

5.11 NUSINERSEN, 12mg/5mL injection, Spinraza[®], Biogen Australia Pty Ltd

1 Purpose of application

- 1.1 Authority Required listing for nusinersen for treatment of infantile-onset (Type I) and childhood-onset (Types II & Type III) spinal muscular atrophy (SMA). This was the first application to the PBAC for nusinersen.
- 1.2 The requested basis for listing was a cost-effectiveness analysis of nusinersen and continuation of standard care compared with placebo and continuation of standard care.

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

Component	Description
Population	Patients with infantile-onset and childhood-onset SMA (see Table 3 below for definitions of onset).
Intervention	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	Placebo (for no treatment) when used in conjunction with standard of care.
Outcomes	Infantile-onset (Type I): Percentage of motor milestone responders; event-free survival Childhood-onset (Type II and III): Change from baseline in HFMSE score (Type II and III).
Clinical claim	In patients with infantile- and childhood-onset SMA, nusinersen is superior in terms of comparative clinical effectiveness and no worse in terms of comparative safety, compared to placebo (no treatment).

Source: Table 1.1.2, pp9-10 of the submission

SMA = spinal muscular atrophy; HFMSE = Hammersmith Infant Neurological Examination

2 Requested listing

Table 2: Essential elements of the requested listing

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer	
NUSINERSEN						
Initial treatment						
12mg/5mL injection, 1 x 5mL vial	1	1	3	\$ [REDACTED] (public)	SPINRAZA, Biogen Australia Pty Ltd	
Continuing treatment						
12mg/5mL injection, 1 x 5mL vial	1	1	2	\$ [REDACTED] (private)		
				\$ [REDACTED] (public)		
				\$ [REDACTED] (private)		

As the submission did not suggest a DPMQ for private dispensing, a price for the dispensing of nusinersen in a private hospital setting was calculated during the evaluation.

Condition:	Spinal muscular atrophy (SMA)
PBS Indication:	Treatment of infantile-onset and childhood-onset spinal muscular atrophy
Treatment phase:	Initial treatment – New patients
Restriction:	<input checked="" type="checkbox"/> Authority Required - In Writing

Treatment criteria:	<ul style="list-style-type: none"> The treatment must be prescribed by a neurologist, or by a physician in consultation with a neurologist with expertise in the treatment of spinal muscular atrophy; AND The treatment is administered intrathecally by, or under the direction of, healthcare professionals experienced in performing lumbar punctures; AND The treatment must be given concomitantly with standard of care for this condition.
Clinical criteria:	<ul style="list-style-type: none"> Patient must be diagnosed by a neurologist, or by a physician in consultation with a neurologist with expertise in the treatment of SMA; AND Patient must have genetic documentation of 5q survival-of-motor neuron (SMN) homozygous gene deletion, homozygous gene mutation, or compound heterozygote.
Population criteria:	<ul style="list-style-type: none"> Patient must have onset of clinical signs and symptoms consistent with infantile-onset or childhood-onset SMA.
Prescriber Instructions	<ul style="list-style-type: none"> The authority application must be in writing and must include: <ol style="list-style-type: none"> a completed authority prescription form; and a signed patient acknowledgement; or an acknowledgement signed by a parent or authorised guardian, if applicable; and a copy of the pathology report detailing the molecular testing for 5q SMN homozygous gene deletion, homozygous gene mutation, or compound heterozygote.
Administrative Advice	<ul style="list-style-type: none"> Special Pricing Arrangements apply. No increase in the maximum number of repeats may be authorised.
Treatment phase:	Continuing treatment
Restriction:	<input checked="" type="checkbox"/> Authority Required - In Writing
Treatment criteria:	<ul style="list-style-type: none"> The treatment must be prescribed by a neurologist, or by a physician in consultation with a neurologist with expertise in the treatment of spinal muscular atrophy; AND The treatment is administered intrathecally by, or under the direction of, healthcare professionals experienced in performing lumbar punctures; AND The treatment must be given concomitantly with standard of care for this condition.
Clinical criteria:	<ul style="list-style-type: none"> Patient must have previously received PBS-subsidised initial therapy with nusinersen, given concomitantly with standard of care for this condition.
Population criteria:	<ul style="list-style-type: none"> Patient must have onset of clinical signs and symptoms consistent with infantile-onset or childhood-onset SMA.
Prescriber Instructions	<ul style="list-style-type: none"> The authority application must be in writing and must include: <ol style="list-style-type: none"> a completed authority prescription form; and a signed patient acknowledgement; or an acknowledgement signed by a parent or authorised guardian, if applicable; and a copy of the pathology report detailing the molecular testing for 5q SMN homozygous gene deletion, homozygous gene mutation, or compound heterozygote.
Administrative Advice	<ul style="list-style-type: none"> Special Pricing Arrangements apply. No increase in the maximum number of repeats may be authorised.

2.1 The DUSC noted that the restriction is broader than the trial population as it includes 15-18 year old patients and adults who developed symptoms in childhood. Additionally the age of symptom onset may be subject to recall bias.

2.2 The submission proposed a special pricing arrangement [REDACTED]

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

3 Background

Registration status

- 3.1 TGA status: The submission was made under TGA/PBAC Parallel Process. At the time of evaluation for PBAC consideration, the TGA Delegate's Overview was available.

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 (SMN-1) 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 patients have a varying number of SMN-2 gene copies, there is a clinical spectrum of disease with earlier age of onset being associated with increased severity of symptoms. The disease affects motor function, survival, growth and electrophysiology. Table 3 details the typical features of each SMA type.
- 4.2 The correlation between the number of SMN-2 gene copies and clinical manifestation (i.e. the SMA type) of SMA is poor as other factors such as sequence variations within the SMN-2 gene may modify the phenotype.

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	SMN-2 copy number	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

Source: Table 1.1.1, p5 of the submission

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.

- 4.3 As there is no therapy currently approved for the treatment of SMA, the submission proposed that nusinersen would be used first-line in addition to continuation of standard care. The proposed treatment algorithm included cessation of treatment for patients not meeting the continuation criteria, however continuation criteria were not proposed in the requested restriction. The DUSC considered that patients are likely to

want to remain on treatment long term, noting the lack of alternative treatments and the progressive nature of the condition.

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

5 Comparator

- 5.1 The submission nominated placebo (for no treatment) and continuation of individualised standard care as the main comparator. The submission proposed that nusinersen would be used in addition to standard of care. The submission's nomination of placebo for no treatment as the comparator was considered appropriate. The PBAC considered this was the appropriate comparator.

6 Consideration of the evidence

Sponsor hearing

- 6.1 The Sponsor requested a hearing for this item. The clinician discussed the natural history of childhood-onset SMA in comparison to the clinical evidence in the key trial. The clinician highlighted the benefits of treatment with nusinersen on mortality in infantile-onset SMA and motor function as assessed by the HFMSE in childhood onset SMA. The clinician presented a range of clinical case studies and emphasised the impact of early treatment on the extent of benefit. The clinician explained how the HFMSE is used to assess motor function and clinical progression in patients with SMA. However, the clinician noted that the HFMSE does not capture all aspects of the disease course and that the extent of benefit that is meaningful for older patients was patient specific. The clinician highlighted that in addition to the different SMA types, the condition also encompasses different stages with more severe symptoms in end stage disease. The clinician indicated that the intrathecal injection procedure is well tolerated in most patients, and addressed other matters in response to the Committee's questions. The PBAC considered that the hearing was informative as it provided a clinical perspective on the treatment and progression of this uncommon condition.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (1087), health professionals (33) and organisations (3) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with nusinersen for patients with SMA including increased mobility, improved quality of life and slowing of disease progression.
- 6.3 SMA Australia and the Muscular Dystrophy Association of NSW emphasised the high clinical need for treatment for this patient population which currently has no other treatment options.
- 6.4 The Centre for Community-Driven Research presented a summary of results from a recent patient experience survey in SMA consisting of 50 participants, which aimed to collect data to further understanding of SMA from a patient's perspective. Of the

three SMA Type I participants described as being able to access nusinersen, it was noted that two were described as having improvements in their child in relation to muscle strength while none of the participants noted any side effects associated with treatment. Overall, it was reported that the majority of participants had a high level of anxiety in relation to fear of disease progression and supported access to nusinersen specifically.

