

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

1 Purpose of Application

- 1.1 Section 100, Authority Required, Highly Specialised Drugs Program listing for nusinersen for the pre-symptomatic initiation of treatment of patients with Spinal Muscular Atrophy (SMA) who have up to 3 copies of the survival-of-motor-neuron 2 (SMN2) gene. The patient population would be better described as “patients with SMN1 deletion or mutation with up to 3 copies of SMN2 and no SMA symptoms” as it is not clear that all those meeting the SMN1 and SMN2 criteria would develop SMA (particularly Type I, II or IIIa). For simplicity, pre-symptomatic *initiation of* treatment, is also referred to as ‘early’ treatment.
- 1.2 The requested basis for listing was a cost-utility analysis of early treatment with nusinersen compared to current standard of care treatment with nusinersen according to the current PBS restriction (for simplicity, this is referred to as ‘symptomatic’ treatment).

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

Component	Description
Population	Patients with pre-symptomatic SMA (SMN1 deletion or mutation with SMN2 copy number of 1, 2 or 3). This would be better described as “patients with SMN1 deletion or mutation with SMN2 copy number of 1, 2 or 3 and no SMA symptoms”.
Intervention	Pre-symptomatic <i>initiation of</i> treatment with nusinersen: Nusinersen administered at a dose of 12mg via intrathecal injection with four loading doses and two maintenance doses in year 1 and three doses per year thereafter
Comparator	Symptomatic treatment with nusinersen: Nusinersen (administered as above) to patients with a diagnosis of SMA and who had the onset of at least two signs and symptoms prior to 3 years of age (i.e. SMA Type I, II or IIIa). Noting that one “sign and symptom” relates to age of onset.
Outcomes	<ul style="list-style-type: none"> • Time to death or respiratory intervention (Primary endpoint) • Survival and Motor function as assessed by HINE, CHOP INTEND, and WHO instruments • Safety
Clinical claim	In patients with pre-symptomatic SMA [with SMN1 deletion or mutation with SMN2 copy number of 1, 2 or 3 and no SMA symptoms], nusinersen is clinically superior in terms of comparative effectiveness and no worse in terms of comparative safety, compared to current treatment with nusinersen, as detailed by the existing PBS restriction. No evidence is provided for patients with SMN1 deletion or mutation and a SMN2 copy number of 1.

Abbreviations: 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
Source: Table 1.4, p6 of the submission

2 Requested listing

Table 2: Requested restriction for nusinersen

Name, restriction, manner of administration, form	Maximum quantity (packs)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
NUSINERSEN Initial treatment			\$110,000 (public)	
12mg*/5mL injection, 1 x 5 mL vial	1	3	\$110,047.39 (private)	Spinraza, Biogen Australia Pty Ltd
Continuing treatment			█ (effective price)	
12mg*/5mL injection, 1 x 5 mL vial	1	2	\$110,000 (public)	
			\$110,047.39 (private)	
			█ (effective price)	

Category/Program:	Section 100 – Highly Specialised Drugs Program
PBS indication:	Treatment of <u>pre-symptomatic</u> , infantile-onset and childhood-onset SMA
Treatment phase:	Initial – New patients
Restriction:	Section 100 – Highly Specialised Drugs Program <input checked="" type="checkbox"/> Authority Required - In Writing
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 5q homozygous deletion, mutation of, or compound heterozygous mutation in the SMN1 gene of Type I, II or IIIa; AND Patient must have experienced at least two of the defined signs and symptoms of SMA Type I, II or IIIa prior to 3 years of age OR <u>Patient must be genetically diagnosed with SMA with a confirmed SMN2 copy number of 1, 2 or 3 prior to onset of signs and symptoms</u> ; AND The treatment must be given concomitantly with standard of care for this condition. AND The treatment must not exceed four loading doses (at days 0, 14, 28 and 63) under this restriction.
Population criteria:	Patient must be 18 years of age or under.

* Submission referred to the strength as 12.6mg/5mL being 12.6mg nusinersen (as heptadecacosodium) in 5mL, which is equivalent to 12mg of nusinersen as the free acid.

Underlined text reflects the change from the current PBS listing.

The continuation criteria remained the same as for the current listing.

Source: Table 1.6 and 1.7, pp14-15 of the submission.

- 2.1 The submission proposed amending the current restriction (underlined text in the restriction) to incorporate the requested population.
- 2.2 A Special Pricing Arrangement was proposed with an effective price of \$█ per 5mL injection. It is unclear whether the sponsor intends to rebate the cost of █; an offer that is in place for the current restriction.
- 2.3 While the clinical evidence presented was in infants aged 6 weeks or less, the proposed restriction did not include an age limit for the requested population. The current restriction has the population criteria of ‘patient must be 18 years of age or under’. An age limit of less than 3 years would be appropriate, however, consideration could also be given as to whether the maximum age for initiation should be 6 weeks for consistency with the clinical trial population. The ESC considered it would be appropriate to limit pre-symptomatic initiation of treatment to patients less than 3

years of age, noting that this was supported in the Pre-Sub-Committee Response (PSCR). The ESC considered it was likely impractical to limit the age for pre-symptomatic initiation of treatment to a maximum of 6 weeks given current SMA screening procedures.

- 2.4 The ESC noted that the sponsor had not requested an MBS item for the SMN2 copy number genetic test, which is currently available as necessary in NSW and ACT via a newborn screening pilot program, and funded by state public hospitals and private payers in other states and territories. The ESC considered there could potentially be equity of access issues to testing if nusinersen were listed for pre-symptomatic initiation of treatment of SMA.

3 Background

Registration status

- 3.1 TGA status: registered for the treatment of 5q SMA, which would include pre-symptomatic initiation of treatment.

4 Population and disease

- 4.1 Spinal muscular atrophy is an autosomal recessive progressive neuromuscular disease caused by mutations or deletions in the Survival-of-Motor-Neuron 1 (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. Respiratory muscle failure is the major cause of morbidity and mortality for patients with SMA. As SMN2 copy number varies from patient to patient, there is a clinical spectrum of the disease where fewer SMN2 gene copies broadly correlate to earlier age of onset and increased disease severity, however due to disease modifying factors in some patients, such correlation is not always apparent.

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

Classification	SMA type	Age at symptom onset	Maximal motor milestone	Likely/Common SMN2 copy numbers	Motor ability and additional features	Prognosis [^]
Pre-natal	0	Pre-natal (before birth)	None	1	Severe hypotonia; Unable to sit or roll*	Death within weeks
Infantile-onset	I	<6 months	None	1, 2, 3	Severe hypotonia; Unable to sit or roll#	Death by 2 years
Childhood-onset	II	6 - 18 months	Sitting	2, 3, 4	Proximal weakness; Unable to walk independently	Survival into adulthood
	III	<3 years (IIIa) >3 years (IIIb) >12 to ≤18 years (IIIc)	Walking	3, 4, 5	May lose ability to walk	Normal lifespan
Adult-onset	IV	>18 years	Normal	4, 5, 6	Mild motor impairment	Normal lifespan

SMA = spinal muscular atrophy; SMN-2 = survival-of-motor-neuron 2 gene.

* Need for respiratory support at birth; contractures at birth, reduced foetal movements.

[^] Prognosis varies with phenotype and standard of care interventions.

Ia joint contractures present at birth; Ic may achieve head control.

Note: The most common number of copies of the SMN-2 gene for each type of SMA is bolded.

Source: Table 1.3, p5 of the submission

4.2 Under the proposed restriction, nusinersen is intended to be used early in patients who are positive for mutations or deletions in SMN1 and who have up to 3 copies of SMN2. The submission claimed that a threshold of up to 3 copies of SMN2 would enable 90.6% (amending errors in extraction of data increased this to 90.8%) of current PBS patients to access treatment early and derive the greatest benefit of treatment. The submission also stated that under the proposed listing, 94.5% (93.9%) of the patients treated before symptoms developed would have become eligible to be treated with nusinersen under the current restriction in due course. These values were not calculated using data from patients currently accessing nusinersen, but from the submission’s literature review.

4.3 It was previously noted in relation to nusinersen that there is poor correlation between the number of SMN2 gene copies and clinical manifestation of the disease, as other factors within the SMN2 gene may modify the phenotype (Paragraph 4.2, Nusinersen Public Summary Document, November 2017). The submission also presented analyses assuming an SMN2 copy threshold of 2 and 4 copies (Table 4). As expected, using a more stringent threshold of 2 copies of SMN2 leads to a lower proportion of ‘false positives’ (1-PPV = 1.5%), compared to a threshold of 3 copies of SMN2 (6.1%), but at the expense of more patients who would have to wait for symptoms to emerge to become eligible for nusinersen under the current listing (46.7% vs 90.8%). Conversely, relaxing the threshold to 4 copies of SMN2 leads to a far greater proportion of false positives (17.7%), but ensures that almost no patients would have had to wait for symptoms to emerge to become eligible for nusinersen under the current restriction (99.9%). The PBAC may wish to consider whether a different threshold than 3 or less SMN2 copies would be more appropriate.

Table 4: Sensitivity, specificity, PPV and NPV of SMN2 testing to capture the current PBS patient population by SMN2 threshold

Parameter	Question	SMN2 ≤3	SMN2 ≤2	SMN2 ≤4
Sensitivity	What proportion of current PBS patients would be detected pre-symptomatically?	90.6% (73.80/81.44)	46.1% (37.53/81.44)	99.9% (81.35/81.44)
	Evaluation's values	90.8% (73.94/81.44) ^a	46.7% (38.05/81.44) ^a	99.9% (81.35/81.44) ^a
Specificity	What proportion of SMA patients not eligible for PBS treatment in current practice would not be treated pre-symptomatically?	76.7% (14.24/18.56)	96.7% (17.94/18.56)	5.9% (1.09/18.56)
	Evaluation's values	74.2% (13.78/18.56) ^a	96.9% (17.98/18.56) ^a	5.9% (1.10/18.56) ^a
PPV	What proportion of patients treated pre-symptomatically, would be eligible for PBS in current practice?	94.5% (73.80/78.13)	98.4% (37.53/38.15)	82.3% (81.35/98.82)
	Evaluation's values	93.9% (73.94/78.73) ^a	96.9% (38.05/38.63) ^a	82.3% (81.35/98.81) ^a
NPV	What proportion of patients not treated pre-symptomatically, would not be eligible for PBS in current practice?	65.1% (14.24/21.87)	29.0% (17.94/61.85)	92.3% (1.09/1.18)
	Evaluation's values	64.8% (13.78/21.27) ^a	29.3% (17.98/61.37) ^a	92.4% (1.10/1.19) ^a

Source: Table 2a-15, p39 of the Submission.

