ ⁵	+340.6%
Assumed duration of treatment effect = 10 years	\$█	0.8232	\$█ ⁶	+119.4%
Assumed duration of treatment effect = 15 years	\$█	1.1277	\$█ ²	+43.5%
Time horizon = 10 years	\$█	1.0212	\$█ ²	+48.6%
Time horizon = 40 years	\$█	1.3399	\$█ ¹	+15.8%

Source: Constructed during evaluation using Cost utility analysis (CUA) workbook (Section 3).xlsx

AE = adverse events; ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life year; SMN = survival of motor neuron.

^a Percentage change from base case presented in the resubmission.

The redacted values correspond to the following ranges:

¹ \$155,000 to < \$255,000

² \$255,000 to < \$355,000

³ \$355,000 to < \$455,000

⁴ \$95,000 to < \$115,000

⁵ \$855,000 to < \$955,000

⁶ \$455,000 to < \$555,000

6.57 The ESC noted that the revised base case ICER was particularly sensitive to changes in the assumed duration of treatment effect and incremental difference in utility.

6.58 Overall, the ICER may be underestimated as:

- The assumption that the clinical benefit in patients with 3 SMN2 copies was identical to that in patients with 2 SMN2 copies was inconsistent with PBAC's opinion that the incremental benefit of pre-symptomatic treatment (with onasemnogene abeparvovec) compared to symptomatic treatment with disease modifying therapies for patients with 3 SMN2 copies would be less than that for patients with 1-2 SMN2 copies due to patients with 3 SMN2 copies likely having better outcomes in the absence of pre-symptomatic treatment (paragraph 7.6, onasemnogene abeparvovec PSD, November 2022 PBAC meeting). The ESC considered this assumption of identical treatment benefit was optimistic;
- Health state costs in patients with 3 SMN2 copies may be overestimated;
- The assumption of a fixed age of onset and distribution of SMA types may favour pre symptomatic treatment;
- It was assumed that no patients with 3 SMN2 copies would have developed SMA Type IV; and
- The assumption that patients in the SoC arm will experience an immediate decrement of 0.2 utility as soon as they become symptomatic (irrespective of SMA

type) whereas patients treated when pre-symptomatic will slowly experience utility decline over 20 years from the time of symptom onset (irrespective of SMA type) favoured pre-symptomatic treatment.

- 6.59 Additionally, the economic evaluation contained the following sources of uncertainty, which could not be quantified during the evaluation:
- The assumption of no mortality in SMA Type I patients with 3 *SMN2* copies may favour pre-symptomatic treatment;
 - The model did not consider discontinuation of treatment. It was unclear whether this favoured pre-symptomatic treatment or SoC as there are complex effects such as unclear disease progression after cessation of treatment and potential for treatment switching to risdiplam in clinical practice;
 - There was no reliable estimate of the incremental benefit of pre-symptomatic treatment compared to SoC in patients with 3 *SMN2* copies;
 - The distribution of SMA types (i.e., the phenotype of patients in the absence of pre-symptomatic treatment) among patients with 3 *SMN2* copies is uncertain.
- 6.60 In relation to onasemnogene abeparvovec the PBAC has previously advised that a lower price for pre-symptomatic treatment in individuals with 3 *SMN2* copies would be required to achieve a similar cost-effectiveness to pre-symptomatic treatment in those with 1-2 *SMN2* copies (paragraph 7.10 onasemnogene abeparvovec PSD, November 2022 PBAC meeting).
- 6.61 The ESC considered that there were substantial limitations to the data available to inform the economic model, leading to significant uncertainty regarding the modelled outcomes. However, there is unlikely to be alternative data or approaches to economic analysis that would provide more robust estimates of the cost-effectiveness. The ESC considered the request for the same price in patients with 3 copies of *SMN2* as for patients with 1-2 copies of *SMN2* was not justified given the PBAC's previous advice, and further because some pre-symptomatic patients may have otherwise been treated under the symptomatic Type IIIb/c listings where there is a lower price. The ESC considered that even if the PBAC accepts that there is comparable benefit in patients with 3 copies of *SMN2*, the price of nusinersen for pre-symptomatic patients with 3 copies of *SMN2* should be no more than the weighted mean price based on expected SMA type (i.e., accounting for the lower price in Type 3B/C symptomatic patients). Assuming 8.34% of patients with 3 copies of *SMN2* would be Type IIIb/c and the remainder Type I-II, the weighted price per dose would be reduced from \$1 to \$1. The ESC noted the PBAC's previous advice that the cost-effective price is likely to be lower in patients with 3 copies of *SMN2* and suggested that, if there is uncertainty regarding comparable benefit in patients with 3 copies of *SMN2*, an acceptable price should reflect that difference. The pre-PBAC response stated that while this approach seemed to oversimplify and overcompensate for the uncertainties in the underlying evidence base, that the approach resulted in a minimal