Clinical trials

- 6.5 The submission was based on two head-to-head trials comparing nusinersen to sham-control:
 - ENDEAR (n=121) in infantile-onset SMA (Type I) and
 - CHERISH (n=126) in childhood-onset SMA (Type II).
- 6.6 Three supplementary single-arm trials were also included in the submission: NURTURE (pre-symptomatic infants) (n=20) and CS3A for (infantile-onset SMA Type I) (n=20), and CS12 for childhood-onset SMA (SMA Types II and III) (n=47).
- 6.7 Details of the trials presented in the submission are provided in Table 4.

Table 4: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
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
Supplementary non-randomised trials		
SM291/NURTURE	A Study of Multiple Doses of Nusinersen (ISIS 396443) Delivered to Infants With Genetically Diagnosed and Pre-symptomatic Spinal Muscular Atrophy [NCT02386553]	10 February 2017
CS3A	A Study to Assess the Efficacy, Safety and Pharmacokinetics of Nusinersen (ISIS 396443) in Infants With Spinal Muscular Atrophy (SMA) [NCT01839656] Finkel et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose escalation study. Finkel et al. Interim results of a phase 2 clinical study of nusinersen (ISIS-SMNRX) in patients with infantile-onset spinal muscular atrophy. Finkel et al. Interim results of a phase 2 clinical study of nusinersen (ISIS-SMNRX) in patients with infantile-onset spinal muscular atrophy. Finkel et al. Results of a phase 2 open-label study of ISIS-SMNRx in patients with infantile (type 1) spinal muscular atrophy. Finkel et al. Results of a phase 2 open-label study of ISIS-SMNRx in patients with infantile (Type 1) spinal muscular atrophy.	21 August 2016 The Lancet 2016. 388 (10063): 3017-3026 Annual of Neurology 2016. 80; S371-372 Neurology 2016. 86 (16); Supplement P5.004 Neurology 2014. 82 (10); Supplement S6.003 Neuromuscular disorders 2014. 24 (9-10); 920
CS12	An Open-label Safety and Tolerability Study of Nusinersen (ISIS 396443) in Participants With Spinal Muscular Atrophy (SMA) Who Previously Participated in ISIS 396443-CS2 (NCT01703988) or ISIS 396443-CS10 (NCT01780246) [NCT02052791] Luu et al. Population Pharmacokinetics of Nusinersen in the Cerebral Spinal Fluid and Plasma of Paediatric Patients With Spinal Muscular Atrophy Following Intrathecal Administrations.	8 June 2017 J Clinical Pharmacology 2017. Epub

Source: Table 2.2.3, p48-49 of the submission

6.8 The key features of the direct randomised trials are summarised in Table 5.

Table 5: Key features of the included evidence, nusinersen versus sham-control

Trial	N	Design/ Median duration of follow-up	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
ENDEAR	121	R, DB, MC 280 days	Low	Infantile-onset SMA (Type I)	EFS, OS, HINE (Section 2)	EFS used as a proxy for OS
CHERISH	126	R, DB, MC 450 days	Low	Childhood-onset SMA (Type II)	HFMSE	HFMSE

DB=double blind; R=randomised; SMA = spinal muscular atrophy; EFS = event-free survival; OS = overall survival; HINE = Hammersmith Infant Neurological Examination; HFMSE = Hammersmith Functional Motor Scale-Expanded

Source: compiled during the evaluation

6.9 As the CHERISH trial did not enrol any patients with Type III childhood-onset SMA, the evidence for nusinersen in this patient population came from the single-arm, non-randomised, open-label CS12 study enrolling 47 patients with Type II and Type III SMA, with 25 patients having SMA Type III. The submission compared the Hammersmith

Functional Motor Scale-Expanded (HFMSSE) results from this study to HFMSSE results reported in studies that investigated the natural history of SMA (Sivo et al, 2015 and Kaufmann et al, 2012).

- 6.10 The HFMSSE assesses 33 functional motor tasks such as sitting, rolling, 4-point kneeling, crawling, transitioning from floor to sitting and sitting to standing, standing with support and assistance, walking with support and assistance and stair ascent and descent. Each item HFMSSE is allocated a score of 2, 1 or 0 according to pre-determined criteria (for a total score of 66). A score of 0 indicates inability to complete the task, a score of 1 meaning the task can be completed with compensation and a score of 2 meaning the task can be completed normally, without compensation.
- 6.11 The submission considered that a 3-point increase in the HFMSSE would be clinically significant for patients with childhood-onset SMA, and that stabilisation of disease without deterioration, as evidenced by a 0-point improvement in HFMSSE would be clinically meaningful. For example, the submission explained that the ability to roll and sit up in bed independently would require a 3-point change in specific items of the HFMSSE.
- 6.12 The nomination of a 3-point change as being clinically significant for patients was based on a publication (Swoboda et al. 2010) using the Modified Hammersmith Functional Motor Scale (MHFMS)-SMA (includes 20 items). The authors reported that the standard deviation for the results of the MHFMS-SMA at 6 months was 3.19 and that a clinically meaningful change in the MHFMS-SMA would be 3-points at 6 months. Thus, while a 3-point change could be statistically significant, the clinical significance of the change has not been established. No data were provided in the submission to substantiate the clinical significance of the 3-point change in HFMSSE. The submission provided illustrative examples of what a 3-point increase in specific items of the HFMSSE would mean for a patient, however the overall clinical significance of a 3-point change is unclear, and the submission acknowledges that an “examination of individual item scores is the only way to understand the clinical significance of 3 point improvements”.
- 6.13 The Pre-Sub-Committee Response (PSCR) (p2) presented results from Pera et al 2017 which outlined individual items of the HFMSSE and how these related to daily activities as perceived by patients and caregivers surveyed during the study. The PSCR (p3) claimed that the results of the study indicates that the HFMSSE assesses motor function tasks which are relevant and meaningful and reiterated the conclusion from Pera et al 2017 that the study findings suggest that ‘any improvement is considered to be meaningful, regardless as to whether the baseline score is very low, in the middle, or very high’.
- 6.14 The PBAC considered that the nomination of a 3-point change in HFMSSE as a MCID was not adequately supported for Type II SMA noting that, in addition to the issues above, the Swoboda et al. 2010 publication from which this figure was based, used the (MHFMS)-SMA consisting of only 20 items rather than the full HFMSSE (consisting of 33 items) for which data was collected in the CHERISH trial.

