6.05 ONASEMNOGENE ABEPARVOVEC, Solution for injection, customised based on patient weight Zolgensma®, Novartis Pharmaceuticals Australia Pty Ltd.

1 Purpose of submission

1.1 The Category 2 submission requested an extension to the Section 100 (Highly Specialised Drugs Program), Authority Required listing of onasemnogene abeparvovec (ONA) for treatment of spinal muscular atrophy (SMA) to include pre-symptomatic patients who are genetically diagnosed with SMA and have 3 copies of the Survival Motor Neuron 2 (*SMN2)* gene.

1.2 Listing was requested on the basis of a cost-utility analysis of ONA versus disease modifying therapies (DMTs) i.e., nusinersen in active treatment of symptomatic patients with SMA.

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

Component	Description
Population	Paediatric patients less than 9 months of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the SMN1 gene and 3 copies of the SMN2 gene
Intervention	Onasemnogene abeparvovec (ONA), administered as a single intravenous infusion through a venous catheter delivered over 60 minutes. The recommended dose is 1.1 x 10^{14} vector genomes per kilogram (vg/kg) of body weight, to be individually made up by the sponsor for each patient. To manage possible liver function abnormalities, all patients should receive oral prednisolone (1 mg/kg) starting one day before ONA infusion and continued for 30 days post. At the end of the 30-day period, for patients with normal liver function, prednisolone dose should be tapered over the next 28 days. For patients with hepatic impairment, oral prednisolone (1 mg/kg per day) should continue until liver function results become unremarkable, at which time prednisolone dose should be tapered over the next 28 days.
Comparator	Usual care / watchful waiting and treat as symptoms appear.
Outcomes	Milestone developments (i.e. standing and walking)
Clinical claim	Pre-symptomatic treatment of patients with SMA with bi-allelic mutations in the SMN1 gene and 3 copies of the SMN2 gene with ONA is superior in terms of effectiveness (development milestones) and non-inferior in terms of safety compared to usual care / watchful waiting and treat as symptoms appear.

Source: Table 1.1, p4 of the submission.
DMT=disease modifying therapy; SMA=spinal muscular atrophy; *SMN1*=survival motor neuron 1; *SMN2*=survival motor neuron 2

2 Background

Registration status

2.1 ONA was registered by the TGA on 4 March 2021 for the following indication:

"Zolgensma® (onasemnogene abeparvovec) is indicated for the treatment of paediatric patients less than 9 months of age with symptomatic or presymptomatic

spinal muscular atrophy with bi-allelic mutations in the survival motor neuron 1 (*SMN1*) gene and 1 to 3 copies of the *SMN2* gene."

Previous PBAC consideration

2.2 Currently, DMTs for SMA listed on the PBS include nusinersen and risdiplam for ongoing treatment of symptomatic Type I, II or IIIa and nusinersen for pre-symptomatic initiation of treatment in patients with SMA and 1 to 2 copies of *SMN2*. Nusinersen was also listed on 1 August 2022 for patients with adult onset SMA who were diagnosed before 19 years of age (primarily SMA Types II and III). In September 2022 nusinersen was listed for patients with symptomatic Type IIIb/c SMA. SMA with symptom onset after 19 years is considered to be Type IV SMA and is not PBS-subsidised.

2.3 ONA was listed on the PBS in May 2022 as a once-off treatment in patients aged less than 9 months with symptomatic SMA Type I or pre-symptomatic SMA with 1 to 2 copies of *SMN2* on a cost minimisation basis versus risdiplam, which was the least costly DMT for SMA. If listed, ONA would become the first DMT available for patients who are pre-symptomatic with 3 copies of *SMN2*.

2.4 In the May 2021 addendum to the November 2020 meeting, the PBAC noted the proposed population for ONA was revised to patients aged less than 9 months, with 1-3 copies of the *SMN2* gene. The PBAC also noted that pre-symptomatic patients with 3 copies of *SMN2* were not eligible for treatment with nusinersen. The PBAC considered the request for inclusion of pre-symptomatic patients with 3 copies of *SMN2* was not adequately supported and at the requested price ONA was unlikely to be cost-effective in these patients, noting that some patients with 3 copies of *SMN2* may manifest with later onset of symptoms and less severe disease phenotype (SMA Type II or III) (paragraphs 8.1 and 8.5, onasemnogene abeparvovec Public Summary Document (PSD), November 2020 PBAC meeting with May 2021 and September 2021 Addendum). The ESC noted that despite this advice the sponsor had requested a substantially higher price for ONA in pre-symptomatic patients with 3 copies of *SMN2* than was accepted by the PBAC as being cost-effective for patients with 1-2 copies of *SMN2*.

2.5 Nusinersen was previously considered by the PBAC for pre-symptomatic initiation of treatment of patients with 1-3 *SMN2* copies in July and November 2019, proposed changes were not recommended due to uncertain incremental benefit versus symptomatic treatment. The PBAC also noted advice from MSAC that while *SMN2* copy number variation offers some prognostic value, it was more reliable for infants with two or less copies of *SMN2* compared to three or less copies of *SMN2* (paragraph 11.2, nusinersen PSD, Nov 2019 PBAC meeting). Pre-symptomatic initiation of treatment with nusinersen was ultimately recommended by the PBAC in July 2020 for infants with two or less copies of *SMN2* after a resubmission in this subpopulation (paragraph 7.1, nusinersen PSD, July 2020 PBAC meeting).

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
ONASEMNOGENE ABEPARVOVEC					
Onasemnogene abeparvovec Liquid in vial 1.1 x 10^{14} vg/kg	$	1	1	0	Zolgensma®

Category / Program: Section 100 – Highly Specialised Drugs Program (Public hospital code only)
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (in writing only via post/HPOS upload)
Administrative Advice: No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply. Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for 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 Other disease modifying therapies for this condition are: (i) nusinersen, (ii) risdiplam. Recognised hospitals in the management of SMA are Queensland 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. Accredited treatment centres and suppliers are those organisations accredited by the Gene Technology Regulator under section 92 of the Gene Technology Act 2000. The following website provides a list of accredited organisations and may update without notice: https://www.ogtr.gov.au/what-weve-approved/accredited-organisations
Indication: Spinal muscular atrophy (SMA)
Treatment Phase: Use in a patient untreated with disease modifying therapies for this condition
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:
Patient must have experienced at least two of the defined signs/symptoms of Type 1 SMA specified below; or
The condition must be presymptomatic SMA, with genetic confirmation that there are 1 to 3 copies of the survival motor neuron 2 (*SMN2*) gene
Treatment criteria:
Must be treated by a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic, 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
Treatment criteria
Patient must be undergoing treatment with this pharmaceutical benefit once only in a lifetime
AND

Treatment criteria
Patient must not be undergoing treatment with this pharmaceutical benefit through this listing where prior treatment has occurred with any of: (i) nusinersen, (ii) risdiplam
Population criteria:
Patient must be no older than 9 months of age
Population criteria:
Patient must have symptomatic Type 1 SMA; or
Patient must have presymptomatic SMA
Prescribing Instructions: In the relevant PBS Authority Application form, specify the following: (i) the SMA type being treated: symptomatic Type 1 SMA, or, pre-symptomatic SMA; (ii) for Type 1 SMA, the signs/symptoms that the patient has experienced, together with the patient's age at the onset of these signs/symptoms. State the weight of the patient in kilograms and request the appropriate product pack presentation with respect to the mix of 5.5 mL and 8.3 mL vials. Confirm that genetic testing has been completed to demonstrate the following in support of an SMA diagnosis: (i) 5q homozygous deletion of the survival motor neuron 1 (SMN1) gene; or (ii) deletion of one copy of the SMN1 gene in addition to a pathogenic/likely pathogenic variance in the remaining single copy of the SMN1 gene. If the condition is pre-symptomatic SMA, confirm that there is genetic test finding that substantiates the number of SMN2 gene copies determined by quantitative polymerase chain reaction (qPCR) or multiple ligation dependent probe amplification (MLPA). Quote the date, pathology provider name and any unique identifying serial number/code that links the genetic test result to the patient. 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.
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.

Source: Table 1.13, pp28-30 of the submission.

3.1 The requested restriction was based on ONA's current PBS restriction, with exception of the following modification: "The condition must be presymptomatic SMA, with genetic confirmation that there are 1 to ~~2~~*3* copies of the survival motor neuron 2 (*SMN2*) gene".

3.2 The proposed effective price for ONA treatment in patients with 3 copies of *SMN2* gene ($) is higher than the current published price for ONA in the treatment of symptomatic SMA Type I or pre-symptomatic SMA with 1 to 2 copies of *SMN2* (published price $2,557,773.87). A special pricing arrangement (SPA) also applies to the current PBS listing of ONA, with an effective price of $, including a performance rebate as part of a risk sharing arrangement (RSA). No SPA was proposed in the current submission.

3.3 The requested substantially higher price for ONA in this submission was inconsistent with the request to expand the restriction to patients with potentially less severe

phenotype where the benefit is likely to be smaller. The PBAC agreed with the ESC that as the proportion of patients who would benefit and the magnitude of any benefit are unknown based on the evidence presented, the price requested was not adequately justified.

3.4 The submission proposed a risk sharing arrangement (RSA) where the Commonwealth would be reimbursed for the high upfront expenditure in cases where expected outcomes were not achieved. The submission proposed that the current outcomes-based RSA for ONA for SMA Type I and pre-symptomatic patients with 1 or 2 copies of *SMN2* gene will apply to the proposed population of pre-symptomatic patients with 3 copies of *SMN2*, whereby [redacted]

3.5 The submission indicated that the process for genetic testing of *SMN1* and *SMN2* will be through the newborn bloodspot screening (NBS) program, which has a 99.9% coverage based on newborn screening in NSW. However, there are likely varying proportions of patients diagnosed pre-symptomatically, given SMA screening is currently discrepant across the states and territories of Australia with varying implementation timeframe for NBS. See paragraphs 4.9 to 4.11 below.

For more detail 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 *SMN1* gene on chromosome 5q. Alterations to this gene result in deficiency of SMN protein, which in turn, results in loss of motor function and respiratory failure. SMA is classified into types (0, I, II, III and IV) and subtypes (a, b, c) based on age of onset and maximal motor function achieved. There is also a clinical spectrum of disease associated with the number of copies of *SMN2* gene with earlier age of onset associated with lower number of *SMN2* copies and increased severity of symptoms. Patients with SMA typically develop weak muscles and may have trouble walking and breathing.

4.2 The submission's target population was SMA patients who were identified prior to symptom development, with 3 copies of *SMN2* gene. There are currently no published studies on the natural history of this population and their progression through life. While infants with a later age of onset have better functional ability initially, their condition deteriorates over time and often results in disability, regardless of SMA type.

4.3 Prior to the development of therapies, the traditional classification of SMA was by its phenotypes. However, there is significant overlap in patient clinical status across different phenotypes as it also depends on the stage of the disease (e.g., severe SMA Type II in advanced stages can be more severe compared with a patient in early stages of SMA Type I). Emerging DMTs, in particular SMN-dependent treatments for SMA, their adjacent clinical trials and natural history studies have shown that classification

based solely on motor assessment at the initial presentation was limited. For example, patients who were classified at diagnosis as Type I or II but achieved motor milestones (sitting or ambulation, respectively) would thus cross the boundaries of the traditional classifications. Children with Type III could learn to walk unassisted and retain this ability for a variable amount of time. In Type III non-ambulatory patients, the majority with an age of onset before 3 years lose the ability to walk in childhood or early adulthood. Type IV is rare (<1% SMA cases), adult onset SMA (age >18 years) and on the mild end of the SMA spectrum. Patients usually gain and keep their ability to walk and live a normal lifespan.

4.4 Guidelines and consensus statements (Mercuri et al 2018[1], Finkel et al 2018[2], Kirschner et al 2020[3]) have recommended an update to the classification of SMA, acknowledging the SMA phenotypes as a continuum and that classification by types alone is not sufficient to define the patient populations who might benefit most from gene therapy. In symptomatic patients, the age at onset, disease duration (interval between symptom onset to starting treatment) and motor function status at the start of treatment are the most important factors that predict response to treatment, whereas in pre-symptomatic patients, *SMN2* copy number is the most important predictor of clinical severity and age of onset (Kirschner et al 2020). The new classification system consists of non-sitters, sitters, and walkers. Figure 1 presents clinical forms of SMA according to the new and original classifications and their correlations with *SMN2* copy numbers based on a review study by Wirth et al 2020[4].

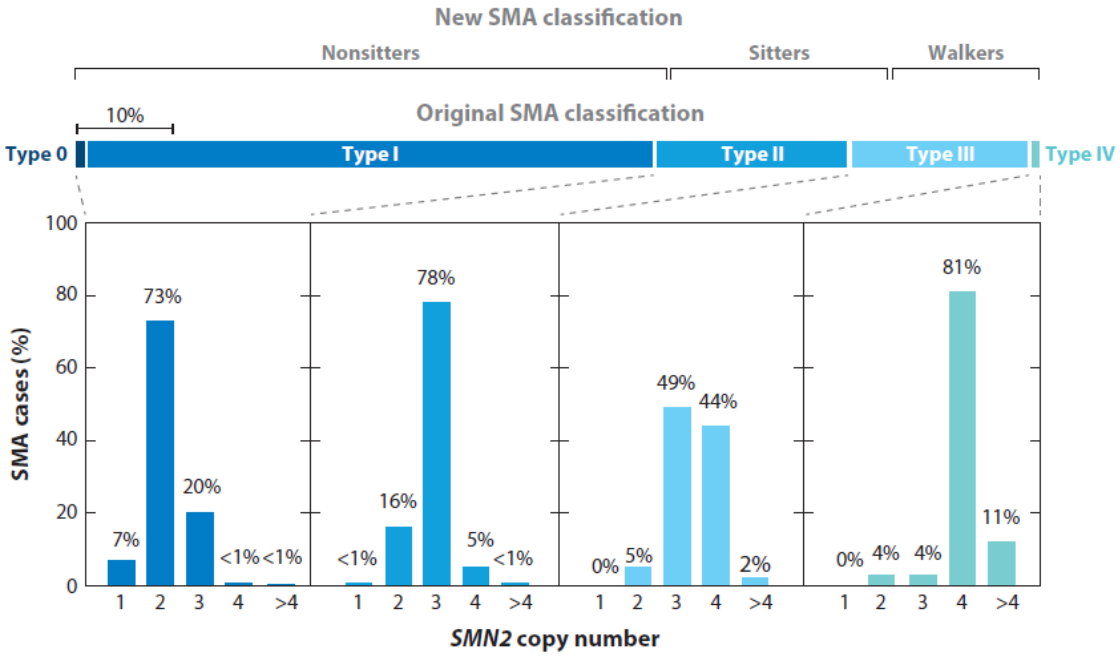
[1] Mercuri E, Finkel RS, Muntoni F, et al. 2018. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscular Disorders 28:103–115.

[2] Finkel RS, Mercuri E, Meyer OH, et al. 2018. Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. Neuromuscular Disorders 28:197–207.

[3] Kirschner J, Butoianu N, Goemans N, et al. 2020. European ad-hoc consensus statement on gene replacement therapy for spinal muscular atrophy. European Journal of Paediatric Neurology 28:38-43.

[4] Wirth B, Karakaya M, Kye MJ, Mendoza-Ferreira N. 2020. Twenty-Five Years of Spinal Muscular Atrophy Research: From Phenotype to Genotype to Therapy, and What Comes Next. Annual Review of Genomics and Human Genetics 21:231-261.

Figure 1: Clinical forms of SMA based on the new and original classifications and their correlations with *SMN2* copy numbers.



Source: Figure 1, Wirth et al 2020.
SMA=spinal muscular atrophy; SMN=survival motor neuron;
Non-sitters include all Type 0 and Type I patients and some Type II patients who are unable to sit independently.
Sitters include the remaining Type II and some Type III patients who are unable to walk independently.
Walkers include the remaining Type III and all Type IV patients.
The correlations between clinical severity and SMN2 copy numbers are depicted according to the original classification, as no correlation studies for the new classification are available. Type 0 SMA cases reported so far always carry one SMN2 copy, and in most studies these were included under type I.

4.5 Although the severity of the SMA phenotype is influenced mainly by the *SMN2* copy number, with more copies resulting in a milder phenotype, this correlation is not absolute. The Pre-Sub-Committee Response (PSCR) noted data from Cusco et al 2020 found an 'unexpected discordance' between copy number and disease severity with children with 3 or 4 copies of the gene showing more severe disease than expected. Wirth et al 2020 reported that the predictive value of 3 copies of *SMN2* is less than that of 2 or 4 copies. In consideration of the prognostic value of *SMN2* copy number for the severity of SMA to determine eligibility for nusinersen in pre-symptomatic patients (MSAC application number 1589, 2019), the Medical Services Advisory Committee (MSAC) also noted that three copies of *SMN2* resulted in infants developing all types of SMA, from Type I (most severe) to Type IV (least severe), with most developing Type II. Based on a meta-analysis of world-wide data, Calucho et al 2018 reported that in patients with 3 *SMN2* copies, the majority would develop SMA Type II (53%) and Type III (30%) and 17% would develop the more severe Type I and would never sit. The PBAC had also previously noted that for SMA Type I, while the majority of patients (80%) had ≤2 copies of the *SMN2* gene, 20% had 3 copies of SMN2. Patients with 3 copies of the *SMN2* gene could also manifest as either Types III or IV

SMA (paragraph 4.3, onasemnogene abeparvovec PSD, November 2020 PBAC meeting).

4.6 The PBAC noted that descriptions of SMA Type and phenotype reflect the natural history of disease and don't reflect a scenario where patients are treated with DMTs pre-symptomatically or soon after symptoms appear. At the November 2020 meeting, the PBAC noted that while ONA (and nusinersen) improved motor function, neither treatment was able to cure SMA, with patients in the trials remaining significantly disabled (paragraph 6.23, onasemnogene abeparvovec PSD, November 2020 PBAC meeting).

4.7 The difference between the current and proposed clinical management was earlier treatment with ONA in patients diagnosed with 3 copies of *SMN2* prior to symptom development. Currently, these patients would receive PBS listed treatments when symptoms are present. The pre-PBAC response stated that the international standard is to treat upon diagnosis of SMA (with or without symptoms), in order to minimise the loss of irreplaceable motor neurons. The ESC considered that the move to pre-symptomatic treatment in patients who may have otherwise gone on to develop less severe disease represents a substantial shift to preventive treatment. The ESC considered this may require a different approach to consideration of cost-effectiveness compared with when DMTs first became available as potentially life-saving treatments for patients with severe disease.

