

7.03 NUSINERSEN, Solution for injection 12.6 mg in 5 mL, Spinraza[®], Biogen Australia Pty Ltd

1 Purpose of resubmission

- 1.1 The resubmission requested a Section 100 (Highly Specialised Drugs Program), Authority Required listing for nusinersen for the treatment of adult patients diagnosed with spinal muscular atrophy (SMA). This listing was requested as an extension to the existing paediatric restrictions for nusinersen.
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis of nusinersen (and standard of care) versus standard of care alone in adult patients (>18 years of age) diagnosed with 5q SMA with symptom onset prior to 19 years of age (≤18 years of age). Table 1 provides a summary of the key components of the resubmission.

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

Component	Description
Population	Treatment of adult patients (aged >18 years) genetically diagnosed with 5q SMA with symptoms of SMA prior to 19 years of age.
Intervention	Nusinersen administered at a dose of 12 mg via intrathecal injection with four loading doses and two maintenance doses in year 1 and three doses per year thereafter.
Comparator	Standard of care (for no treatment)
Outcomes	Key efficacy endpoints – motor function: • HFMSE • RULM • 6MWT Key efficacy endpoints – respiratory function: • FVC • Peak cough flow Safety
Clinical claim	Nusinersen has superior efficacy and non-inferior safety compared to standard of care.

FVC = forced vital capacity; HFMSE = Hammersmith Functional Motor Scale-Expanded; 6MWT = 6 minute walk test; RULM = revised upper limb module; SMA = spinal muscular atrophy

Source: Table 1.2, p15 and Table 2.30, p139 of the resubmission

2 Background

Registration status

- 2.1 Nusinersen was TGA registered for the treatment of 5q spinal muscular atrophy (SMA) on 2 November 2017.

Previous PBAC consideration

- 2.2 Nusinersen has been considered by the PBAC on several occasions. The first submission was considered at the PBAC meeting in November 2017. Listing was

requested in a broad SMA population comprising patients with infantile-onset (Type I) and childhood-onset (Types II & Type III) with no restrictions proposed regarding the age of nusinersen commencement. This was not recommended by the PBAC.

- 2.3 A minor resubmission was considered at the March 2018 PBAC meeting for symptomatic SMA patients. At this meeting nusinersen received a positive recommendation from the PBAC and was listed for the treatment of patients aged 18 years or less at initiation of treatment, who have had at least two of the defined signs and symptoms of SMA Type I, II or IIIa prior to 3 years of age.
- 2.4 In November 2020, the first resubmission was made to request extending the nusinersen listing to include adults with SMA, specifically in patients with symptom onset prior to 19 years of age and removal of the upper age limit of 18 years for initiation of treatment. This was not recommended by the PBAC.
- 2.5 The current resubmission requests extending the current PBS listing of nusinersen to include adults with SMA (>18 years of age) who have experienced signs and symptoms of SMA prior to 19 years of age (≤ 18 years of age). For this patient population, the key matters of concern from the November 2020 PBAC meeting are summarised in Table 2.

Table 2: Summary of outstanding matters of concern

Matter of concern (November 2020 PBAC Meeting)	How the March 2021 resubmission addressed it
PBS restriction The resubmission had not adequately defined the appropriate adult population for nusinersen and PBAC considered that alternative criteria could be considered that identify patients most likely to benefit (e.g. based on level or type of disability). Specialist clinical input would be required to help determine such criteria and thus define the appropriate patient population (paragraphs 7.1 and 7.2).	The sponsor received specialist clinical advice from two adult SMA Advisory Boards. The resubmission stated that clinicians indicated that functional status in adults with SMA is the most clinically relevant factor in determining patient capacity to benefit from treatment, with adults less severely affected by the disease and those who have more function to preserve (e.g. ambulant patients) expected to have the potential to gain the most from treatment. Partially addressed. The resubmission did not propose listing criteria based on a subpopulation of SMA patients who are most likely to benefit from treatment with nusinersen but clinical data and the economic model was presented based on ambulation status. The ESC considered that this matter of concern was not adequately addressed in the resubmission and the focus on gross motor outcomes in the clinical data and economic model may not reflect the most clinically relevant outcomes for many patients.
Clinical effectiveness The incremental benefit of nusinersen was unclear due to: • lack of randomised comparative data and lack of statistical analyses for the indirect naïve comparisons presented; • lack of transitivity between studies, particularly for the studies used to support the outcome of HFMSE noting the unknown impact of variables such as ambulant / non ambulant status, age of patient and rate of decline across types of SMA; • potential for a placebo effect and inappropriate exclusion of studies (paragraph 7.7)	Not addressed. No randomised comparative data or additional statistical analyses for the indirect naïve comparison were presented in the resubmission. Concerns regarding the transitivity between studies remain applicable. The potential for a placebo effect remained.
The magnitude and durability of benefit of nusinersen in adults with SMA was not able to be quantified and clinical input may be required to better understand the clinical significance of the outcomes in adults (paragraphs 7.9 and 7.10).	Not addressed. The clinical results provided in the resubmission appear consistent in direction with data previously presented to the PBAC but still did not allow for a reliable quantification of the incremental benefit of nusinersen treatment in adults with SMA. No long-term data was presented.
The claim of non-inferior comparative safety was not adequately supported by the data as there may be long term implications from repeated lumbar puncture administrations (paragraph. 7.11).	Not addressed. The resubmission again made a claim of non-inferior comparative safety but did not support this claim with a comparison of nusinersen to standard of care with respect to safety.

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Matter of concern (November 2020 PBAC Meeting)	How the March 2021 resubmission addressed it
Cost-effectiveness	
The economic model was uncertain and ICER high based on issues relating to (i) model inputs (transition probabilities, resource use estimates, utility weights), (ii) approach used to extrapolate duration of benefit for nusinersen, and (iii) cost effectiveness of nusinersen in non-adult patients with symptom onset between 3 and 18 years of age (paragraph 7.13).	The economic evaluation was updated with results presented for a range of adult patient populations defined by age, motor function status and age of onset of SMA. Listing in non-adult patients with symptom onset between 3 and 18 years was not requested in the resubmission. Partially addressed. Transition probabilities, utility weights and the duration of benefit for nusinersen remain uncertain.
Financial estimates	
The PBAC considered financial estimates were uncertain due to (i) assumed uptake and discontinuation rates, (ii) estimated number of patients with Type II and III SMA, (iii) average age of patients likely to access nusinersen and distribution of Type IIIa or IIIb patients, (iv) potential use beyond the requested restriction in adult patients with Type IV SMA (paragraphs 7.15 – 7.17).	The resubmission presented updated financial estimates but used the same uptake and discontinuation rates as in the November 2020 resubmission. While the previous resubmission proposed that the existing RSA for nusinersen in the paediatric setting be extended to include financial estimates for adults, the current resubmission proposed a separate RSA for adults with SMA. Partially addressed.

RSA= risk share arrangement

Source: Table 0.1, p4 of the resubmission.

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

3 Requested listing

Name, restriction, manner of administration, form	Maximum quantity (packs)	No. of repeats	Dispensed price for maximum quantity for adult SMA^	Proprietary name and manufacturer
NUSINERSEN				
Initial loading dose			\$110,000 published price	Spinraza,
12*mg/ 5 mL injection, 5ml vial	1	3	\$ [REDACTED] effective price	Biogen Australia Pty
Maintenance treatment			\$110,000 published price	Ltd
12*mg/ 5 mL injection, 5ml vial	1	0	\$ [REDACTED] effective price	

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Category/Program:	Section 100 – Highly Specialised Drugs Program
Prescriber type:	☒ Medical Practitioners
Condition:	Spinal muscular atrophy (SMA)
PBS Indication:	Treatment of SMA (Adults)
Treatment phase:	Initial – New patients
Restriction:	☒ Authority Required - In Writing
Treatment criteria:	Must be treated by a specialist medical practitioner experienced in the diagnosis and management of SMA; or in consultation with a specialist medical practitioner experienced in the diagnosis and management of SMA.
Clinical criteria:	The condition must be 5q homozygous deletion, mutation of, or compound heterozygous mutation in the SMN1 gene; AND Patient must have experienced signs and symptoms of SMA prior to 19 years of age; AND The treatment must not be used in combination with other SMA disease-modifying treatments; 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 over 18 years of age.
Administrative Advice	Special Pricing Arrangements apply. No increase in the maximum number of repeats may be authorised.
Treatment phase:	Continuing treatment - Maintenance
Treatment criteria:	Must be treated by a specialist medical practitioner experienced in the diagnosis and management of SMA; or in consultation with a specialist medical practitioner experienced in the diagnosis and management of SMA.
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition; AND The treatment must be given concomitantly with standard of care for this condition; AND The treatment must be ceased when the patient experiences a clinically significant decline in motor function resulting in loss of function or when invasive permanent assisted ventilation is required in the absence of a potentially reversible cause while being treated with this drug**.
Population criteria:	Patient must be over 18 years of age.

* The resubmission refers to the strength as 12.6mg/5mL.

^ Effective price applicable only to SMA patients who initiate nusinersen as adults. The effective price for treatment initiation as paediatric patients with SMA continues at \$ [REDACTED] per dose. The proposed list price for nusinersen for the treatment of adult patients with SMA is the same as the current PBS list price for nusinersen.

** In alignment with the current PBS restriction, invasive permanent assisted ventilation means ventilation via tracheostomy tube for greater than or equal to 16 hours per day. However, the proposed inclusion for the requirement for a decline in motor function is only applicable to adults; it is not applicable to the current PBS continuation criteria for nusinersen in the paediatric setting.

Source: Tables 1.5, 1.6 and 1.7, p31, 34 and 36 of the resubmission.

3.1 The revised pricing for adult SMA patients proposed in the resubmission included:

- In addition to the current special pricing arrangement (SPA), a further [REDACTED]% rebate was offered for the adult population (resulting in an effective price for the adult population of \$ [REDACTED]/vial); and
- [REDACTED] for all adults with SMA initiating nusinersen therapy; and
- [REDACTED] for nusinersen.

3.2 The proposed restriction did not include initiation of nusinersen in patients aged 18 years or younger who are not currently covered by the existing symptomatic listing for nusinersen (i.e. patients with Type IIb SMA) where onset of symptoms commenced

between 3 and 18 years of age. This was in contrast to the resubmission in November 2020 where listing for paediatric patients with Type IIIb SMA was requested. Consequently, under the current requested PBS restriction, patients whose symptoms began at between 3 and 18 years of age would not receive PBS funded nusinersen until they turn 18 years of age; for example, a patient who experienced initial symptoms of SMA at 4 years of age would need to wait until they were aged over 18 years to be eligible for PBS-listed nusinersen. Such a delay may be considered clinically inappropriate and the resulting discontinuity could potentially lead to confusion and a perceived inequity for those paediatric patients who remain ineligible despite being symptomatic. The Pre-Sub-Committee Response (PSCR) acknowledged that the resubmission was not able to present evidence specific to this population due to a lack of available data, but stated that the sponsor would welcome a pragmatic approach to addressing this issue via a risk share agreement. The ESC agreed that the exclusion of patients aged <18 years with Type IIIb SMA, where onset of symptoms commenced between 3 and 18 years of age, was not clinically appropriate and was likely to lead to confusion and inequity. The ESC advised that consideration should be given to including this population as part of any extension to nusinersen listings based on this submission. As such, the ESC advised that PBAC should give consideration to the cost-effectiveness of treatment in this population to the extent possible given the limitations of the data. The pre-PBAC response proposed including paediatric patients with Type IIIb SMA in the existing Risk Sharing Arrangement (RSA) for nusinersen, noting the size of the eligible paediatric Type IIIb SMA patient population is expected to be small.

- 3.3 The PSCR noted that the Secretariat suggested updating the proposed clinical criteria of the PBS restriction, to require adults with SMA to have documented evidence of symptom onset prior to 19 years of age, in order to reduce the potential use of nusinersen in adults with Type IV SMA. The PSCR stated the sponsor is willing to work with the Department and the Australian SMA clinical community to further refine the proposed restriction.
- 3.4 The ESC noted that the resubmission proposed continuation criteria for nusinersen to ensure patients are responding to treatment: “The treatment must be ceased when the patient experiences a clinically significant decline in motor function resulting in loss of function” in addition to requiring invasive permanent assisted ventilation. The ESC advised that further clinician input is required to determine the most appropriate outcomes for inclusion in the continuation criteria, given the heterogeneity of the PBS population in terms of disease severity, age and level of functioning at treatment initiation.
- 3.5 The PSCR noted that as the Sponsor has recently commenced an early access program for adults with SMA who meet the proposed PBS eligibility criteria to have access to nusinersen treatment prior to PBS listing, consideration to transitioning arrangements would be required. The pre-PBAC Response confirmed that the eligibility criteria for this program are aligned with the proposed PBS eligibility criteria. The pre-PBAC

response stated that the early access program commenced in May 2021, and that as of 25 June 2021, there were [REDACTED] adult SMA patients in the program, [REDACTED].

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

4 Population and disease

- 4.1 SMA is a rare autosomal recessive progressive neuromuscular disease caused by mutations or deletions in the survival 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, muscle weakness and complications such as respiratory issues, contractures and scoliosis. Patients with SMA typically develop weak muscles and may have trouble walking and breathing. SMA is classified into types (0, I, II, III and IV and subtypes (a, b, and sometimes by subgroup c) based on age of onset and maximal motor function achieved.
- 4.2 There is a clinical spectrum of disease with earlier age of onset being associated with lower numbers of survival motor neuron 2 (*SMN2*) gene copies and increased severity of symptoms. Table 3 provides an overview of the classification of SMA.

Table 3: Classification of SMA

Terminology	SMA type	Age at symptom onset	Highest motor function achieved	Average life expectancy
Pre-natal	0	Prenatal	None – unable to sit or roll	Death within weeks
Infantile onset	I	<6 months	None – unable to sit or roll	Death within 2 years
Childhood onset	II	6-18 months	Sitting – unable to walk independently	Survival into adulthood
	III	<3 years (IIIa) >3 years (IIIb) >12 to ≤18 years (IIIc)*	Independently stand and walk, may lose ability to walk over time	Normal lifespan
Adult onset	IV	>18 years	Normal – mild motor impairment	Normal lifespan

*Recent publications distinguish between Type IIIb and IIIc SMA with Type IIIc being defined as when symptoms develop after 12 years but before 19 years, although Type IIIb is commonly used to describe onset of SMA symptoms from after 3 years to 18 years of age.

SMA = spinal muscular atrophy

Source: Table 1.1, p7 of the resubmission

- 4.3 Nusinersen is an antisense oligonucleotide that increases the proportion of exon 7 inclusion in *SMN2* messenger ribonucleic acid (mRNA) transcripts by binding to *SMN2* pre-mRNA, thus increasing the level of SMN protein. Nusinersen is delivered intrathecally, directly into the cerebrospinal fluid, with or without image guidance. Four loading doses are given (days 0, 14, 28 and 63) and then maintenance doses are administered once every 4 months.
- 4.4 The PSCR stated that clinical advice indicates that achieving disease stabilisation is the main treatment goal for adults with SMA, which contrasts to the treatment goal in paediatric SMA. The ESC noted that the submission indicated that specialist clinical advice suggested functional status in adults with SMA is the most clinically relevant

factor in determining patient capacity to benefit from treatment, with adults less severely affected by the disease and those who have more function to preserve (e.g. ambulant patients) expected to have the potential to gain the most from treatment. However the ESC considered that the emerging literature suggests that for many patients, particularly those with less function at baseline, functional status is unlikely adequately capture treatment benefit (see also paragraph 6.38).

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

5 Comparator

- 5.1 The submission nominated standard of care (for no treatment) as the main comparator. This nomination was based on the absence of an alternate disease-modifying therapy available on the PBS for the treatment of adults with SMA (as of February 2021); however, the resubmission acknowledged that two new treatments for SMA (risdiplam and onasemnogene abeparvovec) are currently proceeding through registration and reimbursement processes.
- 5.2 The previous submission (November 2020) presented standard of care as the main comparator for adults with SMA. The PBAC considered that standard of care was an appropriate comparator (paragraph 7.5, p.33 nusinersen Public Summary Document (PSD), November 2020).
- 5.3 The PSKR stated that development of the consensus treatment guidelines for adults with SMA is proceeding. Following a meeting of neurologists with expertise in neuromuscular conditions, convened by the Sponsor in 2020, a summary of considerations for an Australian adult SMA consensus guideline was developed and preparation for clinician-led focus groups with adults with SMA, to gather information regarding their perspectives on the proposed guideline, has now commenced (noting that the consensus treatment guidelines are still in development and will require input from patients). The PBAC considered that the draft treatment guidelines would be informative for any future consideration of treatments for adults with SMA.

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

6 Consideration of the evidence

Sponsor hearings

- 6.1 The sponsor requested a hearing for this item. The clinician noted that the pool of untreated adults with SMA is diminishing, as most paediatric patients are accessing treatment. The clinician emphasised the unmet clinical need for effective treatments for adults with SMA. The clinician indicated that from treatment, adult patients hoped to maintain stable employment, participation in society, dignity and independence. The clinician described the outcomes of the Hammersmith motor function scale – expanded (HFMSE), revised upper limb module (RULM) and six minute walk test (6MWT) from Hagenacker 2020 and highlighted the clinical significance of these

outcomes for adult patients.