Comparative effectiveness

Type I SMA

- 6.15 Results for the primary outcome of motor milestone response (MMR) based on the Hammersmith Infant Neurological Examination (HINE) in the ENDEAR trial for patients with Type I SMA are summarised in Table 6. A responder was defined as ≥ 2 -point increase in motor milestone (MM) category of ability to kick or achievement of maximal score in that category (touching toes) or ≥ 1 -point increase in MM of head control, rolling, sitting, crawling, standing or walking AND improvement (as defined previously) in more categories than worsening (worsening defined as ≥ 2 -point decrease or decrease to lowest score of kicking or ≥ 1 -point decrease in any other category).
- 6.16 The results based on the final analysis set showed that patients treated with nusinersen experienced significant improvement in the ability to acquire milestones as well as in the number of milestones achieved. There was a significant difference in the percentage of MMR between the two groups of 50.68% (95% CI: 31.81%, 66.48; $p < 0.0001$ Fisher's exact test). The results were consistent with those from the interim analysis, which showed a difference in percentage of responders of 41% (95% CI: 18%, 61%).
- 6.17 The total number of motor milestones achieved over time from baseline increased from a mean change of [REDACTED] for nusinersen treated patients and [REDACTED] for sham-control patients at Day 64 to [REDACTED] and [REDACTED] respectively, by Day 394, with a mean difference in favour of nusinersen of [REDACTED].

Table 6: Results of motor milestone response for the ENDEAR trial

Analysis population	Efficacy set	
	Sham-controls	Nusinersen
Treatment group		
Number of evaluable subjects ^a , N (%)	37 (100)	73 (100)
Number of subjects who died ^b , n (%)	16 (43)	13 (18)
Number of subjects withdrawn for reasons other than death ^b	1 (3)	2 (3)
Ability to kick:		
At least a 2-point increase	█	███
Achievement of touching toes	█	██
Head control: at least a 1-point increase	█	███
Rolling: at least a 1-point increase	███	███
Sitting: at least a 1-point increase	█	███
Crawling: at least a 1-point increase	█	██
Standing: at least a 1-point increase	█	███
Walking: at least a 1-point increase	█	█
Number of patients (%) ^d	0	37 (51)
Difference in percentage of responders (nusinersen - control)	50.68	
(95% CI) ^e	31.81, 66.48	
p-value (compared to control) ^f	<0.0001	

CI = confidence interval; N = number

^a Subjects with opportunity for at least a 6-month (Day 183) assessment

^b Subjects who died or who were withdrawn are considered non-responders

^c Subjects with 6-month (Day 183), 10-month (Day 302), or 13-month (Day 394) data. The last available assessment is used.

^d Endpoint used for analysis. For category of ability to kick, similar to the definition of improvement, worsening is defined as at least 2-point decrease or decrease to the lowest possible score of no kicking. For the other 6 categories, worsening is defined as at least 1-point decrease.

^e Exact unconditional confidence interval.

^f From Fisher's exact test.

Source: Table 2.5.2, p107 of the submission

6.18 Table 7 and Figure 1 present the results for the primary outcome of event-free survival from the ENDEAR trial.

Table 7: Summary of event-free survival based on Expert Advisory Committee review – ITT analysis, ENDEAR trial

Parameter	Sham-controls	Nusinersen
Number of patients (%)	41 (100)	80 (100)
Number of events (%)	28 (68)	31 (39)
Median time to event	22.6 weeks	Not reached
95% CI for median time to event	██████████	██████████
Event rate ^a at:		
3 months	██████████	██████████
6 months	██████████	██████████
9 months	██████████	██████████
12 months	██████████	██████████
13 months	██████████	██████████
p-value compared to control ^b	0.0046*	
Hazard ratio of nusinersen to controls (95% CI)	0.530 (0.3156, 0.8902)	
p-value compared to control ^c	0.0164	

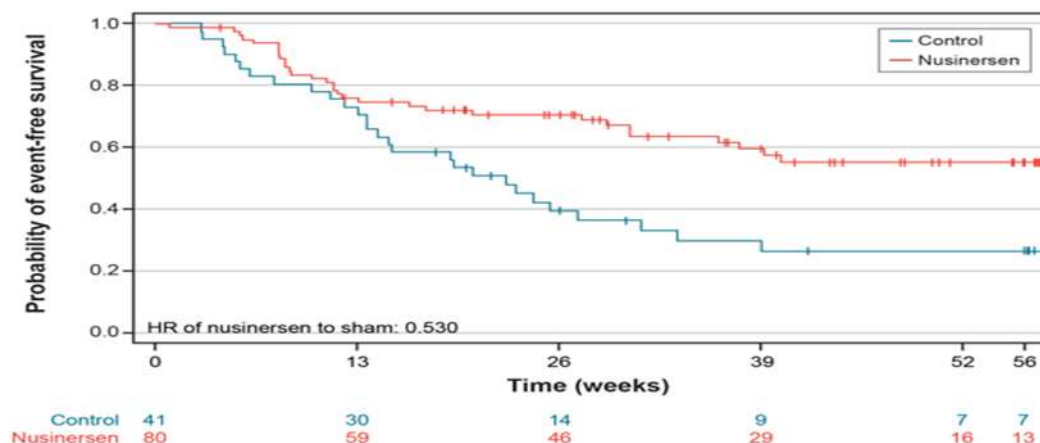
Notes: ^aBased on the Kaplan-Meier product-limit method.

^bBased on log-rank test stratified by disease duration.

^cBased on Cox proportional hazards model adjusted for each subject's disease duration at screening.

CI = confidence interval.

Source: Table 2.5.6, p112 of the submission

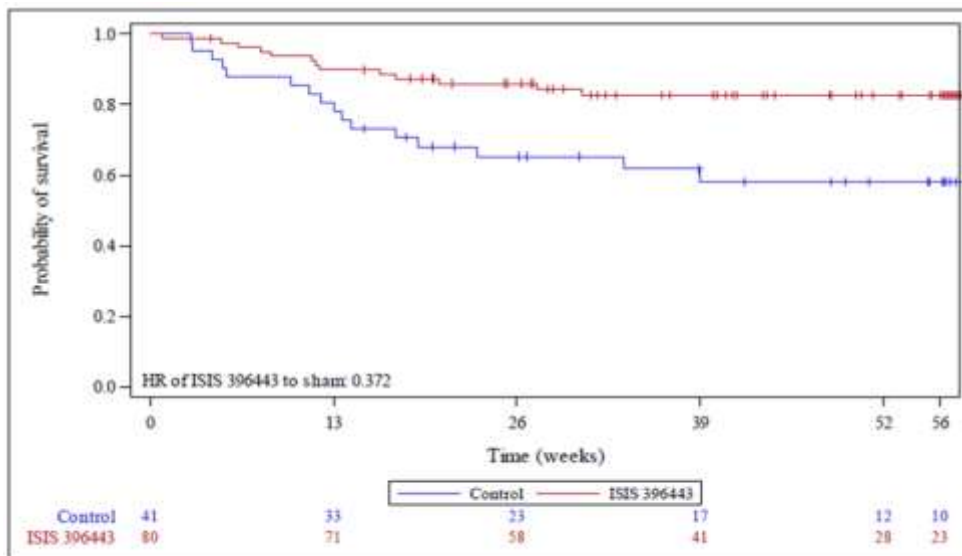
Figure 1: Kaplan-Meier curves for event-free survival - ITT analysis, ENDEAR trial

Source: Figure ES.2, p5 of the submission

6.19 The data showed that time to death or permanent ventilation was prolonged in patients treated with nusinersen: there was a 47% reduction in the risk of death or permanent ventilation compared to patients who received the sham-control procedure ($p=0.0046$) based on the ITT analysis. The median time to an event was 22.6 weeks in the sham-control group (██████████), with median time to an event not being reached in the nusinersen treatment arm (██████████) at the time of the analysis (16 December 2016). Based on a Cox proportional hazards model that adjusted for disease duration at screening, the hazard ratio was 0.530 (95% CI: 0.316, 0.890; $p=0.0164$), indicating a 47% reduction in the risk of death or permanent ventilation following treatment with nusinersen.