4.8 ONA is a once per life-time gene replacement therapy consisting of a non-replicating recombinant adeno-associated viral (AAV_9) vector containing the human SMN gene under control of the chicken beta-actin promoter. It is designed to deliver a copy of the gene encoding the human SMN protein. ONA is administered as a single-dose intravenous (IV) infusion delivered over 60 minutes. The recommended dose is 1.1 x 10^{14} vector genomes per kilogram (vg/kg) of bodyweight. All patients should receive oral prednisolone (1 mg/kg) to manage possible liver function abnormalities, started one day prior to treatment, and for at least 30 days post-treatment.

Newborn bloodspot screening (NBS)

4.9 NBS will identify and diagnose patients with SMA for treatment prior to symptom development. However, NBS funding is not available in all states and territories. An estimated 90% of the population would be screened for SMA by end of 2023 based on the jurisdictions that have indicated fully funded programs (New South Wales and Australian Capital Territory) and program commencement in December 2022-June 2023 (Western Australia, Victoria and Queensland). This would increase to 97% coverage if South Australia was included. A variable proportion of the patient population will likely be diagnosed based on NBS and based on symptoms given that the current status of SMA screening is discrepant across the states and territories of Australia with varying implementation timeframes.

4.10 NSW and ACT have continued SMA screening following a pilot. All children born in NSW/ACT are offered screening within 48-72 hours of birth, with a 0.1% opt-out rate.

The process of SMA screening in the NBS involved a first-tier screening test on dried blood sample to determine homozygous deletion of *SMN1* and a second-tier test was performed on those positive at first tier. Second tier screening screens for *SMN1* homozygous deletion on a second dried blood sample and *SMN2* copy number on the first and second dried blood sample. The NBS pilot protocol on all tested dried bloodspot cards had a sensitivity of 100%, specificity greater than 99.9%, false-positive rate less than 0.001%, and positive predictive value of 95.5%.

4.11 As of January 2021, this pilot had detected 22 children from 252,081 babies screened (Newson et al 2022). However, the potential incidence of SMA may potentially reduce over time with reproductive genetic carrier screening and prenatal diagnosis of SMA on the horizon, which may change reproductive/intervention options. In July 2020, the MSAC recommended for reimbursement (but not yet implemented) pre-conception genetic carrier testing for inherited conditions including SMA (application number 1573). MSAC has also considered the expanded reproductive carrier screening of couples for joint carrier status of genes associated with autosomal recessive and X-linked conditions, which encompasses SMA (application number 1637, Application form and PICO confirmation).

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

5 Comparator

5.1 The submission nominated watchful waiting and treat as symptoms appear as the main comparator. Patients identified with pre-symptomatic SMA and 3 copies of *SMN2* currently wait to show symptoms before receiving treatment with DMTs on the PBS. Currently, the period of wait-to-treat may vary (from 0 days to 18 years) depending on symptom onset, with potential delays in the mean time between symptom onset and genetic diagnosis of 3.6, 14.3 and 43.6 months for SMA Types I, II and III, respectively (Davidson et al 2022)[5]. However, early detection of SMA, such as NBS, will likely reduce this delay and expediate initiation of treatment. Table 2 summarises the age of symptomatic and pre-symptomatic treatments with DMTs on the PBS.

[5] Davidson JE, Farrar MA. 2022. The changing therapeutic landscape of spinal muscular atrophy. Australian Journal of General Practice. 51(1-2):38-42.

Table 2: Age of symptomatic and pre-symptomatic treatment with DMTs on the PBS

Age of pre-symptomatic treatment by SMN2 copy				Age of symptomatic treatment by SMA Type				
Likely SMN2 copy number			ONA	NUSI	Type	Age at symptom onset	ONA	NUSI	RISD
1			≤9 months	≤36 months	0	Prenatal	n/a	n/a	n/a
1	2	3	≤9 months	≤36 months	I	<6 months	≤9 months	≤3 years	≤3 years
2	3	4	≤9 months	≤36 months	II	6-18 months	n/a	≤18 years	≤3 years
3	4		n/a	n/a	IIIa	18 months to 3 years	n/a	≤18 years	≤3 years
	4		n/a	n/a	IIIb	>3 years	n/a		n/a
	4		n/a	n/a	IIIc	>12 to ≤18 years	n/a		n/a

Grey shading indicates SMN2 copy number treated by DMTs (ONA and NUSI) listed on the PBS in pre-symptomatic treatment.
Source: compiled during the evaluation.
DMT=disease modifying therapy; NUSI=nusinersen; ONA=onasemnogene abeparvovec; RISD=risdiplam; n/a=not available; SMA=spinal muscular atrophy; SMN2=survival motor neuron;

5.2 The submission also appropriately nominated nusinersen and risdiplam as near market comparators. Although nusinersen is available on the PBS for pre-symptomatic treatment in patients with 2 copies of *SMN2*, neither drug is currently PBS-listed for pre-symptomatic treatment in 3 copies of *SMN2*. However, studies of nusinersen and risdiplam in pre-symptomatic patients with 2 or 3 copies of *SMN2* were identified in the submission. Of note, the PBAC previously considered that "on balance ONA would likely deliver similar clinical outcomes to [nusinersen] in matched patients" (paragraph 7.1, onasemnogene abeparvovec PSD, November 2020 PBAC meeting). Risdiplam was recommended for listing on PBS on the basis of a cost-minimisation analysis versus nusinersen (paragraph 7.1, risdiplam PSD, March 2021 PBAC meeting).

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The hearing included a paediatric neurologist, an advocate for SMA patients and a parent of a child with SMA. The clinician noted that the available evidence across all current DMTs indicate better outcomes for patients the earlier they are treated. The clinician considered that patients should receive treatment as early as possible irrespective of whether they have 2 or 3 copies of *SMN2*, noting that pathological processes of SMA begin in utero. The SMA patient advocate noted that because no treatments are currently available for pre-symptomatic patients who are genetically diagnosed with SMA and have 3 *SMN2* copies, there have been situations where not all children within a family of carriers have been able to receive treatment. The SMA patient advocate considered that availability of ONA for pre-symptomatic treatment of patients with 3 copies of *SMN2* would ensure equity of access. The parent of a child with SMA with 3 copies of *SMN2*, who was diagnosed at 11 months noted the significant improvements their child experienced after receiving treatment. Despite treatment, at 6 years of age the child requires use of a wheelchair at times, depending on safety considerations and her level of fatigue. The parent noted that outcomes may have been different for the

child if treatment had been available earlier and strongly supported making ONA available to treat children as early as possible.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (22), health care professionals (4) and organisations (2) via the Consumer Comments facility on the PBS website. The comments emphasised the importance of early intervention in the treatment of SMA in order to prevent irreversible motor neuron loss. The comments noted that while the side effect profile of ONA was not yet completely understood, the treatment demonstrated a favourable safety profile in clinical trials. It was also noted that the prevention of SMA symptoms through early treatment may reduce future healthcare costs. Comments from parents of children genetically diagnosed with SMA who were treated with ONA shortly after birth, described benefits of treatment including remaining asymptomatic and meeting normal developmental milestones. Comments from parents of children with SMA who were treated with ONA following the development of symptoms indicated a perception that their child would have even better outcomes if treated prior to symptom onset.

6.3 The National Paediatric Medicines Forum (NPMF) noted that minimal adverse events have been reported for ONA so far across paediatric facilities. The NPMF noted that with paediatric sites developing facilities to prepare and administer gene therapies, as well as the formation of state based newborn screening programs, many more children would be able to receive treatment quickly if the listing was recommended by the PBAC.

6.4 Spinal Muscular Atrophy Australia strongly supported expanding the current PBS listing of ONA to include the pre-symptomatic treatment of patients genetically diagnosed with SMA who have 3 *SMN*2 copies. Spinal Muscular Atrophy Australia noted that while advances in diagnostics and treatments has changed the SMA landscape considerably over the last few years, access to treatment is not equitable for all children genetically diagnosed with SMA. Spinal Muscular Atrophy Australia noted that treating children with SMA who have 3 *SMN*2 copies after the development of symptoms could mean these children would not achieve the same outcomes as children who are currently eligible to receive subsidised treatment earlier, and highlighted the distress that watching and waiting for symptoms has on parents and families.

Clinical studies

6.5 The submission was based on one single-arm study of ONA in pre-symptomatic patients (SPR1NT) and its long-term follow-up (LT-002, interim data), and 12 studies for symptomatic SMA treatment with DMTs on the PBS for patients with SMA Types I to III. These included 4 open-label studies of ONA as symptomatic treatment: START and its long-term follow-up START-LTFU (also known as LT-001) and STRIVE-US, STRIVE-EU, and their long-term follow-up (also in LT-002). There were 6 studies for

nusinersen: 2 sham-controlled RCTs (ENDEAR and CHERISH), 2 dose-escalating studies (CS2 and CS3A) and 2 open-label follow-up extension studies (CS2/CS12 and SHINE (interim data)). Patients in CS2 who continued in the open-label safety study CS12 were analysed in CS2/CS12 (Darras et al 2019). SHINE was a long-term extension study which enrolled patients from shorter term nusinersen studies ENDEAR, CHERISH, EMBRACE, CS12 and CS3A. The submission included two studies for risdiplam: FIREFISH and SUNFISH, both comprising an exploratory dose finding part and a second open-label efficacy part using the risdiplam dose from the first part (interim data).

6.6 All the studies were considered by the PBAC in previous submissions of DMTs for SMA or the Review of SMA 'whole of disease' treatment evidence March 2021 commissioned and provided by Biogen (Attachment 14 of the submission).

6.7 The submission identified in "Attachment 8 Near market comparator analysis", two ongoing studies of DMTs for treatment in pre-symptomatic patients: nusinersen (NURTURE) and risdiplam (RAINBOWFISH), which were excluded from the main analysis on the grounds of 'wrong population'. Given the scarcity of data for pre-symptomatic treatment with DMTs, these studies were included during the evaluation to provide context, particularly the likely difference in efficacy between pre-symptomatic and symptomatic treatment using the same drug, given that information is lacking for ONA in symptomatic treatment of patients with Type II or III SMA. Both NURTURE and RAINBOWFISH were previously presented and considered by the PBAC and included patients with 2 or 3 copies of *SMN2* who received treatment pre-symptomatically and reported comparable outcomes such as motor functions and survival at 24 months.

6.8 The submission also identified six systematic reviews evaluating the efficacy and safety of nusinersen in symptomatic paediatric or adult patients with SMA, in terms of motor milestones, survival and adverse events.

6.9 In addition, four SMA natural history studies were identified and used in the modelled economic evaluation:

- National Network for Excellence in Neuroscience Clinical Trials (NeuroNext) a US prospective, multicentre, natural history study (Kolb 2017), that enrolled 53 SMA patients between November 2012 and September 2014 and were followed for 24 months;
- Paediatric Neuromuscular Clinical Research Network for SMA (PNCR) cohort study investigating the natural history of SMA (Finkel 2014), 79 patients (34 Type I and 45 Type II) enrolled between May 2005 and April 2009 were followed for 36 months;
- Gregoretti 2013, Italian medical records on 194 patients with SMA Type I reviewed from 1992-2010; and
- Zerres 1997, German natural history data since 1985, 569 patients (240 Type II and 329 Type III).

NeuroNext, PNCR and Gregoretti 2013 were previously considered by the PBAC in the November 2021 submission of ONA for symptomatic Type I SMA.

6.10 Details of the studies presented in the submission are provided in the table below.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Pre-symptomatic treatment of SMA		
ONA		
SPR1NT NCT03505099 (completed)	AVXS-101-CL-304. A global study of a single, one-time dose of AVXS-101 delivered to infants with genetically diagnosed and presymptomatic spinal muscular atrophy with multiple copies of SMN2. Strauss et al. Onasemnogene abeparvovec for presymptomatic infants with three copies of MSN2 at risk for spinal muscular atrophy: The Phase III SPR1NT trial.	October 2021. Nature Medicine 2022; 28(7):1390-1397.
LT-002 NCT04042025 (interim)	AVXS101/AV101 (onasemnogene abeparvovec). Summary of data from long-term follow-up studies. [Study LT-001 and Study LT-002]. Long-term Follow-up Study of Patients Receiving Onasemnogene Abeparvovec-xioi	October 2021.
NUSI		
NURTURE NCT02386553 (ongoing)	De Vivo D, Bertini E, Swoboda K, et al. Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study.	Neuromuscular Disorders 2019; 29(11):842-856.
RISD		
RAINBOWFISH NCT03779334 (ongoing)	Finkel RS, et al. RAINBOWFISH: Preliminary efficacy and safety data in risdiplam-treated infants with presymptomatic SMA.	MDA Clinical and Scientific Conference 2022, poster 76.
Symptomatic treatment of SMA		
ONA		
START NCT02122952 (completed)	AVXS-101-CL-101 Clinical Study Report. Phase I Gene Transfer Clinical Trial for Spinal Muscular Atrophy Type 1 Delivering AVXS-101. Mendell JR, et al. Single-dose gene-replacement therapy for spinal muscular atrophy.	August 2018 New England Journal of Medicine 2017; 377(18):1713-1722.
START-LTFU (LTFU) NCT03421977 (interim)	AVXS101/AV101 (onasemnogene abeparvovec). Summary of data from long-term follow-up studies. [Study LT-001 and Study LT-002]. Mendell JR, et al. Five-Year Extension Results of the Phase 1 START Trial of Onasemnogene Abeparvovec in Spinal Muscular Atrophy.	October 2021. JAMA Neurology 2021; 78(7): 834-841.
STR1VE-US NCT03306277 (completed)	AVXS-101-CL-303 Clinical Study Report. Phase 3, Open-label, Single-arm, Single-dose Gene Replacement Therapy Clinical Trial for Patients with Spinal Muscular Atrophy Type 1 with One or Two SMN2 Copies Delivering AVXS-101 by Intravenous Infusion. Day JW, et al. Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy in patients with two copies of SMN2 (STR1VE): an open-label, single-arm, multicentre, phase 3 trial.	March 2020 The Lancet Neurology 2021; 20(4):284-293.
STR1VE-EU NCT03461289 (completed)	AVXS-101-CL-302 Clinical Study Report. Phase 3, Open-Label, Single-Arm, Single-Dose Gene Replacement Therapy Clinical Trial for Patients with Spinal Muscular Atrophy Type 1 with One or Two SMN2 Copies Delivering AVXS-101 by Intravenous Infusion. Mercuri E, et al. Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy type 1 (STR1VE-EU): an open-label, single-arm, multicentre, phase 3 trial.	April 2021 The Lancet Neurology 2021; 20(10):832-841.

Trial ID	Protocol title/ Publication title	Publication citation
NUSI		
ENDEAR NCT02193074	Finkel RS, et al. Nusinersen versus sham control in infantile-onset spinal muscular atrophy.	New England Journal of Medicine 2017; 377(18):1723-1732.
CS3A NCT01839656	Finkel RS, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. Finkel RS, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: final report of a phase 2, open-label, multicentre, dose-escalation study.	Lancet 2016; 388(10063):3017-3026. The Lancet Child and Adolescent Health 2021; 5(7):491-500.
SHINE/ENDEAR NCT02594124	Castro D, Finkel RS, Farrar MA, et al. Nusinersen in infantile-onset spinal muscular atrophy: Results from longer-term treatment from the open-label SHINE extension study. [Conference presentation, data presented only for patients who started treatment in the ENDEAR trial]	American Academy of Neurology Annual Meeting 2020.
CHERISH NCT02292537	Mercuri E, et al. Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy [Clinical Trial, Phase III; Comparative Study; Multicenter Study; Randomized Controlled Trial].	New England Journal of Medicine 2018; 378(7):625-635.
CS2 NCT01703988	Chiriboga CA, et al. Results from a phase 1 study of nusinersen (ISIS-SMN Rx) in children with spinal muscular atrophy.	Neurology 2016; 86(10):890-897.
SHINE/CS2A *(CS2/CS12)* NCT01703988	Darras BT, et al. Nusinersen in later-onset spinal muscular atrophy: Long-term results from the phase 1/2 studies [LT extension of CS2/CS12].	Neurology 2019; 92(21):e2492-e2506.
SHINE/CHERISH NCT02594124	Kirschner J, et al. Interim report on the safety and efficacy of longer-term treatment with nusinersen in later-onset spinal muscular atrophy (SMA): Results from the shine study.	Journal of the Neurological Sciences 2019; 405:248-249.
EMBRACE [a] NCT02462759	Acsadi G, Crawford TO, Müller-Felber W, et al. Safety and efficacy of nusinersen in spinal muscular atrophy: The EMBRACE study.	Muscle Nerve 2021; 63(5):668-677.
RISD		
FIREFISH NCT02913482	Baranello G, et al. Risdiplam in type 1 spinal muscular atrophy. Darras BT, Masson R, Mazurkiewicz-Bełdzińska M, et al. Risdiplam-Treated Infants with Type 1 Spinal Muscular Atrophy versus Historical Controls.	New England Journal of Medicine 2021; 384(10):915-923. New England Journal of Medicine 2021; 385(5):427-435.
SUNFISH NCT02908685	Mercuri E, et al. Safety and efficacy of once-daily risdiplam in type 2 and non-ambulant type 3 spinal muscular atrophy (SUNFISH part 2): a phase 3, double-blind, randomised, placebo-controlled trial.	The Lancet. Neurology 2022; 21(1):42-52.
Natural history		
NeuroNext	Kolb SJ, Coffey CS, Yankey JW, et al. Natural history of infantile-onset spinal muscular atrophy.	Annals of Neurology 2017; 82:883-891.
PNCR	Finkel RS, McDermott MP, Kaufmann P, et al. Observational study of spinal muscular atrophy type I and implications for clinical trials.	Neurology 2014; 83: 910-817.
Farrar 2013	Farrar MA, Vuvic S, Johnston HM, et al. Pathophysiological insights derived by natural history and motor function of spinal muscular atrophy.	The Journal of Paediatrics 2013; 162:155-159.
Gregoretti 2013	Gregoretti C, Ottonello G, Beatrice M et al. Survival of patients with spinal muscular atrophy type I.	Pediatrics 2013; 131(5):e1509-e1514.
Zerres 1997	Zerres K, Rudnik-Schöneborn S, Forrest E, et al. A collaborative study on the natural history of childhood and juvenile onset proximal spinal muscular atrophy (type II and III SMA): 569 patients.	Journal of the Neurological Sciences 1997; 146(1):67-72.