Abbreviations: NPV = negative predictive value; PPV = positive predictive value; SMN = survival of motor neuron

Sensitivity = true positives / all those treated under current practice

Specificity = true negatives / all those not treated under current practice

PPV = true positives / all those treated under proposed listing

NPV = true negatives / all those not treated under proposed listing

^a Evaluation's values which correct for errors in extraction of data

4.4 The ESC noted that lowering the threshold for SMN2 copy number to 2 would exclude the proportion of patients with an SMN2 copy number of 3 who, based on the limited interim clinical evidence available, may derive the most benefit from pre-symptomatic initiation of treatment (see paragraph 6.14). However, the ESC considered that the highest clinical need would be in patients with the most severe forms of SMA (generally seen in patients with fewer SMN2 copies).

5 Comparator

5.1 The submission nominated standard of care (i.e. symptomatic treatment with nusinersen upon diagnosis of SMA Type I, II or IIIa and identification of two signs or symptoms of SMA, noting that age of onset is described as a 'sign or symptom' in the current listing) as the main comparator. The nominated comparator was considered appropriate.

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician presented results from the ENDEAR and CHERISH trials which included patients with SMA type I and patients with

SMA Type II respectively, to emphasise the impact of early treatment on the extent of benefit. The clinician noted that in both studies, patients treated earlier achieved better outcomes compared to those treated later. The clinician also presented results from the NURTURE trial, highlighting that the developmental milestones achieved by patients who initiate treatment with nusinersen prior to the onset of symptoms would not be typically achieved in patients with SMA Type I and II. The clinician noted that rapid irreversible motor neuron damage occurs in untreated SMA patients in the first year of life and that this process can begin in patients prior to the development of symptoms. The clinician noted that [REDACTED] SMA positive patients (from [REDACTED] neonates screened) have already been identified through the NSW/ACT newborn screening pilot program and that [REDACTED] of the [REDACTED] neonates who were identified as having 2 SMN2 copies were already symptomatic when seen by a specialist. The clinician noted that [REDACTED] of the [REDACTED] patients who were identified as having an SMN2 copy number of 3 had also developed symptoms at the time of seeing a specialist. The clinician presented results from the Calucho et al., 2008 systematic review of the correlation between SMN2 copy number and SMA type in approximately 3,500 SMA patients, noting that most patients diagnosed with SMA type I or II have an SMN2 copy number of 2 or 3. [REDACTED]

[REDACTED] The PBAC considered that the hearing was of limited usefulness given most of the information presented was either from the submission itself or had previously been considered by the PBAC.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from organisations (2) via the Consumer Comments facility on the PBS website. Spinal Muscular Atrophy Australia and Rare Voices Australia were supportive of treatment with nusinersen being made available to patients prior to the onset of SMA symptoms.

Clinical trials

- 6.3 The submission was based on an interim analysis (dated 15 May 2018) of an ongoing phase 2, non-randomised, non-controlled, open-label study of nusinersen in 25 pre-symptomatic infants with confirmed homozygous or compound heterozygous SMN1, and either 2 or 3 copies of SMN2: the NURTURE trial. Data from the first interim analysis of this trial dated February 2018 was presented as supportive data in the November 2017 PBAC submission. The results should be interpreted with caution due to the lack of a control group. The magnitude of incremental benefit, if any, from pre-symptomatic initiation of treatment with nusinersen compared with initiating treatment under the current PBS restriction (onset of at least two signs or symptoms,

where one 'sign or symptom' is age of onset <3 years) is not informed by NURTURE. The ESC considered the results of NURTURE were difficult to interpret in the context of a condition where treatment would be required for the patient's lifetime given the lack of comparator arm and given the results are based on an interim analysis.

- 6.4 The applicability of the results to patients older than 6 weeks and to patients with only 1 copy of SMN2 are uncertain given the NURTURE trial limited enrolment to patients aged ≤ 6 weeks of age with 2 or 3 SMN2 copies. The PSCR stated that patients with only 1 copy of SMN2 would likely be symptomatic at birth, or become symptomatic shortly after birth, thereby meeting the current PBS criteria and would likely never receive treatment pre-symptomatically. The PSCR acknowledged there was some uncertainty around the applicability of the trial results to the proposed patient population however, argued that older (≥ 6 weeks) pre-symptomatic patients would still derive more benefit if treated compared to a patient treated symptomatically. The ESC considered that the trial population may have less severe disease than the proposed PBS population, which includes patients with 1 copy of SMN2.
- 6.5 The submission relied on a naïve informal comparison of the effect of nusinersen in the NURTURE trial to its effect in patients treated in the ENDEAR and CS3A trials for infantile-onset SMA patients and to its effect in patients treated in the CHERISH trial in childhood-onset SMA patients to inform the clinical claim. Given the transitivity issues associated with the comparison, the reliability of the comparison was considered limited.
- 6.6 ENDEAR (n=121) and CHERISH (n=126) formed part of the key evidence that the PBAC considered for the current listing for nusinersen for the treatment of symptomatic patients with SMA Type I, II or IIIa, with CS3A (n=20) being a supplementary trial in that consideration. ENDEAR and CHERISH were head-to-head trials comparing nusinersen to sham-control. CS3A was a single-arm trial. Longer-term data from these trials was provided in the submission from the open-label extension SHINE trial.
- 6.7 Details of the trials presented in the submission are provided in Table 5.

Table 5: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Non-randomised trial forming the primary evidence		
SM291/ NURTURE	<p>A Study of Multiple Doses of Nusinersen (ISIS 396443) Delivered to Infants With Genetically Diagnosed and Pre-symptomatic Spinal Muscular Atrophy [NCT02386553]</p> <p>Interim Clinical Study Report</p> <p>Interim Clinical Study Report</p> <p>Bertini E, Hwu WL, Reyna SP, Farwell W, Gheuens S, Sun P, et al. Efficacy and safety of nusinersen in infants with presymptomatic spinal muscular atrophy (SMA): Interim results from the NURTURE study.</p> <p>46th Annual Meeting of the Child Neurology Society.</p> <p>Crawford T, De Vivo D, Bertini E, Hwu WL, Foster R, Bhan I, et al. Nusinersen in infants who initiate treatment in a presymptomatic stage of spinal muscular atrophy (SMA): Interim efficacy and safety results from the phase 2 nurture study.</p> <p>De Vivo D, Bertini E, Hwu WL, Foster R, Gheuens S, Farwell W, et al. One-year outcomes following treatment with nusinersen: Interim results from the NURTURE study of presymptomatic infants with genetically diagnosed spinal muscular atrophy (SMA).</p> <p>De Vivo DC, Bertini E, Hwu W, Foster R, Bhan I, Gheuens S, et al. Nusinersen in infants who initiate treatment in a presymptomatic stage of spinal muscular atrophy (SMA): Interim results from the Phase 2 NURTURE study.</p> <p>De Vivo DC, Hwu WL, Reyna SP, Farwell W, Gheuens S, Sun P, et al. Interim efficacy and safety results from the Phase 2 NURTURE study evaluating nusinersen in presymptomatic infants with spinal muscular atrophy.</p> <p>Mercuri E, Finkel RS, Farrar M, Richman S, Foster R, Hughes S, et al. Infants and children with spinal muscular atrophy (sma) treated with nusinersen in clinical trials: An integrated safety analysis.</p> <p>Nct. A Study of Multiple Doses of Nusinersen (ISIS 396443) Delivered to Infants With Genetically Diagnosed and Presymptomatic Spinal Muscular Atrophy.</p>	<p>May 2018</p> <p>February 2017</p> <p>European Journal of Paediatric Neurology. 2017;21:e14</p> <p>Annals of Neurology. 2017;82</p> <p>Annals of Neurology. 2018;84:S392</p> <p>Annals of Neurology. 2017;82:S265-S6</p> <p>Canadian Journal of Neurological Sciences. 2018;45:S12-S3</p> <p>Neurology. 2017;88(16)</p> <p>Developmental Medicine and Child Neurology. 2017;59:16-7</p> <p>https://clinicaltrials.gov/show/nct02386553. 2015</p>
Supplementary trials used for the informal indirect comparison		
CS3B/ ENDEAR	A Study to Assess the Efficacy and Safety of Nusinersen (ISIS 396443) in Infants With Spinal Muscular Atrophy [NCT02193074]	10 February 2017
CS4/ CHERISH	A Study to Assess the Efficacy and Safety of Nusinersen (ISIS 396443) in Participants With Later-onset Spinal Muscular Atrophy (SMA) [NCT02292537]	6 June 2017
CS3A	<p>A Study to Assess the Efficacy, Safety and Pharmacokinetics of Nusinersen (ISIS 396443) in Infants With Spinal Muscular Atrophy (SMA) [NCT01839656]</p> <p>Finkel et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose escalation study.</p> <p>Finkel et al. Interim results of a phase 2 clinical study of nusinersen (ISIS-SMNRX) in patients with infantile-onset spinal muscular atrophy.</p> <p>Finkel et al. Interim results of a phase 2 clinical study of nusinersen (ISIS-SMNRX) in patients with infantile-onset spinal muscular atrophy.</p> <p>Finkel et al. Results of a phase 2 open-label study of ISIS-SMNRx in patients with infantile (type 1) spinal muscular atrophy.</p> <p>Finkel et al. Results of a phase 2 open-label study of ISIS-SMNRx in patients with infantile (Type 1) spinal muscular atrophy.</p>	<p>21 August 2016</p> <p>The Lancet 2016. 388 (10063): 3017-3026</p> <p>Annual of Neurology 2016. 80; S371-372</p> <p>Neurology 2016. 86 (16); Supplement P5.004</p> <p>Neurology 2014. 82 (10); Supplement S6.003</p> <p>Neuromuscular disorders 2014. 24 (9-10); 920</p>

Source: Table 2d.3, p63 of the submission and Table 2.2.3, p48-49 of the November 2017 PBAC submission.