6.20 Time to death in the ITT population of the ENDEAR trial was a secondary endpoint and the Kaplan-Meier curve for this secondary endpoint is presented in Figure 2. The hazard ratio for time to death was 0.372 (95%CI: 0.179, 0.775), indicating a 62.8% reduction in the risk of death with nusinersen in comparison to sham-control ($p=0.0041$).

Figure 2: Kaplan-Meier curve for time to death – ITT population, ENDEAR trial



Source: Figure 2.5.5, p118 of the submission

6.21 The PBAC agreed that the submission reasonably indicated that since patients with Type I SMA requiring permanent ventilation will usually be placed onto palliative care in Australia, that event-free survival was a better proxy for overall survival in the economic evaluation for patients with Type I SMA.

Types II and III SMA

6.22 Results for the primary outcome, change in Hammersmith Functional Motor Scale-Expanded (HFMSSE) score from the CHERISH trial for patients with Type II SMA are presented in Table 8.

Table 8: Change from baseline in HFMSSE to month 15 (multiple imputation) – ITT set, CHERISH trial

Parameter	Sham-controls	Nusinersen
Number of patients in ITT Set	42 (100)	84 (100)
Number of patients with observed Month 15 value	34 (81)	66 (79)
Number of patients with imputed Month 15 value	8 (19)	18 (21)
Change in HFMSSE to Month 15		
Least squares mean (95% CI) ^a	-1.0 (-2.5, 0.5)	3.9 (3.0, 4.9)
SE	0.76	0.49
Least squares mean difference (95% CI) ^a	4.9 (3.1, 6.7)	
SE	0.91	
p-value (compared to control) ^a	0.0000001	

ANCOVA = analysis of covariance; CI = confidence interval; ITT = intention to treat; MI = multiple imputation; S = standard error; HFMSSE = Hammersmith Functional Motor Scale-Expanded

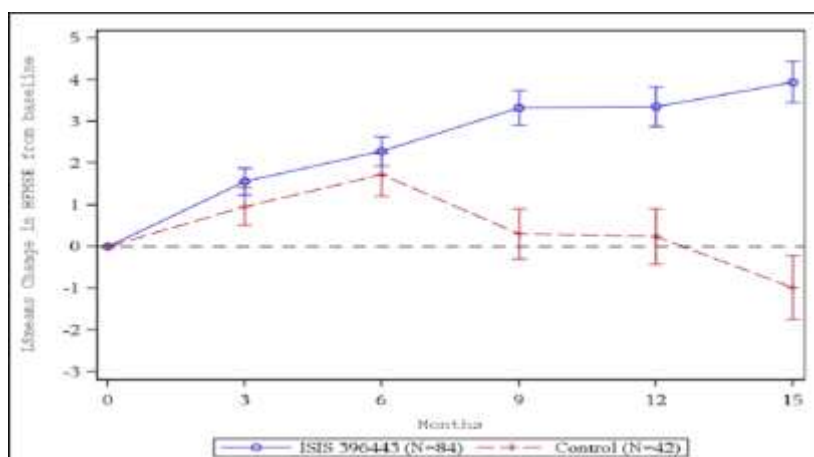
Note: This table is based on multiply imputed data.

^a From MI procedure, based on ANCOVA with treatment as a fixed effect and adjustment for each subject's age at screening and HFMSSE at baseline. These estimates are constructed from fitting the ANCOVA model to each of the imputed datasets.

Source: Table 2.5.16, p142 of the submission

6.23 Figure 3 illustrates the least squares mean change in HFMSSE scores from baseline over time.

Figure 3: Least squares mean change in HFMSE score from baseline (multiple imputation) over time – ITT set, CHERISH trial



Source: Figure 2.5.12. p144 of the submission

- 6.24 Consistent with the natural history of SMA, the results indicate that there was an overall decline in motor function in the sham-control group over time, whereas a difference between nusinersen and the sham-control group emerged after 6 months.
- 6.25 For the secondary endpoint of a three-point increase in HFMSE score, results from the CHERISH trial indicated that at Month 15, a significantly higher proportion of patients treated with nusinersen achieved an increase of 3 or points in HFMSE score compared to sham-control (56.8% vs. 26.3%, $p=0.00006$).
- 6.26 The submission also presented an indirect comparison of data from the phase I study CS12 and data on the natural history of SMA in patients with Types II and III SMA, although no statistical comparisons were presented. Based on this naïve comparison, it appeared that while motor function on average decreased in untreated patients, patients treated with nusinersen achieved maintenance or a small increase in motor function.
- 6.27 The PBAC noted that while this may suggest that nusinersen helps to prevent the decline in motor function that is typical for patients with Type II and III SMA without treatment, given the lack of a randomised comparison and the lack of a statistical analysis, both the existence of a benefit and the degree of any benefit of nusinersen in terms of motor function based on this data is unclear. The unknown distribution of Type IIIA and Type IIIB SMA in the CS12 study also limits the interpretation and comparison with natural history data. In addition, while the submission suggested that maintenance of motor function constitutes a minimally clinically important difference (MCID), it did not present sufficient data to justify this assertion.
- 6.28 The PBAC noted that the CHERISH and C12 trials both utilised a 6 monthly dosing regimen whereas the Product Information recommends 4 monthly dosing. The PBAC considered that the incremental benefit of using more frequent dosing in Types II and III SMA is unknown.

Comparative harms

- 6.29 The comparative harms for nusinersen and sham-control are summarised as follows: There were some variations in the treatment-emergent adverse events (TEAEs)

between treatment groups in the ENDEAR and CHERISH trials, but in general the results did not reveal that nusinersen was associated with greater annualised rates overall than sham-control in the ENDEAR trial. In the CHERISH trial, nusinersen was associated with a greater incidence of back pain and vomiting (annualised rates of █% for nusinersen versus █% for sham-control for back pain, and █% versus █% for vomiting respectively).

6.30 The PBAC noted that maintenance doses in the CHERISH trial were administered every 6 months in comparison to the 4 monthly doses recommended in the draft Product Information. The PBAC considered that in clinical practice, the rate of adverse events may be higher than those reported in the CHERISH trial based on more frequent administrations.

6.31 While adverse event rates appeared similar for sham-control compared to nusinersen in the ENDEAR and CHERISH trials, in clinical practice patients will receive standard care without a sham-control procedure and there are likely to be reactions associated with administration via lumbar puncture, including a risk of infection that would not occur in patients who receive standard care.

Benefits and harms

6.32 A summary of the comparative benefits and harms for nusinersen versus sham-control is presented in Table 9.

Table 9: Summary of comparative benefits and harms for nusinersen and sham-control

Benefits							
Motor milestone responder							
Trial	Nusinersen	Sham-controls	RR (95% CI)	Events/100 patients		RD (95% CI)	
				Nusinersen	Sham-controls		
ENDEAR*	37/73	0/37	Not calculable	50.7	0	0.507 (0.318, 0.665)	
Continuous Outcome I: Change from Baseline to Month 15 in HFMSE score							
Trial	Nusinersen			Sham-controls			Least squares mean difference*
	n	Least squares mean Δ Baseline HFMSE	SE	n	Least squares mean Δ Baseline HFMSE	SE	
CHERISH	84	3.9	0.49	42	-1.0	0.76	4.9 (3.1, 6.7)
Time-to-event : Event-free survival in the ENDEAR trial**							
Event	Nusinersen	Sham-controls	Absolute Difference		HR (95% CI)		
Number of events, n (%)	31/80 (39)	28/41 (68)	29%		0.53 (0.32 to 0.89)		
Time-to-event : Death in the ENDEAR trial							
Event	Nusinersen	Sham-controls	Absolute Difference		HR (95% CI)		
Number of events, n (%)	13/80 (16)	16/41 (39)	23%		0.37 (0.18 to 0.78)		

*Based on Hammersmith Infant Neurological Examination (HINE) Section 2; HFMSE = Hammersmith Functional Motor Scale-Expanded; RD = risk difference; RR = risk ratio; SE = standard error

**Median duration of follow-up 280 days

Source: Compiled during the evaluation/Tables 2.5.1-2.5.16, pp105-142 of the submission

6.33 On the basis of direct evidence presented by the submission, for every 100 patients with Type I SMA treated with nusinersen in comparison to sham-control:

- Approximately 51 additional patients would be classified as a motor milestone responder¹ over a median duration of follow-up of 280 days.
- Approximately 23 additional patients would remain alive over a median duration of follow-up of 280 days.
- Approximately 29 more patients would remain alive or ventilator-free over a median duration of follow-up of 280 days.