[a] *potentially relevant study included in the review but excluded from the submission was the EMBRACE study (NCT02462759)6. The submission excluded EMBRACE due to 'wrong population', however the phase 2 randomised sham-controlled study enrolled young children (N=21) with 2 or 3 copies SMN2 and onset of symptoms consistent with SMA*
Source: Table 2.5, pp37-48 of the submission and Attachment 8 Near market comparator analysis.docx.
NUSI=nusinersen; ONA=onasemnogene abeparvovec; RISD=risdiplam; SMA=spinal muscular atrophy; *SMN1*=survival motor neuron 1; *SMN2*=survival motor neuron 2;

6.11 Table 4 summarises the key features of the included studies.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Bias	Treatment arms	Population	Outcome(s)	S3
Pre-symptomatic treatment of SMA							
ONA							
SPR1NT	15[a]	MC, NC, OL up to 24 mths of age	High#	ONA IV 1.1 x 10^{14} vg/kg	3 copies of *SMN2*, age ≤6 wks	1°: motor milestone - standing (24 mths) 2°: motor milestones, EFS	✓
LT-002 (SPRINT)^	18[b]	MC, OL extension 15 yrs May 2021 data cut: median (range) age 29.2 (25.2, 35.1) mths, time since treatment 28 (24.5, 34.8) mths	High#	As in SPR1NT	SMA 2-3 copies of *SMN2*	1°: motor milestone (24 mths) 2°: motor milestones, EFS	-
NUSI							
NURTURE^	25	MC, OL, NC, 5y March 2019 data cut: median (range) age 34.8 (25.7-45.4) mths	High#	NUSI IC 12 mg	2 or 3 (n=10) copies of *SMN2*, age ≤6 wks	1°: EFS 2°: OS, motor milestones	-
RISD							
RAINBOWFISH^	18	MC, OL, NC 2 yrs / 3 yrs July 2021 data cut: median (range) age 26.5 (16-40) months	High#	RISD oral target dose	≥2 copies of *SMN2*, age ≤6 wks	1°: motor milestone - sitting (12 mths)[c] 2°: motor milestones, EFS	-
Symptomatic treatment of SMA							
ONA							
START	15[d]	NC, OL 2 yrs	High#	ONA IV 6.7 × 10^{13} vg/kg ONA IV 1.1 × 10^{14} vg/kg	SMA Type I (2 copies of *SMN2*), age ≤6mths	1°: safety 2°: motor milestones, EFS, OS	-
START-LTFU (LT-001)^	15[d]	OL extension 15yrs June 2020 data cut, mean (range): age: 38.9 (25.4-48) mths, time since treatment: 4.8 (4.6-5.6) yrs	High#	As in START	SMA Type I (2 copies of SMN2)	1°: safety 2°: motor milestones, EFS	-
STR1VE-US	22	MC, NC, OL up to 18 mths of age	High#	ONA IV 1.1 x 10^{14} vg/kg	SMA Type I (1-2 copies of *SMN2*); age <6 mths	1°: motor milestone – sitting	-

[6] Acsadi G, Crawford TO, Müller-Felber W, et al. Safety and efficacy of nusinersen in spinal muscular atrophy: The EMBRACE study. Muscle Nerve 2021; 63(5):668-677.

Trial	N	Design/ duration	Bias	Treatment arms	Population	Outcome(s)	S3
						(age 18 mths), EFS (age 14 mths) 2°: motor milestones, OS	
STR1VE-EU	33	MC, NC, OL up to 18 mths of age	High#	ONA IV 1.1 x 10^{14} vg/kg	SMA Type I (1-2 copies of *SMN2*); age <6 mths	1°: motor milestone – sitting (age 18 mths) 2°: EFS, OS Other: motor milestones	-
LT-002^ (STR1VE-US, STR1VE-EU)	27[b]	MC, OL extension 15 yrs May 2021 data cut: median (range) age 41.7 (38.5-45.5) mths from STR1VE-US, 34.1 (29.4-36) mths from STR1VE-EU	High#	As in STR1VE	SMA Type I (1-2 copies of *SMN2*)	1°: motor milestone (24 mths) 2°: motor milestones, EFS	-
NUSI							
ENDEAR	121	R, DB, MC 13 mths	Low	NUSI IC 12 mg Control (sham)	SMA Type I (2 copies of *SMN2*); age ≥2 yrs	1°: motor milestone response – HINE-2, EFS (13 mths) 2°: motor milestones, OS	✓
CS3A	20	MC, OL 36 mths	High#	NUSI IC 6 mg + 12 mg maintenance NUSI IC 12 mg	SMA Type I (2-3 copies of *SMN2*); age 3 wks to 6 mths	1°: motor milestones – HINE-2 (36 mths) 2°: motor milestones, EFS, OS	-
CS2	34	MC, OL 8.4 mths[g]	High#	NUSI IC 3, 6, 9 or 12 mg	SMA Type II or III (2-4 copies of *SMN2*); age 2-14 yrs	1°: safety other: motor milestones, PedsQL	-
CS2/CS12	24[h]	OL 25 mths	High#	NUSI IC 12 mg	As in CS2	1°: motor milestones other: safety, concomitant drugs	✓
CHERISH	126	R, DB, MC 16 mths	Low	NUSI IC 12 mg Control (sham)	SMA Type II or III (2-4 copies of *SMN2*); age 2-12 yrs	1°: motor milestones HFMSE (15 mths) 2°: motor milestones, safety	-
EMBRACE	21	R, DB, MC 14 mths[i] / 28 mths	Unclear	NUSI IC 12 mg Control (sham)	2-3 copies SMN2[k]	1°: safety other: motor milestones	-
SHINE^	292[e]	OL extension 5 yrs August 2019 data cut: in ENDEAR/SHINE patients median age 2.6-2.7 yrs, time on treatment 1.34-2.08 yrs, and in	High#	NUSI IC 12 mg	SMA Type I and Type II patients from ENDEAR, CHERISH, CS3A, CS12, EMBRACE	1°: safety 2°: motor milestone, EFS, OS	✓[f]

Trial	N	Design/ duration	Bias	Treatment arms	Population	Outcome(s)	S3
		CS2/CS12/SHINE patients median time on treatment was 6.3 yrs					
RISD							
FIREFISH^	41	MC, OL 24 mths / 3 yrs [m]	High[#]	RISD oral target dose	SMA Type I (2 copies of *SMN2*); age 1-7 mths	1°: motor milestone – sitting (12 mths) 2°: motor milestones, EFS, OS	-
SUNFISH^	180[n]	R, DB, MC, PC 12 wks + 12 mths / OL 12 mths [m] / 3 yrs	Low	RISD oral 5 mg/kg RISD oral 0.25 mg/kg placebo	SMA Type II and Type III, non-ambulant; age 2-25 yrs	1°: motor milestone – sitting (12 mths) 2°: motor milestones, EFS, OS	-
Natural history							
NeuroNext	53	Enrolled between Nov 2012 to Sept 2014	-	-	SMA (n=26) and healthy infants, USA	Motor milestones, EFS, OS	✓
PNCR	79	Enrolled between 2005-09	-	-	SMA Type I (n=34) and Type II, USA	Motor milestones, EFS, OS	-
Gregoretti 2013	194	Followed up 1992-2010	-	-	Type I SMA, Italy	OS	✓
Zerres 1997	569	Enrolled since 1985 Germany and 1960 Poland	-	-	SMA Type II (sitters, n=240), Type IIIa (walkers SMA onset before 3yrs, n=195) and Type IIIb (walkers SMA onset 3-30 yrs, n=134) Germany and Poland	Motor milestones, OS	✓

Green shading represents study population consisting only of patients treated pre-symptomatically, unshaded rows represent studies in symptomatic patients.
Source: Table 2.8, pp60-61 and Tables 2.9 and 2.10, pp6.7-68, of the submission.
BSID-GM=Bayley scales of infant and toddler development – gross motor subtest; CMAP=compound muscle action potential; DB=double blind; EFS, event-free survival (survival without permanent ventilation); HFMSE=Hammersmith functional motor scale expanded; HINE=Hammersmith Infant Neurological Examination; IC=intracathel; IV=intravenous; MC=multi-centre; NC=non-comparative single arm study; NUSI=nusinersen; OL=open label; ONA=onasemnogene abeparvovec; OS=overall survival; PC=placebo-controlled; PedsQL=paediatric quality of life; R=randomised; RISD=risdiplam; SMA=spinal muscular atrophy; *SMN1*=survival motor neuron 1; *SMN2*=survival motor neuron 2; mth=month; yr=year; wk=week;
S3 indicates studies used in the modelled economic evaluation (Section 3).

^ ongoing study.

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

a Patients with 3 copies of *SMN2* only. The study population consisted of two cohorts: Cohort 1 (n=14) with 2 copies of *SMN2* and Cohort 2 (n=15) with 3 copies of *SMN2* and 1 patient with 4 copies of *SMN2*.

b LT-002 enrolled 59 patients: n=18 (2-3 copies of SMN2) from SPR1NT (CL-304), n=20 from STR1VE-EU (CL-302), n=7 from STR1VE-US (CL303), n=1 from CL-306 and n=13 from STRONG.

c primary efficacy population included patients with 2 copies of SMN2 and CMAP ≥1.5 mV at baseline.

d In START, n=3 received low dose ONA 6.7×10^{13} vg/kg and n=12 received therapeutic dose ONA 1.1×10^{14} vg/kg. All 15 enrolled in START were recruited to START-LTFU, but results reported for 13 patients (3 low dose and 10 therapeutic dose), as 2 discontinued.

e SHINE enrolled 292 patients: n=82 (60 NUSI, 22 SHAM) from ENDEAR, n=24 from CS12 that started in CS2, n=125 (83 NUSI, 42 SHAM) from CHERISH, n=20 from EMBRACE and n=11 from CS3A.

f The modelled economic evaluation used data from ENDEAR-SHINE.

g Patients were assessed 9-14 months after initial dose at enrolment to transition into the long-term extension study (CS12). Time between CS2 and CS12 studies varied by patient (196-413 days).

h CS12 included 52 patients previously enrolled in CS2 or CS10. 24 children in CS2 completed treatment in CS12. However, all (n=28) children in CS2 were eligible to continue in CS12. To be eligible for CS12, patients had to have completed dosing CS2 or CS10 ≥6 months (180 days) and ≤13 months (396 days) before Screening.

i EMBRACE was halted due to demonstrated efficacy in ENDEAR (data cutoff 30 March 2017). Eligible patients were transferred to amended open-label protocol (termed Part 2) for approx. 28 mths (24 mths NUSI and follow-up ~4 mths after last dose). For patients initially randomized to NUSI, median (range) time in the study (Parts 1 and 2 combined) was 995 (890-1010) days. For those randomized to control, the median (range) time in Part 1 was 302 (230-366) days, followed by NUSI treatment in Part 2 of 656 (653-659) days.

k Patients not eligible for ENDEAR and CHERISH were included in EMBRACE: 2 copies SMN2 (age ≤6 mths symptom onset, >7 mths at screening), 3 copies SMN2 (age ≤6 mths symptoms onset), 2-3 copies SMN2 (age ≥6 mths symptom onset, ≤18 mths at screening).
m Two-part study: Part 1 was exploratory dose finding and Part 2 investigated efficacy of RISD for 24 mths at the dose selected in Part 1. After completion of the 24-month treatment period, individuals could continue in the open-label extension for up to 3 years.

6.12 Except for ENDEAR, CHERISH, SUNFISH and EMBRACE which were RCTs that included a control arm (sham or placebo), all studies were open-label, non-comparative single arm design using TGA approved doses. Only SPR1NT, NURTURE and RAINBOWFISH were conducted in patients with pre-symptomatic SMA, which were small studies and included a total of 35 patients with 3 copies of SMN2. The ESC noted that of the studies provided, there was limited evidence relevant to informing the comparison of pre-symptomatic treatment with ONA vs symptomatic treatment in patients with 3 copies of SMN2 and no disaggregated outcomes specific to symptomatic patients with 3 copies of SMN2 were presented.

6.13 At the time of the evaluation, seven studies were ongoing (LT-002, START-LTFU, SHINE, NURTURE, RAINBOWFISH, FIREFISH and SUNFISH) with some interim results reported.

6.14 Overall, the risk of bias for ENDEAR, CHERISH and SUNFISH was low as they were RCTs. There was unclear risk of bias for the EMBRACE study, which was changed from a single double blind RCT design to become a two-part study that included a double-blind phase and an open-label extension.

6.15 The other studies were considered to be at high risk of bias due to the nature of their study design, being small, single arm, non-comparative studies. Also, while survival or death was an objective outcome, the other outcomes such as the assessment of motor milestone attainment were subject to variation between clinicians/studies, with associated high risk of bias, particularly given there were no comparative control arms in these studies.

6.16 There were some important differences across the studies:

<u>Studies in pre-symptomatic patients</u>

- The SPR1NT (ONA), NURTURE (nusinersen) and RAINBOWFISH (risdiplam) studies were designed for pre-symptomatic patients who were younger and healthier than patients in the symptomatic studies. The mean age at treatment was consistently less than 30 days across the pre-symptomatic studies. In SPR1NT and RAINBOWFISH, no patients required ventilatory support at baseline. While motor function on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) was not assessed for the cohort with 3 copies of SMN2 in SPR1NT, in NURTURE and RAINBOWFISH (interim data for three patients with >2 SMN2 copies), the scores at baseline were generally higher (>40, indicating a lack of SMA symptoms).

Studies in symptomatic patients

- Age at the start of dosing: Mean age at first dose (at screening) was younger in the studies with Type I patients compared to those with Types II and III patients;
- Disease duration (interval between symptom onset to starting treatment): Mean duration was shorter in the studies with Type I patients compared to those with Type II and III patients;
- SMA type or SMN2 copy numbers: All patients in the ONA studies had 2 copies of *SMN*2, as did the majority of patients in studies of nusinersen and risdiplam in infantile or early childhood. There was a higher proportion of patients with 3 copies of *SMN*2 in CHERISH, CS2, EMBRACE and SUNFISH; and
- There were baseline differences between the studies in terms of: motor milestones (ability to sit alone and ability to walk alone), ventilatory support, and nutritional support.

6.17 All studies included dosing regimens consistent with the dosage recommended in the PI, however, there were minor deviations in some studies. Dose adjustments for children aged less than 2 years were allowed in ENDEAR and in START, CS2 and CS3A, some patient cohorts/groups received lower or higher doses of study drugs than recommended in the PI. FIREFISH and SUNFISH were two-part studies in which the dosage regimen used in Part 2 was based on the doses determined in Part 1 (dose finding).

6.18 Across the symptomatic studies, there were notable differences in the interval between symptom onset and treatment initiation, with generally larger intervals for studies in SMA Types II and III. For example, in symptomatic patients with SMA Type I, the mean age range at the start of treatment in the ONA studies (3.1-4.1 months) was lower than in nusinersen studies (4.6-6.0 months). However, in CS2/CS12 (Types II and III, 2-4 SMN2 copies), the interval between the mean age at symptom onset and mean age at first dose was 3.5 years in Type II and 7.1 years in Type III, and in CHERISH (Types II and III, 2-4 SMN2 copies) median disease duration was 3.2 years (first dose at 4 years). In EMBRACE (2-3 SMN2 copies), median disease duration was 11.2 months at baseline (first dose at 16.7 months of age).

6.19 The duration of treatment follow-up in the ONA studies (up to 2 years) was generally longer than the nusinersen studies. However, patients in ONA and nusinersen studies are rolled over into long term follow up studies at the end of the shorter-term study, with the long-term study for ONA, START-LTFU (LT-001) and LT-002 planning to follow patients for 15 years (at May 2021 data cut, patient mean age was 6.2 and 2.1-4.8 years, respectively). The long-term follow-up study for nusinersen, SHINE, plans to follow patients up to 5 years (currently up to 4.2 years of follow-up from first dose of nusinersen in ENDEAR at August 2019 data cut). All risdiplam studies are ongoing, with median treatment period of 2 years and open label extension for 3 years.

Comparative effectiveness

6.20 Considering untreated patients with 3 copies of SMN2 are mostly likely to develop either SMA Type II (sitters) or Type III (walkers) and are not at an imminent risk of death, the most important outcomes for the comparison between pre-symptomatic treatment and watchful waiting/symptomatic treatment may be the attainment and maintenance of motor milestones. The improvement from sitting to walking may be particularly important treatment outcomes for Type II patients. The submission made a claim of superior efficacy based on developmental motor milestones.

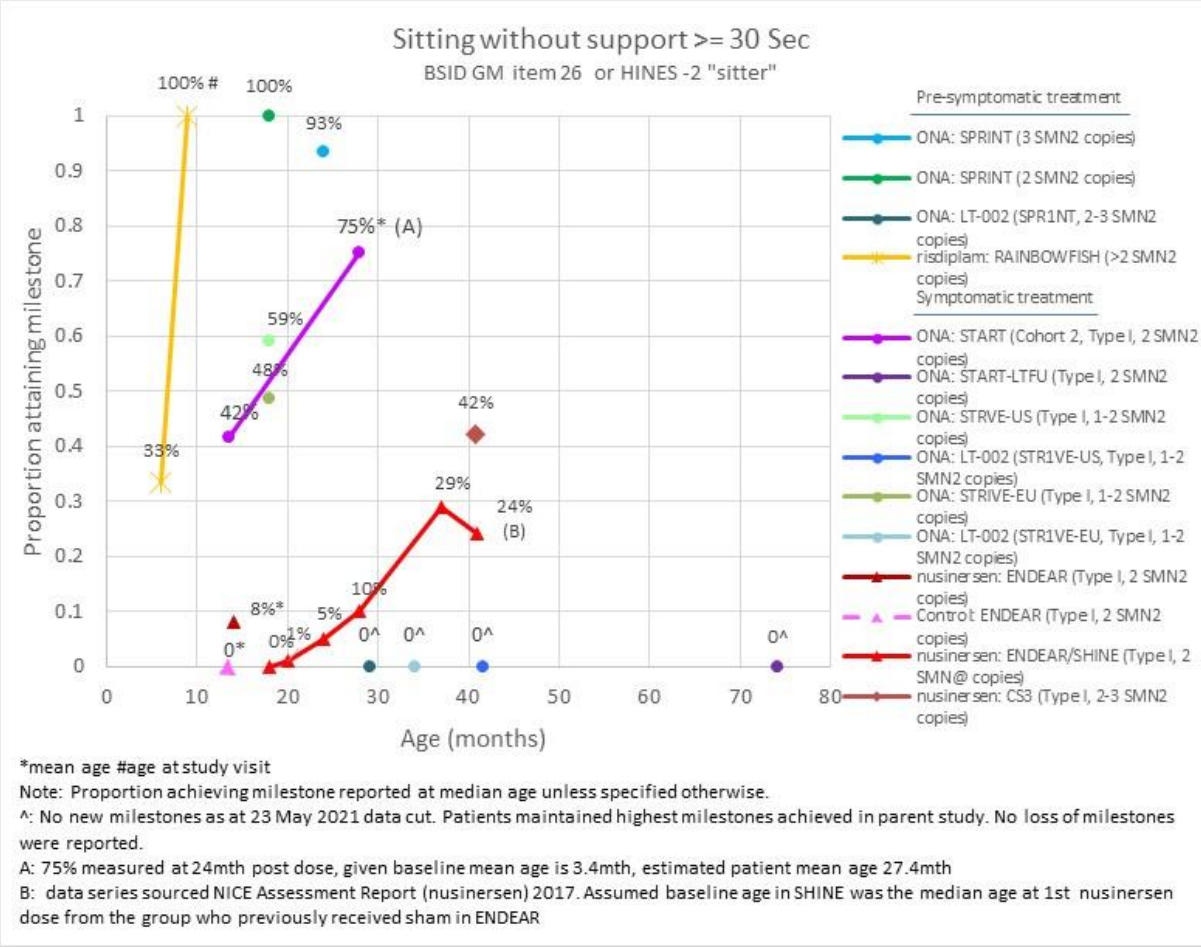
6.21 All the included studies assessed motor function, OS and EFS outcomes as either primary or secondary outcomes, however there were differences in their definitions and the measures used. The PBAC had previously considered all these outcomes in the November 2020 ONA submission. While the motor milestones reported in this submission included the ability to stand, ability to walk and ability to sit (≥30 seconds and for all definitions combined), there were some differences between pre-symptomatic and symptomatic studies in primary development milestones endpoints measured. For example, in SPR1NT (pre-symptomatic ONA), the primary and key secondary outcome for those with 3 copies of SMN2 was meeting the Bayley Scale for Infant Development (BSID) gross motor (GM) subtest for stand alone and walk alone, but for patients with 2 copies of SMN2 this was independent sitting on the BSID. The developmental milestones measured in symptomatic studies also varied (i.e., for Type I it was the ability to sit alone, but for Type II or III SMA this included either maintenance or improvement from baseline in motor milestones (assessed using a variety of scales such as BSID, Hammersmith Infant Neurological Examination (HINE-2) or WHO criteria).