6.8 The key features of the included evidence are summarised in Table 6.

Table 6: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
NURTURE	25	OL, NC, 5 years Interim analysis 27.14 months	High*	Age <6 weeks with SMA and no symptoms: 2 or 3 SMN2 copies	EFS, OS, Motor milestones, CHOP Intend	Not used
ENDEAR	121	R, DB, MC 13 months	Low	Infantile-onset SMA (Type I)	EFS, OS, HINE (Section 2)	
CHERISH	126	R, DB, MC 16 months	Low	Childhood-onset SMA (Type II)	HFMSE	
CS3A	20	OL, MC, NC, multi-dose 3.7 years	High*	Infantile-onset SMA (Type I)	Motor milestones	
SHINE	142 Type I SMA and 182 Type II SMA patients	OL, extension trial 5 years total from enrolment in first trial	High*	Type I and Type II SMA patients from the ENDEAR, CHERISH, CS3A or CS12 trials	EFS, OS, HINE (Section 2), CHOP Intend, Motor milestones, HFMSE, quality of life	

Abbreviations: O, open label; OS, overall survival; EFS, event-free survival; NC, non-comparative; R, randomised; DB, double-blind; MC, multi-centre; SMA, spinal muscular atrophy; HINE, Hammersmith Infant Neurological Examination; HFMSE, Hammersmith Functional Motor Scale-Expanded.

* Considered to be high risk of bias being open-label and non-comparative studies.

Source: Section 2 of the submission and Table 5 in the November 2017 PBAC commentary; SHINE CSR p107.

Comparative effectiveness

SMA symptom onset in patients initiating treatment while still pre-symptomatic

6.9 The proportion of patients who experienced symptoms of SMA at 13 months and 24 months in the NURTURE trial is detailed in Table 7.

Table 7: SMA symptoms in patients – Efficacy set, NURTURE

	At 13 months			At 24 months		
	2 SMN2 copy	3 SMN2 copies	Total	2 SMN2 copy	3 SMN2 copies	Total
Number of patients (N)	15	10	25	11	5	16
No. Patients with percutaneous gastric tube inserted, n (%)	■ (■)	■	■ (■)	■ (■)	■	■ (■)
No. patients with weight below the 5th percentile, n (%)	■ (■)	■	■ (■)	■ (■)	■	■ (■)
No. patients with weight dropping 2 or more major percentiles over 6 months, n (%)	■ (■)	■	■ (■)	■ (■)	■	■ (■)
No. patients who lose a WHO milestone or fail to demonstrate all expected WHO milestones, n (%)	■ (■)	■ (■)	■ (■)	■ (■)	■	■ (■)
No. patients with manifestation of SMA symptoms, n (%)	■ (■)	■ (■)	■ (■)	■ (■)	■	■ (■)
Proportion, (95% CI)	(■ ■)	(■ ■)	(■ ■)	(■ ■)	(■ ■)	(■ ■)

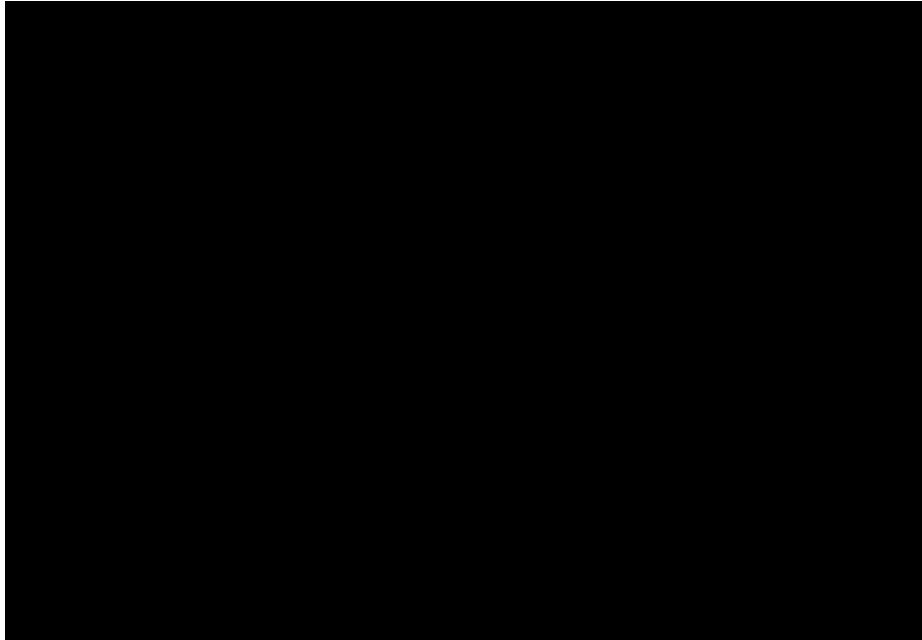
Source: SM201 NURTURE CSR Interim 4, Table 20, p102-103 and Table 92, p554-555.

- 6.10 The efficacy of pre-symptomatic initiation of treatment with nusinersen in SMA patients for the outcome of SMA symptom onset by SMN2 copy numbers 1, 2 or 3 (the proposed population) can be summarised as:
- SMN2 copy number = 1: No data. Completely unknown efficacy or benefit.
 - SMN2 copy number = 2: ■/■ (■%) developed SMA symptoms by 13 months of age and, of the 11 patients who had reached 24 months of age, ■ (■%) patients developed SMA symptoms. Longer term course of disease and outcomes are unknown. The ESC noted these results did not support a clear effect on symptom onset with pre-symptomatic initiation of treatment for patients with an SMN2 copy number of 2. Many patients with an SMN2 copy number of 2 would experience symptom onset prior to 6 months of age, but others could have a later onset of symptoms (see Table 3).
 - SMN2 copy number =3: ■/■ (■%) developed SMA symptoms by 13 months of age, but ■ of the ■ patients who had reached 24 months of age developed SMA symptoms. However, it is plausible that the follow-up period was insufficient for symptom onset in this patient population to be observed in the trial. Longer term course of disease and outcomes are unknown. The ESC considered the extent to which symptom onset was delayed for patients with an SMN2 copy number of 3, if any, was uncertain as patients with an SMN2 copy number of 3 may develop symptoms after 24 months of age.
- 6.11 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. Additionally, even if patients remained asymptomatic or if symptoms developed after 36 months (i.e. SMA Type IIIb or IV) it would remain unknown if pre-symptomatic initiation of treatment with nusinersen altered the course of disease or if the patient would have developed symptoms/remained asymptomatic irrespective of treatment.

Event-free survival

- 6.12 Results for the primary outcome of event-free survival in NURTURE at the updated interim analysis date of 15 May 2018 are presented in Figure 1. Event-free survival was defined as the time to respiratory intervention (invasive or non-invasive ventilation for 6 or more hours per day continuously for 7 or more consecutive days; or tracheostomy) or death.

Figure 1: Kaplan-Meier curve for age at death or respiratory intervention - ITT set



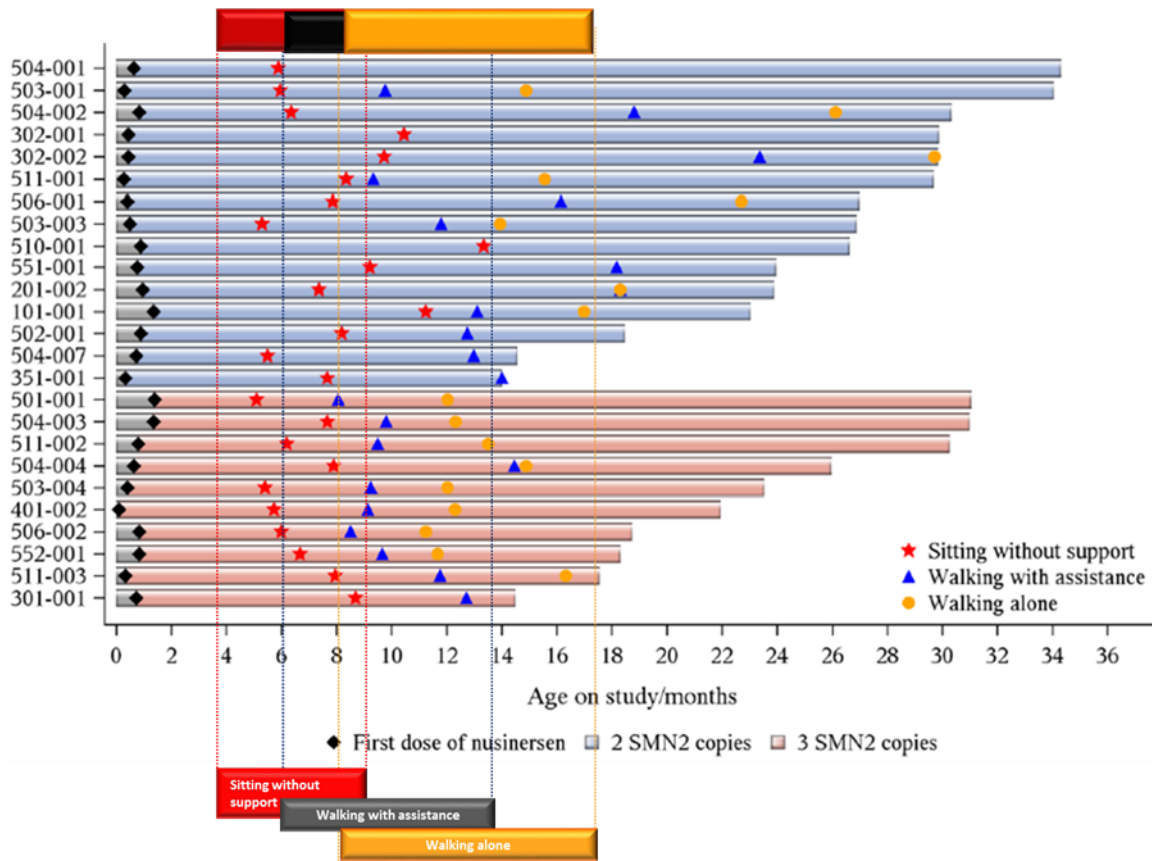
Source: Figure 2d-2, p79 of the submission.

6.13 At the interim time-point no patient had died, and four patients with 2 SMN2 copies met the primary endpoint of death or respiratory intervention, with the respiratory intervention having been initiated for acute, reversible infections. No patient required permanent ventilation.

WHO motor milestones

6.14 Individual patient results for WHO milestones are presented in Figure 2, with the red, grey and yellow shaded bars at the base of the figure representing the expected timeframe for achievement of these milestones in normal healthy infants.

Figure 2: Achievement of WHO motor milestones based on caregiver observation with confirmation by site at subsequent visit – ITT set



Source: Figure 2d-5, p89 of the submission.