6.34 On the basis of direct evidence presented by the submission, treatment with nusinersen in comparison to sham-control in patients with Type II SMA over 450 days resulted in an improvement in HFMSE score (least squares mean difference) of 4.9.

Interpretation of clinical evidence

6.35 The submission claimed that nusinersen was superior in terms of comparative effectiveness compared to sham-control and no worse in terms of safety for the treatment of patients with SMA.

6.36 The PBAC considered that claim of superior comparative effectiveness of nusinersen compared to sham-control was adequately supported by the evidence for patients with Type I SMA. However, the extent of benefit in terms of event free survival was not yet known and it was not clear whether the observed would persist over the longer-term or whether similar benefits to those seen in the ENDEAR trial could be expected initially for the likely PBS population.

6.37 The PBAC considered the claim of superior comparative effectiveness was not well supported for patients with Type II SMA as the clinical relevance of a 4.9 point difference in HMSE is not clear and as it is not clear if this benefit is sustained for a longer period.

6.38 The PBAC considered the claim of superior comparative effectiveness was not supported for patients with Type III SMA, with a lack of randomised comparative evidence in this patient population compared to sham-control.

6.39 The PSCR (p2) indicated that data from the current ongoing phase 3, open label extension study (SHINE) which aims to assess efficacy and safety of nusinersen over 3 years in patients (n=274) with SMA previously in the ENDEAR, CHERISH, CS3A and CS12 trials would address uncertainty of the long-term benefit of treatment with nusinersen. The PBAC considered that while data from the SHINE study may support an effect over a longer period, it would not address its concerns regarding comparative effectiveness over a lifetime.

6.40 The PBAC noted that in relation to safety, while adverse event rates appeared similar for sham-control compared to nusinersen in the ENDEAR and CHERISH trials, in clinical practice there would not be a sham-control procedure and there could be reactions associated with administration via lumbar puncture, including a risk of infection that would not occur in patients receiving standard care. Overall, it was not apparent that

¹ Defined as more categories of improvement than worsening where improvement is defined as ≥ 2 -point increase in category of ability to kick or achievement of maximal score in that category (touching toes) or ≥ 1 -point increase in MM of head control, rolling, sitting, crawling, standing or walking. Worsening defined as defined as ≥ 2 -point decrease or decrease to lowest score of kicking or ≥ 1 -point decrease in any other category.

nusinersen would be no worse compared to placebo (no treatment), and it was particularly not apparent that the claim would be supported over the longer-term.

Economic analysis

6.41 The submission presented a separate cost-effectiveness evaluation for each of the three SMA Types (Types I, II and III). A summary of the modelled economic evaluation presented for SMA Type I is presented in Table 10.

Table 10: SMA Type I; Summary of model structure and rationale

Component	Summary
Time horizon	100 years in the model base case versus 13 months in trial
Outcomes	LYG
Methods used to generate results	SMA Type I: A partitioned survival model with two health states (alive or dead). Kaplan Meier data from the standard care arm of ENDEAR (13 month trial) was extrapolated by fitting a Weibull model of the survival data from a natural history study of SMA (Farrar 2013) which was fitted to the Kaplan Meier data at 12 months. Survival for nusinersen patients was estimated by applying the HR for overall survival (0.372). As the submission claimed the more appropriate outcome is Event Free Survival (EFS), the correct HR would be the HR for EFS (0.530).
Health states	SMA Type I modelled two states, alive or dead
Utilities	No utilities were used in the submission
Cycle length	4 months which is consistent with the dosing interval in the draft PI
Transition probabilities	Not applicable

Source: reference sections/tables/spreadsheets within the submission

6.42 The evaluations of SMA Types II and III were restricted to trial based evaluations of CHERISH and CS12, and were reported as a cost per responder, defined differentially as a ≥ 3 -point increase over 15 months or ≥ 0 -point increase in the HFMSE score over two years for SMA Types II and III, respectively.

6.43 All cost-effectiveness analyses were based on the special pricing arrangement proposed in the submission, [REDACTED].

Type 1 SMA

6.44 The key drivers of the SMA Type I model are shown in Table 11.

Table 11: Key drivers of the model for SMA Type I

Description	Method/Value	Impact
Cost of nusinersen	Proposed price (including special pricing arrangement)	High, favours placebo (standard care)
Extrapolation	Treatment effect continued beyond 13 month trial period for up to 100 years (although median survival is predicted to be only a 2-3 years);	High, favours nusinersen
Utilities	No utility values are used	High, favours nusinersen

Source: compiled during the evaluation

6.45 For SMA Type I, the submission presented a number of 'steps' both in the main body of the submission (and in the Excel file 'Section 3 Nusinersen July 2017 PBAC Type I.xlsx') including some which are more appropriately considered to be sensitivity analyses. The key steps are shown in Table 12.

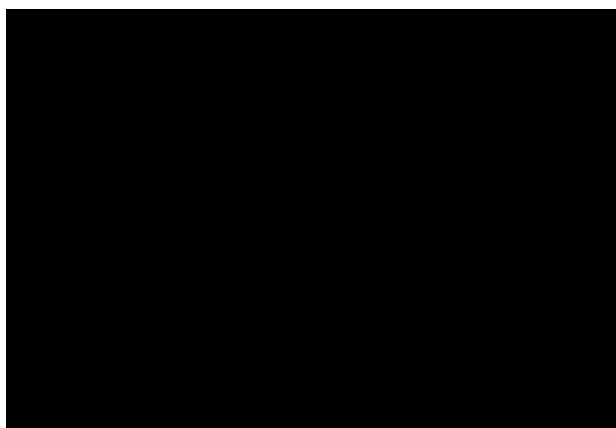
Table 12: SMA Type I: Results of the stepped economic evaluation

Step and component	Nusinersen	Placebo (standard care)	Increment
Step 1: ENDEAR-based costs and outcomes			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Responder	51%	0%	51%
Incremental cost/extra responder gained			\$ [REDACTED]
Step 2: ENDEAR evidence transformed to clinical outcome (using Weibull model of trial outcome of EFS)			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYG	0.7096	0.5144	0.19525
Incremental cost/extra LYG			\$ [REDACTED]
Step 3: ENDEAR evidence extrapolated to the appropriate time horizon (using Weibull model of trial of EFS)			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYG	2.7733	0.6478	2.1254
Incremental cost/extra LYG			\$ [REDACTED]
Step 4: ENDEAR evidence extrapolated to and translated to the Australian population/setting (Farrar 2013)			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYG	3.5685	1.0858	2.4827
Incremental cost/extra LYG			\$ [REDACTED]

Source: Table 3.8.2, p284 of the submission

6.46 The submission’s predicted survival for nusinersen versus standard care (referred to as SoC in the submission) is shown in Figure 4.