Motor functioning

6.22 Figure 2 and Figure 3 present the motor development milestone outcome of ability to sit in the included studies. The milestone was reported as sitting without support (≥30, ≥10 or ≥5 seconds) assessed on either the BSID GM item 26, WHO Multicentre Growth Reference Study (WHO-MGRS) or HINE-2. The main outcome measure used to assess the ability to sit were BSID in the ONA studies and HINE-2 in the nusinersen and risdiplam studies.

6.23 The ESC noted that there were apparent differences in the proportion of patients reaching the milestone of sitting without support for ≥30 seconds for the pre-symptomatic ONA studies compared with the symptomatic treatment studies. However, the cohorts included in these studies were not necessarily comparable in terms of SMA Type and/or SMN2 copy number.

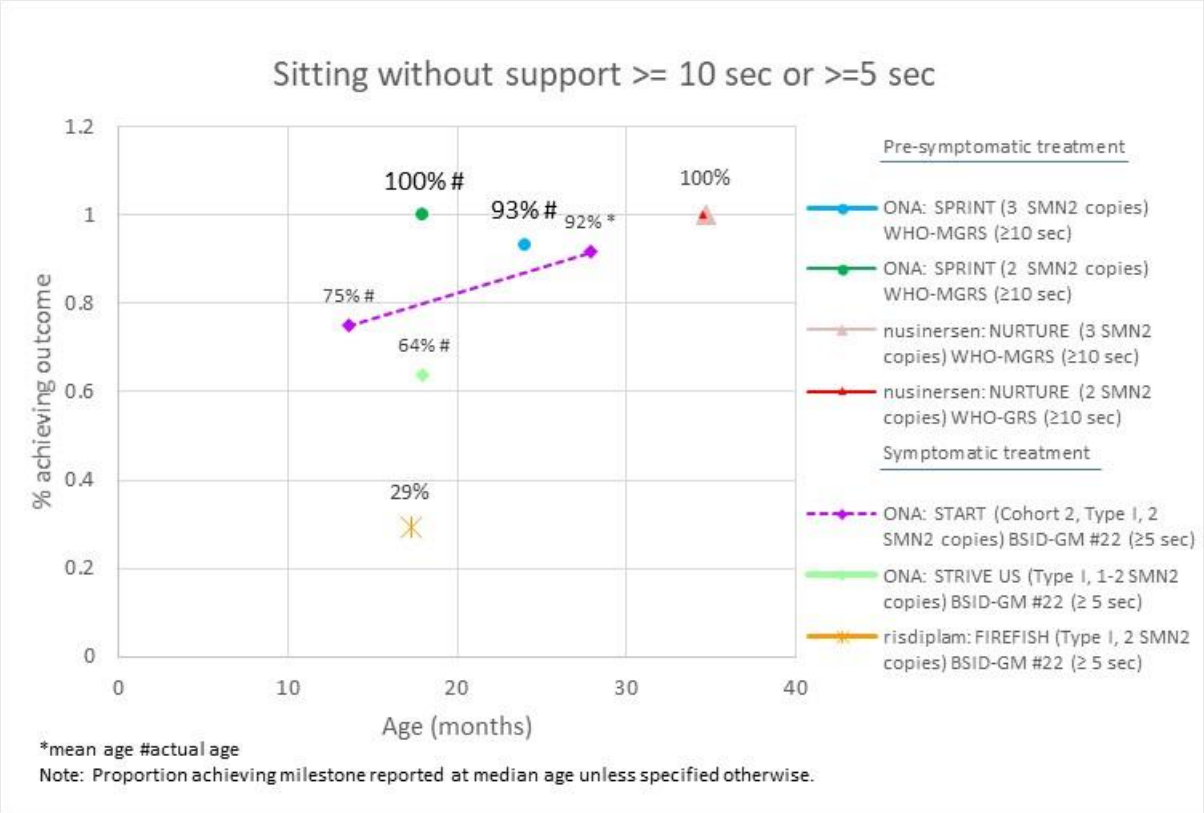
Figure 2: proportion of patients sitting without support (≥30 seconds as defined by BSID GM #26 video confirmed) in the ONA studies and "sitter" (by HINES-2) in nusinersen and risdiplam studies.



*mean age #age at study visit
Note: Proportion achieving milestone reported at median age unless specified otherwise.
^: No new milestones as at 23 May 2021 data cut. Patients maintained highest milestones achieved in parent study. No loss of milestones were reported.
A: 75% measured at 24mth post dose, given baseline mean age is 3.4mth, estimated patient mean age 27.4mth
B: data series sourced NICE Assessment Report (nusinersen) 2017. Assumed baseline age in SHINE was the median age at 1st nusinersen dose from the group who previously received sham in ENDEAR

Source: constructed during the evaluation from Table 2.36 and Table 2.37, pp126-127 of the submission.
BSID-GM=Bayley Scale for Infant Development (gross motor scale); HINE-2=Hammersmith Infant Neurological Examination (Section 2); ONA=onasemnogene abeparvovec;

Figure 3: proportion of patients sitting without support ≥10 seconds as defined by WHO-MGRS and ≥5 seconds as defined by BSID-GM #22.



Source: constructed during the evaluation from Table 2.36 and Table 2.37, pp126-127 of the submission.
BSID-GM=Bayley Scale for Infant Development (gross motor scale); ONA=onasemnogene abeparvovec; WHO-MGRS=World Health Organisation – Multicentre Growth Reference Study;

6.24 Table 5 summarises the motor development milestone outcomes of ability to stand unsupported across the included studies.

Table 5: Motor development milestones (ability to stand)

Treatment	Outcome	ONA n/N (%)	Control n/N (%)	NUSI n/N (%)	RISD n/N (%)	S3
Ability to stand alone (BSID[a], WHO-MGRS[b], HINE-2[c])						
ONA	Pre-symptomatic treatment					
	SPR1NT– BSID					
	2 *SMN2* copies, 18 months of age	11/14 (78.6%)	-	-	-	-
	3 *SMN2* copies, 24 months of age	15/15 (100%)	19 (23.5%)^	-	-	✓
	% achieved within window	14/15 (93.3%)	-	-	-	-
	Median (range) age at earliest achievement, 12.6 (9.5-18.3) months					
	Symptomatic treatment					
	START – BSID/WHO-MGRS (Type I, 2 *SMN2* copies)					
	13.6 months of age	2/12 (16.7%)	-	-	-	-
	24 months post dose	2/12 (16.7%)				
	STR1VE-US (Type I, 1-2 *SMN2* copies) – BSID, 14.7 months of age	1/22 (4.5%)	-	-	-	-
	STR1VE-EU (Type I, 1-2 *SMN2* copies) – BSID/WHO-MGRS, 18 months of age	1/33 (3%)	-	-	-	-
NUSI	Pre-symptomatic treatment					
	NURTURE (2-3 *SMN2* copies)	-	-	NR	-	-
	Symptomatic treatment – HINE-2					
	ENDEAR (Type I, 2 *SMN2* copies) median follow-up: NUSI 280 days, control 187 days	-	0/40 (0%)	*0/84 (0%)*[f]	-	✓
	CS3A (Type I, 2-3 *SMN2* copies) median (range) time on study 36.2 (2-46.9) months	-	-	*1/19 (5.3%)*[g]	-	-
	CS2 (Type II or III, 2-4 *SMN2* copies)	-	-	NR	-	-
	CS2/CS12 (Type II or III, 2-4 *SMN2* copies)	-		NR	-	✓
	CHERISH (Type II or III, 2-4 *SMN2* copies) WHO-MGRS, 79% in NUSI and 81% in control completed 15-month assessment	-	1/42 (2.4%)	1/84 (1.2%)	-	-
	EMBRACE (Part 1) (2-3 *SMN2* copies) 14-month assessment	-	2/7 (28.6%)	2/14 (14.3%)	-	-
RISD	Pre-symptomatic treatment					
	RAINBOWFISH – HINE-2					
	2 copies of SMN2, ≥12 months treatment[e]	-	-	-	2/4 (50%)	-
	>2 copies of SMN2, ≥12 months treatment[e]	-	-	-	3/3 (100%)	-
	Symptomatic treatment					
	FIREFISH (Part 2) (Type I, 2 *SMN2* copies) BSID, 12-month assessment	-	-	-	0/41 (0%)	-
	SUNFISH (Part 2) (Type II or III, non-ambulant)	-		-	NR	-

Green shading represents study population consisting only of patients treated pre-symptomatically. Unshaded rows represent studies in symptomatic patients. *Italics* indicate results extracted during the evaluation. *Italics* indicate results extracted during the evaluation.
Source: Tables 2.33 and 2.34, pp124-125 of the submission.
BSID=Bayley Scale for Infant Development; MGRS=Multicentre Growth Reference Study, NUSI=nusinersen; ONA=onasemnogene abeparvovec; RISD=risdiplam; *SMN2*=survival motor neuron 2; WHO=World Health Organisation;
S3 indicates studies used in the modelled economic evaluation (Section 3).
^ comparison with PNCR (natural history) control population.
A Bayley GM item 40: stands alone ≥3 seconds (after you release his/her hands).
B WHO-MGRS: standing alone ≥10 seconds. Child stands upright position on both feet (not toes) with back straight. Legs support 100% weight. No contact with a person or object.
c HINE-2: "standing unaided"
d No child was reported to stand alone as the highest achieved milestone while being in the extension study.
e In RAINBOWFISH the preliminary exploratory analysis at the July 2021 data cut was for 7 infants treated with RISD for ≥12 months.

f Result corrected during the evaluation. ENDEAR reported 1 patient achieved HINE-2 standing milestone: stands with support (1%) and stand unaided (0). The submission reported 1 patient achieved ability to stand alone.

g Result corrected during the evaluation. CS3 (Finkel 2021) final analysis reported 4/19 (21%) could stand (3 with support and 1 unaided). The submission reported 5/20 (25%) patients achieved ability to stand alone.

6.25 Table 6 summarises the motor development milestone outcomes of ability to walk unsupported across the included studies.

Table 6: Motor development milestones (ability to walk)

Tx	Outcome	ONA n/N (%)	Control n/N (%)	NUSI n/N (%)	RISD n/N (%)	S3
Ability to walk alone (BSID[a], WHO-MGRS[b], HINE-2[c])						
ONA	**Pre-symptomatic** treatment					
	SPR1NT– BSID					
	2 *SMN2* copies, 18 months of age	9/14 (64.3%)	-	-	-	-
	3 *SMN2* copies, 24 months of age	14/15 (93.3%)	17 (21%)^	-	-	✓
	% achieved within window	11/15 (73.3%)	-	-	-	-
	Median (range) age at earliest achievement, 14.1 (12.1-18.8) months					
	Symptomatic treatment					
	START (Type I, 2 *SMN2 copies*)– WHO-MGRS					
	13.6 months of age	2/12 (16.7%)	-	-	-	-
	24 months post dose	2/12 (16.7%)				
	STR1VE-US (Type I, 1-2 *SMN2* copies) – BSID, 15.3 months of age	1/22 (4.5%)	-	-	-	-
	STR1VE-EU (Type I ,1-2 *SMN2* copies) – BSID/WHO-MGRS, 18 months of age	1/33 (3%)	-	-	-	-
NUSI	**Pre-symptomatic** treatment					
	NURTURE (2-3 *SMN2* copies) – WHO-MGRS					
	2 copies of *SMN2*, 34.5 months of age	-	-	12/15 (88%)	-	-
	3 copies of *SMN2*, 24.7 months of age	-	-	10/10 (100%)	-	-
	Symptomatic treatment – HINE-2					
	ENDEAR (Type I, 2 *SMN2* copies)	-	-	NR	-	✓
	CS3A (Type I, 2-3 *SMN2* copies) median (range) time on study 36.2 (2-46.9) months	-	-	1/19 (5.3%)[g]	-	
	CS2 (Type II or III, 2-4 *SMN2* copies)	-	-	NR	-	-
	CS2/CS12 (Type II or III, 2-4 *SMN2* copies) - 6MWT	-			-	✓
	Type II, mean age at assessment 4.6 years[h]	-	-	1/11 (9.1%)	-	-
	Type III, mean age at final assessment 12.8 years			2/4 (50%)[j]		
	CHERISH (Type II or III, 2-4 *SMN2* copies) WHO-MGRS, 79% in NUSI and 81% in control completed 15-month assessment	-	*NR*[k]	*NR*[k]	-	-
	EMBRACE (Part 1) (2-3 *SMN2* copies) *14-month assessment*	-	0/7 (0%)	1/14 (7.1%)	-	-
RISD	**Pre-symptomatic** treatment					
	RAINBOWFISH – HINE-2					
	2 copies of SMN2, ≥12 months treatment[e]	-	-	-	1/4 (25%)	-
	>2 copies of SMN2, ≥12 months treatment[e]	-	-	-	3/3 (100%)	-
	Symptomatic treatment					
	FIREFISH (Part 2) (Type I, 2 *SMN2* copies)	-	-	-	0/41 (0%)	-

Tx	Outcome	ONA n/N (%)	Control n/N (%)	NUSI n/N (%)	RISD n/N (%)	S 3
	- BSID, 12-month assessment					
	SUNFISH (Part 2) (Type II or III, non-ambulant)	-		-	NR	-
Natural History	Zerres 1997 Type II (sitters) Type IIIa (walkers, SMA onset <3yrs) 10-year FU Type IIIb (walkers, SMA onset 3-30yrs) 10-year FU	-	0 (70.3%) (96.3%)	-	-	✓

Green shading represents study population consisting only of patients treated pre-symptomatically. Unshaded rows represent studies in symptomatic patients.

Source: Table 2.35, p126 of the submission. BSID=Bayley Scale for Infant Development; FU= follow up; MGRS=Multicentre Growth Reference Study, NUSI=nusinersen; ONA=onasemnogene abeparvovec; RISD=risdiplam; *SMN2*=survival motor neuron 2; tx=treatment; WHO=World Health Organisation; 6MWT=six-minute walk test; NR=not reported;

S3 indicates studies used in the modelled economic evaluation (Section 3).

^ comparison with PNCR (natural history) control population.

a Bayley GM item 43: walks alone. Child takes ≥5 steps independently, displaying coordination and balance.

b WHO-MGRS: walking alone. Child takes ≥5 steps independently in upright position with back straight. One leg moves forward while the other supports most of the body weight. There is no contact with a person or object.

c HINE-2: "walking independently"

d No child was reported to stand alone as the highest achieved milestone while being in the extension study.

e In RAINBOWFISH the preliminary exploratory analysis at the July 2021 data cut was for 7 infants treated with RISD for ≥12 months.

g Result corrected during the evaluation. CS3 (Finkel 2021) final analysis reported 2/19 (11%) could walk (1 with support and 1 unaided). The submission reported 2/20 (10%) patients achieved ability to walk alone.

h Calculated from age 2.1 years at first dose in CS2, plus 8.8 months follow-up, then enrolled in CS12 with Day 650 visit when the child first completed 6MWT.

j In CS2/CS12, 2/4 children with SMA Type III who were previously able to walk but had lost that ability before the baseline CS2 assessment regained the ability to walk independently during the course of CS2/CS12 studies. All children with SMA type III (n=17) had previously walked, but 4 lost that ability; thus, 13 were ambulatory at CS2 baseline.

k Result corrected during the evaluation. CHERISH reported 1/84 NUSI patient achieved ability to walk with assistance. The proportion who achieved ability to walk alone was not reported. However, 13/84 children in NUSI group and 2/42 control group achieved ≥1 new WHO motor milestone at 15 months assessment.

6.26 Table 7 summarises the results from longer term extension studies for ONA (START-LTFU and LT-002) and nusinersen (ENDEAR/SHINE).