- 6.2 The clinician stated that adult patients have actively been engaged to enrol in the Australian SMA registry. The clinician stated that clinical experts were currently working to determine which patient reported outcome tool would be most relevant for Australian patients and that this would be further discussed in the clinician-led focus groups with adults with SMA. The clinician noted that while the registry would be useful for collating data on patient outcomes, the collection of HFMSE and RULM data is challenging as most adult neuromuscular clinics in Australia are not multidisciplinary with few having access to physiotherapy resources which are required for HFMSE and RULM assessment.

Consumer comments

- 6.3 The PBAC noted and welcomed the input from individuals (72), health care professionals (2) and organisations (3) via the Consumer Comments facility on the PBS website. The comments described the progressive loss of muscle strength and motor function associated with SMA and the significant impact of this deterioration on daily life (e.g. ability to work, and ability to self-care). The comments also noted that the fear of disease progression and uncertainty of access to treatment had a detrimental impact on patients' mental health. The comments emphasised that even though nusinersen may not be curative, slowing or stabilising disease progression is important as it could allow patients to maintain a level of independence and improve patient quality of life. Many of the comments also raised issues of equity around access to treatment and expressed frustration that nusinersen was only subsidised for paediatric patients.
- 6.4 The Muscular Dystrophy Association of NSW, Duchenne Australia and SMA Australia strongly supported expanding access of nusinersen to all patients with SMA. The organisations highlighted the high demand for effective treatments for adult patients with SMA. The Muscular Dystrophy Association of NSW noted that many patients valued even a small improvement in functioning as this could mean maintenance of employment and independence. The Muscular Dystrophy Association of NSW also noted the high caregiver burden in families of adult patients with SMA.

Clinical trials

- 6.5 No head-to-head trials of nusinersen versus standard of care were available in adult patients with SMA. The resubmission was based on a naïve comparison of nusinersen studies with natural history studies of SMA patients.
- 6.6 Data for nusinersen in adults with SMA was informed by eight real-world studies in 317 adults with a mean follow-up of up to 17 months (Maggi 2020, Hagenacker 2020, Walter 2019, Duong 2021, De Wel 2020, Jochmann 2020, Veerapandiyani 2019 and Yeo 2020), and data pooled from three European SMA registries (referred to as SMA Registry from herein) in 252 adults (Cohort 1), of which a subset of 75 patients reported results before and after initiation of nusinersen (Cohort 2). Mean follow-up

before and after nusinersen initiation in Cohort 2 in the SMA registry was 131 weeks and 52 weeks, respectively.

- 6.7 Natural history data from ten studies (Mercuri 2016, Montes 2018, Pera 2019, Wadman 2019, Coratti 2020a, Coratti 2020b, Wijngaarde 2020a, Querin 2021, Mazzone 2013 and Bonati 2017) were presented to inform the naïve indirect comparison.
- 6.8 In the November 2020 resubmission only two real-world studies of nusinersen in adults with SMA (Hagenacker 2020 and Walter 2019) and four natural history studies of patients with SMA (Montes 2018, Pera 2019, Wadman 2018 and Mercuri 2016) were presented, and the European SMA registry data was not available at the time of the evaluation. The PSCR contended that the body of real-world clinical evidence presented in this resubmission for nusinersen in adults with SMA is comprehensive for a rare disease therapy. The ESC noted that the resubmission included a substantially increased body of clinical evidence for nusinersen in adults with type II and III SMA, though the duration of follow-up was not substantially increased. The ESC noted that the evidence in patients with type III SMA was not broken down into the subtypes IIIa and IIIb, which prevents separate consideration of the outcomes for patients with these subtypes.
- 6.9 Details of the studies presented in the resubmission are provided in Table 4.

Table 4: Studies and associated reports presented in the resubmission

Study ID	Protocol title/ Publication title	Publication citation
Non-randomised studies of treatment with nusinersen in adult patients		
Maggi 2020	Nusinersen safety and effects on motor function in adult spinal muscular atrophy type 2 and 3.	Journal of Neurology, Neurosurgery and Psychiatry 2020;91(11):1166-1174.
Hagenacker 2020	Nusinersen in adults with 5q spinal muscular atrophy: a non-interventional, multicentre, observational cohort study.	The Lancet Neurology 2020; 19(4),317-325.
Duong 2021	Nusinersen Treatment in Adults with Spinal Muscular Atrophy.	Neurology: Clinical Practice 2021; pp.10.1212/CPJ.0000000000001033.
Walter 2019	Safety and Treatment Effects of Nusinersen in Longstanding Adult 5q-SMA Type 3 - A Prospective Observational Study."	Journal of Neuromuscular Diseases 2019; 6(4): 453-465.
	P.354Treatment effects of nusinersen in longstanding adult 5q-SMA type 3 - a prospective observational study over 10 months.	Neuromuscular Disorders 2019; 29: S185.
De Wel 2020	Nusinersen treatment significantly improves hand grip strength, hand motor function and MRC sum scores in adult patients with spinal muscular atrophy types 3 and 4.	Journal of Neurology 2020;268(3):923-935.
	THERAPY: P.279 Efficacy and safety of nusinersen treated adult patients with spinal muscular atrophy (SMA) types 2-3-4.	Neuromuscular Disorders. 2020;30:S128. 10.1016/j.nmd.2020.08.276
Jochmann 2020	Experiences from treating seven adult 5q spinal muscular atrophy patients with Nusinersen.	Therapeutic Advances in Neurological Disorders 2020;13, p.1756286420090780.
Yeo 2020	Prospective Cohort Study of Nusinersen Treatment in Adults with Spinal Muscular Atrophy	J Neuromuscul Dis. 2020;7(3):257-268.
	Outcome measures for nusinersen efficacy in adults with spinal muscular atrophy.	Neurology 2019;92(15):S5.008.
Veerapandiyan 2019	Nusinersen for older patients with spinal muscular atrophy: A real-world clinical setting experience.	Muscle Nerve 2020;61(2):222– 226.
	Intrathecal nusinersen in older children and adults with spinal muscular atrophy.	Neurology 2019;92(15).S5.001.
SMA Registry	Characterisation of patients with spinal muscular atrophy based on data of SMA registries (SMARtCARE, ISMAR, CuidAME)	No publication cited. (Referred to as SMA Registry 2020 Analyses Report)
Data on the natural history of SMA in untreated patients		
Mercuri 2016	Patterns of disease progression in type 2 and 3 SMA: Implications for clinical trials	Neuromuscular Disorders 2016: 26(2): 126-131.
Montes 2018	Ambulatory function in spinal muscular atrophy: Age-related patterns of progression	PLoS ONE 13(6): e0199657
Pera 2019	Revised upper limb module for spinal muscular atrophy: 12 month changes	Muscle and Nerve 2019: 59(4): 426-430.
Wadman 2018	Muscle strength and motor function throughout life in a cross-sectional cohort of 180 patients with spinal muscular atrophy types 1c-4	European Journal of Neurology 2018: 25(3): 512-518.
Coratti 2020a	Clinical Variability in Spinal Muscular Atrophy Type III.	Annals of Neurology. 2020;88(6):1109-1117. 10.1002/ana.25900
Coratti 2020b	Age and baseline values predict 12 and 24-month functional changes in type 2 SMA.	Neuromuscular Disorders. 2020;30(9):756-764. 10.1016/j.nmd.2020.07.005
Wijngaarde 2020a	Muscle strength and motor function in adolescents and adults with spinal muscular atrophy	Neurology. 2020;95(14):e1988-e1998. 10.1212/WNL.00000000000010540
Querin 2021	Development of new outcome measures for adult SMA type III and IV: a multimodal longitudinal study.	Journal of Neurology. 2021. 10.1007/s00415-020-10332-5

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Study ID	Protocol title/ Publication title	Publication citation
Mazzone 2013	Six minute walk test in type III spinal muscular atrophy: A 12month longitudinal study	Neuromuscular Disorders 23(8): 624-628.
Bonati 2017	Longitudinal characterization of biomarkers for spinal muscular atrophy	Annals of Clinical and Translational Neurology 4(5): 292-304.

Source: Tables 2.5 and 2.9 and 2.9, pp 67-68 and 83 of the resubmission and compiled during the evaluation from Section 2.2 of the resubmission.

Gray shaded cells indicate studies previously presented in the November 2020 resubmission.

- 6.10 The key features of the included studies are summarised in Table 5 below, including the risk of bias which was assessed using the ROBINS-1 tool for nonrandomised studies.

Table 5: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Nusinersen						
Maggi 2020	116	Retrospective cohort study single arm 14 months	High	Type II and III SMA	HFMSE, RULM, 6MWT	HSFME, RULM and 6MWT responder rates, baseline age
Hagenacker 2020	124	Prospective, observational cohort study, single arm 14 months	High	Type II and III SMA	HFMSE, RULM, 6MWT	Discontinuation rate used, baseline age
Duong 2021	42	Prospective observational study, single arm Mean treatment duration 12.5 months	High	Type II and III SMA	HFMSE, RULM, 6MWT	Not used
Walter 2019	19	Prospective, observational, single-arm, 10 months	High	Type III SMA	HFMSE, RULM, 6MWT	Not used
De Wel 2020	16	Prospective observational cohort study and retrospective study of natural history data, 14 months	High	Type III and IV SMA	HFMSE, RULM, 6MWT	Not used
Jochmann 2020	7	Prospective case series 10 months	High	Type II and III SMA	HFMSE, RULM, 6MWT	Not used
Yeo 2020		Prospective cohort study Mean 17 months	High	Type III SMA	HFMSE, RULM, 6MWT	Not used
Veerapandiyan 2019	12	A retrospective cross- sectional study Mean 17.4 months	High	Type III SMA	RULM	Not used
SMA registry ^a	Cohort 1: 252 Cohort 2: 75 (subset of cohort 1)	Descriptive observational study within prospective, multi-centre disease registries Median follow up: cohort 1 18 months (mean NR), cohort 2 10 months (mean 57 weeks)	High	Type III and IV SMA	HFMSE, RULM, 6MWT	Not used
Natural history data						
Mercuri 2016	268	Natural history data	High	Type II and III SMA	HFMSE	Not used
Montes 2018	73		High	Type II sitters to Type IIIb SMA	6MWT	Not used
Pera 2019	108		High	Type II to Type III SMA	RULM	Not used
Wadman 2018	180		High	Type IIa to Type IV SMA	HFMSE	Not used
Coratti 2020a	182	Natural history data	High	Type III SMA	HFMSE	Not used
Coratti 2020b	267		High	Type II SMA	HFMSE	Not used
Wijngaarde 2020a	250		High	Type 1c to IV SMA	HFMSE	Not used
Querin 2021	14		High	Type III and IV SMA	6MWT	Not used
Mazzone 2013	38		High	Type III SMA	6MWT	Not used
Bonati 2017	18-		High	Type III SMA	6MWT	Not used

HFMSE=Hammersmith Functional Motor Scale– Expanded; 6MWT=6 min walking test; NR=not reported; RULM=Revised Upper Limb Module; SMA=spinal muscular atrophy.

^aThe resubmission reported that it is likely there was an overlap between the 77 SMA Type III patients included by Hagenacker 2020 and the SMA Type III patients in the SMARtCARE SMA registry. The results presented for these studies therefore do not represent distinct data sets.

Cells shaded grey represent studies presented in the nusinersen November 2020 resubmission.

Source: Compiled from Section 2 of the resubmission.

- 6.11 The nusinersen studies were considered to have a high risk of bias, as they were open label, non-comparative and non-randomised studies. For similar reasons, the natural history studies were also considered to have a high risk of bias due to the lack of matching comparison, lack of blinding and likely selection bias (as patients selected for retrospective studies were selected based on available data).
- 6.12 Overall, the SMA patients included in the nusinersen studies were a highly heterogeneous population, with large variations in time of SMA onset, baseline motor functional scores and ambulatory status. Nonetheless, with the exception of a few type IV patients in whom symptom onset would be after the patient turned 18 years of age, the patients in the included nusinersen studies were likely to be representative of the proposed PBS population.
- 6.13 There was insufficient information on the baseline demographics of adult patients with SMA with symptom onset from before 18 years (i.e. SMA types I, II or III) from the natural history studies to be able to conduct any meaningful comparisons with the included nusinersen studies to determine whether the transitivity assumption may hold for the naïve comparison that is relevant to the current resubmission. The ESC considered that the heterogeneity of the populations within and across the trials, in terms of patient age, degree of disease progression and the extent of function at baseline, made it difficult to draw clear or meaningful conclusions regarding treatment outcomes.
- 6.14 A naïve comparison was presented for three outcomes: the Hammersmith motor function scale – expanded (HFMSE), revised upper limb module (RULM) and six minute walk test (6MWT).
- 6.15 As per the November 2020 resubmission, the current resubmission proposed that a ≥ 3 point change in HFMSE, or a ≥ 2 point change in RULM, or a ≥ 30 metres change in 6MWT were clinically meaningful. The ESC has previously considered that the importance of these outcomes (and the relevance of changes in these scores) in terms of clinically meaningful benefits for adult patients with SMA was unclear. The ESC considered that it was unclear which motor changes impact quality of life in adults and noted that consumer preferences tended to be around maintenance of upper limb function (e.g. for basic self-care, using devices, steering a wheel chair) and that, for many non-ambulant patients, mobility in terms of transfer movements in and out of chairs was clinically meaningful (paragraph 6.23, p13 nusinersen PSD, November 2020).
- 6.16 While respiratory outcomes (forced vital capacity (FVC) and peak cough flow) were

listed as key efficacy outcomes, no naïve comparison with standard of care was provided, and no MCIDs were defined by the resubmission. Quality of life was measured in one study (Jochmann 2020) using the EuroQol 5D (EQ-5D-5L). The PSCR stated that preventing progressive loss of independence has a significant impact on adult patients and their carers' quality of life and maintaining optimal lung function is prudent for all adults with SMA, as respiratory infection a significant cause of morbidity and mortality.

- 6.17 In the SMA registry data presented in the submission the analyses were combined by SMA type regardless of the current functional status of the patients. The PSCR noted that commonly used SMA outcome measures, such as HFMSE and RULM, are not optimised and sensitive for severely affected individuals, generally non-ambulant patients, which has most likely affected the annualised motor function scores. In the trials and registry data, given the heterogeneity of adult SMA patients in terms of age, disease severity and baseline levels of function, the ESC considered there is no single outcome reported in the trials that captures the most meaningful changes. The ESC noted that, in addition to gross motor outcomes, stabilisation of disease in terms of outcomes such as lung function, hand motor function and grip strength or endurance in activities of daily living may be more sensitive measures for quantification of treatment benefit in adults with SMA.
- 6.18 None of the studies included statistical adjustments for multiple testing, despite reporting results at multiple time points and reporting p-values for each time point. As such, the p-values reported by the included studies (which refer to change from baseline) should be interpreted with caution, as the threshold for significance may be less than the conventional 5%.

Comparative effectiveness

- 6.19 The results of the naïve comparison for HFMSE from the nusinersen studies and the natural history studies are presented in Table 6.