Figure 4: Predicted survival (EFS outcome)



Source: Excel file Worksheet Cost per LY (modelled analysis) in ‘Section 3 Nusinersen July 2017 PBAC Type I.xlsx’ accompanying the submission

6.47 The ICERs in the submission for SMA Type I were consistently very high. Although the submission reasonably assumed that event-free survival (EFS; a combination of overall survival and permanent ventilation-free survival) was a better proxy for overall survival (OS) given patients in Australia requiring permanent ventilation will usually be placed onto palliative care, the hazard ratio applied to EFS in the model was that for OS from ENDEAR (HR=0.372), rather than that for EFS (HR=0.530).

6.48 The PBAC agreed with its ESC that the application of the hazard ratio for EFS to the model may have been more appropriate. The ESC also noted that when the hazard ratio for EFS (HR=0.530) was applied to the model, the predicated gain in survival

changed to 1.78 years. Application of the EFS HR resulted in an ICER of more than \$200,000/life year (LY) gained compared to the base case of more than \$200,000/LY gained.

6.49 The PBAC noted it would be reasonable to assume that if utility values had been used, that the ICERs would be significantly higher again. Indeed plausible utility values increased the ICER to more than \$200,000/QALY for SMA Type I. The results of sensitivity conducted during the evaluation using assumed utility values for SMA Type I are shown in Table 13 below.

Table 13: Sensitivity analysis using assumed utility values for SMA type I

Base case incremental cost	Base case incremental Life-years	Utility value tested (assumed values)	QALYs	Cost/QALY ^a
\$ [REDACTED]	2.48	0.9	2.23	\$ [REDACTED]
		0.8	1.99	\$ [REDACTED]
		0.7	1.74	\$ [REDACTED]

^a Base case = more than \$200,000 per life-year gained.

Source: Compiled during evaluation

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

6.50 The ESC noted that although the lifetime horizon (100 years) applied in the model for SMA Type I was not appropriate, the time horizon applied in the model was effectively 15-20 years as all patients had died by this time. The ESC noted that the resulting ICERs from sensitivity analyses which applied model durations of 10 and 20 years were similar (more than \$200,000/QALY).

Types II and III SMA

6.51 The ICERs estimated for SMA Type II and III were more than \$200,000/responder (defined as those with a ≥3-point increase in HFSME over 15 months) and more than \$200,000/responder (defined as those with a ≥0-point increase in HFSME over two years), respectively.

6.52 Limitations of the results were the submission’s assumption that the effect size for nusinersen would remain constant over life-expectancy in each of the three SMA indications and the failure to use utility values for adolescent and adult stages of life in the SMA Type I model. The ICERs were also subject to limitations from omitted costs associated with standard care given the incremental survival in the nusinersen + standard care arm. In addition to these limitations, the ESC considered that the results of the economic analysis for SMA Type II and III were uncertain due to the following issues:

- The time horizons for SMA Type II and III are restricted to the CHERISH trial duration of 15 months and CS12 trial duration of two years respectively. The ESC considered this was inappropriate for evaluating the cost-effectiveness of nusinersen over a 20-40 year period for this patient population, noting it was unlikely that patients have reached a ‘steady state’.
- The difference in the threshold for ‘responder’ for SMA Type II (achieving a ≥3-point gain on the HFMSE) and Type III (achieving a ≥0-point gain on the HFMSE) was not justified. Moreover, the ESC considered the nomination of a 3-point change as being clinically significant was poorly supported (see paragraph 6.7).

- The maintenance dosing regimen in the CHERISH trial was every 6 months, in contrast to the assumed 4 monthly maintenance dosing regimen. The PSCR (p5) claimed that this biases against nusinersen. The PBAC considered that while this was likely to be bias against nusinersen, the cost-effectiveness of nusinersen in this setting with a 4 monthly maintenance dosing context is unknown.
- Utility values were not incorporated into the economic models even though the only claim to benefit for SMA Type II and III is improved quality of life in the absence of gain in survival. The PSCR (p5) argued that a cost per responder approach instead of cost per QALY was used due to challenges associated with evaluating quality of life in young children. The PBAC agreed with its ESC and considered this did not justify the cost per responder approach as patients with SMA Types II and III are predicted to spend most of their life expectancy as adults.
- The comparative efficacy for SMA Type III is poorly supported as the only data presented in the submission is from 20 patients in a single-arm study (trial CS12).

Drug cost/patient/year

6.53 The drug cost of on-going treatment with nusinersen for all three SMA indications is \$ [REDACTED]/year, based on three maintenance doses per year at the DPMQ of \$ [REDACTED]/vial (public).

Estimated PBS usage & financial implications

6.54 The submission was considered by DUSC.

6.55 The submission took an epidemiological approach, whereby the incident rate of each SMA subtype was applied to the number of live births each year in Australia. Patient survival for each disease subtype was then applied so as to capture the number of prevalent patients for each disease type at the time of nusinersen listing on the PBAC.

6.56 The submission estimated the prevalence of SMA to be less than 10,000 people in 2018 (less than 10,000 Type I, less than 10,000 Type II and less than 10,000 Type III). The number of patients proposed to commence PBS subsidised treatment with nusinersen is shown in Table 14.

6.57 The submission estimated a net financial cost to the PBS for SMA of \$60 - \$100 million in the first year of listing, increasing to more than \$100 million in year 6 of listing. In year 1 this includes \$10 - \$20 million for Type I, \$30 - \$60 million for Type II and \$30 - \$60 million for Type III SMA. The year 6 estimates include \$20 - \$30 million for Type I, \$60 - \$100 million for Type II and \$60 - \$100 million for Type III SMA. Given the average life expectancy of Type II patients is into adulthood and Type III patients have a normal lifespan, DUSC highlighted that the cost of this treatment will escalate beyond Year 6 as patients will remain on treatment long term and the treated prevalent population will grow.

Table 14: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of Type I SMA patients initiating PBS nusinersen per year	■	■	■	■	■	■
Number of Type II SMA patients initiating PBS nusinersen per year	■	■	■	■	■	■
Number of Type III SMA patients initiating PBS nusinersen per year	■	■	■	■	■	■
Total patients treated each year (patient years) ^a	■	■	■	■	■	■
Number of scripts dispensed ^b	■	■	■	■	■	■

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year.

Estimated financial implications of nusinersen						
Cost to PBS/RPBS	■	■	■	■	■	■
Copayments	■	■	■	■	■	■
Cost to PBS less copayments	■	■	■	■	■	■
Net financial implications						
Net cost to PBS	■	■	■	■	■	■
Net cost to MBS	■	■	■	■	■	■
Net cost to PBS/MBS	■	■	■	■	■	■

^aThe submission did not provide the total number of patients on treatment in each year, rather the number of patient years of treatment was presented.

^b Assuming 2 scripts in year 1 for initiating patients (the 2 rebated scripts in year 1 were not included in these estimates) and 3 scripts per year from year 2 onwards, in surviving patients, as estimated by the submission.

Source: Table 13 of Commentary Executive Summary, Tables 4.2.2-4.2.15, and Table 4.5.2-4.5.3, pp309-320 of the submission and Section 4 MS Excel Workbook, Sheet 3c

6.58 The estimated incidence of Type I SMA was based on Australian data and is reasonable. The number of people with Type II or III SMA is uncertain due to a lack of Australian incidence data. The PSCR (p7) reiterated that a comprehensive and systematic epidemiological approach has been employed in Section 4 to provide a robust estimate of the cost of nusinersen to the PBS/MBS. The DUSC agreed and considered that the estimated number of patients in Australia that would be eligible for nusinersen is based on the best available data.

6.59 The Sponsor acknowledged that some residual uncertainty may remain and expressed a willingness to work with the PBAC and Department of Health to develop an appropriate RSA to address any residual areas of uncertainty (PSCR p5). The DUSC noted that the size of the population over 18 years old is highly uncertain. These patients are estimated to account for 32% of expenditure in Year 1.