Table 7: Highest milestone attained in long-term follow-up, for ONA (SPRINT, START-LTFU, LT-002) and NUSI (ENDEAR/SHINE)

n/N(%)	None	Sit with support	Sit without support	Hand & knees crawling	Stand with assistance	Walk with assistance	Stand alone	Walk alone	Co admin NUSI/RISD
SPR1NT/LT-002 (3 SMN2 copies)									
- End of SPR1NT (up to age 24 mth)	-	-	-	-	-	-	1/15 (7%)	14/15 (93%)	None[a]
- LT-002 23 May 2021 data cut: mean age 29.6 mth[b]	-	-	-	-	-	-	-	5/8 (63%)[c]	None
SPR1NT/LT-002 (2 SMN2 copies)									
- End of SPR1NT (up to age 18 mth)	-	-	-	-	2/14 (14%)	1/14 (7%)	2/14 (14%)	9/14 (64%)	None
- LT-002 23 May 2021 data cut: mean age 29.9 mth[d]								4/7 (57%)[e]	1/7 (14%)
START/START-LTFU (Type I, 2 SMN2 copies)									
- end of START (≥20 mth of age, mean age 27.9 mth)	4/15 (27%)	11/15 (73%)	9^/15 (60%)	NR	2/15 (13%)	2/15 (13%)	2/15 (13%)	2/15 (13%)	None
- START-LTFU 19 Aug 2019 data cut: mean age 4.8 yrs*	2/15 (13%)	1/15 (7%)	5/15 (33%)	NR	3/15 (20%)	-	-	2/15 (13%)	7/15 (47%)
- START-LTFU 23 May 2021 data cut: mean age 6.5 yrs*	2/15 (13%)	-	6/15 (40%)	NR	3/15 (20%)	-	-	2/15 (13%)	8/15 (53%)
ENDEAR/SHINE (Nusinersen in ENDEAR) (Type I, 2 SMN2 copies)									
- 2.08 yrs since 1st dose	NR	NR	22/59 (37%)	1/59 (2%)	5/59 (8%)	3/59 (5%)	0/59 (0%)	0/59 (0%)	-
- 3.4 yrs since 1st dose of nusinersen	NR	NR	37/58 (64%)	3/58 (5%)	11/58 (19%)	4/58 (7%)	1/58 (2%)	1/58 (2%)	-
ENDEAR/SHINE (Sham control in ENDEAR) (Type I, 2 SMN2 copies)									
- 1.34 yrs since 1st dose	NR	NR	0/22 (0%)	0/22 (0%)	0/22 (0%)	0/22 (0%)	0/22 (0%)	0/22 (0%)	-
- 2.65 yrs since 1st dose of nusinersen	NR	NR	1/20 (5%)	0/20 (0%)	0/20 (0%)	0/20 (0%)	0/20 (0%)	0/20 (0%)	-

Green shading represents study population consisting only of patients treated pre-symptomatically. Italics indicate results extracted during the evaluation.

Source: Compiled during the evaluation from Castro 2020 (p8), AVXS-101-LT-001 and LT-002 LTFU report OCT2021.pdf

NUSI=nusinersen; ONA=onasemnogene abeparvovec; RISD=risdiplam; yr=year;

^ Patients sitting ≥30 seconds are included in the totals for ≥15 seconds, ≥10 seconds, and ≥5 seconds.

* 2 patients discontinued from START LTFU, but % still expressed out of the original N.

a Based on the study exclusion criteria. Also, concomitant use of therapy for treatment of SMA e.g. NUSI was prohibited during the study.

b 8 patients with 3 copies of SMN2 from SPR1NT were included in the interim analysis, however, no data were available for 3 patients.

c Patients maintained the highest developmental milestone achieved (walk alone) from the parent study SPR1NT.

d 7 patients with 2 copies of SMN2 from SPR1NT were included in the interim analysis, however, no data were available for 3 patients.

e one patient with 2 copies of SMN2 reported highest milestone of ability to walk alone in LT-002, from previous milestone of walk with assistance in SPR1NT.

Pre-symptomatic

6.27 In SPR1NT, all 15 (100%) patients with 3 copies of SMN2 treated pre-symptomatically with ONA achieved at least one developmental milestone at 24 months of age post

dose, with the highest milestone as the ability to stand alone or walk alone assessed on either BSID or WHO-MGRS. The median age at earliest achievement was 12.6 and 14.10 months, respectively. A total of 14/15 (93.3%) achieved the ability to sit without support.

6.28 In the pre-symptomatic studies, motor function attainment (particularly the ability to walk) appeared to improve with increasing SMN2 copy number; more patients with 3 copies of SMN2 achieved the ability to walk than those with 2 SMN2 copies (93.3% versus 73.3% in SPR1NT for ONA and 100% versus 88% in NURTURE for nusinersen).

Symptomatic

6.29 For symptomatic patients, motor function attainment varied by SMA type, disease duration and baseline motor function. The highest motor function attainment also appeared to increase with higher SMA type and SMN2 copy number. In the studies of infantile onset SMA (4.6-6 months of age at baseline), ENDEAR (Type I, 2 SMN2 copies) reported no patient achieved the ability to stand, whereas in CS3A (Type I, 2-3 copies) 5.3% achieved the ability to stand or walk independently. Across the studies that included later-onset SMA, CHERISH (Type II or III, 2-4 SMN2 copies) reported 1.2% achieved the ability to stand independently at 15 months of treatment versus 2.4% in control, however, at baseline, mean age at treatment was 3-4 years (disease duration of 2.1-3.2 years) and all patients could sit independently, and a proportion of patients already attained the ability to walk with support (24% in nusinersen vs 33% in control). In CS2/CS12 2/4 (50%) patients with SMA Type III (2-4 SMN2 copies) were assessed as having regained the ability to walk alone during the study at 12.8 years, versus 1/11 (9.1%) patients with Type II (2 SMN2 copies) that newly achieved the ability to walk alone at 4.6 years.

6.30 There were large intervals between age at symptom onset (11 months for Type II and 22 months for Type III) and age at screening/first dose (4.4 years in Type II and 8.9 years in Type III). The ESC considered this evidence is unlikely to represent clinical practice given availability of DMTs on PBS, as patients are expected to be treated soon after symptom onset and likely with better outcomes.

6.31 All patients with SMA Type III in CS2 had the ability to walk but 4 lost that ability prior to CS2 baseline, whereas all those with Type II had the ability to sit alone and 2 (18%) could walk with support at CS2 baseline. In EMBRACE (patients with 2-3 SMN2 copies), 14.3% of children were able to stand and 7.1% could walk independently after 14 months of treatment. Compared to CS2, these patients were younger (median age at first dose was 16.7 month) and treated sooner (disease duration 11.2 months with 57% able to sit alone). However, the different milestone measures and timepoints for the reported data makes comparisons difficult. The ESC noted the outcomes for patients with 3 SMN2 copies in the NUSI trials were presented as aggregated outcomes which included those for patients with 2 and/or 4 SMN2 copies. The ESC considered that the lack of disaggregated outcomes for symptomatic patients with 3 SMN2 copies meant that comparisons were of limited value.

6.32 Natural history data from Zerres 1997 indicated that 70.3% and 96.3% of SMA IIIa and IIIb patients followed up retained their ability to walk at 10 years versus 0% for those with Type II SMA (the study referred to SMA Type II patients as sitters, so by definition they were not able to walk). The ESC noted that the data presented indicated the majority of patients with Type III SMA would achieve and retain the motor milestone of ability to walk. The ESC considered that the magnitude of benefit of pre-symptomatic treatment was particularly uncertain for Type III SMA patients noting that a substantial proportion of patients with Type III SMA have 3 SMN2 copies (see Figure 1).

6.33 Symptomatic studies of ONA were limited to patients with SMA Type I (1-2 copies of SMN2). In these studies, few patients achieved the ability to stand or walk (3-16.7%), but more patients were able to sit (42-75%). For Type I patients treated with nusinersen, few achieved the ability to sit (8% in ENDEAR), the ability to stand (0-14.3%) and ability to walk (5.3-20%). Interim analysis of risdiplam from FIREFISH which also enrolled Type I SMA patients, showed 29% of patients achieved the ability to sit unsupported at the 12-month assessment (age range 14.5-18.9 months) but none achieved the ability to stand or walk.

6.34 The ESC noted that long-term data were very limited for patients with Type I SMA (START-LTFU (n=10) includes data for patients up to 6.6 years since dosing with ONA) and were not available for pre-symptomatic studies or symptomatic studies involving patients with SMA Type II or III.

6.35 Longer term follow-up from START (Type I, 2 SMN2 copies), showed that all patients (10/10) from Cohort 2 of START who received the therapeutic dose of ONA have maintained all previously attained milestones with 3 patients gaining new milestones ('stands with assistance' from previous sit alone for either ≥15 or 30 sec), however for two patients this may be due to concomitant nusinersen or risdiplam use. Use of concomitant nusinersen/risdiplam was high in START-LTFU, with 8/13 (61.5%) and 5/10 (50%) patients from the overall and the START Cohort 2 populations having received concomitant therapy respectively, with the majority to have started post START but prior to enrolment in START-LTFU. Therapy was initiated independent of the sponsor in each case.

6.36 Long-term data from SHINE (interim analysis), showed that for patients who began nusinersen in ENDEAR (Type I, 2 SMN2 copies) and continued in SHINE, additional improvements in total and specific HINE-2 motor milestones, such as head control and sitting alone were observed. In the patients who received sham control in ENDEAR and began nusinersen in SHINE, new improvements in total HINE-2 motor milestones were also observed. The highest milestone attained in this group at 3.4 years after first dose of nusinersen included 1/58 (2%) that could walk alone, 4/58 (7%) that could walk with assistance, 1/58 (2%) that could stand alone, 11/58 (19%) that could stand with assistance and 37/58 (64%) that could sit without support.

Overall Survival (OS) and Event Free Survival (EFS, survival without permanent ventilation)

Pre-symptomatic

6.37 In SPR1NT, all 15 (100%) patients with 3 copies of SMN2 receiving pre-symptomatic treatment of ONA remained alive and free from permanent ventilation at 24 months of age. At the interim data cut (23 May 2021) those patients (n=8) that enrolled in the long-term extension study LT-002 also remained alive and free of permanent ventilation (mean age 29.6 months).

Symptomatic

6.38 In the symptomatic studies, EFS outcomes were only reported for studies in SMA Type I patients, where the reported survival was generally higher in the ONA studies (>90%) versus those reported in the nusinersen and risdiplam studies (55%-85%). As noted at the November 2020 PBAC meeting, the results were difficult to compare due to important differences across the studies and the high likelihood of bias due to evidence coming from small single arm studies for ONA (paragraph 6.21, onasemnogene abeparvovec PSD, November 2020 PBAC meeting).

Comparative harms

6.39 Limited adverse events (AEs) data were available from the ongoing studies. In SPR1NT, all 15 (100%) patients with 3 copies of *SMN2* experienced at least one AE with 3 (20%) patients reporting serious AEs up to 24 months of age (i.e., increased alanine aminotransferase, ear infection and rash). The most commonly reported AEs were pyrexia, upper respiratory tract infection, cough and nasopharyngitis. Most AEs were moderate in severity. There were no deaths reported during the study. Treatment-related AEs were reported for 8 (53.3%), and the most frequent were increase in aspartate aminotransferase and amino alanine aminotransferase. AEs of special interest were related to hepatotoxicity, thrombocytopenia, cardiac AEs, thrombotic microangiopathy and sensory abnormalities suggestive of ganglionitis, and most were graded mild to moderate in severity.

6.40 Table 8 presents a comparison of the common AEs reported in SPR1NT and NURTURE for children with 3 copies of SMN2 who received pre-symptomatic treatment with ONA and nusinersen, respectively. In NURTURE, 2/10 (20%) patients had at least one event that was determined by investigators as possibly or definitely related to the lumbar puncture procedure. In RAINBOWFISH, the preliminary safety data showed no treatment-related serious AEs in pre-symptomatic infants treated with risdiplam for up to 18.1 months.

Table 8: Common AEs in SPR1NT and NURTURE (patients with 3 copies of SMN2)

AEs, n/N (%)	SPR1NT ONA (n=15)	NURTURE NUSI (n=10)	RR (95%CI)
AE possibly or definitely related to lumbar puncture procedure**	0	2 (20)	3.0 (0.3, 29.0)
Pyrexia	11 (73.3)	7 (70)	1.0 (0.6, 1.6)
Upper respiratory tract infection	9 (60.0)	7 (70)	1.2 (0.7, 2.1)
Cough	4 (26.7)	5 (50)	1.9 (0.7, 5.3)
Nasopharyngitis	3 (20.0)	4 (40)	2.0 (0.6, 7.1)
Vomiting	2 (13.3)	3 (30)	2.3 (0.5, 11.1)
Hypotonia	2 (13.3)	0[a]	0.3 (0.0, 5.5)
Rash	2 (13.3)	1 (10)[b]	0.8 (0.1, 7.2)

Green shading represents study population consisting only of patients treated pre-symptomatically. unshaded rows represent studies in symptomatic patients.

Source: Table 17, Attachment 8 Near Market comparator analysis.docx.

AE=adverse event; NUSI=nusinersen; ONA=onasemnogene abeparvovec; RISD=risdiplam; NR=not reported;

** Assessed by the investigator; included events that were possibly related or related to the lumber puncture procedure.

a reported as muscular weakness.

b reported as rash possibly related to study drug.

6.41 Across the studies of symptomatic treatment, most ONA treated patients experienced at least one AE, with 25% to 54.5% of those events deemed to be related to ONA treatment, and 45.5% to 83.3% reported serious AEs, including pneumonia, upper respiratory infection, respiratory distress, bronchiolitis and respiratory failure. Two deaths were reported in the STRIVE studies, but none in START and the long-term follow-up studies (START-LTFU and LT-002). In the nusinersen studies, the incidence of AEs was similar between nusinersen group vs sham control for ENDEAR, CHERISH and EMBRACE. For patients treated with nusinersen, 16.7-81.3% experienced serious AEs. The most frequently reported serious AEs in the ENDEAR study were respiratory failure and distress (25% and 26%, respectively), and pneumonia (24%). Interim analysis from SHINE (data cut: 15 October 2018)[7] indicated safety was maintained for nusinersen treated ENDEAR/SHINE patients for median of 997.5 days (approx. 33 months), and the most common AEs during SHINE were consistent with ENDEAR: pyrexia (66%), upper respiratory tract infection (38%), pneumonia (31%); nasopharyngitis (29%), and ear infection (26%).

6.42 For patients treated with risdiplam, 92.5% to 100% reported any AEs, and 20% to 58% experienced serious AEs. The most common serious AEs included pneumonia, hypotonia and respiratory failure. In FIREFISH, three patients had fatal respiratory complications that are characteristic of Type I SMA.

6.43 The ESC noted that all DMTs for SMA were associated with a high probability of experiencing an AE.

[7] Darras BT, De Vivo DC, Farrar MA, et al. Safety Profile of Nusinersen in Presymptomatic and Infantile-Onset Spinal Muscular Atrophy (SMA): Interim Results from the NURTURE and ENDEAR-SHINE Studies (1659). Neurology 2020. 94(15 Supplement)

Benefits/harms

6.44 The submission did not present comparative efficacy or safety data to allow for a quantitative comparison of the benefits and harms of treatment between ONA in pre-symptomatic patients with 3 copies of *SMN2* and DMTs in active treatment of symptomatic patients with SMA. Accordingly, benefits/harms table was not presented.

Clinical claim

6.45 The submission described ONA as superior in terms of effectiveness on developmental milestones (i.e., standing and walking) compared to symptomatic treatment with DMTs (ONA, nusinersen and risdiplam) and non-inferior in terms of safety for pre-symptomatic treatment of SMA in children with 3 copies of *SMN2* gene.

6.46 The clinical evidence for the effectiveness of ONA in patients with 3 copies of SMN2 was uncertain due to:

- Limited long-term data: While the result from SPR1NT showed that most patients with 3 copies of SMN2 who were treated with ONA prior to symptoms achieved age-appropriate motor milestones (ability to stand or walk alone) at 24 months of age, the extended follow-up data were only available for 5.6 months (29.6 months of age) from LT-002 (interim data cut 23 May 2021).
- Limited comparative data: There were limited data for symptomatic treatment of patients with SMA Types II or III, this was a concern given it is likely to be the predominant phenotype of patients with 3 copies of SMN2. The Type II or Type III symptomatic treatment studies (CS2/CS12 with nusinersen) may also lack applicability to the PBS population given patients were treated approximately 3.5 or 7.1 years after symptom onset respectively rather than soon after symptom onset, so patients may have had poorer outcomes as a result.
- Heterogenous population, outcome assessment and design: The clinical data comprised mostly of small nonrandomised studies with significant heterogeneity including potential treatment effect modifiers such as SMN2 copy numbers within phenotype, age at treatment initiation, disease duration, baseline motor function, disease duration, as well as difference in milestone measurement and assessment timepoints making comparisons difficult.
- Counter factual SMA type: Given the counterfactual phenotype of patients treated pre-symptomatically with ONA will never be revealed, and that patients with 3 SMN2 copies may adopt a range of phenotypes from never sitting and imminent death without treatment (Type I) to normal life span and minor motor deficits (Type IV), any benefit will also depend on the expected composition of these phenotypes in Australia, which may vary from estimates in natural history.

6.47 The ESC considered that the claim of superior effectiveness compared to symptomatic treatment with DMTs was not adequately supported by the available evidence. The

ESC noted there were limited data available to inform the comparison and it was unknown whether the effects of ONA would be maintained over a lifetime given the limited long-term data. The ESC considered it was difficult to quantify any benefit as the disease trajectory of pre-symptomatic patients was unknown.

6.48 The ESC considered the claim of non-inferior safety was reasonable.

6.49 The PBAC accepted the claim of superior comparative effectiveness for pre-symptomatic treatment of patients with 3 copies of *SMN2*, on the basis that pre-symptomatic treatment would be expected to prevent or reduce the irreversible loss of motor neurons and therefore result in superior outcomes for patients. However, the PBAC noted that the magnitude of benefit could not be discerned from the limited clinical data.

6.50 The PBAC recalled it previously noted that safety data presented for ONA and nusinersen indicated that ONA had a similar or greater proportion of patients with any AE, serious AEs, and treatment related serious AEs and noting the black box safety warning for the risk of acute serious liver injury (para 7.6 ONA PSD, November 2020 PBAC meeting). The PBAC considered that the claim of non-inferior comparative safety for pre-symptomatic treatment with ONA compared with watchful waiting was not reasonable, where some patients (albeit a small proportion) may not require symptomatic treatment with DMTs.

Economic analysis

6.51 The submission presented a test and treat cost-utility analysis for patients with 3 copies of *SMN2* comparing 'the proposed strategy' (pre-symptomatic treatment with ONA) versus 'status quo' initiating treatment as symptoms emerge. The modelling approach was a Markov cohort analysis (7 health states) with an associated decision tree incorporating *SMN2* testing accuracy in the pre-symptomatic arm and splitting patients by SMA type in status quo. Overall, the model structure was overly ambitious for the limited clinical data.

6.52 The clinical evidence supporting the model was poor as it comprised mostly of small non-randomised studies with significant heterogeneity including potential treatment effect modifiers such as *SMN2* copies within phenotype, age at treatment initiation, disease duration, baseline motor function, intervals between symptom onset and treatment, as well as differences in milestone measurement and assessment timepoints. The evidence was particularly sparse for symptomatic treatment of Types II and III SMA, this was a concern given Types II and III SMA are the most common phenotypes of patients with 3 copies of *SMN2*. Further, there were no disaggregated outcomes specific to symptomatic patients with 3 copies of *SMN2*.