Table 6: HFMSE change from baseline across published studies

Study	Type	N	Mean Age in years (SD)	Mean Baseline HFMSE (SD)	Annualised change from baseline (mean (SD); median (range)), p-value
Nusinersen studies					
Maggi 2020 ^a	Type II + III (All)	51	36.8 (13.3), n=116	26.5 (21.7), n=116	+5.38 (NR); +8.5 (NR)
	Non-ambulatory Type II	5	26.3 (7.5), n=13	1.46 (2.82), n=13	+1.2 (2.68); 0 (0 to 6), p>0.05
	Non-ambulatory Type III sitters	19	40.8 (14.0), n=51	11.41 (9.6), n=51	+3.53 (3.67); +3 (-3 to 11), p=0.0014
	Ambulatory Type III walkers	27	35.5 (12.2), n=52	47.56 (11.3), n=52	+2.37 (2.22); +2 (-2 to 6), p=0.00016
Hagenacker 2020 ^a	Type II + III (All)	57	33 (11)	24.7 (21.8)	+3.12 (4.02); NR (2.06 to 4.19), p<0.0001
	Type II	19	28.9 (9.41)	4.8 (8.5)	+1.1 (1.4); 0 (0.4 to 1.7) p=0.0059
	Type III	38	35.7 (11.6)	34.6 (19.5)	+4.2 (4.5); 3 (2.7 to 5.7) p<0.0001
Hagenacker 2020 ^a (subgroup analysis)	Ambulant patients	23	NR	NR	+4.6 (4.4); NR (NR), p<0.0001
	Non-ambulant patients	34	NR	NR	+2.1 (3.4); NR (NR), p<0.0001
Duong 2021	Type II + III (All)	31	33.7 (NR) n=42	median 19 (range 0- 60) n=42	+0.86 (95%CI -0.52 to 2.24); NR (NR)
	Type II	11			+0.66 (95%CI -1.63 to 2.95); NR (NR)
	Type III	20			+0.99 (95%CI -0.77 to 2.74); NR (NR)
	Non-sitter	9			-0.24 (95%CI -3.57 to 3.09); NR (NR)
	Sitter	11			+1.13 (95%CI -1.11 to 3.36); NR (NR)
	Walker	11			+1.09 (95%CI -1.26 to 3.44); NR (NR)
Walter 2019 ^b	Type III (All)	19	35.2 (11.7)	35.16 (21.1)	+4.34 (NR); NR (NR) p=0.201
De Wel 2020 ^a	Type III (n=14) + IV (n=2) (All)	16	Median 37.5 (range 22-66)	27.3 (19.8)	+2.1 (NR); NR (NR) p=0.31
Jochmann 2020 ^b	Type II and III	6	41.2, N=7*	13.9 (NR)*	+5 (6.5); NR (NR)
Yeo 2020 ^a	Type III	6	Median 29.9 (range 24.9-65.5)	Median 35 (range 21, 53)	+2 (NR); NR (1 to 5)
Natural history studies					
Mercuri 2016	Type II	17	26.6 (7.5)	4.84	-0.059 ^c (NR); NR (NR)
	Type III ^c	12	29.4 (12.9)	55.2	-0.17 ^c (NR); NR (NR)
Wadman 2018	Type IIa	44 ^e	15-30	1.93 ^d	-0.129 (NR); NR (NR)
			30+	0.00 ^d	0.000 ^f (NR); NR (NR)
	Type IIb	36 ^e	15-30	6.09 ^d	-0.030 (NR); NR (NR)
			30+	NR	-0.165 (NR); NR (NR)
	Type IIIa	40 ^e	15-30	30.74 ^d	-1.643 (NR); NR (NR)
			30+	NR	-0.085 (NR); NR (NR)
	Type IIIb	36 ^e	15-30	64.9 ^d	-1.178 (NR); NR (NR)
			30+	NR	-0.940 (NR); NR (NR)
Coratti 2020 ^{a,g}	Type III (>20y)	49	23.99 (2.67)	30.42 (18.70)	-1.65 (3.42); NR (NR)
	Ambulant	18	23.67 (2.94)	51.94 (7.63)	-1.56 (3.96); NR (NR)
	Non-ambulant	31	24.19 (2.53)	17.93 (9.38)	-1.70 (3.14); NR (NR)
	Type IIIa (>20y)	27	24.18 (2.24)	23.07 (17.47)	-2.18 (3.54); NR (NR)

Study	Type	N	Mean Age in years (SD)	Mean Baseline HFMSE (SD)	Annualised change from baseline (mean (SD); median (range)), p-value
	Ambulant	8	24.45 (1.66)	47.63 (6.12)	-3.25 (4.89); NR (NR)
	Non-ambulant	19	24.07 (2.48)	12.74 (6.77)	-1.74 (2.84); NR (NR)
	Type IIIb (>20y)	22	23.77 (3.16)	39.45 (16.34)	-1.00 (3.24); NR (NR)
	Ambulant	10	23.04 (3.63)	55.40 (7.14)	-0.20 (2.53); NR (NR)
	Non-ambulant	12	24.38 (2.73)	26.17 (6.66)	-1.67 (3.70); NR (NR)
Coratti 2020b	Type II (all)	652 ^j	9.41 (6.32)	11.55 (9.24)	-0.68 (3.28); NR (-13 to +12)
	Type II (>13yr)	117	20.21 (5.75)	3.21 (3.79)	-0.26 (1.37); NR (-10 to 3)
	Type II (>18y) ^h	54	24.24 (5.10)	NR	-0.15 (1.28); NR (NR)
Wijngaarde 2020a ⁱ	Type IIa	68	13.4 (5.9-21.2)	9.27 (1.09)	-0.29 (95%CI -0.39, -0.18); NR (NR)
	Type IIb	50	15.0 (7.0-24.7)	20.58 (2.07)	-0.46 (95%CI -0.61, -0.30); NR (NR)
	Type IIIa	63	25.2 (6.2-47.6)	44.53 (2.74)	-0.73 (95%CI -0.88, -0.58); NR (NR)
	Type IIIb	40	42.8 (26.7-48.3)	60.01 (7.06)	-0.56 (95%CI -0.93, -0.19); NR (NR)

^aData reported for patients who had 14 month assessment only. Baseline values include all patients enrolled

^bData represents 10 month assessment expressed. Mean age of patients and baseline HFMSE in Jochmann 2020 recalculated during evaluation

^cDerived from Mercuri Figure 1 in patients ≥ 18 ; change over 12 months. The resubmission excluded the one patient aged 17.64.

^dThe resubmission stated that these values were assumed to be the mean ages captured in the slope. This could not be verified.

^eAge group sizes not reported, consequently, the N presented here includes patients across all ages for each SMA type

^fChange of zero due to a mean of zero in this patient group

^g12 month changes reported for the >20 subgroup in supplementary table 1 in Coratti 2020a.

^hEstimates are based on IPD (*not defined by resubmission*) analysis extracted from figure 2 of source document (Nb. overlapping data points, particularly at 0 change means that not all data points may have been captured in analysis).

ⁱBaseline and annualised change in HFMSE are based on intercept (SE) and slope from model parameter estimates as reported in table 2 of source document

^j652 12 month assessments taken from 267 patients (150 males and 117 females)

^kValues calculated during evaluation.

CI = confidence interval HFMSE=Hammersmith motor function scale – expanded; NR=not reported; SD=Standard deviation; SMA=spinal muscular atrophy

Cells shaded grey represent studies presented in the nusinersen November 2020 resubmission.

Source: Table 2.80, p255 of the resubmission

6.20 There were inconsistencies reported by the resubmission for Maggi 2020. For example, the median annualised change from baseline provided in the resubmission for all the subgroups (+1.2 for non-ambulatory type II SMA patients, +3.53 for non-ambulatory type III sitters and +2.37 for ambulatory type III walkers) were all smaller than the annualised change for all patients (+5.38), which was implausible. This appeared to be due to inconsistencies between the values reported by Maggi 2020 in the publication and in the published supplementary data. As such, the results of all patients in Maggi 2020 may be uncertain.

6.21 Apart from Maggi 2020, the included nusinersen studies report that adult patients treated with Type II or III SMA with nusinersen experienced a mean annualised HFMSE improvement from baseline between 0.66 to 4.6 points based on a mean period of 10 to 14 months of treatment (six to seven doses), but a number of patients may continue to experience motor function decline. The natural history study data suggested that HFMSE may remain stable or decline in adult patients without treatment (mean

annualised change from baseline ranging from 0.00 to -3.25), although some patients may experience an improvement from baseline (e.g. Coratti 2020b reported that 11.0% and 9.5% of patients showed an improvement in HFMSE of >2 points after 12 months and 24 months, respectively).

6.22 However, the comparison of HFMSE in nusinersen treated versus untreated patients was complicated by differences between the study populations that were likely to have caused heterogeneity and were not adequately addressed by the resubmission. In particular, as the rate of change in HFMSE appeared to be dependent on a number of factors, such as type of SMA, whether the patient is ambulant or non-ambulant and age of the patient, the naïve comparison was considered to be limited by the differences in regard to these variables between the nusinersen treatment studies and the natural history data. The comparison may also have been limited by the different time periods for assessment of the outcome in terms of months of treatment/follow-up.

6.23 The change in HFMSE reported in the SMA registry is presented in Table 7.

Table 7: HFMSE change from baseline in SMA Registry

Type	N	Mean Age in years	Mean Baseline HFMSE	Weekly rate of change (95%CI)	Annualised change from baseline – mean slope – p-value ^b
Nusinersen treatment					
Cohort 1: Treated Type III + IV	235	NR ^a	NR ^a	0.029 (0.019, 0.039)	+1.51 p<0.0001
Cohort 2: Treated Type III + IV	75	37.6	29.15 n=47	0.026 (0.0010, 0.041)	+1.34 p=0.0011
Natural history					
Cohort 1: Untreated Type III + IV	17	NR ^a	NR ^a	-0.011 (-0.033 0.010)	-0.59 p=0.305
Cohort 2: Before treatment Type III + IV	75	37.6	29.15 n=47	-0.00006(-0.010,0.009)	-0.00312 p=0.9903

Note: The total cohort 1 comprises of 252 patients:

- Treated cohort 1, adults: n=235 – SMA Type III: n=228 (97.02%) and SMA Type IV: n=7 (2.98%)

- Untreated cohort 1, adults: n=17 – SMA Type III: n=14 (82.35%) and SMA Type IV: n=3 (17.65%).

The total cohort 2 comprises of 75 patients: All patients are SMA Type III (n=74, 98.7%) and IV (n=1, 1.3%).

^aAge and HFMSE score at baseline was not available for adults only for cohort 1

^bAnnualised change from baseline was estimated multiplying the weekly rate of change by 52 to give an approximate change per year.

HFMSE=Hammersmith motor function scale – expanded; NR=not reported

Source: Table 2.81, p257 of the resubmission, Tables 3.1.2.2 and 3.2.2.1, SMA Registry 2020 Analyses Report

6.24 The results from the SMA Registry were consistent in direction with the results from the published studies. A small decrease in HFMSE was observed for untreated patients while a small increase in HFMSE was observed for patients treated with nusinersen. It may be not have been appropriate to multiply a weekly rate by 52 to derive an annual rate, instead of estimating an annual rate with the available data (as was done for other nusinersen studies). Due to the non-comparative nature of the data, these results do not allow for an accurate quantification of HFMSE benefit when treated with nusinersen. Nonetheless, the before and after results in Cohort 2 may indicate a higher quality of evidence than the naïve comparison as it may be argued that each patient acted as their own control. An incremental annualised change in HFMSE of +1.34 was reported in patients after nusinersen treatment compared to before

treatment. It was noted that this was less than the ≥ 3 point of change required for a minimally clinically important difference proposed by the resubmission.

- 6.25 The results of the naïve comparison for RULM from the nusinersen studies and the natural history studies are presented in Table 8.

Table 8: RULM change from baseline across published studies

Study	Type	N	Mean Age in years (SD)	Mean Baseline RULM (SD)	Annualised change from baseline (mean (SD); median (range)) – p-value
Nusinersen studies					
Maggi 2020 ^a	Type II + III (All)	50	36.8 (13.3), n=116	25.2 (11.6), n=114	+2.4 (NR); +1.5 (NR)
	Non-ambulatory Type II	5	26.3 (7.5), n=13	6.42 (8.4), n=12	+1.6 (1.52); 2 (0 to 3), P>0.05
	Non-ambulatory Type III sitters	19	40.8 (14.0), n=51	20.16 (8.6), n=51	+1.47 (2.5); 2 (-6 to 5), p=0.018
	Ambulatory Type III walkers	25	35.5 (12.2), n=52	34.71 (36), n=51	+0.4 (1.83); 0 (-3 to 6), P>0.05
Hagenacker 2020 ^a	Type II + III (All)	57	33 (11)	23.85 (12.16), n = 58	+1.09 (±1.75); NR (0.62 to 1.55) p<0.0001
	Type II	19	28.9 (9.41)	12.3 (9.0)	+1.6 (±2.0); NR (0.7 to 2.5) p=0.0049
	Type III	38	35.7 (11.6)	29.5 (9.1)	+0.7 (±1.7); NR (0.2 to 1.3) p=0.01
Duong 2021	Type II + III (All)	39	33.7 (NR) n=42	18.2 (range 0-37) n=42	+0.11 (95%CI -0.45, 0.67); NR (NR)
	Type II	16			+0.43 (95%CI -0.44, 1.31); NR (NR)
	Type III	23			-0.12 (95%CI -0.81 to 0.57); NR (NR)
	Non-sitter	16			-0.17 (95%CI -1.09 to 0.74); NR (NR)
	Sitter	12			+0.74 (95%CI -0.32 to 1.80); NR (NR)
	Walker	11			-0.01 (95%CI -1.02 to 0.99); NR (NR)
Walter 2019 ^b	Type III (All)	19	35.2 (11.7)	32.32 (7.39)	+0.74 (0)p=0.048
De Wel 2020 ^a	Type III + IV (All)	16	Median 37.5 (range 22-66)	27.1 (8.10)	+1.06 (95%CI-0.79 to 2.91); NR (NR) p=0.24
Jochmann 2020	Type II and III	6	41.2, N=7 ^{e*}	11.7 (NR) ^{e*}	+7.7 (9.3); NR (NR)
Yeo 2020	Type III	6	Median 29.9 (range 24.9-65.5)	31.5 (range 22–37)	+1.8(NR); NR (0, 3), p < 0.05
Veerapandiyan 2019	Type I, II and III	4	35.8 (NR)N=4	16.7 (NR)	+1.6 ^d (NR); NR (NR)
Natural history studies					
Pera 2019 Patients ≥18 years ^c	All	24	NR (NR)	22.0 (NR)	-0.7 (2.5); NR (NR)
	Type II	11	NR (NR)	11.8 (NR)	+0.6 (1.9); NR (NR)
	Type III non-ambulant	6	NR (NR)	22.7 (NR)	-1.7 (2.4); NR (NR)
	Type III ambulant	7	NR (NR)	36.0 (NR)	-1.4 (2.7); NR (NR)

^aData represents 14 month assessment expressed. Baseline values include all patients enrolled^bData represents 10 month assessment expressed^cData extracted using DigitizerIT Software.^dIncrease from baseline to last assessment. Last assessment varied from 9 to 26 months.^eMean age of patients and baseline RULM in Jochmann 2020 recalculated during evaluation

* Values calculated during evaluation.

Data shaded grey was presented in the nusinersen November 2020 submission.

CI = confidence interval; NR = not reported; RULM=Revised upper limb module; SD=Standard deviation; SMA=spinal muscular atrophy

Source: Table 2.82, p259 of the resubmission

- 6.26 As for HFMSE, the results reported for all patients in Maggi 2020 were not consistent with the results for the subtypes, with a mean change in RULM for all patients being greater than the value in each of the SMA subgroups.
- 6.27 The ambulant SMA Type III walkers in Maggi 2020 and Type III (All patients) in Walter 2019 both had a median baseline score of 37 points, which is the maximum possible score on the RULM scale. Patients then generally maintained this functionality for the duration of follow up. The resubmission reasonably reported that an observed ceiling effect indicated that RULM may not be sensitive enough to capture functional gains attributable to nusinersen treatment in this patient population.
- 6.28 The resubmission stated that the naïve comparison appeared to indicate that adult SMA patients treated with nusinersen reported disease stabilisation or a modest improvement when measured using RULM, whereas a decline was reported in natural history studies of adults with SMA. However, given the non-comparative nature of the data, limited amount of natural history data available with which to compare nusinersen data, the heterogeneity of the population, the inconsistencies in the follow up period of the nusinersen studies, the data inconsistencies observed with the Maggi 2020 study and the ceiling effect observed for the RULM outcome, it was difficult to draw any reliable conclusions from the available RULM data in the naïve comparison.
- 6.29 The results of change in RULM from baseline for the SMA registry are summarised in Table 9.

Table 9: RULM change from baseline in SMA Registry

Type	N	Mean Age in years	Mean Baseline RULM	Weekly rate of change (95%CI)	Annualised change from baseline – mean slope – p-value ^b
Nusinersen treatment					
Cohort 1: Treated Type III + IV	235	NA ^a	NA ^a	0.012 (0.005, 0.018)	+0.61 p=0.0007
Cohort 1: Treated Type III + IV (excl. ceiling effect)	NA			0.016 (0.007, 0.025)	+0.84 p=0.0007
Cohort 2: Treated Type III + IV	75	37.6 n=75	26.15 n=45	0.003 (-0.005,0.010)	+0.13 p=0.5227
Cohort 2: Treated Type III + IV (excl. ceiling effect)	53			0.005 (-0.007, 0.016)	+0.24 p=0.4275
Natural history					
Cohort 1: Untreated Type III + IV	17	NA ^a	NA ^a	0.004 (-0.010, 0.018)	+0.21 p=0.5875
Cohort 1: Untreated Type III + IV (excl. ceiling effect)	NA			0.026 (-0.034, 0.086)	+1.36 p=0.3929
Cohort 2: Before treatment Type III + IV	75	37.6 n=75	26.15 n=45	-0.007(-0.014,-0.0009)	-0.39 p=0.0259
Cohort 2: Before treatment Type III + IV (excl. ceiling effect)	53			-0.014 (-0.026, -0.003)	-0.75 p=0.0115

Note: The total cohort 1 comprises of 252 patients:

• Treated cohort 1: n=235 – SMA Type III: n=228 (97.02%) and SMA Type IV: n=7 (2.98%)

• Untreated cohort 1: n=17 – SMA Type III: n=14 (82.35%) and SMA Type IV: n=3 (17.65%).

The total cohort 2 comprises of 75 patients: All patients are SMA Type III (n=74, 98.7%) and IV (n=1, 1.3%).