6.15 As caregivers noted the age at first achievement of WHO motor milestones and confirmation was provided by the site at subsequent visits, this outcome may have been subject to some subjectivity. Visually it appeared from the data presented that all patients with 3 copies of SMN2, except for patient 504-004, achieved the motor milestones in the expected timeframe for normal healthy infants. However, given that two thirds of patients with 2 copies of SMN2 in NURTURE failed to meet expected WHO milestones at 13 months of age, the submission’s clinical claim that “Infants genetically diagnosed with SMA and treated with nusinersen prior to symptom onset continue to develop milestones that are consistent with the expectation for healthy infants without SMA” was considered to be unsupported. The PSCR clarified that the claim was to convey that patients treated early with nusinersen achieved milestones that are consistent with normal development observed in infants without SMA, albeit somewhat delayed in some patients. The PSCR stated that treated infants with SMA have been able to reach milestones that are rarely achieved by untreated or symptomatically treated patients.

- 6.16 The ESC considered that the interim analysis results did not adequately support a benefit with pre-symptomatic initiation of treatment in patients with an SMN2 copy number of 2. While the ESC considered there was some indication that initiation of treatment in pre-symptomatic patients may lead to better outcomes in terms of WHO milestones in patients with less severe disease (i.e. patients with an SMN2 copy number of 3), the ESC considered the interpretation of these results were considerably uncertain given the limited follow-up and in the absence of meaningful comparative data. Further, the ESC were uncertain of the applicability of the trial results to the proposed PBS population which does not preclude patients with an SMN2 copy number of 1.

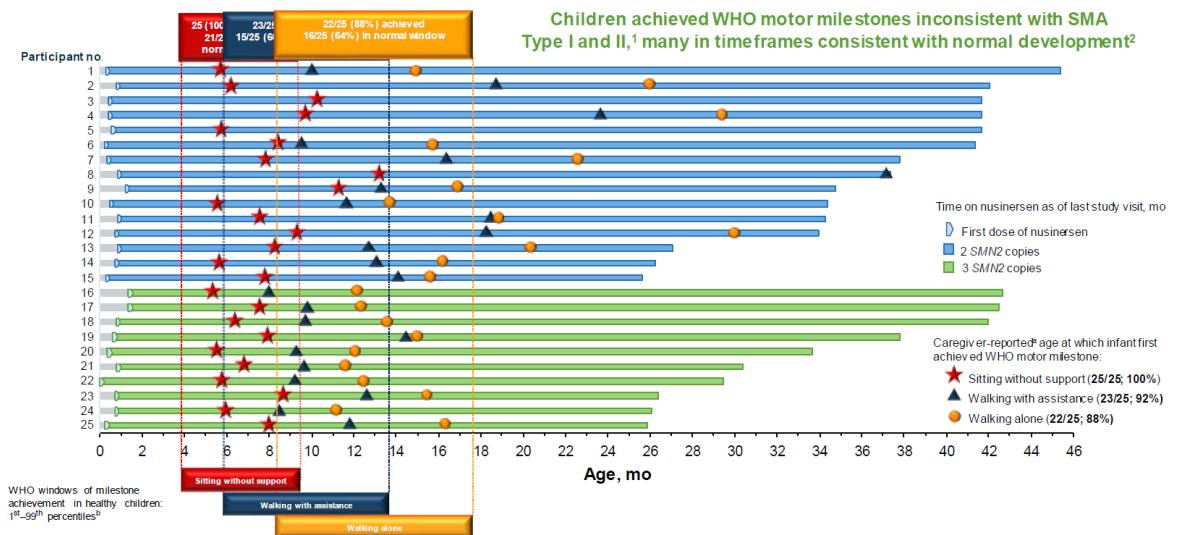
Naïve indirect comparison

- 6.17 The submission presented a naïve numerical comparison of outcomes reported in NURTURE and the outcomes reported in the clinical trial program of nusinersen in symptomatic infantile-onset (Type I) and early childhood-onset (Type II or IIIa).
- 6.18 Given there were significant differences between the patients enrolled in the trials that were used to form the basis of the indirect comparison (ENDEAR, CS3A and CHERISH, as well as extension data from patients in these studies in the SHINE study) and patients in the NURTURE trial, it was considered inappropriate to compare their results in an indirect comparison. Key differences in patient characteristics included:
- NURTURE enrolled patients with SMN2 copy numbers of 2 and 3 whereas ENDEAR enrolled only patients with SMN2 copy number of 2 AND who had the most severe form of disease (Type I SMA). Patients enrolled in ENDEAR were likely to have worse outcomes than those enrolled in NURTURE, which was reflected in the mortality rate (13/80, 16%) in nusinersen treated patients in ENDEAR compared to NURTURE in which no deaths were observed; and
 - The mean age of patients in CHERISH at screening (3.8 years) was older than the oldest patient enrolled in NURTURE at interim cut off (847 days, or 2.3 years), indicating that the patients enrolled in CHERISH and NURTURE were at completely different developmental stages. The PSCR argued that the NURTURE trial population largely represents the patient population for whom nusinersen is currently available in terms of distribution of SMA type. The ESC considered that patient age would likely have a significant impact on the achievement of developmental milestones.
- 6.19 The ESC noted that, while patients in NURTURE had better outcomes including the highest rates of survival, event-free survival and the lowest rates of permanent ventilation of the patients in the CS3A and ENDEAR trials (with SHINE extension), the patients in NURTURE were healthier, having not yet developed any symptoms of SMA. Overall, the ESC considered that it was not possible to determine the magnitude of incremental benefit, if any, of pre-symptomatic initiation of treatment versus

symptomatic treatment from the indirect comparisons given differences between the patient populations in the NURTURE, ENDEAR and CHERISH trials outlined above.

6.20 The pre-PBAC Response presented an updated interim analysis of the NURTURE trial from March 2019 which had a median follow up of 33.8 months. The pre-PBAC Response noted that at this latest follow up, no patients had died or required permanent ventilation. The pre-PBAC Response further noted that most patients had reached the maximum CHOP-INTEND score and that most patients had achieved the WHO motor milestones of sitting without support, walking with assistance and walking alone (see Figure 3).

Figure 3: Achievement of WHO motor milestones based on caregiver observation with confirmation by site at subsequent visit – ITT set (March 2019 interim analysis)



Source: p3 of the Pre-PBAC Response

Comparative harms

6.21 The adverse events experienced by patients in the NURTURE trial are detailed in Table 8.

Table 8: Summary of adverse events in the NURTURE trial

	N (%)
Number of patients dosed	25
Number of patients with adverse event	25 (100)
Number of patients with a moderate or severe event	18 (72)
Number of patients with a severe event	5 (20)
Number of patients with an event, possibly related or related to:	
Study treatment	6 (24)
Lumbar puncture	6 (24)
Number of patients with an event related to:	
Study treatment	0
Lumbar puncture	6 (24)
Number of patients with a serious event	9 (36)

Number of patients with a serious event related to study treatment	0
Number of patients discontinuing treatment due to an event	0
Number of patients withdrawing from study due to an event	0

Source: Table 2d-20, p92 of the submission.

6.22 Of the serious adverse events experienced, the most frequently reported events were pneumonia in four patients, respiratory syncytial virus bronchiolitis in two patients, and respiratory distress in two patients. One serious adverse event was related to post-lumbar puncture syndrome due to failed lumbar puncture procedure on Day 4.

6.23 No patients discontinued the study prematurely due an adverse event and there were no deaths. The ESC noted that the long-term safety of a lifetime of treatment with nusinersen was unknown.

Benefits/harms

6.24 The naïve indirect comparison presented in the submission did not allow for a quantitative comparison of the benefits and harms of early use of nusinersen and symptomatic use. Accordingly, a benefits/harms table has not been presented.

Clinical claim

6.25 The submission concluded that infants genetically diagnosed with SMA and treated with nusinersen prior to symptom onset continue to develop milestones that are consistent with the expectation for healthy infants without SMA, and that the magnitude of benefit from pre-symptomatic initiation of treatment is greater compared with symptomatic treatment.

6.26 The therapeutic conclusion presented in the submission was not adequately supported by the evidence presented in Section 2 of the submission as:

- NURTURE was a single-arm study with no control group, which did not allow for an estimation of the incremental benefit of pre-symptomatic initiation of treatment with nusinersen compared to nusinersen treatment under the current PBS restriction, and there were significant differences in the patients enrolled in ENDEAR and CHERISH with those in NURTURE which did not allow any meaningful indirect comparisons;
- NURTURE enrolled only patients with 2 or 3 copies of SMN2, therefore the efficacy of pre-symptomatic initiation of treatment with nusinersen of patients with just 1 copy of SMN2 is unknown;
- █/█ (█%) of patients with 2 copies of SMN2 in NURTURE developed SMA symptoms and failed to meet the age appropriate WHO milestones by 13 months of age, which was inconsistent with the submission’s clinical claim;
- After an average follow-up of more than 2 years, while infants genetically diagnosed with 3 copies of SMN2 who were treated early with nusinersen attained

WHO motor milestones at time points that were generally within the time ranges expected by the WHO for normal healthy infants, the date of first attainment of motor milestones was subjective, being based on caregiver observation. The ESC considered that, while there may be some potential for bias in the assessment of motor milestones, caregivers of patients with SMA would likely be well placed to assess the attainment of milestones such as those reflected in Figure 2 above.

- The comparison to symptomatic treatment was informed by a naive indirect comparison with multiple transitivity issues and was considered unlikely to be meaningful or reliable.

6.27 The PBAC agreed with the evaluation that the clinical claim was not supported by the clinical data presented on the basis of the issues noted above. The PBAC considered that any magnitude of benefit versus symptomatic treatment could not be determined from the indirect comparisons presented.

Economic analysis

6.28 The submission presented a modelled cost-utility analysis to compare the scenario where nusinersen is available to patients genetically diagnosed with SMA with SMN2 copy numbers of 1, 2 or 3 (early treatment), to current practice where nusinersen is only available upon diagnosis of SMA in patients who have two SMA symptoms that occurred prior to 3 years of age (symptomatic treatment).

6.29 The model was considered overly simplistic and likely to be unfit for purpose as there were no health states considered and no changes in QALYs over time (except for discounting at 5%). Table 9 provides a summary of the model structure and rationale.

Table 9: Summary of model structure and rationale

Component	Description	Justification/comments
Type of analysis	Cost-utility analysis	This was considered appropriate.
Outcomes	Quality-adjusted life years	While this was appropriate, the magnitude of any incremental QALY gain was uncertain.
Time horizon	80 years in the model vs 27.1 months in the key trial	Likely insufficient data to justify the time horizon.
Methods used to generate results	Cohort expected value	Reasonable
Software package	MS Excel 2010	Reasonable

Source: Section 3 of the submission.