difference in overall price for individuals with pre-symptomatic SMA with 3 *SMN2* copies. The PBAC noted the pre-PBAC response stated that the sponsor would not be able to progress if the listing required a price reduction.

Drug cost/patient /year

Table 19: Drug cost per patient for proposed and comparator drugs

	Pre-symptomatic initiation			Symptomatic initiation		
	Proposed drug Trial dose and duration	Proposed drug Model ^b	Proposed drug Financial estimates ^c	Comparator Trial dose and duration	Comparator Model	Comparator Financial estimates
Mean dose	12 mg at days 0, 14, 28 and 63, then every 4 months after confirmed <i>SMN1</i> deletion/mutation			12 mg at days 0, 14, 28 and 63, then every 4 months after symptom onset		
Mean duration	Life-long					
Cost/patient/dose	\$█			Type 1: \$█ Type II-IIIa: \$█ (█ rebated) Type IIIb/c: \$█ (█ rebated)		
Cost/patient/year ^a	Initiation year: \$█ Subsequent years: \$█			Initiation year: \$█ Subsequent years: \$█		

Source: Constructed during the evaluation using Section 1.4 of the resubmission.

^a The first year of treatment includes 6 doses of nusinersen (4 loading doses plus 2 maintenance doses) but calculations include a rebate for █ in patients with SMA and 3 copies of *SMN2* commencing pre-symptomatic treatment. Subsequent years (maintenance) require 3 doses per year.

^b The economic model base case assumed a 100% uptake rate of nusinersen for pre-symptomatic treatment in paediatric patients diagnosed with SMA with 3 copies of *SMN2*.

^c The resubmission's financial estimates assumed a nusinersen uptake rate of 97% in year 1, increasing to 99% in year 4, with 99% uptake maintained over years 5 and 6.

Estimated PBS usage & financial implications

6.62 This submission was not considered by DUSC. The resubmission used an epidemiological approach for the financial estimates for the listing of nusinersen for pre-symptomatic initiation.