^aAge and RULM score at baseline is not available for adults only for cohort 1

^bAnnualised change from baseline was estimated multiplying the weekly rate of change by 52 to give an approximate change per year.

RULM=Revised Upper limb module; SMA=spinal muscular atrophy

Source: Table 2.83, p262 of the resubmission, Tables 3.1.2.3, 3.1.2.3.2, 3.2.2.2.1 and 3.2.2.2.2, SMA Registry 2020 Analyses Report

- 6.30 The data for the SMA registry found that RULM score increased by +0.61 points annually in the nusinersen-treated patients compared to the untreated patients (Cohort 1). It should be noted however, that an increase in RULM by +0.21 per year was seen in untreated patients, going against the expectation that untreated patients will slowly experience motor decline over time. An even greater increase in RULM (+1.36 per year) was seen when patients in cohort 1 with a ceiling effect were excluded from the analysis. In Cohort 2 of the SMA registry, the RULM scores showed an annualised decrease in slope of -0.39 points before initiation of nusinersen treatment and a +0.13 points annualised increase after treatment with nusinersen. It was unclear why the change in RULM was so different when comparing the untreated patients in cohort 1 (whose RULM increased over time), to the patients in cohort 2 before treatment (whose RULM decreased over time).
- 6.31 Assuming that the before and after treatment effects in Cohort 2 were representative of an incremental benefit, the change in RULM from the first year of nusinersen treatment was +0.52 points (+0.99 when excluding ceiling effect), which was less than the ≥2 point change in RULM that was proposed to represent a clinically meaningful change.
- 6.32 While the data appears to suggest that adult SMA patients treated with nusinersen experience a small increase or at least no decline in RULM scores, in the absence of a direct comparative study, it was not possible to elicit an incremental benefit for

treatment with nusinersen compared to best supportive care. This was consistent with the PBAC's previous consideration that while a claim of superior comparative effectiveness of nusinersen to standard of care was reasonable, the magnitude and durability of benefit was not able to be quantified based on the data presented (paragraph 7.10, p34 nusinersen PSD, November 2020).

- 6.33 The results of the naïve comparison for 6MWT from the nusinersen studies and the natural history studies are presented in Table 10.

Table 10: Change in 6MWT from baseline across studies

Study	Type	N	Mean age in years (SD)	Mean baseline 6MWT metres (SD)	Annualised change from baseline (mean (SD); median (range)) – p-value
Nusinersen studies					
Maggi 2020 ^a	Ambulatory Type III walkers	24	35.5 (12.2), n=52	308 (140), n=48	+23.11 (51.2); 20 (-101 to 111) p=0.016
Hagenacker 2020 ^a	Type III	25	35.7 (11.6)	371.43 (210.34) ^g	+46.0 (49.91); 46 (25.4 to 66.6) ^h p<0.0001
Duong 2021	Walkers	10	33.7 n=42	300 (123.8) n=42	+3.29 (95%CI -28.04 to 34.62); NR (NR)
Walter 2019 ^b	Type III (All)	11	35.2 (11.7)	369.5 (126.6)	+8.25 (NR); NR (NR) p=0.01
De Wel 2020 ^a	Type III + IV (All)	7	Median 37.5	296 (199)	+7 (95%CI -38.42 to 53.27); NR (NR) p=0.71
Yeo 2020	Type III	4	Median 29.9 (range 24.9-65.5)	249 (range 74, 429)	NR [No results clinically or statistically meaningful.]
Natural history studies					
Montes 2018	Type III	15	>20 years	NR (NR)	-9.7 (NR); NR (-19.3 to -0.1), p=0.05
Querin 2021 ^c	Type III + IV	14	43.5 (12.1)	341.3 (247.6)	-4 (NR); NR (NR) p=0.318 ⁱ
Mazzone 2013 ^d	Type IIIa	2	>18 years	NR (NR)	+17.06 (NR); NR (NR)
	Type IIIb	6	>18 years	NR (NR)	+22.35 (NR); NR (NR)
Bonati 2017 ^e	Type III	19	32 (13) (range 11-51)	460.05 (138.12) n=18	+38.88 (based on a final assessment of 498.93m available in 14 of 18 patients)

^aData represents 14 month assessment expressed

^bData represents 10 month assessment expressed

^cAnnualised change was estimated from mean baseline and 24 months values reported in Table 1 of Querin 2021.

^dEstimates are based on IPD analysis extracted from figure 1a of source document.

^ePreviously excluded due to insufficient baseline data on underlying disease; not all patients were adults (the composition of group of patients by age is unclear), and no subgroup data presented.

^fJochmann 2020 reported 6MWT results for one patient only. This data has therefore not been included in the table.

^gThe result provided is the figure reported in the publication by Hagenacker 2020. The supplementary appendix to Hagenacker 2020 shows this result to be 356 (212.9).

^hThe result provided is the figure reported in the publication by Hagenacker 2020. The supplementary appendix to Hagenacker 2020 shows the median result to be 46 (0-71).

ⁱLikely estimated as half the difference between the point estimate at baseline (341.3m) and at 24 months (333.3m)

CI = confidence interval; NR=not reported; RULM=Revised upper limb module; SD=Standard deviation; SMA=spinal muscular atrophy
Source: Table 2.84, p264 in the resubmission.

- 6.34 The results reported in the resubmission for the 6MWT in the nusinersen studies were highly variable, ranging in change from baseline from +7 metres (m) in De Wel 2020

to +46.0 m in SMA Type III patients in Hagenacker 2020. The 6MWT results for the natural history studies varied in a similar manner, ranging from -9.7 m (Montes 2018) to +38.88 m (Bonati 2017). The inconsistency between studies within the nusinersen and natural history studies made it difficult to draw any conclusions from the naïve comparison for the 6MWT outcome.

6.35 The results of the 6MWT from the SMA registry are summarised in Table 11.

Table 11: 6MWT change from baseline in SMA Registry

Type	N	Mean age in years (SD)	Mean baseline 6MWT metres(SD)	Weekly rate of change (95%CI)	Annualised change from baseline – mean slope – p-value ^b
Nusinersen treatment					
Cohort 1: Treated Type III + IV	NR	NR ^a	NR ^a	0.263 (0.099, 0.427)	+13.69 p=0.0018
Cohort 2: Treated Type III + IV	13	37.6 n=75	383.40 n=16	-0.034 (-0.437, 0.369)	-1.78 p=0.8675
Natural history					
Cohort 1: Untreated Type III + IV	NR	NR ^a	NR ^a	-0.715 (-1.279,-0.151)	-37.17 p=0.0133
Cohort 2: Before treatment Type III + IV	13	37.6 n=75	383.40 n=16	-0.239 (-0.349,-0.130)	-12.44 p<0.0001

Note: The total cohort 1 comprises of 252 patients:

• Treated cohort 1: n=235 – SMA Type III: n=228 (97.02%) and SMA Type IV: n=7 (2.98%)

• Untreated cohort 1: n=17 – SMA Type III: n=14 (82.35%) and SMA Type IV: n=3 (17.65%).

The total cohort 2 comprises of 75 patients: All patients are SMA Type III (n=74, 98.7%) and IV (n=1, 1.3%).

^aAge and 6MWT score at baseline is not available for adults only for cohort 1 table.

^bAnnualised change from baseline was estimated multiplying the weekly rate of change by 52 to give an approximate change per year.

6MWT=Six minute walk test; NR=not reported; SMA=spinal muscular atrophy

Source: Table 2.85, p264 of resubmission and Tables 3.1.2.4 and 3.2.2.3, SMA Registry 2020 Analyses Report

6.36 In Cohort 1 of the SMA Registry, nusinersen-treated patients showed an increase in distance of +13.69 m annually, while the untreated patients decreased by 37.17 m. The results for cohort 2 showed that both patients before treatment and when treated with nusinersen experienced a decrease in 6MWT scores but the decline in 6MWT was smaller for patients treated with nusinersen. It should be noted that only 13 patients reported results for the 6MWT in Cohort 2. The incremental difference in the annualised rate of change in the 6MWT before and after nusinersen treatment in Cohort 2 was +10.66 m, though this should be expressed as a smaller decrease rather than an increase.

6.37 In November 2020 the PBAC considered that:

- ‘...the incremental benefit of nusinersen in the requested population was unclear due to the lack of randomised comparative data and lack of statistical analyses for the indirect naïve comparisons presented; lack of transitivity between studies, particularly for the studies used to support the outcome of HFMSE noting the unknown impact of variables such as ambulant / non ambulant status, age of patient and rate of decline across types of SMA; the potential for a placebo effect; and the inappropriate exclusion of studies.’ (paragraph 7.7, p.33 nusinersen PSD, November 2020); and
- ‘...while the claim of superior comparative effectiveness compared to standard of care was reasonable, the magnitude and durability of benefit was not able to be

quantified based on the data presented’ (paragraph 7.10, p.34 nusinersen PSD November 2020).

No additional randomised comparative data or longer term clinical data that would allow these issues to be addressed was provided in this resubmission. The clinical results provided appear consistent in direction with data previously presented to the PBAC but still did not allow for a reliable quantification of the incremental benefit of nusinersen treatment in adults with SMA. Given the numerous inconsistencies in the data and the lack of comparative data, it was difficult to make specific conclusions about the efficacy of nusinersen for the treatment of SMA in adults, particularly using the endpoints RULM (due to the ceiling effect observed and the resulting insensitivity of this measure) and 6MWT (due to the highly variable nature of the results reported between studies). It should also be noted that not all patients improve or remain stable with nusinersen, which can be observed in the reported ranges of differences from baseline for each outcome. Similarly, some patients who were untreated reported improvements in scores.

- 6.38 Responder analysis from Maggi 2020 is presented in Table 12. Responders were defined as a patient who experienced at least one of: ≥ 3 -point HFMSE score change, ≥ 2 -point RULM score change or a ≥ 30 m distance change in the 6MWT from baseline. The responders for each of these endpoints was assessed individually, then patients who were a responder in at least one of these three outcomes was defined as an ‘overall responder’.

Table 12: Proportion of responder for HFMSE, RULM and 6MWT in Maggi 2020.

	All SMA			SMA II			SMA III "Sitters"			SMA III "Walkers"		
	T6	T10	T14	T6	T10	T14	T6	T10	T14	T6	T10	T14
n of responders	33	32	25	1	1	1	14	14	11	18	17	13
HFMSE Total n	116	84	51	13	9	5	51	35	19	52	40	27
Responder %	28%	38%	49%	8%	11%	20%	27%	40%	58%	35%	43%	48%
n of responders	24	22	17	3	5	3	15	13	10	6	4	4
RULM Total n	114	80	49	12	9	5	51	33	19	51	38	25
Responder %	21%	28%	35%	25%	56%	60%	29%	39%	53%	12%	11%	16%
n of responders	NA	NA	NA	NA	NA	NA	NA	NA	NA	14	16	10
6MWT Total n	NA	NA	NA	NA	NA	NA	NA	NA	NA	48	35	24
Responder %	NA	NA	NA	NA	NA	NA	NA	NA	NA	29%	46%	42%
responder n	61	53	35	3	5	3	26	21	15	32	27	17
Overall total n	116	84	51	13	9	5	51	35	19	52	40	27
responder %	53%	63%	69%	23%	56%	60%	51%	60%	79%	62%	68%	63%

Red colour code corresponds to population size at given time points (months from the beginning of treatment) for different subgroups (SMA Type II, SMA Type III sitters and walkers), with intense red corresponding to relatively large populations. Green colour code corresponds to % of responders (ie, patients considered by Maggi 2020 to have a clinically meaningful improvement) at a given time point, with intense green corresponding to high responder rates.

HFMSE=Hammersmith Functional Motor Scale– Expanded; 6MWT=6 min walking test; RULM=Revised Upper Limb Module; SMA=spinal muscular atrophy; T6=6 months from the beginning of treatment; T10=10 months from the beginning of treatment; T14=14 months from the beginning of treatment.

Source: Figure 2.15, p178 of the resubmission

- 6.39 While Maggi 2020 reported that the proportion of responders increased over time, this was misleading because the total number of patients evaluated at each time point progressively decreased, likely because patients who were non-responders

disproportionately were more likely to stop treatment. For each patient subpopulation, the actual number of responders generally decreased over time. For example, for HFMSE responders for all SMA patients there are 33 responders at 6 months, 32 responders at 10 months and 25 responders at 14 months, but this rate of decline was lower than the decrease in total evaluable patients. Therefore, the increase in the percentage of responders over time was likely driven by the decreasing number of patients who have elected to continue to receive nusinersen rather than an actual increase in response over time. A more reasonable approach would be to use the same number of evaluable patients for all time points based on the number of patients enrolled (i.e. an intention to treat approach). Also importantly, as no adjustment for multiple testing was considered, the significance of each of the response rates at each time point was uncertain.

- 6.40 Responder rates for all outcomes in Hagenacker 2020 (presented in the previous resubmission) were reasonably consistent with Maggi 2020. Both Maggi 2020 and Hagenacker 2020 reported that patients with less advanced disease and better motor function at baseline showed greater improvement. The responder rate from Maggi 2020 was the only clinical evidence which was used in the economic evaluation, and was used to inform the proposed utility benefits of treatment with nusinersen.
- 6.41 Respiratory outcomes were reported in several nusinersen studies (Maggi 2020, Duong 2021, Walter 2019, De Wel 2020 and Jochmann 2020). No naïve comparison with natural history was presented by the resubmission. Overall, there was limited evidence to suggest that respiratory function changed from baseline after initiation of nusinersen treatment in the included studies.
- 6.42 The ESC noted that additional recent publications of nusinersen were available, and along with those identified in the submission, these publications focussed on more sensitive measures of benefit for adult patients with SMA. These studies suggest that commonly used SMA outcomes such as the HFMSA and RULM are not meaningful for more severely affected individuals. For example:
- De Wel (2021)¹ reported nusinersen treatment outcomes in terms of changes in hand grip strength and hand motor function scores in adult patients with SMA, which may have greater relevance to patient independence and therefore quality of life.
 - In Veerapandiyan (2020)² 12 patients aged 12-52 years were treated with nusinersen, with subjective improvements in endurance, hand strength and bulbar

¹ De Wel et al (2021). Nusinersen treatment significantly improves hand grip strength, hand motor function and MRC sum scores in adult patients with spinal muscular atrophy types 3 and 4. *J Neurol* 2021 Mar;268(3):923-935.

² The additional publication to Veerapandiyan (2019), as it is referred to in the submission (see Table 4).

functioning critical for activities in daily living reported in 8/12 patients after 17.4 months mean follow up.

- In Eisheikh (2021)³ 19 severely affected, non-ambulatory adults with SMA were treated with nusinersen, with stability of outcome measures of ventilator muscle function, muscle strength and function reported (although the primary outcome forced vital capacity did not demonstrate improvement the authors noted the lack of decline may suggest a mild positive effect). HFMSE and RULM were not feasible in the majority of patients.

6.43 The ESC also noted that natural history of lung function in SMA as reported in Wijngaarde (2020b)⁴ indicated that in early-onset SMA types (1c-3a), there was progressive decline of lung function at younger ages with relative stabilisation during adulthood whereas normal values were maintained in later-onset SMA types 3b and 4 throughout life, indicating that lung function may be more stable than skeletal muscle strength. The ESC considered that, though an important outcome, there was variability across patients with SMA in terms of impact on lung function and therefore this outcome may not capture treatment benefit for all SMA patients.

6.44 Jochmann 2020 was the only nusinersen study to report quality of life (QoL) data. The study by Jochmann incorporated the EQ-5D-5L Index that was self-evaluated by each patient. Table 13 shows the patient level data from Jochmann 2020. QoL data from Jochmann 2020 was not used in the economic model.

Table 13: Patient level data from Jochmann 2020

Patient	Age	SMA Type	Change in RULM (baseline, 10 months)	Change in HFMSE (baseline, 10 months)	Change in 6MWT (baseline, 10 months)	Change in EQ-5D-5L utility (baseline, end of study)
1	45	3	0 (15, 15)	-1 (29, 28)	NA	+0.38 (0.39, 0.77)
2	50	2	+1 (4, 5)	0 (0, 0)	NA	+0.11 (-0.02, 0.09)
3	20	3	-2 (37, 35)	+3 (60, 63)	+68 (275, 343)	+0.21 (0.60, 0.81)
4	57	2	NA (1, NA)	NA (0, NA)	NA	+0.12 (0.06, 0.18) ^a
5	68	3	+20 (17, 37)	+17 (6, 23)	NA	+0.07 (0.06, 0.13)
6	31	2	+11 (5, 16)	+5 (2, 7)	NA	-0.12 (0.18, 0.06) ^b
7	22	2	+16, (3, 19)	+6 (0, 6)	NA	0 (0.18, 0.18)

^a last assessment at 2 months

^b last assessment at 6 months

NA = not applicable

Source: Table 1, Jochmann 2020

6.45 While patients in Jochmann 2020 reported an increase in EQ-5D-5L, patient numbers were very low therefore applicability was limited. However, Jochmann 2020 demonstrated that quality of life may not be correlated with improvements in RULM

³ Eisheikh et al (2021). Safety, Tolerability, and Effect of Nusinersen in Non-ambulatory Adults With Spinal Muscular Atrophy. *Front Neurol.* 2021 Apr 16;12:650532.