6.30 The ESC noted that a cost-effectiveness analysis conducted by the Institute for Clinical and Economic Review of pre-symptomatic initiation of treatment with nusinersen compared to best supportive care included multiple health states which affect mortality and different utility values. The ESC considered that the economic model presented in the submission did not incorporate all information available.

6.31 The ESC considered that a time horizon of 80 years was highly uncertain and not sufficiently justified by the available evidence in the submission.

6.32 The key drivers of the model are highlighted in Table 10.

Table 10: Key drivers of the model

Description	Method/Value	Impact
Extrapolation	Treatment effect continued beyond 27.1-month trial period for up to 80 years.	High, favoured early use of nusinersen.
Utilities	High ongoing incremental utility assumed of 0.91 versus 0.71 for symptomatic treatment, and no disutility for adverse events for incremental period of treatment.	High, favoured early use of nusinersen
Duration of early treatment	Assumed to be 1 year of early treatment required on average before patients would have become eligible and started treatment with nusinersen under the current PBS restriction (symptomatic treatment).	High, favoured early use of nusinersen
Cost savings	A saving of \$4,380 per year for 80 years for lower healthcare expenses was assumed. There was no basis for the assumption of an ongoing cost saving.	High, favoured early use of nusinersen
False positive rate	False positive rate of 5.5% assumed. Amendments to errors identified in data extraction increased this to 6.1% and use of alternative data estimated a 10% rate.	High, favoured early use of nusinersen

Source: Section 3 of the submission.

6.33 The submission offered to rebate the cost to the Government for treating patients who the submission estimated would not have developed a symptom of SMA prior to 3 years of age (“false positives”). Note: Age of onset of symptoms of less than 3 years is a ‘sign or symptom’ in itself, and therefore for the current restriction only one additional symptom is required for patients to be able to access nusinersen. The results of the economic evaluation are presented in Table 11.

Table 11: Results of the economic evaluation

Component	Early treatment with nusinersen	Symptomatic treatment with nusinersen	Increment
Excluding false positive patients			
Cost: nusinersen plus administration and SMN2 testing	\$ [redacted] ^a	\$ [redacted] ^b	\$ [redacted]
Incremental cost/QALY gained			\$ [redacted]
Total costs including other direct medical costs	\$ [redacted]	\$ [redacted] ^c	\$ [redacted]
QALYs	3.9193	0	3.9193
Incremental cost/QALY gained			\$ [redacted] ^d
Including false positive patients^h			
Cost: nusinersen plus administration and SMN2 testing	\$ [redacted]	\$ [redacted] ^e	\$ [redacted]
Incremental cost/QALY gained			\$ [redacted]
Total costs including other direct medical costs	\$ [redacted]	\$ [redacted] ^{e,f}	\$ [redacted]
QALYs	3.7023	0	3.7023
Incremental cost/QALY gained			\$ [redacted] ^g

^a 3 injections per year for 80 years, discounted at 5% per annum to 19.6 years

^b 3 injections per year for 79 years, discounted at 5% per annum to 18.6 years

^c 3 injections per year for 80 years, discounted at 5% per annum to 19.6 years; if assume 18.6 discounted years, total cost is \$ [redacted]

^d ICER is \$ [redacted]/QALY if assume 18.6 discounted years for symptomatic nusinersen treatment (total cost=\$ [redacted])

^e reduces to account for the fact that only 94.5% of patients who would be treated early are treated symptomatically

^f 3 injections per year for 80 years, discounted at 5% per annum to 19.6 years. If assume 18.6 discounted years, total cost is \$ [redacted]

^g ICER is \$ [redacted]/QALY if assume 18.6 discounted years for symptomatic nusinersen treatment (total cost=\$ [redacted])

^h costs attributed to false positives likely overestimated as apply 20.6 years of nusinersen treatment

Source: Calculated during the evaluation and Table 3-5, p119 of the submission.

The redacted table shows ICERs in the range of \$15,000/QALY to \$200,000/QALY.

6.34 The incremental increase in utility of 0.2 (0.91 minus 0.71 (with 0.71 being the utility accepted by the PBAC for patients currently treated with nusinersen on the PBS)) for every year that a patient who was treated early with nusinersen lived, was an assumption without any evidence base. Further, the assumption that there would be this increase and that such an increase would be maintained for the patient’s lifetime was not substantiated. The PSCR contended that the incremental increase in utility of 0.2 is reasonable as it is less than one third of that for the incremental increase in utility for symptomatic treatment versus no treatment (0.71 and 0.04 respectively) presented in the March 2018 minor submission. The ESC considered the application of a 0.2 increase in utility each year for patients initiating treatment pre-symptomatically was inappropriate in the absence of evidence to support the incremental utility increase or that such an increase would be maintained over the time horizon of 80 years.

6.35 The submission estimated that an incremental duration of treatment of 0.91 years would be required for early versus symptomatic treatment, and it used a duration of 1 year in the model. The manner by which the submission derived the incremental duration was considered to be potentially biased and overall, the incremental duration of treatment used in the model was considered to have been underestimated. A longer timeframe for treatment is likely. Data received from the Department showed that for the period from June 2018 to end February 2019 that at least 65% of patients initiated on nusinersen were aged 5 years or more at the date of

their first prescription (although this included grandfathered patients). The PSCR claimed that the maximum duration of early treatment for any individual is three years as patients currently eligible for treatment must have developed symptoms by three years of age. The PSCR stated that based on the expected distribution of symptom onset where 55% of patients are Type I where symptoms develop at 6 months of age, the time frame from early treatment to symptomatic treatment is, on average, slightly less than one year. The ESC noted that the current listing does not preclude patients older than three years of age from treatment as it only specifies that symptoms need to be present prior to three years of age. As such, the ESC considered the sponsor's claim that the maximum duration for early treatment (i.e. pre-symptomatic initiation of treatment) is three years is incorrect. In this regard, the ESC considered the incremental duration of treatment of 1 year used in the model was likely an underestimate. Further, the ESC considered the submission's calculation of the incremental duration of pre-symptomatic treatment was inappropriate as the proportions of patients with Types I, II or IIIa SMA used in the calculation were derived from the studies presented in submission used to inform SMN2 copy number by SMA type, most of which did not report across the full spectrum of SMA, did not differentiate between Types IIIa and IIIb, and had potentially biased recruitment.

- 6.36 A threshold analysis was undertaken during the evaluation to investigate the effect of a longer treatment period as well as the incremental utility gain required to be maintained per year to result in the same ICER as that accepted by the PBAC for the current restriction. The number of additional doses of nusinersen required in Year 1 was left as 3 doses, pending confirmation from the sponsor whether the cost of [REDACTED] (the submission inconsistently, assumed four additional doses in its financial estimates). The ESC advised that the ICER previously accepted for symptomatic treatment may be less relevant for pre-symptomatic initiation of treatment noting the available evidence for pre-symptomatic initiation of treatment is substantially more uncertain than that available for symptomatic treatment.
- 6.37 The ICER included an ongoing reduction in healthcare costs for patients treated early on the basis of SMN2 copy numbers (i.e. 1, 2 or 3 copies of SMN2) of an assumed \$4,380 per year. Whether there would be an ongoing lower cost for healthcare expenditure was considered uncertain. The ESC noted that the cost offsets were not based on evidence, but rather on an assumption that the cost per patient initiating treatment pre-symptomatically per year was \$10,000 (based on the health care expenditure per person of \$7,096 estimated by AIHW in 2015/2016) compared to \$14,380 for a patient treated symptomatically. As such, the ESC considered that the inclusion of the cost savings in the economic analysis was not justified.
- 6.38 The base case assumed a 5.5% (6.1% after correcting for errors) false positive rate (i.e. 6.1% who would receive treatment under the proposed restriction would never have met the current eligibility criteria). The economic model presented was highly

sensitive to changes in the “false positive” proportion. Increasing the “false positive” proportion to 6.5% of all treated patients increased the ICER by 11% from a base case of \$105,000/QALY - \$200,000/QALY to \$105,000/QALY - \$200,000/QALY. The ESC considered the submission’s estimated false positive rate to be unreliable noting that not all studies from which the rate was calculated reported on SMN2 copy number across the full spectrum of SMA, differentiated between Types IIIa and IIIb, and some studies may have had biased recruitment. The ESC noted that using only values from studies which enrolled patients across different SMA types and reported Types IIIa and IIIb patients separately along with the PBS data of the proportion of patients with SMA Type I, II or IIIa who were treated with nusinersen (from end of June 2018 to end of February 2019) under the current listing increased the false positives rate to 10% and the ICER to \$105,000/QALY - \$200,000/QALY. The pre-PBAC Response stated that the analysis which increased the false positives rate to 10% assumes 50% of patients treated on the PBS are Type IIIb which is incorrect as Type IIIb patients have an age of onset of SMA later than 3 years of age and therefore do not meet the current PBS restriction criteria. The PBAC noted that the pre-PBAC Response had misinterpreted the assumptions used to derive the 10% rate of false positives. The PBAC noted the pre-PBAC Response had misinterpreted the analysis as the analysis did not assume 50% of patients treated on the PBS are Type IIIb. The PBAC noted the number of Type IIIb patients was derived based on the estimated proportion of Type IIIa and IIIb patients (based on the studies that reported both Type IIIa and Type IIIb patients) and the number of Type IIIa patients treated on the PBS.

- 6.39 The submission assumed that there would be no difference in adverse events between early and symptomatic treatment with nusinersen. The ESC considered that the exclusion of adverse event costs from the economic analysis was not appropriate, particularly given there would likely be an increase in adverse events associated with more administrations for patients initiating treatment pre-symptomatically compared with patients treated symptomatically.
- 6.40 The submission did not include the cost of any repeat tests for SMN2. This may not have been appropriate if the laboratories that verify positive tests also charged a fee, given the statement on page ii of the submission that any positive tests are repeated for verification at a different laboratory. The ESC considered that exclusion of the cost for repeat tests for SMN2 was not appropriate.
- 6.41 Of further consequence to the reliability of the estimated ICER was that the model did not include the costs of any increase in screening for SMN1. With the availability of a treatment for patients identified as SMN1 positive and with up to 3 copies of SMN2, there is likely to be an increase in the number of patients being screened. The ESC agreed with the evaluation that there would likely be an increase in the number of patients being screened for SMN1 with the availability of pre-symptomatic initiation of treatment. The ESC considered that the cost of increased screening may be substantial noting that, if uptake in Year 6 was 100% as per the submission’s

assumption, the cost would be \$79 million annually (based on a cost of \$220 per test according to the VGS website) if all live births (estimated at 362,706) were screened by Year 6. The ESC considered that data on the costs of the newborn screening pilot program currently being implemented in the NSW and ACT newborn screening pilot may provide an informative indication of costs of screening nationwide.