6.53 Limiting symptomatic treatment in the status quo arm of the model to NUSI was inconsistent with the clinical evaluation which also considered ONA and risdiplam for symptomatic treatment. The PSCR stated NUSI can be considered representative of SMA treatments in the symptomatic setting given ONA and RISD were recommended

for listing by the PBAC on a cost-minimisation basis to NUSI and the clinical evidence presented demonstrates at least non-inferior efficacy and safety across ONA, NUSI and RISD for symptomatic SMA. The PSCR also stated that incorporating each DMT would add uncertainty and complexity to the economic evaluation. The ESC considered that limiting symptomatic treatment in the status quo arm to NUSI was unlikely to adequately represent outcomes and costs in clinical practice.

6.54 A summary of the key components of the economic evaluation is presented in Table 9.

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

Component	Summary
Population	Patients with genetically confirmed SMA and 3 copies of SMN2. In the status quo arm, these patients were assumed to adopt either symptomatic Type I, II, IIIa or IIIb/IV SMA (note despite the labelling, Type IV was not allocated any patients, for clarity, this group is referred to as Type IIIb herein). The phenotypes of patients likely to be treated on PBS were unknown, however based on natural history, patients with 3 SMN2 copies are most likely to develop Type II or III SMA.
Treatments	'Proposed strategy' (pre-symptomatic treatment with ONA) vs 'status quo' initiating NUSI as symptoms emerge. Inappropriate for status quo given patients are also able to access ONA (Type I, ≤ 9mth of age) or RISD (Types I-IIIa) on PBS. This is also inconsistent with the financial estimates which include offsets for NUSI and RISD.
Time horizon	30 years in the model base case versus 24 months in the SPR1NT study.
Outcomes	Life years (LYs) and quality-adjusted life years (QALYs) gained.
Methods used to generate results	Markov cohort expected value.
Health states	7 health states: - 1. Non sitter (PAV) - 1. Non sitter - 2. Sitter (including sub-state "Loses sitting") - 3a. Delayed Walker (including sub-state "Loses walking") - 3b. Experiences later onset SMA (including sub-state "Loses walking") - Broad range of normal development (BRND) - Death The model's base case assumed no motor milestone regressions. This may not be reasonable over a 30-year time horizon.
Cycle length	One month.
Starting health states assumed	**SMA type** / **Starting health state** Pre-symptomatic (ONA) / 'BRND' Symptomatic Type I SMA / '1.Non sitter' Symptomatic Type II SMA / '2.Sitter' Symptomatic Type IIIa, IIIb SMA / 'BRND' Inappropriate and favoured ONA.
Transition probabilities (source)	- Diagnostic accuracy of genetic SMN2 testing (MSAC application 1589). The source for diagnostic accuracy for SMN2 testing was inappropriate as they related to predictive accuracy of SMN2 copy number ≤3 in selecting patients for treatment with nusinersen based on its requested listing rather than accuracy of the genetic test for SMN2 copy number, which, based on the submission (p12) was close to 100%. - Motor milestone achievement for pre-symptomatic treatment (SPR1NT). - Motor milestone achievement for symptomatic treatment (NUSI studies). - Health state-specific mortality: assumed to follow population mortality in the proposed strategy arm, and in the symptomatic arm to follow natural history data in the "1.non sitter' and '2.Sitter' health states and

<table>
<tr><th>Component</th><th>Summary</th></tr>
<tr><td></td><td>general population mortality for '3a. Delayed Walker', '3b. Experiences later onset SMA' and 'BRND' health states.
It was inappropriate to apply natural history OS data to patients treated with DMTs (both arms) for long term survival.</td></tr>
<tr><td>Extrapolation method (survival)</td><td>For natural history data, parametric functions were fitted to the empirical data to extrapolate survival, with the Weibull function selected in the base case for '1.Non-sitter' based on what was considered the most appropriate distribution in the NICE model. The Generalised Gamma function was selected in the base case for '2. Sitter', based on goodness of fit (AIC, BIC and visual inspection), and clinical plausibility.

Proportion of QALYs and costs in the extrapolated period (end of clinical study period to end of model duration of 30 years)
<table>
<tr><th></th><th>End of trial period</th><th>Costs in extrapolated period</th><th>QALYs in extrapolated period</th></tr>
<tr><td>Pre-symptomatic</td><td>24 months</td><td>24.5%</td><td>88.0%</td></tr>
<tr><td>Symptomatic Type I</td><td>46 months</td><td>65.2%</td><td>83.3%</td></tr>
<tr><td>Symptomatic Type II</td><td>85 months</td><td>71.3% (74.4% drug)</td><td>59.9%</td></tr>
<tr><td>Symptomatic Type IIIa</td><td>76 months</td><td>75.3% (77.2% drug)</td><td>65.3%</td></tr>
<tr><td>Symptomatic Type IIIb^</td><td>N/A</td><td>N/A</td><td>N/A</td></tr>
</table></td></tr>
<tr><td>Health related quality of life (QoL)</td><td>Literature-based sources were used for QoL:
<table>
<tr><th>Health state</th><th>Utility (source)</th><th>Alternative utility values</th></tr>
<tr><td>1.Non sitter</td><td>0.19 (Thompson et al 2017)</td><td rowspan="2">1. 0.756, 2. 0.764 - CHERISH,
1. 0.104, 2. 0.067 - Chambers et al 2020.</td></tr>
<tr><td>2.Sitter</td><td>0.60 (Teppenden et al 2018)</td></tr>
<tr><td>3a. Delayed walker; 3b. Experiences later onset SMA; BRND</td><td>General population utility (Ara & Brazier 2010)</td><td>0.878, 0.72, 0.54 - Malone et al 2019</td></tr>
<tr><td>Loses walking (Experiences later onset SMA / Delayed walker)</td><td>0.764 (CHERISH)</td><td></td></tr>
<tr><td>Death</td><td>0 (Assumption)</td><td></td></tr>
</table>
These sources were the same as used in previous published SMA models and the November 2020 ONA submission for SMA Type I, with the distinction that the November 2020 submission also included utility benefits for achieving interim milestones, 0.1 for '1. Non sitter' on-treatment and 0.05 for '2. Sitter' on-treatment.</td></tr>
<tr><td>Healthcare costs (disease management costs)</td><td>Australian SMA QoL and burden of disease study (Chambers et al 2020)</td></tr>
</table>

Italics indicate results generated during the evaluation.

Source: Table 3.1, p163 of the submission.

AIC=Akaike information criterion; BIC=Bayesian information criterion; BRND=broad range of normal development; NUSI=nusinersen; ONA=onasemnogene abeparvovec; OS=overall survival; PAV=permanent assisted ventilation; QoL=quality of life; RISD=risdiplam; SMA=spinal muscular atrophy; SMN=survival of motor neurone.

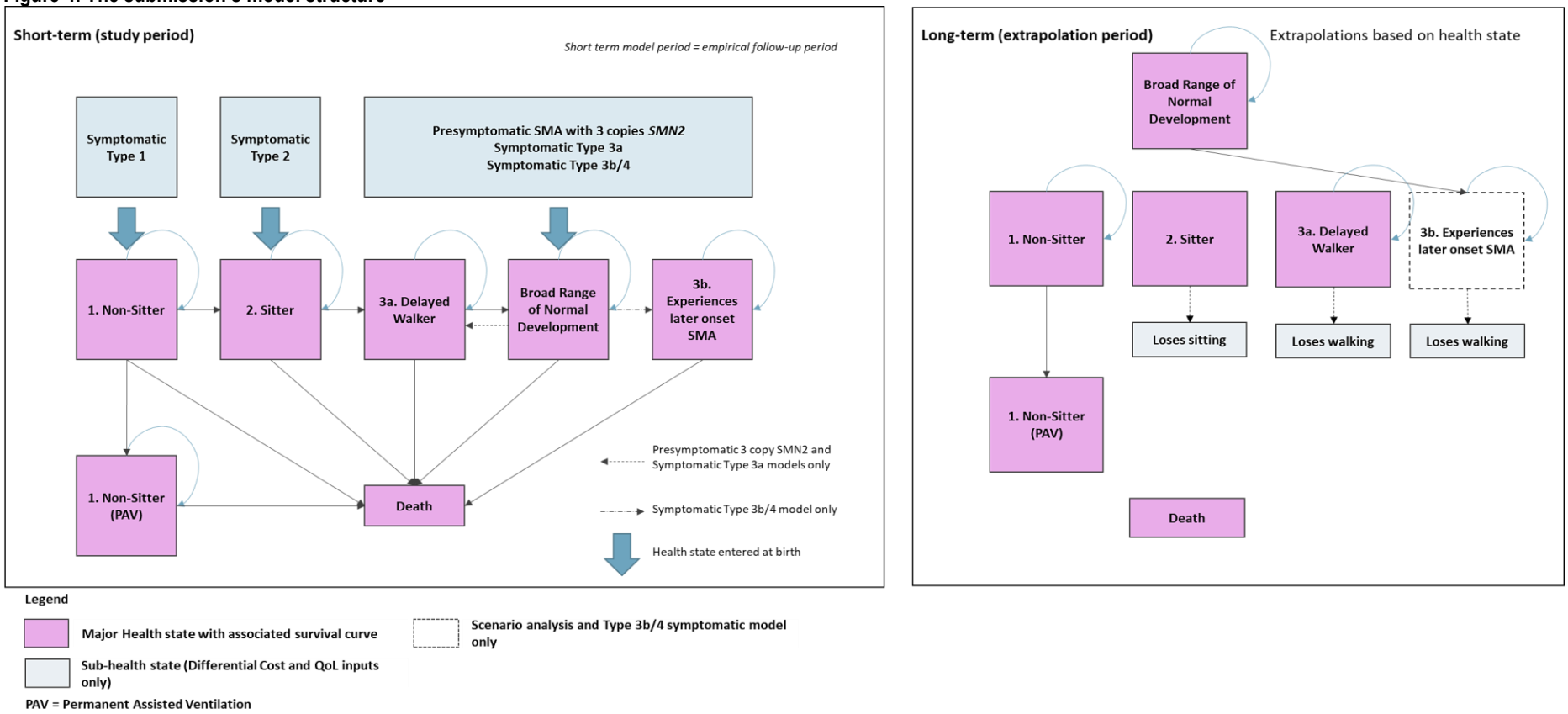
^ No trial transition probabilities were applied to this population, hence no "extrapolated period" applies here. The model assumed that all patients in this group started treatment at 18 years, transitioned to the '3b. Experiences later onset SMA' health state and remained in this state for the model duration.

6.55 The ESC noted that the utilities applied in the model were from a number of different sources. The ESC noted the utility values varied substantially between the sources (e.g., the health state utility for patients with Type II SMA varied from 0.764 in CHERISH to 0.067 in Chambers et al 2020). The ESC also noted that for the utility values applied in the model there was wide variation between the most and least severe states, which was not seen in the utilities derived from CHERISH or the European

burden of illness study (though neither of these sources reported utility values that appear to be plausible). In addition, the use of general population utilities for the BRND state assumed that patients who met development milestones were the same as the general healthy population. The ESC considered that this was not reasonable given the potentially high levels of residual disability associated with SMA despite treatment, and favoured ONA pre-symptomatic treatment. The ESC noted that application of alternative values (e.g. case vignette values using EQ-5D (Lloyd et al; reported in Malone et al 2019)) had a substantial impact on the ICER and therefore utility values were a significant source of uncertainty in the economic evaluation.

6.56 Figure 4 illustrates the model structure and health state transitions.

Figure 4: The submission's model structure



Source: Figure 3.3, p176 of the submission.
PAV=permanent assisted ventilation; SMA=spinal muscular atrophy; SMN=survival motor neuron.
Note: Despite the labelling, no symptomatic Type IV patients were included in the model, so 'Type 3b/4' represents only Type IIIb symptomatic patients.

6.57 The model's base case assumed no patient experienced regression for motor milestones achieved (sitting and walking) and no subsequent treatments were included for either arm. The ESC noted that PBS-subsidised subsequent treatment with nusinersen or risdiplam following ONA is only allowed where patients have a documented loss of milestone. Although no child in the long term follow-up studies for ONA has lost a milestone so far (PSCR, pre-PBAC response), the ESC considered this assumption was highly uncertain over a model duration of 30 years. The model's assumption favoured ONA pre-symptomatic treatment. The ESC considered that there is likely to be some use of sequential treatments where patients experience loss of motor milestones, though this is likely to be lower in patients with 3 copies of SMN2 where the phenotype is less severe, on average.

6.58 Prior to treatment initiation, patient outcomes in the status quo arm were assumed to follow natural history by SMA Type. Once treated, patients were assumed to follow outcomes from the clinical studies ('short-term model period' in the submission) however beyond the trial follow ups, outcomes (mainly survival) were extrapolated based on natural history data ('long term model period' in the submission). The reliance on natural history data to predict patient outcomes for symptomatic SMA for the long term model period resulted in significantly reduced survival for patients with Type I and Type II SMA, which was inconsistent with the clinical data suggesting improved survival of Type I and II SMA patients with DMT treatment.

6.59 Assumptions in the model also favoured the proposed strategy particularly for patients with Type I and Type II SMA, for example, all pre-symptomatic patients in the proposed strategy entered the model from 'BRND' (i.e., the best possible health state) whereas Type I and Type II SMA patients in the status quo arm were assumed to be symptomatic from birth and took residence in a lower motor milestone heath state e.g., '1.Non sitter' for Type I patients, this was not appropriate and favoured ONA. There was also a lack of clinical data supporting the 'BRND' health state, although most patients in SPR1NT (pre-symptomatic ONA) were able to walk by 24 months, given walking was assessed as the ability to take ≥ 5 steps this was unlikely to equate to 'BRND'. There was also a lack of long-term data to justify the assumed sustained benefit over time.

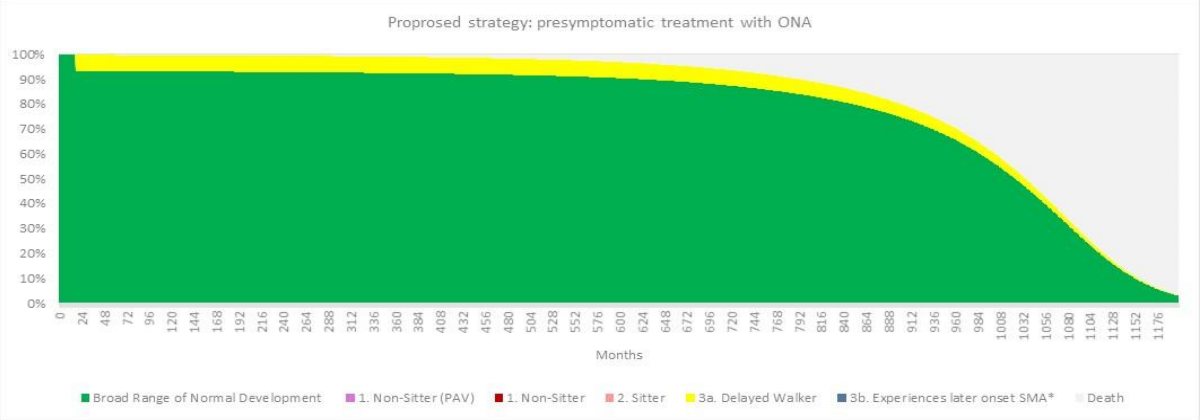
6.60 In the status quo arm, the age at the start of treatment was based on data from the clinical studies for Type I, II and IIIa, although the age definition varied for SMA types and was inconsistent, i.e., from age at study baseline (Type I) screening (Type II) and age at diagnosis (Type IIIa). This was important particularly for Types II and III where there were large gaps between symptom onset, age of diagnosis and age at study screening. Given symptomatic patients entered the model via a symptomatic health state, delays to treatment would bias the results in favour of the proposed strategy. Given the availability and increased testing for SMA, in clinical practice patients are likely to receive treatment soon after symptom onset. The PSCR acknowledged that outcomes for the status quo in Australia are likely to be better than observed in the NUSI trials due to earlier treatment after symptom onset.

6.61 The assumption that costs were lower in the 'BRND' health state compared to the '3a. Delayed walker' health state may also not be reasonable, particularly as patients were assumed to switch from '3a. Delayed walker' to 'BRND' at the end of the study period thus artificially creating a change in costs. A sensitivity analysis exploring this assumption moderately impacted the ICER, although this was a relatively minor cost component compared to drug costs.

6.62 Figure 5 illustrates the model trace for the proposed strategy arm (pre-symptomatic treatment). The figure illustrates that with the exception of a small proportion (1/15, i.e., 6.7%) of patients transitioning to the '3a.Delayed walker' health state before 2 years of age, all patients remained in 'BRND' for the entire model duration except for death due to general population mortality. It may not be plausible for the majority of patients in the pre-symptomatic treatment arm to remain in the 'BRND' health state for 30 years.

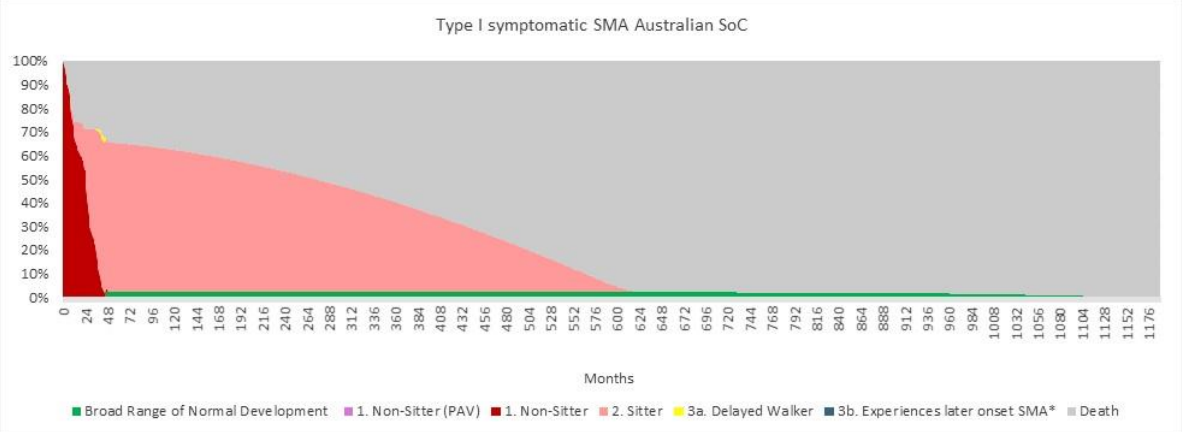
6.63 Figure 6, Figure 7, Figure 8 and Figure 9 illustrate the model traces for symptomatic treatment of patients with Types I, II, IIIa and IIIb SMA, respectively in the status quo arm. These results were in stark contrast with modelled events in the proposed strategy arm. Patients with SMA Types I and II were assumed to experience immediate symptom onset at birth (which was not plausible), and only improved with treatment (but only to '2. Sitter' for the majority) before an early death following natural history. Survival for patients with SMA Type IIIa and IIIb was assumed to be similar to the proposed strategy arm (all following general population mortality), however patients in the status quo arm were assumed to spend more time in the poorer mobility health states and accrue greater costs. The PSCR considered that the natural history study, which Type I SMA survival was based on, may be prone to survivorship bias given the high mortality of these patients. As such, the PSCR contended that it would be inappropriate to assume general population mortality (which is applied in the 'BRND' health state) for Type I SMA prior to initiation treatment. The PSCR noted that pre-symptomatic treatment with ONA remained less costly and more effective compared to status quo when symptomatic Type I and Type II SMA patients were assumed to enter the model in the 'BRND' health state until they receive treatment. The ESC noted that the proposed strategy would remain less costly than status quo over the 30 year horizon with the current assumptions around sequential treatments.