⁴ Wijngaarde et al (2020b). Natural history of lung function in spinal muscular atrophy. *Orphanet J Rare Dis.* 2020 Apr 10;15(1):88.

or HFMSE. The greatest improvements in RULM and HFMSE were seen in patients 5, 6 and 7, but paradoxically they had the lowest quality of life gain from baseline. Patients 1 and 3, who experienced almost no change in either RULM or HFMSE, reported the highest quality of life gains which were multiples greater than in patient 5, who reported the best improvements in both HFMSE and RULM. As only one 6MWT result was available, no inferences regarding the correlation to quality of life could be made. As such, there may be reason to question whether changes in HFMSE and RULM were relevant outcomes to adult patients in SMA, or if QoL in this patient population were driven by other measures. The PSCR argued that it is highly unlikely any meaningful conclusions can be drawn from the correlation between motor function assessments and quality of life given the small number of patients in this study.

- 6.46 The PSCR stated that the benefits of nusinersen extend beyond motor function, reducing clinical decline over the long term in respiratory function and activities of daily living. The ESC considered that alternative, more sensitive measures of quality of life, fatigue, exercise tolerance, stability and activities of daily living are clearly needed to capture treatment benefit for adults with SMA, as suggested by Yeo et al (2020).

Comparative harms

- 6.47 The resubmission presented an overview of the safety reported for each of the nusinersen studies but did not provide a naive comparison with respect to safety. As a claim of non-inferior safety was made by the resubmission, the lack of a comparative safety assessment was inappropriate.
- 6.48 Adverse events (AEs) were reported in 41.4% of patients in the Maggi 2020 study and in 47% of patients in the Hagenacker 2020 study. AEs relating to lumbar puncture were frequently observed with post-procedure headaches most commonly reported (Maggi 2020 37.1%; Hagenacker 2020 20%; Duong 2021 14.3%; Walter 2019 21%; De Wel 25%). Other administration-related adverse events such as lumbar puncture pain (Maggi 2020 8.6%) and back pain (Hagenacker 2020 9%, De Wel 64.3%) were also reported. It was noted that two patients in Maggi 2020 discontinued treatment after six months due to lack of subjective benefit and poor tolerability of repeated lumbar puncture and two patients in Hagenacker 2020 withdrew from treatment due to drug related AEs.
- 6.49 The SMA registry reported that no new types of AEs, serious AEs, nusinersen-related AEs or other safety issues have been reported in the post-marketing setting. The analysis of safety data from the European SMA registry shows that the incidence of AEs and SAEs was not statistically significantly different in the nusinersen treated patient population, compared with the untreated patient population.
- 6.50 The AEs experienced by adult patients treated with nusinersen were similar to those experienced by children in whom AEs were also commonly related to lumbar puncture administration (headache, vomiting, back pain).

- 6.51 In November 2020 the PBAC detailed that there may be long term implications from repeated lumbar puncture administrations, particularly in patients who may not have had nusinersen otherwise (i.e. Type IIIb and Type IV patients). The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data (paragraphs 6.47 and 7.11, p19 and 34, nusinersen PSD, November 2020). No data was provided in the current resubmission to demonstrate the long-term safety of repeated nusinersen administration or to support the claim that nusinersen is non-inferior to standard of care with respect to safety for the requested patient population.
- 6.52 The PSCR argued that evidence from the periodic safety update report (PSUR) indicated no long-term adverse implications from repeated lumbar puncture and all adverse events were aligned with the safety profile for nusinersen.

Benefits/harms

- 6.53 The naïve indirect comparison presented in the resubmission did not allow for a quantitative comparison of the benefits and harms of treatment with nusinersen and standard of care in the requested patient populations. A benefits/harms table was consequently not presented.

Clinical claim

- 6.54 The resubmission described nusinersen for the treatment of adult patients diagnosed with SMA as superior in terms of effectiveness and non-inferior in terms of safety compared with standard of care. The therapeutic conclusion was only partially supported by the evidence presented in the resubmission because:
- The incremental benefit of nusinersen in adult SMA patients remains uncertain, as there was no higher quality comparative evidence presented. The PBAC has previously noted that while a claim of superior comparative effectiveness of nusinersen to standard of care was reasonable, the magnitude and durability of benefit was not able to be quantified based on the data presented (paragraph 7.10, p34 nusinersen PSD November 2020). No new randomised studies were presented in the current resubmission to address this, and as in the November 2020 nusinersen submission, no statistical analysis or incremental benefit was calculated for the naïve indirect comparisons between patients treated with nusinersen and the natural history of patients with SMA;
 - Limited data from the SMA registry for adult patients with SMA Type III and IV who had motor score values from before and after nusinersen treatment initiation, reported an annualised increase of + 1.34 points for HFMSE and +0.52 points (+0.99 when excluding ceiling effect) for RULM, with both of these outcomes failing to meet the proposed clinically meaningful threshold of ≥ 3 points for HFMSE and ≥ 2 points for RULM;

- It was uncertain if HFMSE and RULM were patient relevant outcomes in adult SMA patients, given the differences between patients in terms of age, disease severity and baseline levels of function, there is no single outcome reported in the trials that can capture the most meaningful changes for these patients; and
 - The PBAC had previously noted the short duration of follow-up in the included studies in the context of long-term treatment and considered that the durability of response with nusinersen in adults with SMA was unknown (paragraph 7.8, p33 nusinersen PSD, November 2020), with data up to 14 months of treatment being available. The additional studies included in this resubmission did not provide any longer term data to better inform the durability of benefit with nusinersen.
- 6.55 The ESC noted that the PSCR claimed that the evidence presented “demonstrates that nusinersen enables all adult patients to maintain or improve their current functional state”. The ESC disagreed with this statement and considered that not all patients maintain or improve functional status in the same way and the evidence presented reflect variation in response to nusinersen treatment. The PSCR also stated that the claimed clinical benefit aligned with the evidence in clinical trials and observational data in around 11,000 SMA patients treated for up to 6.5 years. The ESC noted that the vast majority of the evidence for nusinersen in terms of both the number of patients and the duration of treatment was in the paediatric population.
- 6.56 The PBAC had previously considered that the claim of non-inferior comparative safety was not adequately supported by the data and that there may be long term implications from repeated lumbar puncture administrations, particularly in patients who may not have had nusinersen otherwise (i.e. Type IIIb patients) (paragraphs 6.56 and 6.58, p20-21, nusinersen PSD November 2020). The resubmission did not provide a comparative safety assessment to support a claim of non-inferiority, and only provided limited information regarding potential safety concerns with repeated lumbar punctures. It was noted that two patients in Maggi 2020 discontinued treatment after six months due to lack of subjective benefit and poor tolerability of repeated lumbar puncture and two patients in Hagenacker 2020 also discontinued due to drug related adverse events.
- 6.57 The PBAC considered that the claim of superior comparative effectiveness was reasonable however, the PBAC considered that the magnitude and durability of benefit remained uncertain, noting no new comparative data was presented in the resubmission.
- 6.58 The PBAC considered that the claim of non-inferior comparative safety remained unreasonable and not adequately supported by the data.

Economic analysis

- 6.59 The PSCR stated that “an assessment of the cost-effectiveness of nusinersen in adults is only necessary because of a historical PBAC decision to introduce a PBS age

restriction in June 2018 for which, based on age, this group of patients would otherwise be eligible for PBS funded nusinersen treatment.” The ESC noted that the cost effectiveness of treating patients with type II and IIIa SMA who have survived to adulthood without disease modifying treatments, and the cost-effectiveness of treating any patients with type IIIb SMA, has not been established in previous submissions to the PBAC. Without such an analysis the PBAC is unable to recommend listing on the PBS.

- 6.60 The only nusinersen study presented by the resubmission that was used to inform the economic evaluation, was Maggi 2020. The responder rates from Maggi 2020 were used to calculate utility benefit of patients who were treated with nusinersen in the model. The resubmission stated that Maggi 2020 was used because, unlike Hagenacker 2020 (which was used in the economic evaluation in the November 2020 resubmission), it provided response rates for 6MWT, HFMSE, RULM by motor function status.
- 6.61 The natural history studies used in the naïve comparison were not relied upon by the resubmission in the economic model. Instead, results from one natural history study, Wadman 2017, were used to inform the progression of disease in patients treated with standard of care.
- 6.62 Wadman 2017 was a study of 200 patients with genetically confirmed SMA Type I to IV, with *SMN2* copy numbers varying from 1 to 5 copies. Wadman 2017 did not report on the treatments received by patients, but as patients were recruited between September 2010 and August 2014, likely predating nusinersen availability therefore it was unlikely that patients were treated with nusinersen which was approved in 2016. The age at symptom onset, motor milestones (sitting, standing, walking), respiratory support and other key events were reported for these patients, providing information on the progression of disease in SMA patients. It was excluded from the clinical evidence as it did not report HFMSE, RULM or 6MWT results (though it is noted that results for some of these patients may have been reported by Wadman 2018).
- 6.63 The resubmission excluded patients with SMA Type II from the economic analysis, arguing that Type II SMA made up only a small proportion of adult SMA patients in Maggi 2020 (13/116, 11%) and that Type IIIa patients were a suitable proxy for Type II patients. This may not be appropriate, particularly given that the requested restriction does not exclude patients with SMA Type II. While there may be some similarities between Type II and Type IIIa patients, there are numerous important differences such as life expectancy and degree of disability at any given age. As such, the progression and incremental benefit from treatment would differ. Further, both Hagenacker 2020 (45/124, 36%) and Duong 2021 (18/42, 42%) enrolled a much larger proportion of Type II patients compared to Maggi 2020. It was noted that Type II patients were included in the November 2020 resubmission.

- 6.64 The omission of Type II SMA patients likely favoured nusinersen and underestimates the true ICER across the whole cohort as patients with Type II SMA were likely to start treatment at a more disabled health state, which may limit the potential utility gain from treatment with nusinersen in the current model due to a floor effect. Maggi 2020 reported no significant differences ($P > 0.05$) for change from baseline in HFMSE or RULM and as such, it would have been unreasonable to have claimed any quality of life benefit based on HFMSE or RULM response rates in these patients based on the resubmission's nominated approach.
- 6.65 The ESC considered that the changes in structure from the previous model were generally appropriate and reflected availability of additional clinical evidence, however the changes also introduced additional sources of uncertainty.
- 6.66 As the resubmission proposed that the cost of [REDACTED] loading doses of nusinersen will be rebated, the economic model included only the cost of [REDACTED] loading doses of nusinersen.
- 6.67 The resubmission presented a cost-utility analysis. Table 14 provides a summary of the model structure and key inputs.

Table 14: Summary of model structure and rationale

Component	Summary
Time horizon	A lifetime time horizon was used in the model base case compared to 14 months follow up for Maggi 2020. Given the short duration of the nusinersen studies, the lifetime time horizon used in the model increased uncertainty of the results.
Outcomes	QALYs
Methods used to generate results	Markov model
Treatments	Nusinersen and continuation of standard of care versus standard of care alone
Medical condition of the population	100% SMA patients Type III. This is in contrast to Maggi (SMA Type III 11% (other), Type III sitters (44%), Type III walkers (45%)) and Wadman 2017 (SMA Type I (26%), Type II (30%), Type III (41%), Type IV (3%)).
Health states	A total of nine unique health states: A separate health state was created for on or off nusinersen treatment for the below health states (except for the Dead health state) - Walking/standing: unaided – starting state assumed 34.3% of patients in this health state - Walking/standing: aided – starting state assumed 24.5 % of patients in this health state - Non-ambulatory: able to sit – starting state assumed 33.2% of patients in this health state - Non-ambulatory: unable to sit – starting state assumed 8% of patients in this health state - Dead – starting state assumed 0% of patients in this health state The proportion of patients starting in each health state was based on the proportion of Type III SMA patients in each ambulatory state from Wadman 2017.
Cycle length	1 year
Transition probabilities	The transition probabilities were dependent on age, SMA subtype and current health state, and treatment status. In the base case, a weighted proportion of each SMA subtype was assumed (50% Type IIIa, 35% Type IIIb with onset <12 years and 15% Type IIIb with onset >12 years) and this weighting was used to create one single survival curve for all patients to inform transition probabilities. The transition probabilities were calculated for each of the possible health state transitions in the

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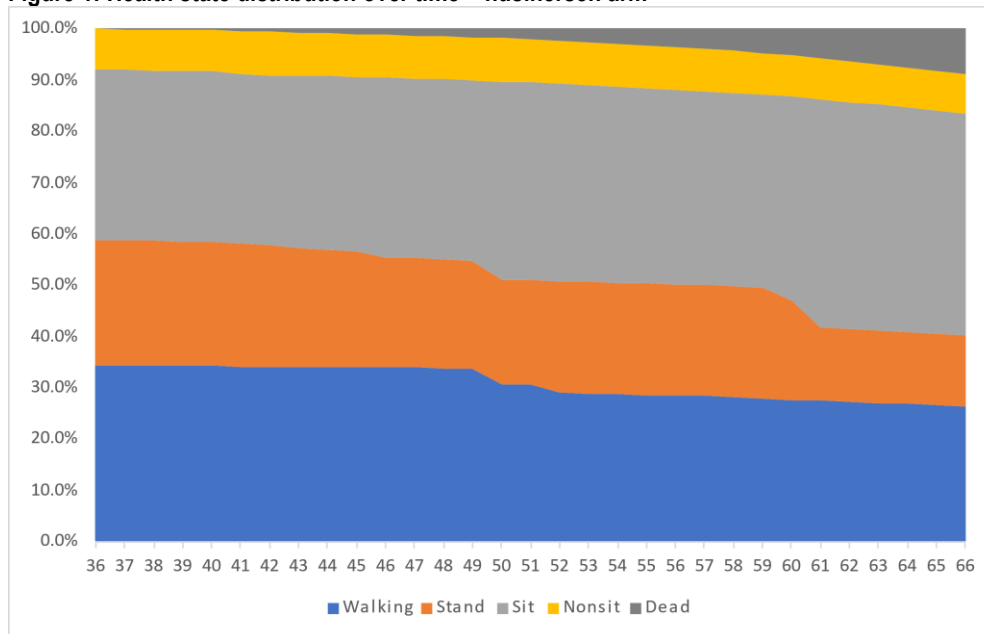
Component	Summary																																									
	model using the health state survival curves from Wadman 2017. The Markov model is structured such that patients can only move down through a single health state at a time. An annual discontinuation rate of 3.7% was applied in the model to account for nusinersen patients ceasing treatment. This figure used is subject to considerable uncertainty. Mortality was assumed to be the same for nusinersen and standard of care patients which was considered reasonable. The model assumed that, while treated with nusinersen, patients would not decline into a less functional alive health state. While the resubmission claimed that this assumption was supported by the continuation rule proposed in this resubmission, this was previously considered unreasonable by ESC as data presented from Hagenacker 2020 and Walter 2019 indicated that some nusinersen treated patients experience a decline in motor function while receiving nusinersen treatment (Table 9, nusinersen PSD, November 2020).																																									
Extrapolation method	The economic model extrapolated the survival curves from Wadman 2017 using the average annual probability of an event of the five years of the available data, resulting in zero or exceedingly small probabilities of progression through the health states after the end of the Wadman data (50 to 80 years depending on health state and type). This methodology was likely to be conservative but generally reflective of changes in the small patient numbers reported by Wadman 2017 and is unlikely to have substantial impact on the ICER.																																									
Utilities	Two types of utilities were included. Firstly, the utility of a particular health state was informed by Belter 2020, and secondly, patients treated with nusinersen were assumed to have a utility benefit from being on treatment which was informed by the responder rates from Maggi 2020 (Table 12). The resubmission considered Belter 2020 to be a more appropriate source of utility values than used in the November 2020 resubmission (Lloyd 2019), as they were collected directly from SMA Type III patients, in line with the patient population and were categorised by patient motor function, in line with the modelled health states. The ESC noted that the utility values used in the resubmission were more conservative than those in the November 2020 submission because the increments between health states were smaller, however the addition of the treatment specific utility increment was less conservative than the November 2020 submission.																																									
	<table><tr><th rowspan="2">Health state</th><th colspan="3">Utility application in current resubmission</th><th colspan="3">Utility application in previous resubmission (Nov 2020)</th></tr><tr><th>SOC</th><th>NUSI</th><th>Increment</th><th>SOC</th><th>NUSI</th><th>Increment</th></tr><tr><td>Walking/standing: unaided</td><td>0.64</td><td>0.6817</td><td>0.0417</td><td>0.72</td><td>0.7221</td><td>0.021</td></tr><tr><td>Walking/standing: aided</td><td>0.35</td><td>0.4214</td><td>0.0714</td><td>0.39</td><td>0.411</td><td>0.021</td></tr><tr><td>Non-ambulatory: able to sit</td><td>0.23</td><td>0.3014</td><td>0.0714</td><td>-0.04</td><td>-0.019</td><td>0.021</td></tr><tr><td>Non-ambulatory: unable to sit</td><td>0.14</td><td>0.2114</td><td>0.0714</td><td>-0.12</td><td>-0.099</td><td>0.021</td></tr></table>	Health state	Utility application in current resubmission			Utility application in previous resubmission (Nov 2020)			SOC	NUSI	Increment	SOC	NUSI	Increment	Walking/standing: unaided	0.64	0.6817	0.0417	0.72	0.7221	0.021	Walking/standing: aided	0.35	0.4214	0.0714	0.39	0.411	0.021	Non-ambulatory: able to sit	0.23	0.3014	0.0714	-0.04	-0.019	0.021	Non-ambulatory: unable to sit	0.14	0.2114	0.0714	-0.12	-0.099	0.021
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	Walking/standing: aided	0.35	0.4214	0.0714	0.39	0.411	0.021																																			
	Non-ambulatory: able to sit	0.23	0.3014	0.0714	-0.04	-0.019	0.021																																			
Non-ambulatory: unable to sit	0.14	0.2114	0.0714	-0.12	-0.099	0.021																																				
SOC = standard of care, NUSI = nusinersen																																										
Source: Table 3.20, p354 of the resubmission, table 9, p21-22 and paragraph 6.70, p25 nusinersen PSD November 2020.																																										
The use of response rates from Maggi 2020 to inform utility benefits with nusinersen, as well as the derivation method, may not be appropriate. The ESC considered that this methodology resulted in some level of double counting of utility gains for the nusinersen treatment arm as some of the assumed utility gain from being a responder would be captured by the individual health state utility. There were no disutilities applied for adverse events in the model, though a disutility for adverse events associated with the lumbar puncture procedure may have been warranted.																																										
Disease state costs	Based on Klug 2016, as for previous resubmission. It was not apparent that the resubmission's application of disease state costs from Klug 2016 would be applicable to the nominated health states, particularly for the assumption that non-ambulatory: unable to sit patients would have the same health state costs as Type I SMA patients in Klug 2016.																																									

Component	Summary
Other nusinersen related costs	Costs for administration and adverse events were based on MBS item costs. As with the November 2020 resubmission, there was no allowance made for monitoring for renal toxicity or thrombocytopenia and there was no allowance made for the cost of an SMN1 gene test, which may not have been appropriate.