6.63 The inputs used for the financial estimates are described in Table 20.

Table 20: Key inputs for financial estimates

Parameter	Value and source	Comment																					
Incidence of SMA	SMA rate 8.66 per 100,000 live births, reported by Kariyawasam 2020. This study reported 9 patients with SMA in 103,903 newborns screened in the first year of screening in the NSW/ACT pilot program.	PBAC considered this was reasonable.																					
Proportion of patients with SMA that have 3 copies of SMN2.	45.81%.	Based on Section 3.3 of the resubmission.																					
Distribution of SMA type for SMN2 3 copies	<table border="1"> <thead> <tr> <th></th> <th colspan="5">SMA type</th> </tr> <tr> <th>SMN2 copy</th> <th>I</th> <th>II</th> <th>IIIa</th> <th>IIIb</th> <th>IV</th> </tr> </thead> <tbody> <tr> <td>3</td> <td>25.4%</td> <td>44.4%</td> <td>22.4%</td> <td>7.8%</td> <td>0.0%</td> </tr> </tbody> </table> <p>Source: Table 4.3, p169 of the resubmission, Sarv 2021</p>		SMA type					SMN2 copy	I	II	IIIa	IIIb	IV	3	25.4%	44.4%	22.4%	7.8%	0.0%	There was uncertainty regarding the distribution of SMA type and SMN2 copy numbers used in the resubmission due to the exclusion of Sarv 2021. Also may not be appropriate to assume no Type IV patients.			
	SMA type																						
SMN2 copy	I	II	IIIa	IIIb	IV																		
3	25.4%	44.4%	22.4%	7.8%	0.0%																		
Nusinersen uptake rate from birth	<table border="1"> <thead> <tr> <th colspan="7">Uptake rate</th> </tr> <tr> <th>2023</th> <th>2024</th> <th>2025</th> <th>2026</th> <th>2027</th> <th>2028</th> <th></th> </tr> </thead> <tbody> <tr> <td>95%</td> <td>97%</td> <td>98%</td> <td>99%</td> <td>99%</td> <td>99%</td> <td></td> </tr> </tbody> </table> <p>Source: Table 4.6, p171 of the resubmission</p>	Uptake rate							2023	2024	2025	2026	2027	2028		95%	97%	98%	99%	99%	99%		This was inconsistent with the economic model where 100% uptake was assumed. Alternate uptake rates were explored in the sensitivity analyses.
Uptake rate																							
2023	2024	2025	2026	2027	2028																		
95%	97%	98%	99%	99%	99%																		
Assumed onset of SMA symptoms/Substituted therapies	<table border="1"> <thead> <tr> <th>SMA Type</th> <th>Age at treatment start (SoC)</th> </tr> </thead> <tbody> <tr> <td>Type I</td> <td>0.5 years</td> </tr> <tr> <td>Type II</td> <td>1 years</td> </tr> <tr> <td>Type IIIa</td> <td>2.25 years</td> </tr> <tr> <td>Type IIIb/c</td> <td>10.5 years (beyond 6-year estimate)</td> </tr> <tr> <td>Type IV</td> <td>Beyond 6-year estimate</td> </tr> </tbody> </table> <p>Source: Table 4.5, p170 of the resubmission</p>	SMA Type	Age at treatment start (SoC)	Type I	0.5 years	Type II	1 years	Type IIIa	2.25 years	Type IIIb/c	10.5 years (beyond 6-year estimate)	Type IV	Beyond 6-year estimate	Consistent with the mean ages for expected symptom onset by SMA type and with the economic evaluation. The assumption that patients begin treatment at symptom onset may slightly overestimate cost offsets for SoC with costs assumed to be incurred earlier than in clinical practice due to a delay between initial symptom onset and the patient receiving their first dose of nusinersen (but expected to be shorter than reported in literature due to screening).									
SMA Type	Age at treatment start (SoC)																						
Type I	0.5 years																						
Type II	1 years																						
Type IIIa	2.25 years																						
Type IIIb/c	10.5 years (beyond 6-year estimate)																						
Type IV	Beyond 6-year estimate																						
Beneficiary type	Based on the current nusinersen paediatric listings, it was assumed 44% of use was by general patients and 56% of use was in the concession category. No RPBS assumed.	During the evaluation the PBS general benefit co-payment was changed to \$30, resulting in an updated weighted mean PBS co-payment of \$16.89. This figure was used in the financial estimates base case and recalculated during the evaluation.																					
Adverse events	The costs and resource utilisation associated with AEs were not included in the financial estimates.	The exclusion of AE-related costs was inconsistent with the economic evaluation where an AE cost per lumbar puncture and costs for hospitalisation due to PLPs were applied. Underestimates financial impact.																					
Nusinersen administration	MBS items 105, 17610, 21945, 23010 and 18216 for a total of \$418.75 per nusinersen administration. The 80% MBS benefit was applied.	Consistent with current MBS costs and the resource costs used in the economic model.																					

Source: constructed during evaluation using information from Nusinersen Economic Model_March2020, p165-176 of the resubmission. ABS = Australian Bureau of Statistics; AE = adverse events; NBS = newborn bloodspot screening; PLPS = post lumbar puncture syndrome; SMA = spinal muscular atrophy; SMN = survival of motor neuron; SoC = standard of care; SPA = special pricing arrangement.