6.60 The DUSC considered that the treatment uptake rates were underestimated. The submission assumed that the uptake rate for incident Type I, II and III patients would be 80%, 100% and 80% respectively. Given the nature of the disease and lack of

alternative treatments, DUSC considered that the uptake rate may approach 100% in all types for incident and prevalent patients.

- 6.61 DUSC considered that the submission may have underestimated the total health care costs, given that costs for adverse events, monitoring, genetic tests and the ongoing cost of standard care in patients who survive for longer on nusinersen were not included in the financial estimates.

Quality use of medicines

- 6.62 The submission stated that the sponsor would be able to provide data from the phase 3, open label extension study (SHINE, CS11) for patients with SMA who previously participated in investigational studies with nusinersen (ENDEAR, CHERISH, CS3A, CS12) and data from the EMBRACE (SM202) ongoing phase 2, double-blind, randomised, sham-controlled study of nusinersen in 21 patients not eligible to participate in ENDEAR or CHERISH, at the request of the PBAC.
- 6.63 The DUSC considered that the availability of nusinersen may encourage screening for the 5q survival-of-motor neuron (SMN) homozygous gene deletion or mutation leading to earlier detection of the condition.
- 6.64 The ESC advised that if recommended for listing, there was a risk that nusinersen would be used in pre-symptomatic patients with a genetic diagnosis of SMA for whom there may be little benefit in early treatment (i.e. Type-IV adult-onset SMA).

Financial management – risk sharing arrangements

- 6.65 The submission proposed a Risk-Sharing Arrangement (RSA) for nusinersen for the treatment of infantile and childhood-onset SMA. There were two elements to the proposed RSA:

- A special pricing arrangement (SPA) [REDACTED]

[REDACTED] The effect of the SPA was incorporated into the economic and financial analysis presented by the submission.

- The submission also stated that the sponsor would be willing to work with the Department of Health to establish an appropriate RSA following feedback from the PBAC on patient eligibility, with the submission acknowledging that the wording of specific criteria to be included in the final restriction has yet to be finalised. The submission also acknowledged that a RSA may be appropriate given the uncertainty surrounding the size of the patient population (particularly in adults) and the likely uptake rate for each patient group.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend the Section 100 (Highly Specialised Drugs Program) listing of nusinersen for the treatment of patients with Infantile-onset (Type I) and

childhood-onset (Types II & III) spinal muscular atrophy (SMA) because of uncertainty about its clinical effectiveness in terms of the extent and durability of response across the spectrum of SMA for which the submission has sought subsidy. In addition, the submission contained insufficient information for the PBAC to form a view on the cost-effectiveness of treatment across the spectrum of SMA.

- 7.2 The PBAC acknowledged that there is a high and urgent clinical need for treatments for SMA, particularly for the most severe forms of the condition. However, the PBAC noted that the consumer input was strongly supportive of a broad PBS listing across all forms of SMA, including adult onset disease. The PBAC considered that the available evidence suggests all patients may receive some benefit from nusinersen, but that this benefit needs to be better quantified.
- 7.3 The PBAC formed the view that the Pharmaceutical Benefits Scheme (PBS) is the most appropriate mechanism for subsidising nusinersen for Australian patients. The PBAC considered that further information on the cost-effectiveness of treatment with nusinersen is necessary in order for it to be able to form a view on the appropriate PBS subsidy price, but that based on the information already available it is likely that a substantial reduction in the proposed price will be required.
- 7.4 The PBAC noted that the submission estimated the prevalence of SMA Type I – III to be less than 10,000 people in 2018 (less than 10,000 Type I, less than 10,000 Type II and less than 10,000 Type III), and that although the submission had used the best available evidence to arrive at this estimate, it is likely that this is an underestimate, particularly of the number of patients over the age of 18 years.
- 7.5 The Committee also noted that targeted therapies are becoming increasingly common, with a number of such therapies being considered for, or added to, the PBS over the past few years. Whilst some targeted therapies are PBS subsidised for larger patient populations than will be treated with nusinersen others are subsidised through the PBS for even rarer conditions.

Further details on the PBS recommendation follow:

Clinical effectiveness of treatment with nusinersen

- 7.6 The PBAC considered that the available evidence suggests all patients with SMA may receive some benefit from nusinersen, but that this benefit needs to be better quantified.
- 7.7 The PBAC noted the clinical spectrum of SMA and the correlation between a worse prognosis and earlier age of onset. However, the PBAC noted that although there is a correlation between SMN-2 gene copies and SMA type, there is significant overlap between SMN-2 copy number and the SMA type that manifests clinically. Therefore, the PBAC noted that the SMA type cannot be diagnosed based on genetic testing prior to symptom onset. Additionally, as diagnosis is clinically based, the age at which a diagnosis is made creates potential equity issues for any subsidy program that limits treatment to specific types of SMA.
- 7.8 The PBAC considered that placebo for no treatment was appropriate as the main comparator.

- 7.9 The PBAC noted that the submission was primarily based on two head-to-head randomised trials comparing nusinersen and sham-control: ENDEAR in Type I SMA and CHERISH in Type II SMA. Both trials are of comparatively short durations in the context of a life-long condition (13 months in ENDEAR and 15 months in CHERISH).
- 7.10 The PBAC noted that the evidence from ENDEAR showed that treatment with nusinersen in patients with Type I SMA resulted in improvements in the primary outcomes of motor milestone response (MRR) and event free survival (EFS) over the duration of follow up in the trial. However the median time to event had not been reached in the nusinersen treatment arm at the last follow up (December 2016), so the extent of the event free survival benefit is not yet clear.
- 7.11 The PBAC noted the mean improvement in Hammersmith Functional Motor Scale – Expanded (HFMSE) score of 3.9 points in the nusinersen treatment group compared to the decline of -1.0 points in the sham-control group in the CHERISH trial. However the PBAC considered further information is needed to establish the clinical relevance of this change. The PBAC considered that the submission’s nomination of 3-point change in HFMSE score as a minimally clinically important difference (MCID) was not adequately supported.
- 7.12 The PBAC also noted that the CHERISH trial only recruited patients up to 12 years of age with a minimal life expectancy of two years or more and HFMSE score of 10 to 54 at screening, which is a narrower patient group than the requested PBS population. Further, the PBAC noted that in addition to SMA type, symptom severity and disease progression was also dependant on the stage of disease. The PBAC noted that the evidence in the submission indicated that the magnitude of benefit from treatment may vary depending on the stage of the disease when treatment is initiated with a larger benefit associated with earlier treatment. However, the PBAC also acknowledged that the magnitude of benefit (i.e change in motor function) that is clinically meaningful may be patient specific. Taken together with its concerns regarding the clinical significance of a 3-point change in HFMSE score, the PBAC considered it difficult to interpret the outcomes of the CHERISH trial.
- 7.13 The PBAC considered that based on the rate of adverse events in the ENDEAR and CHERISH trials, nusinersen was comparable with sham-control in regards to safety. However the PBAC considered that in clinical practice, treatment with nusinersen would be associated with complications related to the lumbar puncture procedure which would not occur in patients receiving standard care. Further, the PBAC considered that in clinical practice, the rate of adverse events may be higher than reported in the CHERISH trial based on more frequent the 4 monthly dosing regimen recommended in the draft product information compared to the 6 monthly dosing regimen in the trial.
- 7.14 The PBAC considered that the evidence presented for Type III SMA, a naïve comparison of the data from 25 patients in the single-arm non-randomised open-label study CS12, versus data on the natural history of SMA was not sufficient to establish comparative efficacy in Type III SMA.
- 7.15 The PBAC considered that the long-term efficacy of treatment with nusinersen for SMA was uncertain given the absence of evidence that the effect of nusinersen would

be maintained beyond the relatively short trial periods. The PBAC noted there is currently an ongoing phase 3, open label extension study (SHINE) which aims to collect long-term efficacy and safety data of nusinersen in patients who previously participated in investigational studies with nusinersen. The PBAC agreed with its ESC that while data from this study may be informative, it would not address concerns regarding efficacy over a life-time.