Source: Compiled during the evaluation from Section 3 of the resubmission.

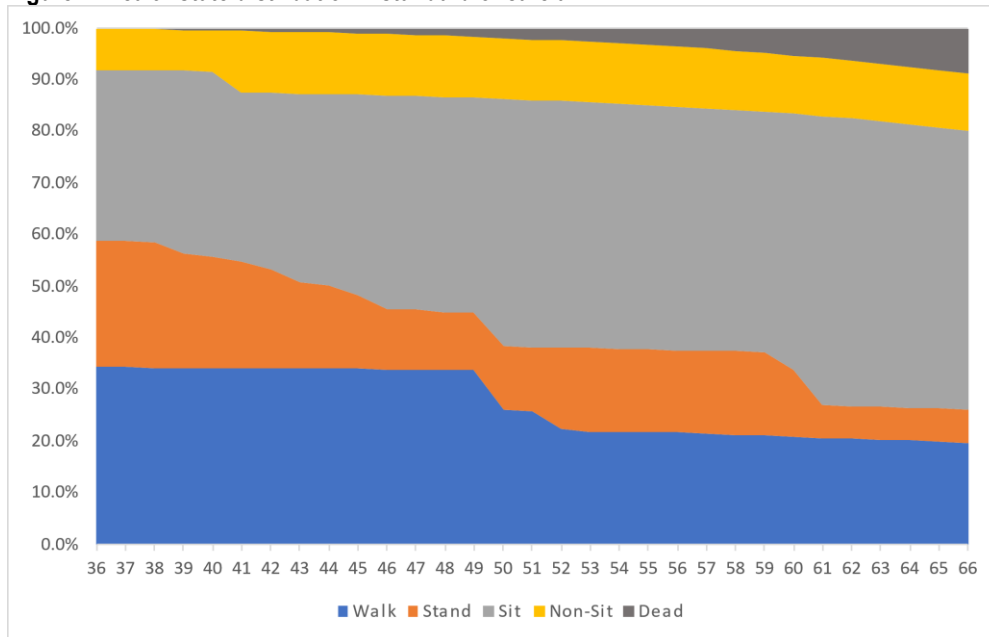
6.68 The health state distributions for patients treated with nusinersen and standard of care are presented in Figure 1 and Figure 2, respectively. Patients remaining on treatment with nusinersen were assumed to not progress. However a 3.7% discontinuation rate was applied in the economic model (derived from the proportion of patients who withdrew from nusinersen treatment in the study reported by Hagenacker 2020), and the patients who discontinue treatment were assumed to progress according to the standard of care probabilities.

Figure 1: Health state distribution over time – nusinersen arm



Source: Figure 3.26, p369 of the resubmission

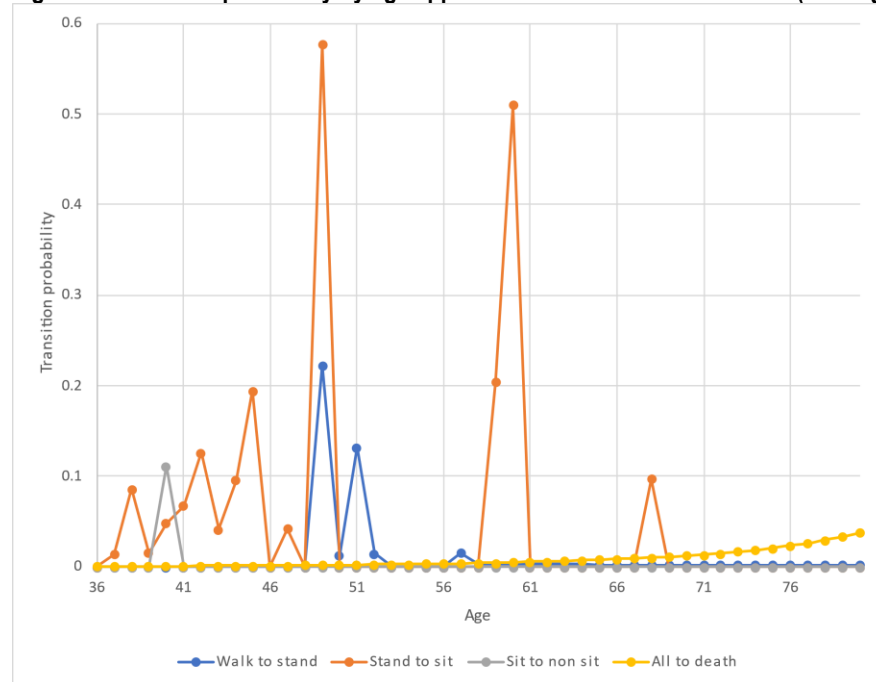
Figure 2: Health state distribution – standard of care arm



Source: Figure 3.27, p369 of the resubmission

- 6.69 As the model applies the specific transitions from Wadman 2017 based on the age of the patient rather than an estimated annualised progression, some rapid changes were observed in the health state distributions, for example, at age 49 of the nusinersen population and at ages 40, 45 and 49 of the standard of care population. These sudden decreases in survival depict disease progression as observed by Wadman 2017. This effect can be more clearly seen when the transition probabilities are graphed by age (Figure 3) with significant spikes at certain ages that reflect the small number of patients in the trial and may not have biological plausibility. It would have been more reasonable to adjust these functions using an annualised rate of decline, or progression being dependent on time spent in a health state, rather than applying the observed results directly. However, the ESC considered that the impact on the ICER of doing so is likely to be modest.

Figure 3: Transition probability by age applied in model to standard of care (from age 36)



Source: Generated during commentary evaluation from model data

6.70 Key drivers of the model are presented in Table 15.

Table 15: Key drivers of the model

Description	Method/Value	Impact
Utility benefit from nusinersen treatment	In addition to utilities applied due to the health state of a given patient, a utility benefit was also applied for patients who were classified as being responders to nusinersen. This led to a potential double counting of utility gains for the nusinersen treatment arm as some of the assumed utility gain from being a responder would have been captured by the individual health state utility. It was also noted that the utility benefit from nusinersen treatment accounted for 63% of the total incremental QALY gain with nusinersen in the base case of the economic model.	High, favours nusinersen. When the utility benefit attributed to nusinersen treatment was removed, the ICER increased by 169%.
Time horizon	A base case of a lifetime time horizon was used. While the time horizon was likely reasonable given the treatment and disease, the lifetime time horizon increased the uncertainty given the limited duration of available clinical data. Use of a shorter time horizons significantly increased the ICER, suggesting that any incremental benefit of nusinersen is dependent on continued use and the assumption of continued efficacy for patients remaining on treatment over the patient's lifetime, as well as the resubmission's assumed rate of progression for standard of care patients.	High, favours nusinersen. When the time horizon was varied to 5, 10 and 20 years, the ICER increased by 71%, 50% and 23%, respectively
Responder rates from Maggi 2020	The responder rates from Maggi 2020 were used to define responders to nusinersen in the resubmission. As discussed in paragraph 6.39, the method of calculation likely biased the results in favour of nusinersen. An ITT approach may have been more appropriate. The ESC noted that without application of utility benefit from nusinersen treatment, responder rates had no impact on the model.	High, favours nusinersen. When an ITT approach was used the ICER increased by 60%.
Assumption of nusinersen efficacy	In the base case, the relative risk of progression for nusinersen was assumed to be 0 (i.e. no progression). This was not supported by the clinical data.	Moderate, favours nusinersen. Assuming a relative risk of 0.5 increases ICER by 26%.

Source: Compiled during the evaluation from Section 3 of the resubmission and calculations undertaken during the evaluation.

6.71 There were significant issues with the application of responder rates from Maggi 2020 to estimate utility benefits associated with nusinersen treatment:

- As discussed in paragraph 6.45, the resubmission's basis for using RULM and HFMSE responder rates to estimate a utility benefit from treatment with nusinersen beyond the arrestment of disease progression may not be justified as there may not be a correlation between RULM and HFMSE and QoL;
- As discussed in paragraph 6.39, the calculation of HFMSE, RULM and 6MWT responder rates by Maggi 2020 was inappropriate as the proportion of responders was based on a patient population that was decreasing in size over time. Using an ITT approach for responder calculations in Maggi 2020 (e.g. 13/116 [11%] response for HFMSE at 14 months instead of 13/27 [48%]) increased the ICER by 60%; and
- This hierarchical approach of applying utility, where utility gains are first applied to patients responding to RULM, then to 6MWT and then to HFMSE (with no patient being awarded a utility gain for more than one measure) likely favoured nusinersen, as the utility gain for a RULM responder was assumed to be 0.12 compared to just 0.03 for a HFMSE responder. If HFMSE response, which had the highest proportion of responders among all three outcomes in Maggi 2020, was given priority and

accounted for first in the 'sitters' population, the ICER increased by 24%.

- It was also likely that there was some degree of double counting as both health state and treatment responder based utilities were included for the nusinersen treatment arm. The ESC noted that health state utility scores were based on the HUI3 instrument (from Belter et al 2020), which includes ambulation and dexterity dimensions which would overlap with the HFMSE and 6MWT measures. However, the ESC also noted that motor outcomes captured with the HFMSE and RULM measures do not necessarily capture QoL benefits for all patients, particularly for patients with more advanced disease at treatment initiation. The ESC and PBAC have previously noted the economic model does not capture changes in fine motor function, which can be important to patients with SMA (paragraph 6.64, nusinersen PSD November 2020). The ESC noted that 37% of QALY gains in the model resulted from health state differences in the model, with the remaining 63% based on the treatment-specific increment in utility. The ESC considered that even if some level of additional utility was not captured in the motor outcomes, the extent of this adjustment in the resubmission model appeared to be implausibly high. The PSCR acknowledged that quantifying utility gains is difficult and they are subject to uncertainty, but were based on reasonable evidence-based estimates where possible. The pre-PBAC response contended that the four-health state structure of the economic model is very broad and only captures changes in gross motor skills and as such, rather than double counting utility gains, the utility gain applied to nusinersen responders is a means of counting the utility gains the four-health state structure of the model otherwise did not capture. The pre-PBAC response considered the model is more likely to underestimate rather than overestimate the benefit of nusinersen to adult patients. The PBAC considered that the utility benefit associated with nusinersen treatment was a major source of uncertainty in the economic model.

6.72 Table 16 provides a summary of the results of the stepped economic evaluation.

Table 16: Results of the stepped economic evaluation of nusinersen versus standard of care in adults with SMA

Treatment arm	Nusinersen	Standard of care	Difference
Trial-based analysis, cost per patient responding to nusinersen on any measure of 6MWT, RULM or HFMSE			
Cost	\$ [redacted]	\$0	\$ [redacted]
Responders	69%	0%	69%
Incremental cost per responder ^a			\$ [redacted] ¹
Extrapolate over patient lifetime			
Cost	\$ [redacted]	\$0	\$ [redacted]
QALYs	7.0053	6.4349	0.5704
Incremental cost per QALY			\$ [redacted] ²
Apply a reduction in the rate of progression through the health states applicable to nusinersen treatment			
Cost	\$ [redacted]	\$0	\$ [redacted]
QALYs	7.5227	6.4349	1.0878
Incremental cost per QALY			\$ [redacted] ²
Incorporate SMA related healthcare (health state) cost			
Cost	\$ [redacted]	\$186,283	\$ [redacted]
QALYs	7.5227	6.4349	1.0878
Incremental cost per QALY			\$ [redacted] ²

6MWT= six minute walking test; HFMSE=Hammersmith Functional Motor Scale Extended; QALY=quality adjusted life year; RULM=revised upper limb module

Source: Table 3.41, p375 of the resubmission

^a Responder defined as a patient who reported an improvement from baseline by one or more of: ≥ 3 points in HFMSE, ≥ 2 points in RULM and/or ≥ 30 m in 6MWT.

The redacted values correspond to the following ranges:

¹ \$355,000 to < \$455,000

² > \$1,055,000

6.73 The base case ICER was estimated by the model to be > \$1,055,000 per QALY. This was likely underestimated as:

- The utility benefit for nusinersen, based on the proportion of responders to the HFMSE, RULM and 6MWT were as reported by Maggi may be inappropriate and likely overestimated (as discussed in paragraph 6.71); and
- The transition probabilities were based on numerous assumptions which favoured nusinersen. This includes the assumption that patients on nusinersen cannot progress to lower health states and the extrapolation of the assumed clinical benefit over a patient's lifetime, while only short-term (up to 14 months) non-comparative data was available. The PSCR argued that the economic model does allow for patients not responding to treatment with nusinersen to discontinue (at a rate of 3.7% per year), at which point they may progress to lower health states. However, the ESC reiterated its previous view that it may not be appropriate to assume no patients would progress to lower health states while receiving ongoing treatment with nusinersen.

6.74 Even if all the favourable assumptions proposed by the resubmission were included, the base case ICER was unlikely to be cost effective, even when compared to the paediatric population. A substantial further price reduction for nusinersen in adult SMA patients will be required in order to achieve an ICER similar to that accepted for the paediatric SMA population. For context, in March 2018, the PBAC noted that the

cost per QALY gained for paediatric patients with Type II/IIIa SMA was \$355,000 to < \$455,000/QALY based on a health care perspective, though at that time the PBAC advised that further negotiations with the sponsor were required to address these uncertainties through a combination of mechanisms including a reduction in price, increased rebates or lower financial caps (Para 6.1 nusinersen PSD, November 2018 PBAC meeting). The PSCR considered that this comparison was fraught because the proposed population (adults with SMA) are in large part a direct subgroup of the original population, and the ICER of \$355,000 to < \$455,000 already implicitly incorporates the high ICER (> \$1,055,000) into the long-term of treatment. The ESC noted there is no overlap in the patients currently eligible for nusinersen (type I, II and IIIa patients who commence treatment prior to 19 years of age) and the proposed patient population in the current submission (type II, IIIa and IIIb patients who commence treatment after 19 years of age). Thus, the proposed population is not a subgroup of the population for which the PBAC previously considered nusinersen would be cost-effective.

6.75 The results of the univariate sensitivity analyses conducted by the resubmission and during the evaluation of the economic model are shown in Table 17.