6.64 The resubmission reasonably claimed that while no therapies would be directly substituted by the proposed listing, pre-symptomatic treatment would bring forward

the treatment of patients who would currently receive nusinersen initiated after the onset of symptoms.

- 6.65 The total cost to the PBS/RPBS of extending the listing of nusinersen to include pre-symptomatic initiation of treatment for patients with SMA with 3 copies of *SMN2* was estimated to be \$0 to < \$10 million in Year 1 and \$0 to < \$10 million in Year 6, with a total of \$20 million to < \$30 million over the first 6 years of listing as presented in Table 21.

Table 21: Estimated utilisation and cost of pre-symptomatic initiation of nusinersen for SMA with 3 SMN2 copies

	2023	2024	2025	2026	2027	2028
Estimation of use and financial impact of pre-symptomatic nusinersen (PBS and RPBS)						
Live births	1	1	1	1	1	1
SMA incidence	2	2	2	2	2	2
Total eligible patients with 3 copies of SMN2	2	2	2	2	2	2
Total incident patients with 3 copies of SMN2	2	2	2	2	2	2
Total prevalent patients with 3 copies of SMN2	2	2	2	2	2	2
Total incident + prevalent patients	2	2	2	2	2	2
Nusinersen vials (excluding)						
Incident patients	2	2	2	2	2	2
Prevalent patients	2	2	2	2	2	2
Total nusinersen scripts	2	2	2	2	2	2
Total, cost of nusinersen (effective)						
Total PBS drug cost	\$ 3	\$ 3	\$ 4	\$ 4	\$ 5	\$ 5
Admin cost for nusinersen	\$ 3	\$ 3	\$ 3	\$ 3	\$ 3	\$ 3
Total MBS/PBS cost of nusinersen, pre-symptomatic initiation	\$ 3	\$ 3	\$ 4	\$ 4	\$ 5	\$ 5
Number of pre-symptomatic nusinersen doses used for SoC ^a						
Year 1 initiation	2	2	2	2	2	2
Year 1 continuation	2	2	2	2	2	2
Year 2+	2	2	2	2	2	2
Total	2	2	2	2	2	2
Total PBS cost offset	\$ 3	\$ 3	\$ 3	\$ 4	\$ 4	\$ 4
Admin cost for nusinersen	\$ 3	\$ 3	\$ 3	\$ 3	\$ 3	\$ 3
Total MBS/PBS cost offsets	\$ 3	\$ 3	\$ 3	\$ 4	\$ 4	\$ 4
Total cost difference	\$ 3	\$ 3	\$ 3	\$ 3	\$ 3	\$ 3
July 2020 submission (≤2 copies of SMN2)	\$ 3	\$ 3	\$ 3	\$ 4	\$ 4	\$ 4

Source: Tables 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 4.10, 4.13, 4.1p168-175; Utilisation and cost model (UCM) workbook (Section 4).xls
 SMA = spinal muscular atrophy; SMN = survival of motor neuron

^a During the evaluation, figures in the workbook sheet '4a. Scripts – affected' were amended to better factor in the assumed treatment delay in the symptomatic setting. The resubmission had multiplied the patients in rows 460 to 468 by a factor to simulate a treatment delay for patients with SMA Type I and IIIa, but during the evaluation this multiplier was removed from the calculation of patient numbers (rows 460 to 468). During the evaluation amendments were made so the treatment delays were factored in by distributing the patients correctly over the years in which they receive treatment, applying treatment delays for scripts calculated for Yr 1 continuation and Yr 2+ and application of the relevant scripts received per year.