6.42 Overall, the ESC considered that the economic analysis presented was not sufficiently reliable to inform the cost-effectiveness of initiating treatment with nusinersen in pre-symptomatic patients on the basis of the following key issues:

- the model structure comprising only a single health state, does not accurately model the disease course of SMA;
- extrapolation of the treatment effect beyond the 21.7 month follow-up period of the NURTURE trial to 80 years was highly uncertain and not appropriate given the lack of long-term data. Further, an incremental benefit of pre-symptomatic initiation of treatment versus symptomatic treatment was not sufficiently supported by the available evidence (see paragraph 6.14);
- the inclusion of a 0.2 utility gain and a saving of \$4,380 in each year of the model for pre-symptomatic initiation of treatment compared to symptomatic treatment were assumptions not adequately supported by evidence;
- the studies used to estimate the incremental duration of treatment of pre-symptomatic treatment (0.91 years) and false positive rate (6.1%) included studies which did not differentiate between Types IIIa and IIIb, did not report SMN2 number across the full spectrum of SMA, and may have had biased recruitment; and
- the assumption of no difference in adverse events between pre-symptomatic initiation of treatment and symptomatic treatment and consequently the exclusion of adverse event costs was not justified (see paragraph 6.35).

6.43 The submission presented a sensitivity analysis varying both the utility rate and the rate of false positive patients. The model was sensitive to both of these factors as well as to the discount rate used and the timeframe of the analysis. The ESC considered that the sensitivity analysis was of limited reliability on the basis that it considered the model itself was not reliable to inform cost-effectiveness.

**Drug cost/patient /extra 1 year of treatment with the cost of [REDACTED]
[REDACTED]: \$ [REDACTED]**

6.44 The incremental cost of nusinersen is for the extra duration of treatment required prior to when the patient would have been diagnosed with SMA and eligible for nusinersen on the PBS under the current restriction. The economic model assumed an additional treatment period of 1 year from initiation of nusinersen. For an extra year

of treatment, 4 doses of nusinersen would be required or 3 doses if the [REDACTED] ([REDACTED]). The drug cost/patient/extra 1 year of treatment is equal to \$ [REDACTED] and \$ [REDACTED] respectively for the 4 or 3 dose scenarios, respectively (see Table 12).

Table 12: Drug cost per patient for proposed and current settings

	Proposed drug Trial dose and duration	Proposed drug Model	Proposed drug Financial estimates
Mean dose	12mg – 4 loading doses then doses every 4 months	12mg	12mg
Mean incremental duration of treatment	Incremental duration of treatment required was not measured	1 year	One extra dose for Type I, 1 extra year for Type II and 2 extra years for Type IIIa SMA patients
Cost/patient/extra 1 year of treatment	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Cost/patient/extra 2 years of treatment *	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

** Undiscounted.

Source: Sections 2, 3 and 4 of the submission.

Estimated PBS usage & financial implications

- 6.45 The submission was considered by DUSC.
- 6.46 The submission used an epidemiological approach whereby the incident population was based on a birth prevalence of 8.5 per 100,000 as reported by Arkblad et al, 2009 for patients in Sweden (and as used in the November 2017 submission for the current restriction). Distribution of SMA patients by type came from the same publication, with an adjustment of 3.35% for Type IV patients. It was not clear how applicable the estimates would be to the Australian population, and there were notable inconsistencies between the estimates assumed and those reported among those currently being treated with nusinersen on the PBS. The DUSC acknowledged that the low proportion of Type I patients in the PBS data compared to the Arkblad et al (2009) data could be due to some of these patients being treated in clinical trials and not on the PBS.
- 6.47 The number of additional patients to be treated with nusinersen under the proposed listing and the corresponding financial impact is shown in Table 13 below.

Table 13: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	■	■	■	■	■	■
Number of scripts dispensed ^a	■	■	■	■	■	■
Estimated financial implications of early use of nusinersen						
Cost to PBS/RPBS	■	■	■	■	■	■
Estimated financial implications for symptomatic use of nusinersen						
Cost to PBS/RPBS	■	■	■	■	■	■
Net financial implications						
Net cost to PBS/RPBS	■	■	■	■	■	■
Net cost to MBS for injection procedures	■	■	■	■	■	■
Net cost to health budget	■	■	■	■	■	■

^a Assuming an additional four doses for 1 year of early treatment, as estimated by the submission.

No copayments assumed.

Source: Table 13, 6.05.COM.21

The redacted table shows that at year 6 the number of patients treated was less than 10,000 and the net cost to PBS/RPBS was less than \$10 million.

6.48 The DUSC considered that estimated utilisation was likely underestimated due to the following:

- The potential for greater patient numbers particularly in Years 1 to 3 of listing due to higher than predicted screening rates. The DUSC considered that screening rates for babies are likely to increase if nusinersen is listed for this indication and be higher than the 30% estimated in Years 1 and 2 after listing. In addition, the submission estimates do not include treatment of patients that may result from screening in older children.
- The DUSC considered that the number of “false positive” patients (i.e. those eligible via genetic testing but who would never qualify under the current restriction) will be greater than predicted if the screening rate is higher than predicted. The DUSC noted that should the number of “false positive” patients be greater than estimated, the additional cost to the PBS would be substantial. Further, the DUSC noted there would be no way of tracking the number of “false positive” patients treated.
- The DUSC considered the duration of incremental treatment may be longer than estimated in the submission.

6.49 Overall, the DUSC considered the financial implications of listing nusinersen for early use to be highly uncertain as there is uncertainty around the premise on which the estimates were based, that SMA patient numbers can be accurately predicted by SMN2 copy number alone.

6.50 The DUSC noted that the cost of testing was underestimated. The submission did not include the cost of the initial and confirmatory SMN1 genetic tests. The cost of SMN2

testing is estimated in the submission, however as this test is only done after a positive SMN1 test, the number of SMN2 tests will be much fewer than the number of SMN1 tests because this is a rare condition.

Quality Use of Medicines

- 6.51 No quality use of medicines issues were identified. The issue of usage in the population beyond the proposed listing (Type IIIb or IV SMA) was considered by the submission and discussed above.
- 6.52 The DUSC considered that the treatment of “false positive” patients should have been addressed by the submission as a QUM issue. The pre-PBAC Response indicated that treatment of “false positive” patients (i.e. patients with Type IIIb or IV SMA) with nusinersen would still be within the approved TGA indication. The PBAC considered that given the milder phenotype associated with Type IIIb and IV SMA and the expected lifespans for these patients, some patients that would be diagnosed with Type IIIb or IV SMA may elect to forgo a lifelong treatment.

Financial Management – Risk Sharing Arrangements

- 6.53 The submission proposed a Risk-Sharing Arrangement for nusinersen. The submission proposed that the cost of patients treated under the proposed restriction who would not have developed symptoms by the age of 3 years could be borne by the sponsor via an appropriate mutually agreed funding mechanism. While the sponsor expected that this would need to be supported by data from the Department of Human Services, capturing patient symptom status at initiation of therapy, it was considered that the number of these patients could not be accurately tracked, since the submission expected that initiating treatment with nusinersen in pre-symptomatic patients would delay the development of symptoms. The submission proposed that one patient annually would fall into this category. The DUSC considered that given there are other significant uncertainties associated with the financial estimates presented and the concerns raised that may contribute to an underestimate of the total cost, additional consideration for further risk sharing beyond the rebate for the estimated usage in patients with Type IIIb or IV SMA may be appropriate.
- 6.54 The PSCR noted that, under the current RSA for nusinersen, [REDACTED]. The PSCR indicated that the Sponsor is willing to consider other appropriate mechanisms for further risk sharing to allay the concern for potential use of nusinersen outside the proposed restriction.
- 6.55 As stated above, it was considered that an annual cap would be appropriate.

7 PBAC Outcome

- 7.1 The PBAC deferred making a final recommendation to extend the current listing of nusinersen to include the pre-symptomatic initiation of treatment of patients who have up to three copies of the survival-of-motor-neuron 2 (SMN2) gene, pending advice from the Medical Services Advisory Committee (MSAC) on the prognostic value of SMN2 copy number for the severity of spinal muscular atrophy (SMA) to help determine eligibility for nusinersen in pre-symptomatic patients. The PBAC considered it would be appropriate to make its final recommendation once the advice it sought from the MSAC was received. However, the PBAC was of a mind to not recommend extending the current listing of nusinersen on the basis there was insufficient evidence to demonstrate pre-symptomatic initiation of treatment with nusinersen would be more effective than treatment with nusinersen following the onset of symptoms of SMA. Further, the PBAC considered that the magnitude of incremental benefit if any, could not be determined from the available evidence.
- 7.2 The PBAC acknowledged there remained a clinical need for treatments for SMA, particularly for patients with the most severe forms of the condition who experience significant disability and poor survival despite treatment. The PBAC noted that a novel gene therapy, administered as a one-time treatment for SMA had been developed and was currently being investigated in an ongoing phase III clinical trial.
- 7.3 The PBAC noted that the key clinical evidence presented in the submission was from the NURTURE trial, an open-label, single arm study of nusinersen in 25 pre-symptomatic infants with confirmed homozygous or compound heterozygous mutation in the SMN1 gene, and either 2 or 3 copies of SMN2. The PBAC noted that most patients with an SMN2 copy number of 2 (10/15) had developed SMA symptoms by 13 months of age. The PBAC noted that while a smaller proportion (2/10) of patients with an SMN2 copy number of 3 had developed SMA symptoms by 13 months of age, it would not be uncommon for patients with an SMN2 copy number of 3 to develop SMA symptoms after this age. Overall, the PBAC considered the results from the NURTURE trial did not adequately support an effect on symptom onset with pre-symptomatic initiation of treatment of patients with an SMN2 copy number of 2 or 3.
- 7.4 The PBAC noted that in the latest March 2019 interim analysis of the NURTURE trial, most patients had reached the WHO motor milestones of sitting without support, walking with assistance and walking alone, though several patients with an SMN2 copy number of 2 met these milestones later than would be expected with normal development (see Figure 3). The PBAC considered these results to be indicative of a treatment effect with pre-symptomatic initiation of treatment however, considered that an incremental benefit of pre-symptomatic initiation of treatment versus symptomatic treatment could not be determined from the available evidence given the lack of appropriate comparative data. The PBAC considered that key differences

between characteristics of the patients enrolled in the ENDEAR, CHERISH and NURTURE trials noted by the ESC (see paragraph 6.18) meant that a comparison of outcomes from these trials could not reliably inform the magnitude of any incremental benefit. On this basis, the PBAC considered that the clinical claim that the magnitude of benefit from pre-symptomatic initiation of treatment is greater compared with symptomatic treatment was not supported by the clinical evidence presented. The PBAC noted that data from the ENDEAR and CHERISH trials supported a larger treatment benefit in symptomatic patients who initiated treatment at an earlier age. However, it considered there was a distinct difference between earlier treatment in symptomatic patients and pre-symptomatic initiation of treatment as the latter involves patients being exposed to an invasive procedure during a period of pre-symptomatic lead time where the additional benefit is uncertain.