Table 17: Key univariate sensitivity analyses

Scenario	Incremental costs	Incremental QALYs	ICER	Change from base case
Base case	\$ [REDACTED]	1.0878	\$ [REDACTED] ¹	-
Time horizon (base case: lifetime)				
5	\$ [REDACTED]	0.2562	\$ [REDACTED] ¹	+71%
10	\$ [REDACTED]	0.4537	\$ [REDACTED] ¹	+50%
20	\$ [REDACTED]	0.7555	\$ [REDACTED] ¹	+23%
30	\$ [REDACTED]	0.9397	\$ [REDACTED] ¹	+10%
Progression relative ratio, Nusinersen versus SoC (base case: RR=0, i.e., no progression on treatment)				
RR=0.1	\$ [REDACTED]	1.0203	\$ [REDACTED] ¹	+5%
RR=0.25	\$ [REDACTED]	0.9273	\$ [REDACTED] ¹	+12%
RR=0.5	\$ [REDACTED]	0.7908	\$ [REDACTED] ¹	+26%
RR=1.0	\$ [REDACTED]	0.5704	\$ [REDACTED] ¹	+64%
Treatment utility benefit (base case: walkers=0.0417, others=0.0714)				
Walkers=0.0834, others=0.1428	\$ [REDACTED]	1.7711	\$ [REDACTED] ¹	-39%
Walkers=0.0209, others=0.0357	\$ [REDACTED]	0.7462	\$ [REDACTED] ¹	+46%
Zero	\$ [REDACTED]	0.4045	\$ [REDACTED] ¹	+169%
Walkers = 0.0417, others = 0.0426 ^a	\$ [REDACTED]	0.08767	\$ [REDACTED] ¹	+24%
Response rates for HSFME, RULM and 6MWT (base case: percentages as reported by Maggi 2020)				
Responder rates using figures from Maggi 2020 using total number of patients as denominator	\$ [REDACTED]	0.6792	\$ [REDACTED] ¹	+60%
Price reduction required to achieve target ICER (base case nusinersen per dose \$ [REDACTED])				
ICER \$ [REDACTED] ² /QALY (same as paediatric Type II/IIIa) ^b – Cost per nusinersen dose \$ [REDACTED]	\$ [REDACTED]	1.0878	\$ [REDACTED] ²	-80%

6MWT = six minute walk test HFMSE = Hammersmith Functional Motor Scale-Expanded; ICER=incremental cost-effectiveness ratio; QALYs=quality adjusted life years; RR=relative risk, RULM = revised upper limb module

Values in *italics* were additional analyses conducted during the evaluation.

^a estimated by calculating responder from HFMSE (58%) first, then assuming remaining 21% of responder were RULM responder rather than the reverse

^b It should be noted that while the nusinersen submission for paediatric patients with Type II/IIIa SMA was previously recommended by the PBAC and presented an ICER of \$ [REDACTED]²/QALY, the PBAC did not accept that this ICER alone demonstrated acceptable cost-effectiveness

of nusinersen for this patient population. "... the PBAC did not accept the proposed price for all SMA types and advised that a price reduction accounting for utilisation in Type II/IIIa patients would be appropriate. The PBAC advised that a combination of reduction in price, increased rebates or lower financial caps, is necessary to achieve a cost-effective listing." (paragraph 6.11, p26 nusinersen PSD, March 2018).

Source: Table 3.53, p385 of the resubmission

The redacted values correspond to the following ranges:

¹ > \$1,055,000

² \$355,000 to < \$455,000

- 6.76 A scenario in which the price of nusinersen was reduced to \$ [REDACTED] (a further 79.5% reduction from the proposed price of \$ [REDACTED]) brought the ICER down to \$355,000 to < \$455,000/QALY, which was consistent with the ICER accepted by the PBAC for the treatment of paediatric patients with Type II and IIIa SMA with nusinersen (Table 6, p18 nusinersen PSD March 2018). The ESC noted that this was a univariate sensitivity analysis and that the assumptions and inputs which lead to an underestimated ICER in the base case would apply, and therefore even at that reduced price, the true ICER would likely exceed that of paediatric Type II and IIIa patients by a sizeable amount (e.g. removal of additional utility from nusinersen treatment based on Maggi 2020 would increase the ICER by 169%).

Drug cost/patient/year

- 6.77 The drug cost per patient for the first year of treatment, including four loading doses ([REDACTED] rebated by the sponsor) and two maintenance doses, was \$ [REDACTED]. The cost per year for nusinersen maintenance was \$ [REDACTED], based on \$ [REDACTED] per dose and three maintenance doses per year. The rebate for [REDACTED] of the four loading doses were included in both the economic evaluation and the financial estimates.

Table 18: Drug cost per patient for proposed drug

	Study dose and duration	Economic Model	Financial estimates
Mean dose	12 mg	12 mg	12 mg
Cost/patient/dose	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Mean duration	~14 months	Lifetime	Lifetime

Estimated PBS usage & financial implications

- 6.78 DUSC did not consider this resubmission. This resubmission used an epidemiological approach based on the same international estimates of prevalence of SMA in patients aged over 18 years that were used for this patient population in the November 2020 and November 2017 PBAC submission for nusinersen.
- 6.79 The estimated financial impact of listing nusinersen on the PBS for the treatment of adult SMA patients with symptom onset before 19 years of age is summarised in Table 19.

Table 19: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimation of use and financial impact of the proposed medicine (PBS and RPBS)						
Prevalent patient population						
Type I	1					
Type II	1					
Type III	1					
Total	1					
Initiators per year ^a						
Type II	1	1	1	1	1	1
Type III	1	1	1	1	1	1
Total	1	1	1	1	1	1
Total patients ^a						
Type II	1	1	1	1	1	1
Type III	1	1	1	1	1	1
Total	1	1	1	1	1	1
Vials/administrations of nusinersen (excluding one free initiation dose received) ^a						
Type II	1	1	1	1	1	1
Type III	1	1	1	1	1	1
Total	1	1	1	1	1	1
Vials/administrations of nusinersen (all doses, including one free initiation dose received) ^a						
Type II	1	1	1	1	1	1
Type III	1	1	1	1	1	1
Total	1	1	1	1	1	1
PBS/RPBS cost less co-pay (eff)						
Type II	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2
Type III	\$ 3	\$ 3	\$ 3	\$ 3	\$ 3	\$ 3
Total	\$ 3	\$ 3	\$ 3	\$ 3	\$ 4	\$ 4
Estimation of changes in use and financial impact of other medicines (PBS and RPBS)						
The resubmission <i>appropriately</i> assumed no therapies were expected to be substituted. This was consistent with the previous November 2020 submission.						
Estimated financial implications for the PBS/RPBS						
Net cost to PBS/RPBS (pub)	\$ 5	\$ 4	\$ 5	\$ 5	\$ 6	\$ 6
Net cost to PBS/RPBS (eff)	\$ 3	\$ 3	\$ 3	\$ 3	\$ 4	\$ 4
Estimated financial implications for the health budget						
MBS administration costs						
Type II	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2
Type III	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2
Total	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2
Adverse events costs						
Type II	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2
Type III	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2
Total	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2
Net cost to Government health budget						
Type II	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2
Type III	\$ 3	\$ 3	\$ 3	\$ 3	\$ 3	\$ 3
Total	\$ 3	\$ 3	\$ 3	\$ 3	\$ 4	\$ 4

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	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
November 2020 submission: Net cost to Government health budget						
Type II	\$ [redacted] ²	\$ [redacted] ²	\$ [redacted] ²	\$ [redacted] ²	\$ [redacted] ²	\$ [redacted] ²
Type III	\$ [redacted] ³	\$ [redacted] ³	\$ [redacted] ³	\$ [redacted] ³	\$ [redacted] ³	\$ [redacted] ⁴
Total	\$ [redacted] ³	\$ [redacted] ³	\$ [redacted] ³	\$ [redacted] ⁴	\$ [redacted] ⁴	\$ [redacted] ⁴

Source: Table 4.3, 4.4, 4.6, p390, 391, 393 of the resubmission and sheet '3a. Scripts – proposed' and '3b. Impact – proposed (pub)' of the financial model workbook.

^aFigures rounded to the nearest whole number. Total figures for Type II + Type III may not add up due to rounding.

Eff = effective; pub = published

The redacted values correspond to the following ranges:

¹ < 500

² \$0 to < \$10 million

³ \$10 million to < \$20 million

⁴ \$20 million to < \$30 million

⁵ \$30 million to < \$40 million

⁶ \$40 million to < \$50 million

6.80 The estimated net cost to the government budget of listing nusinersen on the PBS/RPBS for adult SMA patients with symptom onset before 19 years of age at the proposed effective price was \$10 million to < \$20 million in Year 1, increasing to \$20 million to < \$30 million in Year 6. The total cost over the six year forward estimates was \$100 million to < \$200 million.

6.81 The following points were noted regarding the resubmission's financial model:

- The estimated prevalent population used remained unchanged from the estimates used in the November 2020 and November 2017 submission. The PBAC previously concluded that the prevalent patient population with SMA Types I to III was likely to have been underestimated, particularly for the number of patients over the age of 18 years (Nusinersen PSD, PBAC meeting November 2017, para 7.4);
- Incident patients who would have been covered by this listing when they become eligible (i.e. those with symptom onset between ≥3 years and <19 years, and become over 18 years of age) were not considered in the financial model. Therefore, the number of patients treated with nusinersen may be underestimated.
- The uptake rates of 20% in Year 1, increasing by 5% per year so that 45% of the total prevalent pool would be on treatment with nusinersen by Year 6 of listing, may have been underestimated considering there were no other disease modifying drugs for SMA PBS listed for the proposed population. The resubmission stated that the potential future availability of risdiplam for treatment of adults with SMA was reflected in the uptake rates, although this impact was not quantified, and given that risdiplam is not currently listed for treatment in adult patients with SMA, this may not have been appropriate. For comparison, the uptake rates in paediatric patients were assumed to be 100% and 80% in type II and III SMA, respectively. The PSCR reiterated that some adults may not be considered suitable for intrathecal

administration due to spinal access issues and some adult patients with stable disease may decide against treatment based on their assessment of potential risks and benefits (as per Osmanovic (2020) up to 50% of patients did immediately opt for treatment). The ESC noted the uptake rates appear inconsistent with the large benefit that is required in order for nusinersen to be cost-effective at the price proposed in the submission. The ESC noted that uptake rates in the nusinersen access program may help inform likely uptake rates, though uptake would also be impacted by access programs for risdiplam;

- Patient copayments were not considered in the financial model; however, this was not expected to have a large impact on the financial estimates; and
- While the resubmission estimated that there would be some cost savings associated with keeping more adult patients in higher states of motor function while on nusinersen compared to standard of care in the economic model, this was not considered in the financial estimates. This omission however was not expected to have a large impact on the financial estimates, as the cost difference for health state management (\$17,633 over a patient's lifetime as estimated by the model) was magnitudes lower than the cost of nusinersen.

6.82 Overall, the financial estimates were underestimated as it was likely that the number of eligible patients (a key driver of the financial estimates) may be underestimated. The ESC considered that significant uncertainty around the patient estimates remained due to uncertainty regarding the likely age of patients and the proportion of patients with Type IIIa and IIIb SMA, noting that uptake would vary depending on the relative proportions of cohorts eligible for treatment. The ESC also noted that there was potentially a significant difference in age between patients in the trials and Australian patients (mean 36 years (n=139) in Hagenacker 2020, compared with 45 years (n=181) in the SMA Australia member database). The pre-PBAC response suggested that the uptake and discontinuation rates from the Biogen Free of Charge program for adults could be used in the financial estimates, as it is designed to enrol patients with Type IIIa and IIIb SMA, and that the eligibility criteria used for the program is aligned with the proposed PBS criteria.

6.83 Compared to the most recent submission, November 2020 PBAC meeting, the financial estimates of this resubmission were lower, noting:

- The requested restriction for this resubmission was narrower than the previous submission, although the financial estimates of the previous submission did not consider the use in non-adult patients (aged 18 years or less) who had symptoms of SMA at 3 years of age or more and was limited to the predicted use of nusinersen for the requested listing of adult patients (aged 19 years or more) with SMA on the PBS;

- This resubmission included a discontinuation rate (3.7% per annum, derived from the proportion of patients who withdrew from treatment in Hagenacker 2020) which was not considered in the previous submission;
- This resubmission used a reduced requested price of nusinersen (\$ [REDACTED] vs. \$ [REDACTED] per vial); and
- MBS costs were slightly higher in this resubmission due to increased fees.

Financial Management – Risk Sharing Arrangements

- 6.84 The resubmission proposed a separate Risk Sharing Arrangement (RSA) specifically for adults, independent of the existing RSA for nusinersen in the paediatric setting. This differed from the November 2020 submission which proposed that an amendment be made to the existing Deed of Agreement that exists for nusinersen with the Commonwealth (2018).
- 6.85 There are two elements to the proposed Deed of Agreement with the Commonwealth for nusinersen in the treatment of adults with SMA:
- An additional rebate, specific to adults initiating therapy, requiring a Special Pricing Arrangement (SPA). This reduces the effective price for the adult population by [REDACTED]% (to \$ [REDACTED] per vial) plus [REDACTED] on initiation of treatment. This differed from the November 2020 submission where an additional rebate of [REDACTED]% was proposed plus [REDACTED] on initiation of treatment.
 - Management of uncertainty, with a proposal for an adult-specific expenditure cap.
- 6.86 The [REDACTED] was applied in the economic and financial analysis presented by the resubmission (i.e. the economic model and financial estimates were based on patients requiring [REDACTED], loading doses) and was proposed to be achieved by tracking initiating patients, as occurs for the existing listing.
- 6.87 The PSCR indicated that the Sponsor is willing to work with the PBAC and Department of Health to develop a framework for collecting real-world data for nusinersen in adults via the Australian SMA Registry to provide further confidence in the magnitude and durability of clinical benefit of nusinersen treatment in adults with SMA in the Australian setting. The PSCR stated that this registry has started collecting important medical information on individuals with SMA in Australia. The ESC requested that the sponsor provide an update regarding the number of adult patients currently included in the Australian SMA registry in its pre-PBAC response. The ESC advised that further input is required to determine which outcomes would capture the most meaningful changes for this heterogeneous group of patients, for inclusion in any Pay for Performance or Managed Access Program for nusinersen in the adult population. The pre-PBAC response stated there were currently 55 adult patients participating in the

Australian SMA registry. The pre-PBAC response indicated the sponsor is willing to work with the PBAC and the adult SMA clinical community to identify the outcomes which would capture the most clinically meaningful changes in adults for inclusion in the Australian SMA Registry. The pre-PBAC response noted that if an outcome-based approach is adopted, an appropriate stopping criteria aligned with clinical expert advice will be required to ensure adult patients could only continue nusinersen treatment if they are benefitting from treatment or do not experience a clinically significant decline resulting in loss of function.

- 6.88 The PBAC noted that the pre-PBAC response suggested that the cost of funding paediatric Type IIIb patients could be included in the existing RSA for nusinersen in symptomatic paediatric patients with Type I, II and IIIa SMA. The PBAC agreed with the pre-PBAC response that the size of the eligible paediatric Type IIIb population is likely to be small.

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

7 PBAC Outcome

Adult SMA Population

- 7.1 The PBAC did not recommend extending the listing of nusinersen to include the treatment of spinal muscular atrophy (SMA) in patients with symptom onset prior to 19 years of age, and removal of the age limit of 18 years for initiation of treatment. The PBAC recognised the clinical need for effective treatments for adult SMA. However, the PBAC considered that the adult population most likely to benefit from treatment with nusinersen remained inadequately defined in the resubmission. The PBAC noted that the magnitude and durability of the treatment benefit remained uncertain and considered that the ICER was exceptionally high at the price proposed. The PBAC advised that a substantial price reduction commensurate with the benefit of treatment in adult SMA patients, a Risk Sharing Arrangement (RSA), and a Managed Access Program (MAP) which accounts for the number of patients treated and the number of patients who respond to treatment, would be required to achieve a cost-effective listing for adult SMA patients.
- 7.2 The PBAC noted that nusinersen is a novel medicine and acknowledged there was a high demand for treatments to be made available to adult SMA patients. The PBAC noted the consumer comments indicated that slowing disease progression and even small improvements in functioning were valued by adult SMA patients as these outcomes may allow patients to continue employment and maintain independence. The PBAC noted the condition is substantially debilitating and there are no PBS subsidised therapies available.
- 7.3 The PBAC noted that as per the previous submission, the resubmission was based on a naïve comparison of nusinersen studies with natural history studies of SMA patients for outcomes of HFMSE, RULM and 6MWT. The PBAC noted the data for nusinersen

included eight real world studies consisting of 317 adults in total and data pooled from three European SMA registries in 252 adults, of which a subset (75 patients) reported results before and after initiation of nusinersen. The PBAC noted that although the body of clinical evidence for nusinersen in adult SMA patients was substantially increased compared to the previous submission, the duration of follow-up did not substantially differ to the included studies in the previous submission.