Figure 5: Markov trace for proposed strategy – pre-symptomatic treatment of patients with 3 copies of SMN_2



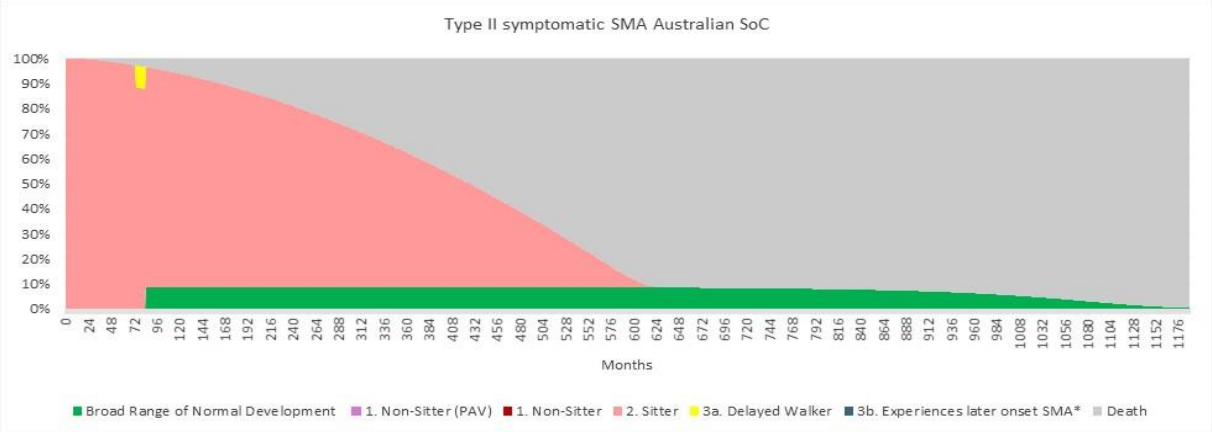
Source: Figure 3.9, p207 of the submission.
PAV=permanent assisted ventilation; SMA=spinal muscular atrophy; SMN=survival motor neuron.

Figure 6: Markov trace for status quo – symptomatic Type I SMA



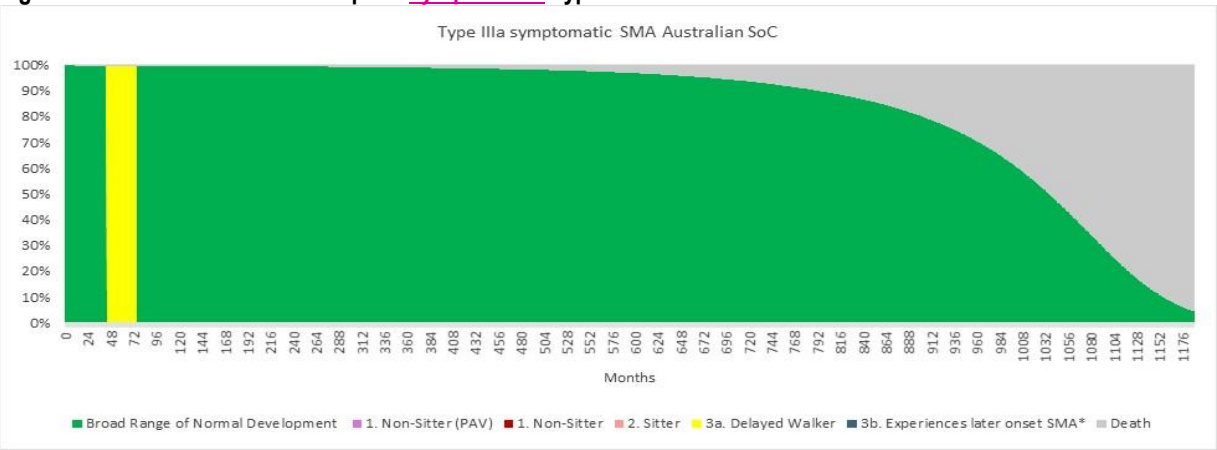
Source: Figure 3.10, p208 of the submission.
PAV=permanent assisted ventilation; SMA=spinal muscular atrophy; SoC=standard of care.

Figure 7: Markov trace for status quo – symptomatic Type II SMA



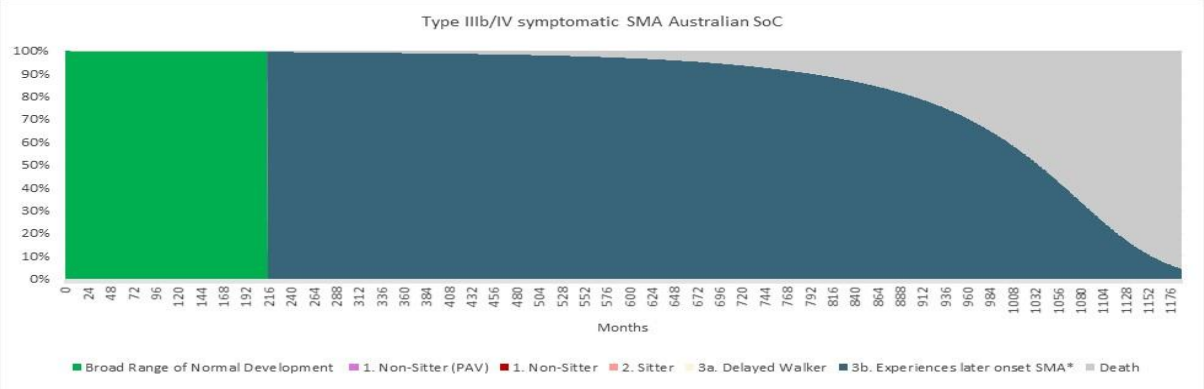
Source: Figure 3.12, p209 of the submission.
PAV=permanent assisted ventilation; SMA=spinal muscular atrophy; SoC=standard of care.

Figure 8: Markov trace for status quo – symptomatic Type IIIa SMA



Source: Figure 3.15, p211 of the submission.
PAV=permanent assisted ventilation; SMA=spinal muscular atrophy; SoC=standard of care.

Figure 9: Markov trace for status quo – symptomatic Type IIIb SMA



Source: Figure 3.16, p211 of the submission.
PAV=permanent assisted ventilation; SMA=spinal muscular atrophy; SoC=standard of care.

6.64 The ESC noted that these traces highlighted the substantially poorer outcomes with respect to survival benefit and motor milestones modelled for patients in the status quo arm compared to the proposed strategy arm. The ESC considered that the modelled incremental benefit was optimistic and not adequately supported by the clinical evidence presented.

6.65 Table 10 provides a summary of the key drivers in the modelled economic evaluation.

Table 10: Key drivers of the model

Description	Method/Value	Impact Base case: Dominant.
Drug costs of sequential DMTs	No sequential treatments were permitted in the model over the full 30 year time horizon	Very high, favoured ONA. A multivariate sensitivity analysis assuming patients could start alternate treatments in the model increased the ICER to [redacted][1]/ QALY gained.
Time horizon	Model assumed a 30-year time horizon, versus 24 months in the SPR1NT study. Due to ONA costs being up front and NUSI's costs to accrue over time, the modelled costs were very sensitive to time horizon.	High, favoured ONA. Assuming a 15-year time horizon increased the ICER to [redacted][2]/QALY.
Survival of sitters	Model assumed the survival curve from natural history data (Zerres et al 1997) for the long term model for patients in the '2.Sitter' health state.	Low to moderate. Assuming survival of general population ('BRND' survival) for patients in the '2.Sitter' health state decreased incremental benefits by 12%.
Healthcare costs (disease management)	Model assumed that patients in the 'BRND' health state had less intensive monitoring compared to patients in the '3a.Delayed walker' health state. The model also assumed no regression in motor milestones in the base case.	Moderate, favoured ONA. Assuming the same healthcare costs for the 'BRND' health state as the '3a. Delayed walker' health state decreased the cost savings for proposed strategy versus status quo arm by around 50%.

Source: compiled during the evaluation.

BRND=broad range of normal development; DMT=disease modifying therapies, NUSI=nusinersen; ONA=onasemnogene abeparvovec; PAV=permanent assisted ventilation; SMA=spinal muscular atrophy; SMN=survival of motor neurone.

[a] This analysis also assumed (i) 100% of patients in the status quo arm had SMA Type II (ii) survival of general population for patients in the '2.Sitter' health state.

The redacted values correspond to the following ranges:

[1] *$155,000 to < $255,000*

[2] *$95,000 to < $115,000*

6.66 Table 11 provides the results of the modelled economic evaluation for the proposed strategy (pre-symptomatic treatment with ONA) versus status quo. The results show that the biggest change in ICER occurred when the model time horizon was extended from 3 years to 30 years, reducing the additional costs for the proposed strategy versus status quo from $0 to < $10 million (in Step 2) to a cost saving per patient (in Step 3). This was primarily due to the upfront drug costs for ONA being offset by the drug costs of nusinersen over a longer time period. The ESC considered the estimated cost saving to be highly uncertain noting these were on the basis of ongoing costs for nusinersen with no subsequent treatments following ONA over the full 30-year time horizon and included significant medical costs prevented.

Table 11: Results of the stepped economic evaluation

Step and component	Proposed strategy	Status quo	Increment
Step 1: trial-based costs and outcomes; 3-year time horizon (37 months in the model)			
Costs	$	$306,554	$
Months standing	36.90mth	9.63mth	27.27mth
Incremental cost/additional months the child was standing			$[1]
Step 2: incorporation of survival			
Costs	$	$306,554	$
LYG	2.80	2.69	0.11
Incremental cost/extra LYG gained			$[2]
Step 3: time horizon extended to 30 years			
Costs	$	$4,299,340	-$
LYG	15.96	14.10	1.86
Incremental cost/extra LYG gained			Dominant
Step 4: incorporation of utilities			
Costs	$	$4,299,340	-$
QALYs	15.20	10.01	5.19
Incremental cost/extra QALY gained (not considering *SMN2* testing accuracy)			Dominant
Step 5: Accounting for *SMN2* testing accuracy			
Costs	$	$4,299,340	-$
QALYs	14.21	10.01	4.20
Incremental cost/extra QALY gained (base case in the model)			**Dominant**

Source: Table 3.38, p215 of the submission.
SMN = survival of motor neurone.
The redacted values correspond to the following ranges:
[1] $95,000 to < $115,000
[2] > $1,055,000

6.67 Table 12 summarises ICERs of the proposed scenario versus each SMA Type in status quo.

Table 12: Disaggregated summary ICER of the proposed scenario versus each SMA Type in status quo.

Type	Drug cost ($)	Admin costs	Medical costs	Total Cost / patient ($)	LYs (discounted)	QALYs (discounted)	ICER ($/QALY)	CE plane quadrant
Proposed scenario								
Pre-symptomatic SMN2 3 copy*		$2,222	$176,045		15.61	14.21	-	-
Status quo								
Type I		$8,771	$779,294		9.91	5.33	Proposed strategy dominant	SE
Type II		$9,471	$765,471		14.48	9.01	Proposed strategy dominant	SE
Type IIIa		$11,259	$132,311		15.96	15.20	[1] Proposed strategy less effective and less costly	SW
Type IIIb		$3,561	$121,708		15.96	15.20	Status quo dominant	NW
Weighted Average		$9,281	$601,767		14.10	10.01	Proposed strategy dominant	SE

Source: generated during the evaluation using the submitted model Zolgensma_3copy_CUA.xlsx.
CE=cost effectiveness, NE=north east, SE=south east, SMA=spinal muscular atrophy, SW=south west.
* Adjusting for test performance (diagnostic accuracy).
The redacted values correspond to the following ranges:
[1] > $1,055,000

6.68 Table 12 illustrates that the ICER for the proposed scenario varied according to SMA Type from dominant (Type I and II) to dominated (Type IIIb). The biggest differences between the treatment strategies in QALYs and LYs were evident for SMA Types I and II (given these patients were assumed to have significantly reduced survival in the status quo arm), otherwise there was little difference in LYs or QALYs for Type IIIa and IIIb SMA, and the different ICERs were therefore driven by the costs accrued for these SMA types, resulting in the proposed strategy being less effective and less costly than status quo for Type IIIa patients and less effective but more costly than status quo for Type IIIb patients.

6.69 ONA is a once off infusion, whilst costs of nusinersen are ongoing from the assumed age of starting treatment to the end of the 30 year model duration, assuming no discontinuations from nusinersen. The PBAC previously considered 11 years to be an acceptable time horizon to consider costs and benefits of ONA versus comparators in the context of (i) an outcomes based RSA and (ii) provision of longer follow-up data to inform the price for a subsequent deed (para 9.11, onasemnogene abeparvovec PSD, November 2020 PBAC meeting September 2021 addendum). The ESC considered that the uncertainties in treatment utilisation, medical costs, survival benefit and motor milestones obtained applied in the model were magnified by extrapolating over the 30 year time horizon.

6.70 The results of key univariate and multivariate sensitivity analyses are summarised in Table 13. Given the submission's base case estimated significant cost savings for the proposed strategy, the results of most sensitivity analyses resulted in negative ICERs with the proposed strategy being dominant. The key drivers in the model were drug costs, subsequent treatment costs, and time horizon.

6.71 A sensitivity analysis assuming patients could start alternate treatments in the model increased the ICER to $155,000 to < $255,000/QALY gained (versus the ICER being dominant in the base case i.e., less costly and more effective), indicating the sensitivity of the ICER to assumptions around drug costs for subsequent treatments. This analysis assumed 50% of pre-symptomatic patients and symptomatic Type I patients treated with ONA will receive sequential treatment with nusinersen (based on START-LTFU). The PSCR argued that children in START who initiated an additional DMT would not be eligible for this subsequent treatment on the PBS without demonstration of the loss of a motor milestone. The sensitivity analysis also assumed that 50% of nusinersen patients treated symptomatically for Type II and IIIa will switch to risdiplam (though the PSCR noted that as costs and outcomes for nusinersen and risdiplam are assumed to be identical this would not be expected to impact the ICER).

6.72 The ESC considered that overall, the economic model presented was not useful for informing the cost-effectiveness of ONA in pre-symptomatic patients with 3 copies of SMN2. The ESC considered that a revised model should include a treatment pathway and outcomes which are more reflective of the current clinical setting.

Table 13: Key Sensitivity Analyses

Analyses	Incremental cost	Incremental QALY	ICER	Δ to cost savings	Δ to incr. QALY
Base case	**-$**	**4.20**	**Dominant**	**-**	**-**
Time horizon (base case 30 years)					
20 years	-$	3.29	Dominant	-73.7%	-21.7%
15 years	$	2.71	$[1]	-130.8%	-35.5%
10 years	$	2.01	$[2]	-204.5%	-52.1%
Discount rate (base case: 5%)					
0%	-$	8.09	Dominant	+350.6%	+92.6%
3.5%	-$	5.00	Dominant	+73.7%	+19.1%
Survival for patients in '2.Sitter'					
Assume survival of general population ('BRND' survival) for patients in the '2.Sitter' health state	-$	3.71	Dominant	+35.0%	-11.7%
Costs					
Assume 'BRND' health state costs are the same as '3a. Delayed walker'	-$	4.20	Dominant	-48.6%	-
Utilities					
Use of case vignette values as reported in Malone 2019.	-$	2.19	Dominant	-	-47.9%
Allow sequential treatment[a]:					
Allow Type I symptomatic patients to be treated with ONA first (at its effective price) Allow sequential treatments: - NUSI following ONA in pre-symptomatic and symptomatic Type I - NUSI treated symptomatically switch to risdiplam in Type II & IIIa[a]	$	4.20	$[3]	-195.1%	-

Source: compiled during the evaluation. BRND=broad range of normal development, ICER=incremental cost-effectiveness ratio, QALY = quality adjusted life year.

[a]Assumed that 50% of pre-symptomatic, symptomatic Type I, II and IIIa patients had sequential treatments.

The redacted values correspond to the following ranges:

[1] *$95,000 to < $115,000*

[2] *$455,000 to < $555,000*

[3] *$155,000 to < $255,000*

Drug cost/patient/course: $[redacted] per patient (once per lifetime).

Table 14: Drug cost per patient for ONA and comparator drugs

	ONA Trial dose and duration	ONA Model	ONA Financial estimates	Comparator Trial dose and duration	Comparator Model	Comparator Financial estimates
Mean dose	$1.1x10^{14}$ vg/kg	Once-off injection	Once-off injection	ONA (once off) NUSI 12 mg^ RISD by age and weight to target exposure	NUSI only: Loading then maintenance (every 4 months)	50% NUSI (12mg), 50% RISD (548-1,826mg (age dependent))
Mean duration	Once-off injection			Varied	Ongoing tx	6 years (ongoing)
Cost/patient/ month	-	$[redacted] per patient	$[redacted] per patient	-	$27,500 in maintenance (NUSI)	$23,976 in maintenance (NUSI/RISD weighted average)
Cost/patient/ year (chronic) or /course	-			-	$330,000 in maintenance (NUSI)	$287,710 in maintenance (NUSI/RISD weighted average)

Source: compiled during the evaluation. NUSI=nusinersen; ONA =onasemnogene abeparvovec, RISD=risdiplam, tx=treatment
^ Dosing frequency varied across the symptomatic and pre-symptomatic studies

Estimated PBS usage & financial implications

6.73 This submission was not considered by DUSC.

6.74 The submission used an epidemiological approach to estimate the financial impact of listing ONA for pre-symptomatic treatment of SMA patents with 3 copies of SMN2 (i.e., the proposed strategy) on the PBS. The submission assumed 100% of pre-symptomatic patients with 3 copies of SMN2 treated with ONA would have otherwise received treatment with nusinersen or risdiplam (i.e., the status quo). In estimating these cost offsets, as was in the modelled economic evaluation, no discontinuation of treatment with either nusinersen or risdiplam was assumed. This was not reasonable, in clinical studies patients did discontinue treatment with nusinersen and in practice patients could discontinue nusinersen and switch to risdiplam treatment. The PSCR noted that only 2 out of 20 patients in CS3A voluntarily discontinued treatment; one patient for reasons not stated, and one patient due to hardship travelling to study site. The PSCR also noted that patients switching from NUSI to RISD would not impact the estimated cost to Government of ONA as the treatments are cost-minimised to one another.