The redacted values correspond to the following ranges:

¹ 300,000 to < 400,000

² < 500

³ \$0 to < \$10 million

⁴ \$10 million to < \$20 million

⁵ \$20 million to < \$30 million

6.66 While the financial estimates would capture patients diagnosed with SMA soon after birth, pre-symptomatic patients who are not identified with SMA as newborns but are diagnosed up to the age of 18 years were not included in the financial estimates. It is expected that this will involve a very small number of patients who are pre-symptomatically diagnosed with SMA at an older age; for example, the diagnosis of an older sibling after their younger sibling is found to have SMA at birth. These patients

- would currently be eligible for nusinersen once they develop SMA symptoms but are not currently eligible for pre-symptomatic treatment.
- 6.67 The resubmission's estimates for delayed substitutions (used to inform cost offsets on the PBS) could not be verified during the evaluation. For example, in year 1, the resubmission estimated that < 500 patients who initiated nusinersen will have developed SMA Type I, and the offset was calculated as half of all initiating patients (< 500) being treated for the full year in year 1 rather than actually delaying the initiation of treatment of all < 500 patients by half a year. During the evaluation, figures were amended to better factor in the assumed treatment delay for the symptomatic setting. For example, the estimates were revised to appropriately consider that < 500 patients who develop SMA Type I will initiate treatment at 6 months, which results in slightly more initiation doses (as there was 11 for symptomatic treatment in SMA Type I) but fewer continuation doses as the duration of treatment was only six months in the first year. These changes resulted in slightly higher total cost offsets than estimated in the resubmission (resubmission estimates for total cost offsets were \$0 million to < \$10 million in Year 1 to \$10 million to < \$20 million in Years 6).
- 6.68 The resubmission recognised that a small proportion of the eligible patients (equalling < 500 individuals initiating treatment each year) would qualify for nusinersen at a later timepoint at a lower price than proposed for the pre-symptomatic setting. This group would consist of SMA phenotype IIIb/c with a *SMN2* copy number of 3. The vial price for patients with SMA Type IIIb/c in the pre-symptomatic setting is \$1 (proposed) compared to \$1 in the symptomatic setting, with both eligible for 1111. As such there would be an additional incremental cost of \$1/year (($\$1 - \1) \times 3 doses/year) for each year of treatment after the patient is expected to become symptomatic. This additional incremental cost was not captured in the financial estimates due to the assumption that patients with SMA Type IIIb/c would experience symptom onset at 10.5 years of age. The resubmission considered this would have minimal financial impact, with the total impact ranging from \$0 million to < \$10 million in year 1 to \$0 million to < \$10 million in year 6. The ESC considered this ongoing additional cost for treating the same patients was not justified.
- 6.69 Of the sensitivity analyses around financial estimates conducted, the financial estimates were most sensitive to changes in:
- The live births assumed: ABS Series B used in base case (\$20 million to < \$30 million over six years), +8.5% for Series A (\$30 million to < \$40 million) and -8.3% for Series C (\$20 million to < \$30 million); and
 - The addition of more patients who may have had Type IIIb/c/IV SMA: assuming < 500 additional patient with Type IIIb in each year increased the total cost over six years to \$30 million to < \$40 million.
- 6.70 Overall, the ESC considered that the financial impact of extending the pre-symptomatic listing to patients with 3 copies of *SMN2* should be relatively minimal, as