- 7.5 The PBAC noted that the majority of adverse events in the NURTURE trial 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.
- 7.6 The PBAC considered that as the clinical landscape for the treatment of SMA continues to change and screening becomes more widespread, the time between diagnosis of SMA and initiation of treatment is likely to decrease. The PBAC noted that patients genetically diagnosed with SMA who develop symptoms of SMA within the first year of life may only receive a few doses of nusinersen under pre-symptomatic initiation of treatment if it were available, prior to becoming eligible for treatment with nusinersen under the current restriction. The PBAC considered that for these patients, the extent of benefit, of a few doses under pre-symptomatic initiation of treatment in addition to treatment over a lifetime was uncertain.
- 7.7 The PBAC considered that the proportion of ‘false positive’ (i.e. Type IIIb and IV) patients that would be treated under pre-symptomatic initiation of treatment of patients with up to three copies of SMN2 was uncertain noting that the proportion of false positive patients who would be treated increased from 6.1% to 10% using alternative values of proportions of SMA types and PBS data of patients treated with nusinersen under the current restriction (see paragraph 6.37). The PBAC agreed with the DUSC that the proportion of false positive patients treated would increase with increased rates of screening. On this basis, the PBAC considered that the incremental duration of earlier treatment, on average, was uncertain. The PBAC considered that while patients with more severe phenotypes would develop SMA symptoms shortly after birth and consequently have a relatively short period of pre-symptomatic initiation of treatment, the period of pre-symptomatic initiation of treatment in other patients and particularly in false positive patients, may be much longer.

- 7.8 The PBAC considered that in the absence of evidence to support a treatment benefit with pre-symptomatic initiation of treatment over symptomatic treatment, the cost-utility analysis presented was of limited relevance to the consideration of the cost-effectiveness of pre-symptomatic initiation of treatment. Irrespective, the PBAC considered the model to be unsuitable for decision making on the basis of the issues outlined in paragraph 6.41.
- 7.9 The PBAC noted that the estimated net cost to the PBS was less than \$10 million in Year 1 increasing to less than \$10 million in Year 6. The PBAC considered the utilisation estimates to be considerably uncertain overall given the submission calculated patient numbers by determining SMA patient numbers by phenotype based on SMN2 copy number alone, which inherently assumes SMN2 copy number accurately correlates to SMA type. The PBAC agreed with the DUSC that the financial impact of extending the existing listing to include pre-symptomatic initiation of treatment, would likely be higher than estimated due to a potentially greater number of true and false positive patients from potentially higher than predicted screening rates and a longer than estimated incremental duration of treatment on average. Further, the PBAC considered that the cost of screening may be substantial noting that if all live births were screened by Year 6 (estimated to be 362,706), the cost would be \$79 million annually.
- 7.10 The PBAC considered there was currently inequitable access to screening for SMA given screening was currently only available through the NSW/ACT newborn screening pilot program with funding in other states and territories being borne by public hospitals and private payers.
- 7.11 The PBAC noted that the range of phenotypes observed for genetic conditions generally broaden as genetic testing becomes more widespread and is carried out in populations beyond those considered to be at risk. The PBAC noted reports of adults with an SMA genotype who have minimal or none of the clinical manifestations typically present in those diagnosed with SMA and that these patients have been reported in two contexts: family members of SMA patients (Helmken et al., 2003)¹ and within a Taiwanese reproductive carrier screening program that screened 107,611 pregnant women (Su et al., 2011)². The PBAC acknowledged these patients are

¹ Helmken C, Hofmann Y, Schoenen F, Oprea G, Rudnik-Schöneborn HRS, Zerres K and Wirth B (2003): Evidence for a modifying pathway in SMA discordant families: reduced SMN level decreases the amount of its interacting partners and Htra2-beta1. *Human Genetics* 114: 11-21

² Su Y-N, Hung C-C, Lin S-Y, Chen F-Y, Chern JPS, et al. (2011): Carrier Screening for Spinal Muscular Atrophy (SMA) in 107,611 Pregnant Women during the Period 2005–2009: A Prospective Population-Based Cohort Study. *PLoS ONE* 6(2): e17067. doi:10.1371/journal.pone.0017067

relatively rare (only 4 of 107,611 pregnant women screened in the Taiwanese study were found to have an SMA genotype with minimal symptoms SMA). However, the PBAC considered that given the rarity of SMA itself, these patients may represent a proportion of patients that would be treated under pre-symptomatic initiation of treatment with nusinersen and become exposed to lifelong treatment with its associated harms and minimal treatment benefit. In this regard, the PBAC requested that the MSAC account for the extent of under ascertainment of false positive patients due to the existence of patients with an SMA genotype without clinical manifestations of SMA, in its provision of advice on the proportion of true and false negative and positive patients that would be expected under pre-symptomatic initiation of treatment with nusinersen. The PBAC considered that the existence of these patients emphasised the effect of other molecular factors in addition to SMN2 copy number on SMA phenotype.

Outcome:

Deferred

November 2019 PBAC addendum to the July 2019 PBAC Minutes:

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

8 Purpose of Item

- 8.1 To consider the advice from the Medical Services Advisory Committee (MSAC) on the prognostic value of SMN2 copy number and advice from clinicians from the Clinical Expert Consultation in relation to the pre-symptomatic initiation of treatment with nusinersen for SMA.

9 Background

- 9.1 At its July 2019 meeting, the PBAC deferred making a final recommendation to extend the current listing of nusinersen to include the pre-symptomatic initiation of treatment of patients who have up to three copies of the SMN2 gene. The PBAC considered it would be appropriate to make its final recommendation following receipt of the advice sought from MSAC on the prognostic value of SMN2 copy number for the severity of SMA to help determine eligibility for nusinersen in pre-symptomatic patients.
- 9.2 The PBAC was of a mind to not recommend extending the current listing of nusinersen on the basis there was insufficient evidence to demonstrate pre-symptomatic initiation of treatment with nusinersen would be more effective than treatment with nusinersen following the onset of symptoms of SMA.

10 Current situation

Advice from MSAC

- 10.1 MSAC considered the prognostic value of the number of copies of the SMN2 gene for the severity of SMA to determine eligibility for nusinersen in pre-symptomatic patients at its meeting on 1 – 2 August 2019.
- 10.2 MSAC considered that SMN2 copy number variation does offer some prognostic value – that is, more copies of SMN2 generally results in less severe SMA, and less copies of SMN2 generally results in more severe SMA. Based on several studies, MSAC noted that having three copies of SMN2 resulted in people developing any type of SMA, from Type I (most severe) to Type IV (least severe), with most developing Type II. However,

infants with two copies of SMN2 usually developed Type I SMA, and less frequently developed Type II or Type III disease. Infants with one copy of SMN2 almost always developed Type I SMA. Thus, MSAC considered that the prognostic value was more reliable for infants with ≤ 2 copies of SMN2 compared with ≤ 3 copies. However, this correlation between SMN2 copy number and disease severity appears to be imperfect. Based on recent data from studies separating SMA Types IIIa and IIIb (Tables 1 and 2), MSAC noted the following proportions of SMA patients would be eligible for pre-symptomatic initiation of treatment with nusinersen based on SMN2 copy number:

- ≤ 2 SMN2 copies: 28.01% of all patients (and an overall ‘false positive’ proportion of 0.56% patients predicted based on the SMN2 result to progress to manifest SMA symptoms sufficient to qualify for the existing PBS listing, but who would not actually have progressed as predicted)
- ≤ 3 SMN2 copies: 80.99% of all patients (and an overall ‘false positive’ proportion of 4.28%).

Table 1: Proportion of SMA patients eligible for nusinersen with pre-symptomatic initiation of treatment and in current practice based on SMN2 copy number threshold of 2 or less, using studies which only reported different SMA types including IIIa and IIIb

		Current practice		
		Eligible	Not eligible	All
Pre-symptomatic initiation of treatment	Eligible	27.45% (True positives)	0.56% (False positives)	28.01%
	Not eligible	57.03% (False negatives)	14.96% (True negatives)	71.99%
	All	84.48%	15.52%	100.00%

Source: August 2019 MSAC Public Summary Document for Application 1589.
Abbreviations: SMA = Spinal Muscular Atrophy, SMN = survival of motor neuron

Table 2: Proportion of SMA patients eligible for nusinersen with pre-symptomatic initiation of treatment and in current practice based on SMN2 copy number threshold of 3 or less, using studies which only reported different SMA types including IIIa and IIIb

		Current practice		
		Eligible	Not eligible	All
Pre-symptomatic initiation of treatment	Eligible	76.72% (True positives)	4.28% (False positives)	80.99%
	Not eligible	7.76% (False negatives)	11.25% (True negatives)	19.01%
	All	84.48%	15.52%	100.00%

Source: August 2019 MSAC Public Summary Document for Application 1589.
Abbreviations: SMA = Spinal Muscular Atrophy, SMN = survival of motor neuron

10.3 MSAC advised that patients with pre-symptomatic SMA and one or two copies of SMN2 could be considered suitable as a prerequisite part of the eligibility criteria for any extended PBS restriction for nusinersen. However, MSAC also advised that patients with pre-symptomatic SMA and three copies of SMN2 should also undergo clinical assessment and electromyography testing by a neuromuscular specialist to detect any early signs of motor abnormality as a prerequisite part of the eligibility criteria for any extended PBS restriction for nusinersen. The purpose of this would be

to reduce some of the negative consequences of incorrectly initiating pre-symptomatic treatment with nusinersen estimated above at 4.28% based on SMN2 copy number alone.