- 7.16 Overall, the PBAC was uncertain of the extent and durability of benefit of treatment with nusinersen in the overall SMA population based on the evidence presented in the submission.

Cost effectiveness of treatment with nusinersen

- 7.17 The PBAC considered that the submission contained insufficient information for the Committee to form a view on the cost-effectiveness of treatment across the spectrum of SMA.
- 7.18 The PBAC noted that the submission presented separate economic evaluations for each SMA type, I, II and III. A modelled evaluation for presented for Type I SMA and trial based evaluations were presented for Type II and III SMA.
- 7.19 The PBAC noted that the base-case ICER for Type I SMA was high at more than \$200,000 per life year (LY) gained. The PBAC agreed with its ESC that it would have been more appropriate to apply the hazard ratio for EFS in the model (HR=0.530) rather than that for OS (HR=0.372) from the ENDEAR trial in the base-case. The PBAC noted that the ICER increased to more than \$200,000per LY gained when the hazard ratio for EFS was applied.
- 7.20 The PBAC considered that the cost per responder estimates presented for Type II and Type III SMA were highly uncertain due to the following issues:
- The time-horizons applied were based on the trial durations (15 months from the CHERISH trial for SMA Type II and two years from CS12 for SMA Type III). Patients are unlikely to have reached a 'steady state' in these time periods as life-expectancy of these patients is expected to extend well beyond the trial periods. Further, no evidence is provided in the submission to support the assumption of constant efficacy over time.
 - The economic analysis for Type II SMA defined responder as a patient achieving ≥ 3 -point improvement in HFMSE score whereas the economic analysis for Type III SMA defined responder as a patient achieving ≥ 0 -point gain in HFMSE score. No justification was provided for the different definitions of responders between the two analyses.
 - The economic analyses assumes a 4 monthly maintenance dosing regimen whereas the maintenance dosing regimen in the CHERISH trial was every 6 months. The PSCR (p5) claimed that this biases against nusinersen. The PBAC considered that while this was likely to bias against nusinersen, the incremental effectiveness of nusinersen in this setting is unknown (and the additional cost associated with an extra dose each year is high at \$ [REDACTED] per patient per year at the proposed price).

- There is a lack of comparative data for Type III SMA. The SMA Type III economic analysis presents a set of efficacy scenarios where the proportion of responders is assumed (assumptions of 0%, 10% and 30%). No justification was provided for the assumed proportions.
- As the submission makes no survival claims for SMA Type II and III, the economic justification for listing relies on gains in quality of life. However, the submission does not identify any utility values. The PBAC noted that while deriving utility values for infants and children is difficult, it considered it was important to include utility values in the economic evaluations for Type II and III SMA, as these patients are predicted to spend most of their life –expectancy as adults. As such, the PBAC agreed with the ESC that the cost per responder approach taken in the economic analysis for Type II and III SMA was not informative.

7.21 The PBAC advised that a resubmission presenting a model based on cost-utility analysis for Types II and III SMA would be required to establish the cost-effectiveness of treatment compared with standard care. Additionally, the PBAC considered that a substantial price reduction would likely be required to render nusinersen cost-effective in the overall SMA population.

Financial impact of subsidising nusinersen

7.22 The PBAC considered the financial impact of listing nusinersen at the proposed price of \$60 - \$100 million in Year 1 increasing to more than \$100 million in Year 6 to be substantial. Additionally, the PBAC considered that the financial impact of listing would likely be higher than estimated on the basis of factors identified by its DUSC including uncertainty around the size of the type II and III SMA population, potential use outside the proposed indication and the likelihood of patients remaining on treatment long term given the lack of alternative treatments and progressive nature of the disease.

7.23 The PBAC noted that the incidence of Type I SMA was estimated based on Australian data and considered this to be reasonable. However, the PBAC considered the estimated number of patients with Type II and III SMA to be uncertain and likely underestimated noting these were based on overseas data due to a lack of Australian data.

7.24 The PBAC noted that SMA is currently diagnosed in Australia using a single diagnostic gene test funded by the state public hospital system at no cost to the patient. The PBAC considered the availability of nusinersen in conjunction with accessible genetic testing would increase the rate of screening for the 5q survival-of-motor neuron (SMN) homozygous gene deletion or mutation, leading to earlier detection. The PBAC agreed with the DUSC that earlier detection may result in use of nusinersen outside the proposed restriction in pre-symptomatic patients. The PBAC considered that while there is some evidence to support a larger benefit of treatment in patients with Type I and Type II SMA who initiate treatment with nusinersen prior to the onset of symptoms, the PBAC considered there was no evidence to suggest that pre-symptomatic treatment with nusinersen would benefit patients with milder forms of SMA (i.e Type III and IV). Given it is currently not possible to precisely identify the SMA

type prior to the onset of symptoms, the PBAC considered that pre-symptomatic treatment with nusinersen may only benefit a proportion of patients.

- 7.25 The PBAC noted the DUSC advice that the submission may have underestimated the total health care costs given that costs for adverse events, monitoring, genetic tests and standard care were not included in the financial estimates. The PBAC considered that incorporation of these costs would have minimal impact on the financial estimates relative to the drug costs.
- 7.26 The PBAC noted the DUSC advice that the cost of treatment would continue to increase beyond Year 6 of listing along with the treated prevalent population given the average life expectancy of Type II patients is to adulthood and Type III patients have a normal lifespan. As such, the PBAC considered that Type II and Type III SMA patient population would account for the majority of treatment costs. Given the uncertainties around the size of the patient population and use of this treatment in clinical practice, the PBAC considered that a tight subsidisation cap through an RSA would be required if nusinersen was recommended for listing.

Rule of Rescue

- 7.27 The PBAC noted the submission requested consideration under the “rule of rescue”.
- 7.28 The PBAC considered that nusinersen may meet the criteria for ‘rule of rescue’ for SMA Type I where the life expectancy of patients without treatment is only two years, however there remains uncertainty about the duration of benefit of treatment in SMA Type I given the duration of follow up on the ENDEAR trial (13 months) .
- 7.29 The PBAC did not consider the ‘rule of rescue’ criteria met for SMA Type II. In particular, criterion four, that ‘the proposed medicine provides a worthwhile clinical improvement sufficient to qualify as a rescue from the medical condition’ is not met for SMA Type II, noting the uncertain clinical significance of a 3-point HFMSE score and uncertain long-term benefit of treatment given the duration of the CHERISH trial (15 months).
- 7.30 The PBAC considered there was insufficient clinical data to ascertain whether the ‘rule of rescue’ criteria would be met for SMA Type III.
- 7.31 As such, the PBAC considered that the ‘rule of rescue’ criteria were not met for nusinersen in the overall SMA population.
- 7.32 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

Biogen is disappointed by the PBAC's decision as this will delay the SMA community's access to SPINRAZA when there are currently no other disease-modifying medicines available to treat this devastating disease. Biogen is confident in the clinical evidence supporting SPINRAZA for the treatment of SMA. Following discussions at the post-PBAC meeting, we have identified next steps and are determined to meet the needs of the PBAC and the SMA community to make SPINRAZA available as soon as possible.