- genetically diagnosed with SMA, noting that NBS programs will soon be introduced across Australia.
- 7.4 The PBAC noted the trajectory of the disease for individuals with 3 copies of *SMN2* in the absence of treatment is uncertain, and that a small proportion would achieve normal milestones in the absence of treatment. The PBAC noted that while the spectrum of disease for patients with 3 copies of *SMN2* is heterogenous and not as severe as for patients with 2 copies of *SMN2*, that it is both biologically plausible, and likely, that if patients are treated with nusinersen earlier that loss of motor neurons will be reduced and a higher level of motor function may be maintained.
- 7.5 The PBAC considered that nusinersen in the symptomatic setting, was the appropriate comparator. The PBAC noted that, while the resubmission had nominated both risdiplam and onasemnogene abeparvovec as near market comparators, at the time of PBAC consideration neither of these treatments were PBS listed for patients diagnosed with 3 copies of *SMN2* prior to the onset of symptoms.
- 7.6 The PBAC noted the clinical evidence presented was primarily based on an updated interim analysis of the NURTURE study of nusinersen initiated pre-symptomatically, and six studies of the use of nusinersen initiated upon development of symptoms. The PBAC noted the studies all had small patient numbers, that the duration of follow-up in the studies was short in the context of a lifelong disease, and considered that all studies had a high risk of bias.
- 7.7 The PBAC noted that patients treated with nusinersen pre-symptomatically in the NURTURE study achieved age-appropriate WHO motor milestones, as of the data cut-off of February 2020, and that while the patients tended to achieve the motor milestones earlier than patients with 2 copies of *SMN2* treated pre-symptomatically, the PBAC considered some of these patients would have achieved these milestones in the absence of treatment.
- 7.8 The PBAC noted advice from the sponsor hearing that suggested that time from symptom onset to initiation of treatment with nusinersen has reduced with the introduction of NBS, with families closely monitoring infants genetically diagnosed with 3 copies of *SMN2* for symptoms so that treatment can commence as early as possible. The PBAC further noted that NBS is expected to be implemented nationally by the end of 2023, allowing for the identification of patients with 3 copies of *SMN2* shortly after birth.
- 7.9 The PBAC noted that based on a naïve numerical and visual depiction of results for change in HINE-2 scores from the symptomatic treatment studies EMBRACE and CS3A, as the delay from symptom identification to initiation of treatment decreased from 15.9 months to 8.6 months (in EMBRACE) and to 2.5 months (in CSA3), mean HINE scores by age approached the mean HINE scores by age for patients treated pre-symptomatically in NURTURE (see Figure 2). The PBAC noted these data suggest that the earlier treatment is commenced, the greater the impact of treatment on mean HINE scores. The PBAC considered that since the delay between symptom

identification and treatment in the EMBRACE study was between 8.6 and 15.9 months, the outcomes would not represent current SoC.

- 7.10 Overall, the PBAC considered that the naïve indirect treatment comparison presented in the resubmission did not allow for an accurate assessment of comparative efficacy. While the PBAC considered it was plausible that pre-symptomatic initiation of nusinersen in patients with 3 copies of *SMN2* would result in greater benefit than initiation of nusinersen commenced symptomatically, the PBAC considered the magnitude of incremental benefit over a lifetime to be uncertain. The PBAC noted that comparative long-term data that would address this uncertainty was unlikely to be available in the future.
- 7.11 The PBAC considered that the claim that pre-symptomatic initiation of nusinersen was no worse, in terms of safety, than nusinersen initiated upon symptom onset in patients with 3 copies of *SMN2* was not supported given the risks associated with lumbar puncture, and because the requested listing would result in more intrathecal injections and further some patients with 3 copies of *SMN2* would not require treatment.
- 7.12 On balance, the PBAC was satisfied that nusinersen initiated pre-symptomatically for patients with 3 copies of *SMN2* was likely to provide a significant improvement in efficacy over initiation of nusinersen in patients once symptomatic. The PBAC considered that while some patients with 3 copies of *SMN2* would not develop symptoms until years after birth, and their disease would be less severe on average, the estimated benefit of early intervention for patients treated pre-symptomatically compared to patients treated symptomatically outweighed the negative impact of treating the small proportion of patients who would not have developed symptoms.
- 7.13 The PBAC noted that the resubmission had presented a modelled cost-utility analysis over a time-frame of 20 years, using the same model structure submitted to support the listing of patients with 1-2 copies of *SMN2*, considered at the July 2020 PBAC meeting. The PBAC recalled that it had previously considered the model results to be uncertain. The PBAC noted the base case ICER was \$155,000 to < \$255,000 per QALY gained, and that this increased to \$155,000 to < \$255,000 when the distribution of SMA types was updated to include patients in the Sarv 2021 study. The PBAC noted the ESC had considered the base case ICER to be underestimated and considered that there remained substantial uncertainty in the modelled ICER due to the limited clinical data available to inform the model.
- 7.14 The PBAC noted the requested price for this listing was the same as the price for pre-symptomatic patients with 1-2 copies of *SMN2*. The PBAC considered that a lower price for pre-symptomatic treatment for a patient with 3 copies of *SMN2* would be required to ensure similar cost-effectiveness to that of treating patients with 1-2 copies given the average incremental benefit of pre-symptomatic treatment in patients with 3 copies of *SMN2* would be less than for patients with 1-2 copies. The PBAC considered that a price reduction of around 10% would be appropriate in this