- 10.4 MSAC noted the alternative methods of SMN2 testing used (multiplex ligation-dependent probe amplification and quantitative polymerase chain reaction) had similar analytic performance. However, neither method detects hybrid SMN1–SMN2 genes, which may have improved the accuracy of this testing for the purposes of the proposed PBS restriction for nusinersen. Further, although variation in SMN2 copy number seems to be the dominant source of prognostic value for SMA severity, MSAC advised that there are several other genetic components besides the SMN2 copy number which also may modify the phenotype to some extent. However, there are limited data available to assess their incremental prognostic value over SMN2 copy number variation.
- 10.5 MSAC advised that there is insufficient evidence on the prevalence of patients who are genotypically abnormal but remain phenotypically normal throughout their life to modify the estimated proportions of pre-symptomatic patients being eligible for nusinersen based on SMN2 copy number.
- 10.6 MSAC accepted that the proportions of patients for whom the SMN2 test results would be inaccurate as a basis to inform the decision of whether to initiate pre-symptomatic treatment with nusinersen ('false positives' and 'false negatives') were quite low, but did not know for sure how many there might be without further information. MSAC noted the trade-off between overtreating patients with false positive results compared with some delay in starting treatment of patients with false negative results, expecting that pre-symptomatic patients with SMN2 results not meeting a defined threshold for subsidised nusinersen would be followed up more intensively as a result of the SMN1-based genetic diagnosis. MSAC considered the prospect of overtreatment with nusinersen to be a more significant risk to patients. MSAC noted that, in the NURTURE trial, 100% of the patients had adverse events (AEs): 18 were moderate or severe, and five were severe. Six of the AEs were related to the lumbar puncture.

The above is a summary of the MSAC consideration. Further details are available in the Public Summary Document 'Application No. 1589 - Prognostic value of the number of copies of the survival of motor neurone 2 (SMN2) gene for the severity of spinal muscular atrophy to determine eligibility for nusinersen in pre-symptomatic patients' on the MSAC website.

Clinical Expert Consultation

- 10.7 Following the July 2019 PBAC meeting, the PBAC Chair and Deputy Chair held a Clinical Expert Consultation with clinicians with expertise in the treatment of SMA to receive advice and clinical perspectives on the pre-symptomatic initiation of treatment of patients with SMA, in the context of the clinical management issues raised at the July 2019 PBAC meeting.
- 10.8 The clinicians considered that the magnitude of treatment benefit with nusinersen was proportional to the number of surviving motor neurons and considered that patients with severe forms of SMA would derive the most benefit from treatment with nusinersen if it were initiated prior to the development of irreversible motor neuron loss. The clinicians noted that motor neuron degeneration begins early in the disease process and considered that even a few weeks of additional early treatment could reduce the morbidity of SMA. The clinicians noted that newborns treated earlier (at 1 week compared with 6 weeks) had better outcomes in the NURTURE study and that these results were consistent with those from the ENDEAR study, where a larger treatment benefit was observed in symptomatic patients who were initiated on treatment at an earlier age. Overall, the clinicians considered that early intervention would reduce motor neuron degeneration and were supportive of pre-symptomatic initiation of treatment for SMA to be available.
- 10.9 The clinicians noted that current knowledge of the distribution of SMA types according to the number of SMN2 copies is mainly from studies in symptomatic patients. However, the clinicians noted that results from prospective population-based newborn screening studies indicate that widespread screening does not result in an increase in the incidence of SMA. The clinicians noted that, based on the available evidence which was consistent with their clinical experience, newborns with 2 or 3 SMN2 copies would develop symptoms in infancy or early childhood with those who have 2 SMN2 copies mostly developing Type I SMA and those who have 3 SMN2 copies mostly developing Type II SMA. The clinicians advised that almost all patients with 2 SMN2 copies would become symptomatic by 5 years of age. On this basis, the clinicians were of the view that all newborns with 2 or 3 copies of SMN2 should receive immediate treatment due to the high probability of presentation with infantile or early childhood-onset forms of SMA. The clinicians further noted that a recent algorithm for the treatment of patients with SMA identified through newborn screening proposed by the SMA newborn screening Multidisciplinary Working group, which comprised 15 SMA experts, recommended that patients with 2 or 3 copies of SMN2 should receive treatment.
- 10.10 The clinicians considered SMN2 copy number variation testing to be reliable. The clinicians noted that in the NSW/ACT newborn screening pilot, digital droplet polymerase chain reaction (PCR) conducted by an Australian National Association of Testing Authorities (NATA) accredited laboratory was used to determine SMN2 copy number and that results were confirmed by NATA accredited Victorian Clinical

Genetics Service using quantitative real-time polymerase chain reaction (qPCR) with 100% concordance of results.

11 PBAC Outcome

- 11.1 The PBAC did not recommend extending the current listing of nusinersen to include the pre-symptomatic initiation of treatment of patients genetically diagnosed with SMA. The PBAC considered it was biologically plausible that pre-symptomatic initiation of treatment with nusinersen would provide an additional benefit for some patients compared with symptomatic treatment, however considered the magnitude of incremental benefit remains uncertain given the lack of appropriate comparative data. Further, the PBAC recalled it considered the economic model previously presented did not provide a reliable basis to inform the cost-effectiveness of pre-symptomatic initiation of treatment with nusinersen and the utilisation estimates to be uncertain.
- 11.2 The PBAC noted the advice from MSAC that SMN2 copy number variation offers some prognostic value and that the MSAC considered the prognostic value was more reliable for infants with two or less copies of SMN2 compared with three or less copies of SMN2. The PBAC noted that although MSAC considered SMN2 copy number to be the main source of prognostic information for SMA severity, the MSAC advised there are several other genetic components besides the SMN2 copy number that may also modify the phenotype to some extent.
- 11.3 The PBAC noted the advice from clinicians through the Clinical Expert Consultation regarding the benefits of pre-symptomatic initiation of treatment with nusinersen. The PBAC recalled its previous consideration that the extent of incremental benefit of a few doses with pre-symptomatic initiation of treatment relative to benefit of treatment starting with development of symptoms was uncertain. However, the PBAC noted the clinicians advised that even a short period of additional early treatment could have a substantial benefit for patients given irreversible motor neuron loss begins early in the disease process. Further, the PBAC recalled it considered that data from the NURTURE trial at a median follow up of 33.8 months was indicative of a treatment effect with pre-symptomatic initiation of treatment, as most patients had achieved the WHO motor milestones of sitting without support, walking with assistance and walking alone. Based on the advice from clinicians and the overall available evidence, the PBAC considered there was likely an incremental benefit from pre-symptomatic initiation of treatment with nusinersen compared with symptomatic treatment however, maintained that the magnitude of incremental benefit could not be ascertained without appropriate comparative data.
- 11.4 The PBAC noted that based on the available evidence, both qPCR and MLPA methods appear to have a high degree of accuracy in determining SMN2 copy number. The PBAC noted that in the first year of the NSW/ACT newborn screening pilot, there was 100% concordance between the results of the second-tier SMN2 copy number

screening test undertaken in patients who were SMN1 deletion positive, and the results of the confirmatory screening tests by qPCR. The PBAC noted there was insufficient information for MSAC to advise on the exact proportions of expected false positives and false negatives in predicting the subsequent severity of SMA, however, agreed with the MSAC that these proportions would likely be low. The PBAC noted that as expected, the estimated false positive proportion increased with increase in the SMN2 copy number threshold. Although the PBAC accepted the false positive proportion was low, it considered the prospect of overtreating any patient who would not benefit from pre-symptomatic initiation of treatment was a significant risk, particularly considering these patients are infants. The PBAC noted a proportion of AEs (32%) in the NURTURE trial were possibly related to the study drug and considered there may be long-term implications from repeated lumbar puncture administrations over a lifetime. Further, the PBAC noted that once treatment is initiated, it would not be possible to determine whether a patient has been overtreated. In this regard, 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 for these patients to those with 2 or less copies of SMN2 to manage the risk of.

- 11.5 The PBAC noted that in the first year of the NSW/ACT newborn screening pilot program, 9 infants of 103,903 newborns screened were genetically confirmed to have SMA. The PBAC noted that the estimated incidence of SMA from the NSW/ACT newborn screening pilot program and from prospective population-based studies in Taiwan and Germany were within the known historical incidence of SMA of 1:6000 – 11,000. However, the PBAC considered it was uncertain whether long-term population based screening would have an impact on the incidence of SMA noting there was a lack of data from long-term population-based screening.
- 11.6 The PBAC recalled it considered the economic model was unsuitable for decision making based on issues around the 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. The PBAC considered the application of an incremental duration of treatment of 0.91 years in the model likely resulted in an underestimate of the costs of pre-symptomatic initiation of treatment, noting clinicians indicated that patients with two SMN2 copies could develop symptoms up to 5 years of age. Based on this advice, the PBAC noted the number of additional doses of nusinersen could be substantially higher than the three additional injections previously assumed. The PBAC considered the assumption of no difference in adverse events between pre-symptomatic initiation of treatment and symptomatic treatment and consequently, the exclusion of AE costs from the model was not appropriate, particularly considering the likely higher number of lumbar puncture related AEs and potential long-term implications of initiating lifelong lumbar puncture administrations in infants. While the PBAC now considered there was likely an incremental benefit from pre-symptomatic

initiation of treatment with nusinersen compared with symptomatic treatment, it considered the extrapolation of the treatment effect beyond the follow up period of the NURTURE trial to 80 years was highly uncertain and likely optimistic. As such, the PBAC also considered the assumption of an improvement in quality of life by 0.2 QALYs every year for a lifetime for every patient treated with nusinersen prior to symptom onset, was likely optimistic. The PBAC advised that any resubmission should provide an updated economic analysis addressing the issues around the economic model outlined above.

- 11.7 The PBAC noted that the sponsor had not confirmed whether the rebate for [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.
- 11.8 The PBAC recalled it considered the estimated financial impact of pre-symptomatic initiation of treatment with nusinersen to be uncertain and potentially underestimated due to an underestimated average duration of treatment (as discussed in paragraph 11.6), and a higher than estimated number of treated patients from higher than predicted screening rates. The PBAC noted there are current clinical trials investigating the efficacy and safety of the oral therapy Risdiplam and gene therapy drug Zolgensma, in infants genetically diagnosed with SMA and noted that some infants genetically diagnosed with SMA through the NSW/ACT newborn screening pilot program may have been enrolled in these trials. The PBAC advised that any resubmission should include revised financial estimates which account for the 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.
- 11.9 The PBAC considered that equity of access to newborn screening for SMA remains an issue as newborn screening costs in states and territories apart from NSW and ACT are currently borne by public hospitals and private payers.
- 11.10 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

12 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.

13 Sponsor's Comment

Biogen is disappointed with the decision and looks forward to working with the PBAC to make nusinersen available for all patients with SMA who could benefit from it.