- 7.4 The PBAC also noted that recent publications for nusinersen suggest that commonly used SMA outcomes such as the HFMSE and RULM are not meaningful for more severely affected individuals. The PBAC noted the ESC's advice that, in addition to gross motor outcomes, outcomes such as lung function, hand motor function and grip strength, fatigue, stability, and endurance in activities of daily living may be more sensitive measures for quantification of treatment benefit and disease stabilisation in adults with SMA.
- 7.5 The PBAC considered that nusinersen provides a minor added benefit, versus standard of care for adult patients with Type II and III SMA, which is clinically relevant. However, the PBAC considered that, there was a low level of confidence in the clinical data in terms of identifying the patients most likely to benefit from treatment, the magnitude of the incremental benefit and durability of benefit. The PBAC considered that these factors remained uncertain and could not be determined from the available data. The PBAC noted there was heterogeneity within and across the nusinersen studies with respect to patient age, ambulation status, degree of disease progression and the extent of function at baseline. The PBAC considered that the naïve comparison with natural history studies indicated that treatment with nusinersen was associated with some improvement in outcomes however, the PBAC noted there was variability in the reported results within and between studies, particularly for the 6MWT outcome.
- 7.6 The PBAC acknowledged that given the rarity of the condition in adults, randomised comparative data would unlikely be forthcoming and that the uncertainty around the magnitude of benefit with nusinersen may need to be managed through other measures.
- 7.7 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data, reiterating its previous consideration that there may be long term implications from repeated lumbar puncture administrations.
- 7.8 The revised economic evaluation presented in the resubmission was based on adults with Type III SMA only and used responder rates from Maggi 2020 to calculate the utility benefit of patients who were treated with nusinersen. Results from one natural history study, Wadman 2017, were used to inform the progression of disease in patients treated with standard of care. The PBAC noted that the changes to the economic model compared with the previous submission reflected the availability of additional clinical evidence, however also noted the changes introduced additional sources of uncertainty. The PBAC considered that the level of confidence in the modelled benefits and the ICER was low, and the ICER was likely underestimated due

to patients treated with nusinersen not being able to progress to lower health states while on treatment and a utility benefit being applied to both nusinersen treatment as well as response. The PBAC further noted the assumption of continued benefit for patients remaining on nusinersen over a lifetime time horizon was considerably uncertain given the available study data had only around 14 months follow-up.

- 7.9 The PBAC noted that while the base case ICER of > \$1,055,000/QALY was substantially lower than that in the previous submission (> \$1,055,000/QALY), it was still considerably higher than the March 2018 indicative ICER of \$355,000 to < \$455,000 estimated for patients with Type II/IIIa SMA (at the time, this ICER was considered uncertain and the PBAC advised that a price reduction would be appropriate). The PBAC considered that to account for the relative benefits across the two populations the ICER for the adult population needs to be consistent with that for the listed (paediatric) population.
- 7.10 The PBAC considered that given the limited clinical data available for nusinersen in adult patients, any economic analysis for this patient population will be associated with substantial uncertainty. As such, the PBAC advised that a substantial price reduction in combination with a MAP would be required to address the uncertainty around the magnitude and duration of clinical benefit associated with nusinersen treatment and achieve a cost-effective listing in adult patients. The PBAC considered that the price reduction should reflect the benefit of treatment in adult patients relative to that for paediatric patients.
- 7.11 The PBAC considered that the MAP should collect data through the Australian SMA Registry and include SMA type, treatment outcomes and number of patients treated. The PBAC advised that the sponsor should consider the following in relation to a MAP proposal:
- Alignment of the MAP criteria with consensus treatment guidelines for adults with SMA.
 - Which outcomes would likely capture the most meaningful changes across the whole population of adult SMA patients in terms of reversal of decline, improvement of motor function and/or preventing/slowing of disease progression? Consideration should also be given to which outcomes would be practical to collect in the clinical setting (e.g. clear functional assessments and guidelines including fine motor skills, endurance, speech and swallowing).
 - The criteria for discontinuing treatment (e.g. worsening of motor function, inability to continue with administration of injections).
 - The timing of the patient assessment schedule (e.g. aligned with clinical visits for nusinersen dosing).
 - The proposed timelines for review. The PBAC considered that 3 years would be appropriate for review of outcomes from the registry.

- 7.12 The PBAC considered that consultation with specialist clinicians would be required to finalise the parameters of any MAP.
- 7.13 The PBAC noted the financial estimates were based on the same estimated prevalent population and uptake assumptions as the previous submission. As such, the PBAC maintained its previous consideration that the financial estimates were uncertain and associated with a low level of confidence. The PBAC reiterated its previous consideration that the estimated number of patients with Type II and III SMA was uncertain, noting these were based on overseas data due to a lack of Australian data. The PBAC considered that the SMA registry may inform these estimates and provide additional confidence in the prevalence estimates.
- 7.14 The PBAC reiterated that the average age of patients likely to access nusinersen under the requested listing and the likely distribution of patients with Type IIIa or IIIb SMA were not adequately defined, noting differences in these patient characteristics between data provided in the resubmission and data provided from the SMA Australian member database, 2020.
- 7.15 The PBAC considered that there may be an increase in the number of patients treated if nusinersen was listed for the treatment of adult SMA patients due to the treatment of patients who are currently not seeking any clinical care for their condition. The PBAC noted that the sponsor proposed an RSA and considered that such an agreement could manage the uncertainties around the number of patients treated.
- 7.16 The PBAC advised that any future resubmission should include a MAP proposal which addresses the considerations in paragraph 7.11. The PBAC noted that the proposed restriction would also need to be revised to align with the criteria of the MAP proposal.
- 7.17 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

Type IIIb SMA Paediatric Population (symptom onset between 3 and 18 years of age)

- 7.18 The PBAC considered it would be appropriate to extend the current listing for nusinersen in symptomatic patients to include all paediatric patients with Type III SMA, including Type IIIb SMA (i.e. all patients with symptom onset between 3 and 18 years of age, which includes the subset with Type IIIc), to allow equity of access to nusinersen across all paediatric patients with SMA. The PBAC considered that extending the listing to include all paediatric patients would be adequately cost-effective if these additional patients were included in the existing RSA for nusinersen without any increase to the existing caps and at the price proposed in this submission (a further [REDACTED] % rebate [REDACTED]).
- 7.19 The PBAC considered that in Type IIIb paediatric SMA patients (with symptom onset

between 3 and 18 years of age) there is a high and urgent clinical need as the condition is seriously debilitating and there are no PBS subsidised therapies available.

- 7.20 The PBAC considered that for patients with Type IIIb SMA nusinersen provides a moderate benefit and there is moderate confidence in the clinical data in terms of magnitude and durability of effect. The PSCR argued that, in the absence of data in patients aged 18 years or less with Type IIIb SMA, the benefit would likely be the same or greater than that observed in adults with Type IIIb SMA as ‘these patients are earlier in the course of the disease and would therefore be able to maintain greater function over their lifetime’. The PBAC noted that in the nusinersen trials results were not presented separately for Type III SMA subtypes (IIIa and IIIb/IIIc) but considered that it was likely that the incremental benefit is reduced in patients with later onset of symptoms but treatment earlier in the course of disease would maximise the benefit from treatment.
- 7.21 The PBAC noted that the pre-PBAC response suggested that the cost of funding nusinersen for paediatric Type IIIb patients could be included in the existing RSA for nusinersen in symptomatic paediatric patients with Type I, II and IIIa SMA. The PBAC agreed with the pre-PBAC response that the size of the eligible paediatric Type IIIb population is likely to be small and considered that the total number of additional patients would be between 5 and 10 patients in each year, based on 11.5% of SMA Type III patients being Type IIIb (paragraph 6.77 risdiplam PSD, March 2021 PBAC meeting) and estimates of Type III SMA patient estimates of 33 to 94 patients in each year (Table 8, nusinersen PSD, March 2018 PBAC meeting). As such, the additional cost to the PBS would be contained and relatively low.
- 7.22 The PBAC noted that the current listing for the treatment of symptomatic patients would need to be revised to reflect the additional paediatric patients for whom PBS listing was recommended. The PBAC advised that specialist clinical input would be required to finalise changes to the current listing, as the typical symptoms for a patient with type IIIb SMA (i.e. with onset between 3 and 18 years of age) may differ from those for type IIIa SMA included in the current listing.
- 7.23 The PBAC advised that the extension to the nusinersen listing to include all paediatric patients could also be flowed onto risdiplam, (recommended in March 2021 for patients with Type I, II or IIIa SMA who are 18 years or under at treatment initiation on a cost-minimisation basis to nusinersen) using the equi-effective doses established for Type I, II and IIIa. The PBAC noted that the same conditions would need to be met as outlined in paragraph 7.18, in terms of pricing and inclusion within the existing nusinersen caps.
- 7.24 The PBAC found that the criteria prescribed by the *National Health (Pharmaceutical and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were met for the extension of the current listing to include all paediatric patients with Type III SMA. Specifically, the PBAC found that in the circumstances of its recommendation to extend the existing listing:

- a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy over standard of care;
- b) The treatment is expected to address a high and urgent unmet clinical need as there are currently no medicines for this patient population; and
- c) It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings.

Outcome:

Recommended

8 Recommended listing

8.1 Amend existing symptomatic spinal muscular atrophy listing (pre-symptomatic restrictions remain unchanged) to:

MEDICINAL PRODUCT medicinal product pack		PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
NUSINERSEN						
nusinersen 12 mg/5 mL injection, 5 mL vial		11363C (Public) 11472T (Private)	1	1	3	Spinraza
Edit Restriction Summary TMP23190 / Treatment of Concept: TMP23189 (current as at 1 July 2021; effective from 1 August 2021)						
		Category / Program: Section 100 – Highly Specialised Drugs Program (Public/Private hospitals)				
		Prescriber type: ☒ Medical Practitioners				
		Restriction type: ☒ Authority Required (written-only via post or electronic upload through Health Professionals Online Services - HPOS)				
		Administrative Advice: No increase in the maximum quantity or number of units may be authorised.				
		Administrative Advice: No increase in the maximum number of repeats may be authorised.				
		Administrative Advice: Special Pricing Arrangements apply.				
		Indication: Symptomatic Type I, II or IIIa spinal muscular atrophy (SMA)				
		Episodicity: Symptomatic				
		Severity: Type I, II, III				
		Condition: spinal muscular atrophy (SMA)				
		Indication: Symptomatic Type I, II or III spinal muscular atrophy (SMA)				
		Treatment Phase: Initial treatment of symptomatic Type I, II or IIIa SMA - Loading doses				
		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				
		AND				
		Clinical criteria:				
		The condition must have genetic confirmation of 5q homozygous deletion of the survival motor neuron 1 (SMN1) gene; or				
		The condition must have genetic confirmation of deletion of one copy of the SMN1 gene in addition to a pathogenic/likely pathogenic variant in the remaining single copy of the SMN1 gene				
		AND				
		Clinical criteria:				

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	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
	The condition must be diagnosed as of one of the following: (a) type I SMA, (b) type II SMA, (c) type III SMA, with the patient experiencing at least 2 signs/symptoms within the age ranges as stated further below; state in this authority application each of: (i) the SMA type, (ii) the signs/symptoms supporting the diagnosis, (iii) the age of onset of SMA signs/symptoms
	AND
	Clinical criteria:
	The treatment must not be in combination with PBS-subsidised treatment with risdiplam for this condition
	AND
	Clinical criteria:
	The treatment must be given concomitantly with standard of care for this condition
	The treatment must be given concomitantly with best supportive care for this condition
	AND
	Clinical criteria:
	The treatment must not exceed four loading doses (at days 0, 14, 28 and 63) under this restriction
	AND
	Population criteria:
	Patient must be 18 years of age or under
	Prescribing instructions: Defined signs and symptoms of type I SMA are: i) Onset before 6 months of age; and ii) Failure to meet or regression in ability to perform age-appropriate motor milestones; or iii) Proximal weakness; or iv) Hypotonia; or v) Absence of deep tendon reflexes; or vi) Failure to gain weight appropriate for age; or vii) Any active chronic neurogenic changes; or viii) A compound muscle action potential below normative values for an age-matched child.
	Prescribing Instructions: Defined signs and symptoms of type II SMA are: i) Onset between 6 and 18 months; and ii) Failure to meet or regression in ability to perform age-appropriate motor milestones; or iii) Proximal weakness; or iv) Weakness in trunk righting/derotation; or v) Hypotonia; or vi) Absence of deep tendon reflexes; or vii) Failure to gain weight appropriate for age; or viii) Any active chronic neurogenic changes; or ix) A compound muscle action potential below normative values for an age-matched child.
	Prescribing Instructions: Defined signs and symptoms of type IIIa SMA are: i) Onset between 18 months and 3 years of age; and ii) Failure to meet or regression in ability to perform age-appropriate motor milestones; or iii) Proximal weakness; or iv) Hypotonia; or v) Absence of deep tendon reflexes; or vi) Failure to gain weight appropriate for age; or vii) Any active chronic neurogenic changes; or viii) A compound muscle action potential below normative values for an age-matched child.
	Prescribing Instructions: Defined signs and symptoms of type III SMA are: i) Onset between 18 months of age to the 18 th birthday (inclusive); and ii) Failure to meet or regression in ability to perform age-appropriate motor milestones; or iii) Proximal weakness; or iv) Hypotonia; or v) Absence of deep tendon reflexes; or vi) Failure to gain weight appropriate for age; or

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	vii) Any active chronic neurogenic changes; or viii) A compound muscle action potential below normative values for an age-matched child.
	Prescribing Instructions: Recognised hospitals in the management of SMA are Lady Cilento Children's Hospital (Brisbane), Royal Children's Hospital Melbourne, Monash Children's Hospital (Melbourne), John Hunter Hospital (Newcastle), Sydney Children's Hospital Randwick, Children's Hospital at Westmead, Adelaide Women and Children's Hospital and Perth Children's Hospital.
	Prescribing Instructions: Application for authorisation of initial treatment must be in writing and must include: (a) a completed authority prescription form; and (b) a completed Spinal muscular atrophy PBS Authority Application Form which includes the following: i) specification of SMA type (I, II or IIIa); and (ii) sign(s) and symptom(s) that the patient has experienced; and (iii) patient's age at the onset of sign(s) and symptom(s).
	Prescribing Instructions: The authority application must be made in writing and must include: (1) a completed authority prescription form; and (2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).
	Administrative Advice: An outcome on the authority application is not immediate but will follow in due course. Electronic upload is encouraged to reduce processing time.
	Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
NUSINERSEN					
nusinersen 12mg/5 mL injection, 5 mL vial	11378W (Public) 11476B (Private)	1	1	0	Spinraza
Edit Restriction Summary TMP23202 / Treatment of Concept: TMP23201 (current as at 1 July 2021; embargo until 1 August 2021)					
	Category / Program: Section 100 – Highly Specialised Drugs Program (Public/Private hospitals)				
	Prescriber type: ☒ Medical Practitioners				
	Restriction type: ☒ Authority Required - immediate/real-time assessment (telephone/online PBS Authorities system)				
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.				
	Administrative Advice: No increase in the maximum number of repeats may be authorised.				
	Administrative Advice: Special Pricing Arrangements apply.				
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).				
	Indication: Spinal muscular atrophy (SMA)				
	Treatment Phase: Continuing/maintenance treatment of either symptomatic Type I, II or IIIa SMA or of a patient commenced on this drug under the pre-symptomatic SMA listing				

	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; or initiated 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
	AND
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition; or
	Patient must be eligible for continuing PBS-subsidised treatment with risdiplam for this condition
	AND
	Clinical criteria:
	The treatment must not be in combination with PBS-subsidised treatment with risdiplam for this condition
	AND
	Clinical criteria:
	The treatment must be given concomitantly with standard of care for this condition
	The treatment must be given concomitantly with best supportive care for this condition
	AND
	Clinical criteria:
	The treatment must be ceased when invasive permanent assisted ventilation is required in the absence of a potentially reversible cause while being treated with this drug
	Prescribing Instructions: Recognised hospitals in the management of SMA are Lady Cilento Children's Hospital (Brisbane), Royal Children's Hospital Melbourne, Monash Children's Hospital (Melbourne), John Hunter Hospital (Newcastle), Sydney Children's Hospital Randwick, Children's Hospital at Westmead, Adelaide Women and Children's Hospital and Perth Children's Hospital.
	Prescribing Instructions: Invasive permanent assisted ventilation means ventilation via tracheostomy tube for greater than or equal to 16 hours per day.
	Prescribing Instructions: In a patient who wishes to switch from PBS-subsidised risdiplam to PBS-subsidised nusinersen for this condition a wash out period may be required.

- 8.2 Flow-on changes to the risdiplam restrictions to permit use of risdiplam for type IIIb and IIIc SMA, in addition to types I, II, and IIIa SMA as recommended by the PBAC in March 2021, are not shown, but will be aligned with those appearing above in nusinersen's restrictions.

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

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the

merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

Biogen welcomes the PBAC's decision to recommend nusinersen for paediatric patients with Type IIIb SMA who have experienced symptom onset between 3 and 18 years of age. Biogen is however deeply disappointed that the PBAC did not recommend nusinersen for adults with SMA aged over 18 years at treatment initiation who have experienced signs and symptoms of SMA prior to 19 years of age. Biogen believes that there is alignment with the PBAC that nusinersen is a novel medicine that provides a clinically relevant benefit for adult patients with SMA, and that there are no current PBS subsidised therapies available for these patients. Biogen is exploring all options available for reimbursement and will collaborate with stakeholders to find a suitable path forward as swiftly as possible. Biogen would like to take this opportunity to thank the SMA community and healthcare professionals who supported the submission.