context for the population with pre-symptomatic SMA with 3 copies *SMN2*. The PBAC also considered that the same loading dose rebate as applies to pre-symptomatic patients with 1-2 copies *SMN2* should apply to patients with 3 copies *SMN2*. The PBAC noted that a submission for ONA in patients with 3 copies *SMN2* was also considered at the July 2023 PBAC meeting and advised that in the event that ONA is recommended and proceeds to PBS listing in this patient population the dose relativities for the current listings for pre-symptomatic patients with 1-2 copies *SMN2* should apply to listings for patients with 3 copies *SMN2*.

- 7.15 The PBAC noted the resubmission had taken an epidemiological approach to estimate use of nusinersen and considered that the approach was generally reasonable. The PBAC noted patients with SMA Type IV had not been accounted for in the distribution of patients with 3 copies of *SMN2*, however considered this to be appropriate in the context of revising the current Risk Sharing Arrangement (see paragraph 6.78) noting also, that this would be expected to be less than < 500 patients per year. The PBAC noted the cost over 6 years was estimated to be \$20 million to < \$30 million, and that overall ESC had considered the impact of listing nusinersen for the requested patient population should be minimal given for most patients it would only be given earlier than it would otherwise be initiated. The PBAC considered that, in the event of PBS listing of ONA for this population, the financial estimates would need to be adjusted to account for the reduced number of patients treated with nusinersen.
- 7.16 The PBAC considered that the uncertainties in the financial estimates could be managed by including the extended listing in the current Risk Sharing Arrangement in place for nusinersen for the under 19 years population. The PBAC advised that any adjustments to the current caps to account for pre-symptomatic initiation of treatment in patients with 3 copies of *SMN2* should be made in conjunction with a corresponding decrease per the financial estimates to account for patients who would have received treatment under the current listing.
- 7.17 The PBAC noted that this submission is not eligible for an independent review as it received a positive recommendation.
- 7.18 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for nusinersen:
- a) Based on the available evidence the magnitude of benefit of initiating treatment with nusinersen pre-symptomatically was not able to be quantified, and therefore the criterion of having a substantial and clinically relevant improvement in efficacy compared to symptomatic initiation was not met;
 - b) The treatment is not expected to address a high and urgent unmet clinical need; and

- c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

Outcome:

Recommended

8 Recommended listing

8.1 Amend existing listings (12176W and 12177X) as follows.

Restriction items: 12176W and 12177X	
	Treatment Phase: Use in a patient untreated with disease modifying therapies for this condition <i>Initial treatment of pre-symptomatic spinal muscular atrophy (SMA) - Loading doses</i>
	Clinical criteria:
	The condition must be presymptomatic SMA, with genetic confirmation that there are 1 to 2 copies of the survival motor neuron 2 (SMN2) gene; <i>OR</i>
	<i>The condition must be presymptomatic SMA, with genetic confirmation that there are 3 copies of the survival motor neuron 2 (SMN2) gene</i>

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

9 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.

10 Sponsor’s Comment

Biogen is pleased that the PBAC acknowledged that SPINRAZA provides a significant improvement when initiated pre-symptomatically in infants and babies with SMA with 3 copies of SMN2.

Biogen will not be in a position to progress with a PBS listing in its current state as the recommendation is conditional on a price reduction (see paragraph 7.14), in addition to scheduled Anniversary price reductions across all SPINRAZA indications in 2024.

SPINRAZA in the pre-symptomatic 3 SMN2 copies population is now reimbursed in over 30 countries, including New Zealand, Canada, France, Italy and Germany.

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Biogen remains willing to work collaboratively with the PBAC and the Department of Health and Aged Care to explore alternative options in order to reach an agreement to expand the listing.