6.75 The submission also assumed no patient treated with ONA would require further treatments (i.e., with nusinersen and risdiplam). This may not have been reasonable, however the ESC considered that such use could be managed with PBS restrictions limiting sequential use.

6.76 The financial estimates presented by the evaluation were corrected by: i) removing rounding from patient numbers, ii) including the prevalent patients in the first year of listing in the cost-offsets and iii) updated all unit costs to reflect prices as of September

2022. The corrected and uncorrected estimates are presented in Table 15. Only corrected results are presented in Table 16.

Table 15: Data sources and parameter values applied in the utilisation and financial estimates

Data	Value		Source	Comment
	Submission	Corrected (if different)		
Eligible population				
Incident patients born from 2023	Yr 1: 12 Yr 2: 13 Yr 3: 13 Yr 4: 13 Yr 5: 13 Yr 6: 13	Yr 1: 13 Yr 2: 13 Yr 3: 13 Yr 4: 13 Yr 5: 13 Yr 6: 13	Applying the following to the estimated ABS population aged 0 in 2023-2029: - 1 in 10,000 diagnosed with SMA (SMA Australia), - 100% identified with NBS, - 38.1% 3 copies of SMN2 identified with NBS (Feldkotetter 2002), - 94% AAV9 eligible (6% AAV9+ve in ONA trials).	Proportion of SMA patients with 3 copies of SMN2 varied each year in the submission as a result of rounding (submission calculated rounded number based of 38.1% then applying that rounded number to the number of SMA patients to estimate the proportion). Submission expected 97% coverage with NBS by end of 2023, financial estimates assume 100% from 2023.
Incident patients born in 2022	Yr 1: 2 Yr 2-6: NA		Estimated ABS Australian birth rates 2022: - 1 in 10,000 diagnosed with SMA - 44% identified with NBS (based on % births in 2020 in NSW, WA, ACT). - 38.1% 3 copies of SMN2 (Feldkotter 2002). - 94% AAV9 eligible - 33.15% <9 months old by ONA listing (assumption based on expected listing date of 1 June 2023: 1 Sept 2022- 31 Dec 2022 represented as a % of the year).	As with incident patients rounding was used inconsistently (though this did not affect whole number of patients).
Total patients eligible to initiate treatment	Yr 1: 13 Yr 2: 12 Yr 3: 12 Yr 4: 12 Yr 5: 12 Yr 6: 12		Incident patients combined.	Calculations were arithmetically correct (though rounding errors would carry through).
Treatment utilisation				
Uptake rate	Yr 1-6: 90%		Based on 23/25 families elected treatment with ONA in pre-reimbursement routes in 2020 (92%).	May be underestimated. However due to rounding the actual uptake implemented equated to 91.7-92.3% for patients born 2023 onwards and 100% for patients born in 2022. Due to rounding errors, increasing uptake in the base case to 95% resulted in a reduction in net costs.
Number initiating treatment	Yr 1: [redacted]1 Yr 2: [redacted]1 Yr 3: [redacted]1 Yr 4: [redacted]1 Yr 5: [redacted]1 Yr 6: [redacted]1		Total eligible multiplied by uptake rate	Calculations were arithmetically correct.

Data	Value		Source	Comment
	Submission	Corrected (if different)		
Number continuing treatment (NUSI/RISD only)	Yr 1: [redacted][1] Yr 2: [redacted][1] Yr 3: [redacted][1] Yr 4: [redacted][1] Yr 5: [redacted][1] Yr 6: [redacted][1]	Yr 1: [redacted][1] Yr 2: [redacted][1] Yr 3: [redacted][1] Yr 4: [redacted][1] Yr 5: [redacted][1] Yr 6: [redacted][1]	Assumption that patients initiating NUSI/RISD will continue to receive treatment indefinitely.	The submission did not include the 2 patients born in 2022 in the first year of the continuing treatments. Prevalent patients each year were based on the rounded numbers who initiated the year before, but those continuing treatment who initiated in the same year were not rounded, leading to slightly different numbers when all the rounding was removed.
Scripts dispensed (ONA)	Yr 1: [redacted][1] Yr 2: [redacted][1] Yr 3: [redacted][1] Yr 4: [redacted][1] Yr 5: [redacted][1] Yr 6: [redacted][1]		ONA is a one-off treatment and therefore one script was required per patients.	This was appropriate.
Subsequent treatments	Not costed		Subsequent treatment following ONA was not discussed in the financial estimates.	This was consistent with the economic model but may not be realistic. Evidence for the long-term benefit of ONA pre-symptomatic treatment is limited and in 53% of patients in START-LTFU received NUSI/RISD post ONA for symptomatic treatment of SMA Type I.
Population split NUSI/RISD	50%:50%		Patients were assumed to be symptomatic from birth, with 50% receiving nusinersen and 50% receiving risdiplam for the length of the financial estimates.	The true split of NUSI and RISD may depend upon patient symptoms, availability, access and preferences for mode of administration etc. Patients who develop Type I symptoms currently would also be eligible for treatment with ONA (approx. 17%). Patients who present with less severe phenotypes may not receive NUSI/RISD until they are older/at all, and therefore it may not be appropriate to assume an additional 6 years of treatment for all patients who do not receive ONA. Costs of RISD may be underestimated, as younger patients will weigh less and therefore have a lower dosage.
PBS/RPBS Costs				
ONA	$[redacted] per dose		DPMQ (effective) (one-off cost)	Requested price.
Prednisolone	$19.28 per 30ml dose	$19.34 per 30ml dose	PBS code 8285C (one-off cost)	Updated for consistency.
NUSI	$110,000 per 12mg/5ml injection		PBS codes 11363C, 11378W (4 initiating scripts then a further 2.96 scripts in initiating year, followed by 3 scripts per year indefinitely).	

Data	Value		Source	Comment
	Submission	Corrected (if different)		
RISD	$12,144.72 per 80ml (60mg)	$10,889.71 per 80ml (60mg)	PBS codes 12610Q, 12606L (548-1,826mg per year depending upon age)	Updated for change in published price. The submission reported an effective AEMP for risdiplam of $[redacted] in its Excel workbook but this was not included in the calculations. The source of the dose by age was not reported.
PBS/RPBS split	100%:0%		Based on existing PBS Item statistics for NUSI and RISD.	
Public/ private split	100%:0%			
Patient copayment	ONA, NUSI, RISD: $18.99		64% patients concessional, 36% general benefit based on PBS Item statistics for NUSI and RISD.	
	Pred: $8.99	Pred $8.02		
MBS costs				
IV administration (1hr)	$101.90	$103.55	Item 14245	Costs were generally reasonable based on June 2022 prices, except: - The submission costed post treatment follow up with a specialist visit for NUSI/RISD at $89.55 (rather than $90.35) with no justification. - Full blood exam (FBE) cost appeared to have included a typographical error. As such, MBS costs were updated for Sept 2022 prices where available.
Intrathecal infusion (up to 1hr)	$195.85	$200.75	Item 18216	
Intrathecal infusion (each subsequent 15 mins)	$19.60	$20.10	Item 18219	
Specialist visit	$90.35	$91.80	Item 104	
Liver function test	$17.70		Item 66512	
Cardiac Troponin test	$20.05		Item 66518	
Full blood count	$152.55	$16.95	Item 65070	
Creatinine	$9.70		Item 66500	

Source: Table 4.1, 4.2, 4.3, 4.11 and Sections 4.2.2, 4.3.1.1, 4.3.1.2 of the submission and compiled during the evaluation
ABS=Australian Bureau of Statistics; IV=intravenous; hr=hour, NBS = newborn bloodspot screening; SMA = spinal muscular atrophy; DPMQ=dispensed price of maximum quantity; MBS=Medicare Benefits Schedule; NA=not applicable, NUSI-nusinersen, ONA=onasemnogene abeparvovec; PBS=Pharmaceutical Benefits Scheme, Pred=prednisolone, RISD=risdiplam, Yr=year
The redacted values correspond to the following ranges:
[1] *< 500*

6.77 In the financial estimates, all patients receiving ONA were assumed to receive no further treatments, but do accrue MBS costs for diagnostic tests and specialist visits. Patients who do not receive ONA are assumed to become symptomatic from birth, with 50% receiving nusinersen and 50% receiving risdiplam for the length of the financial estimates. Some patients will present with symptoms at a later age, or with milder symptoms, and therefore it may not be appropriate to assume an additional 6 years of treatment for all patients who do not receive ONA. The financial estimates were not broken down by type of SMA for status quo, nor did they include treatment discontinuations, subsequent treatments, or the cost of ONA for symptomatic Type 1

patients. The submission also did not include costs for genetic testing (assumed to be covered under NBS) and AAV9 testing (covered by sponsor). Annual healthcare costs for the different phenotypes ranged from $52,019 (Type III) to $192,498 (Type I) in the economic model, suggesting potential additional cost-offsets where symptomatic burden is reduced.

Table 16: Estimation of use and financial impact of the proposed medicine

	2023	2024	2025	2026	2027	2028
Estimation of number of treated patients						
Initiating SMA treatment						
Incident SMA	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Patients with 3 copies of SMN2	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Patients AAV9 eligible	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Patients electing treatment with ONA	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Incident patients born 2022	[redacted]1	-	-	-	-	-
Total initial patients for ONA	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Total ONA scripts	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Net cost of ONA to PBS/RPBS	[redacted]2	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3
Estimation changes in use and financial impact of currently listed treatments						
Patients on comparators displaced by PBS listing of ONA	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Reduction in NUSI scripts	-[redacted]1	-[redacted]1	-[redacted]1	-[redacted]1	-[redacted]1	-[redacted]1
Reduction in RISD scripts	-[redacted]1	-[redacted]1	-[redacted]8	-[redacted]8	-[redacted]8	-[redacted]8
Increase in prednisolone	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Total cost offset to PBS/RPBS	[redacted]4	[redacted]4	[redacted]4	[redacted]4	[redacted]4	-[redacted]4
Estimated financial implications for the PBS/RPBS and the health budget						
Net cost PBS/RPBS (net cost offsets)	[redacted]3	[redacted]5	[redacted]5	[redacted]5	[redacted]6	[redacted]6
Net cost to MBS	[redacted]7	[redacted]4	[redacted]4	[redacted]4	[redacted]4	[redacted]4
Net change to government budget	[redacted]3	[redacted]5	[redacted]5	[redacted]5	[redacted]6	[redacted]6

Source: compiled during the evaluation form Excel workbook 'Utilisation_Cost_Model_ONA_3copy_final.xlsx.

IV=intravenous; hr=hour, SMA = spinal muscular atrophy; MBS=Medicare Benefits Schedule; NUSI-nusinersen, ONA=onasemnogene abeparvovec; PBS=Pharmaceutical Benefits Scheme, RISD=risdiplam, Yr=year

The redacted values correspond to the following ranges:

[1] *< 500*

[2] *$40 million to < $50 million*

[3] *$30 million to < $40 million*

[4] *net cost saving*

[5] *$20 million to < $30 million*

[6] *$10 million to < $20 million*

[7] *$0 to < $10 million*

[8] *500 to < 5,000*

6.78 The submission estimated net costs to the PBS of $30 million to < $40 million in year 1, decreasing to $10 million to < $20 million in year 6, with a combined total net cost to government of approximately $100 million to < $200 million over the first 6 years of listing. The net cost for ONA (without offsets for nusinersen and risdiplam) was estimated to be $40 million to < $50 million in year 1, decreasing to $30 million to < $40 million - $30 million to < $40 million in years 2 to 6, with a total cost of $200 million to < $300 million over the first 6 years of listing.

6.79 The financial estimates may be underestimated because:

- The uptake rate may be underestimated. ONA represents an additional treatment in an area of limited treatments and would be the only treatment for patients with 3 copies of SMN2 available pre-symptomatically. However, uptake would also be dependent on accessibility.
- The rate of SMA identified may be underestimated as the number of patients identified is likely to increase with the newborn screening program. However, in the long term, this may be offset by the introduction of reproductive genetic carrier screening to assist family planning decisions. The PSCR contended the rate of SMA is unlikely to have been underestimated as the estimated incidence applied in the financial estimates (1 per 10,000 infants) is similar to the incidence of 0.83 diagnosed cases of SMA per 10,000 infants screen from the NBS pilot.
- Cost offsets may be lower if patients discontinue nusinersen or risdiplam, or if pre-symptomatic ONA patients go on to develop symptoms (or lose motor milestones) and receive further DMT treatment. The submission argued that some of this risk could be addressed with an RSA. The ESC considered the cost offsets were uncertain and likely over estimated.

6.80 The financial estimates may be overestimated because:

- The estimates do not include offsets for the current cost of ONA to Type I symptomatic patients.
- Symptomatic patients may incur additional healthcare, allied health and support services not costed for in the financial estimates

6.81 The ESC considered the financial estimates to be uncertain and considered it was difficult to determine whether the financial impact was overestimated or underestimated overall.

Quality Use of Medicines

6.82 The submission did not include a quality use of medicines section. However, the submission did list some access issues for ONA including few centres where gene therapy is offered, which may require patients to travel interstate to access ONA. Delays to NBS screening rollout may also limit accessibility to ONA, as patients will not be eligible for ONA if identified after 9 months of age. According to the financial estimates this could affect over half of all incident patients with 3 copies of SMN2 each year the screening is not in place.

Financial Management – Risk Sharing Arrangements

6.83 The submission proposed that the current outcomes-based RSA for ONA in SMA Type I and pre-symptomatic patients with 1 or 2 copies of the *SMN2* gene should apply to the proposed population, such that

[redacted]

6.84 The ESC noted that pre-symptomatic patients with 3 copies of the SMN2 gene are most likely to have Type II or III SMA, for which death is unlikely to occur within 2 years and the loss of motor milestones attained may be more important outcomes for this proposed population rather than deaths. The PSCR considered that the current outcomes-based RSA for ONA would mitigate the risk related to sequential treatments. The ESC considered that the outcomes-based RSA for ONA may not mitigate the risks in the current context as patients may not develop milestone regressions in the proposed RSA time-frame, whereas the economic evaluation assumed patients would not develop milestone regressions over a 30 year horizon.

6.85 The pre-PBAC Response considered that uncertainty around treatment benefit should be addressed via analysis of the clinical data and the price of the treatment determined via cost-effectiveness analysis rather than through an RSA

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

7 PBAC Outcome

7.1 The PBAC did not recommend onasemnogene abeparvovec (ONA) for the treatment of pre-symptomatic patients who are genetically diagnosed with spinal muscular atrophy (SMA) and have 3 copies of the Survival Motor Neuron 2 (SMN2) gene. The PBAC considered that pre-symptomatic treatment with ONA may provide clinical benefit for some patients compared to treatment with existing disease modifying therapies following the onset of symptoms. However, the PBAC noted the magnitude of benefit was unclear from the limited clinical data available. The PBAC considered that the economic model presented was unreliable for informing the cost-effectiveness of ONA. The PBAC noted that the price requested was substantially higher than the current price for patients with 1-2 copies of *SMN2* and considered this to be inconsistent with the reduced incremental benefit that would be observed for patients with 3 copies of *SMN2*. The PBAC considered for ONA to be similarly cost-effective in the expanded population that the price of ONA would need to be substantially less than for the current listing.

7.2 The PBAC noted the strong support from consumers and organisations for ONA to be made available to patients genetically diagnosed with SMA who have 3 *SMN2* copies. The PBAC acknowledged there was a need for equitable access to treatment for all infants genetically diagnosed with SMA, noting that newborn bloodspot screening programs are planned to be rolled out across Australia.

7.3 The PBAC also acknowledged that the clinical landscape of SMA is rapidly changing as the disease, which was previously considered fatal, has now become treatable following the development of effective disease modifying therapies. The PBAC noted that in turn, the clinical approach to SMA is shifting towards early detection and intervention, and disease classification is shifting from SMA types, which was based on the age at which symptoms are identified, towards classification as non-sitters, sitters and walkers, which recognises SMA phenotype as a continuum and is more

focused on current functional status and therapy response. The PBAC noted that the existing restrictions for symptomatic treatment of SMA refer to classification by SMA type, reflecting the various submissions and considerations of cost-effectiveness in various sub-populations. The PBAC considered that the sponsor may wish to consider how the ONA restrictions could be revised to align more closely with current clinical classification and management of SMA in a future resubmission.

7.4 The PBAC agreed with ESC that the move to pre-symptomatic treatment in patients who may have otherwise gone on to develop less severe disease represents a substantial shift to preventive treatment. The PBAC considered this may require a different approach to consideration of cost-effectiveness compared with when DMTs first became available as potentially life-saving treatments for patients with severe disease.

7.5 The PBAC noted that the evidence presented consisted of small single-arm, open label studies and associated follow-up extensions which it had considered in previous submissions for disease modifying therapies for SMA. The PBAC noted the clinical claim of superior effectiveness compared to symptomatic treatment with disease modifying therapies was based on crude comparisons of developmental motor milestones achieved across the studies. The PBAC noted that a higher proportion of patients achieved the highest milestone of walking unsupported in the SPR1NT study (pre-symptomatic treatment with ONA) compared to the studies where patients were treated with disease modifying therapies after symptoms had developed. However, the PBAC noted it was not possible to distinguish between the treatment effect from pre-symptomatic treatment with ONA and the prognosis of SMA patients with 3 *SMN*2 copies from the available evidence. The PBAC noted that in addition to the small sample sizes and heterogeneity across the studies, the lack of data in symptomatic SMA patients with 3 *SMN2* copies treated with ONA, and the lack of disaggregated outcomes specific to symptomatic treatment of patients with SMA 3 *SMN2* copies made it difficult to interpret the results. The PBAC also considered that SMA patients were now likely to be diagnosed more rapidly than before due to increased awareness of the condition and the availability of testing. As such, the studies in symptomatic SMA patients used to represent the comparator do not reflect current clinical practice, where patients would be expected to be treated much earlier. The PBAC considered, overall, although the clinical evidence was very limited, the claim of superior comparative effectiveness may be reasonable on the basis that pre-symptomatic treatment would be expected to prevent or reduce the irreversible loss of motor neurons and therefore result in superior outcomes for patients. However, the PBAC noted that the magnitude of benefit could not be determined with any certainty given the limitations of the available data. The PBAC acknowledged that substantial new clinical data, were unlikely to be forthcoming given the rarity of the condition.

7.6 The PBAC recalled the advice from MSAC that while *SMN2* copy number variation offers some prognostic value, it was more reliable for infants with ≥2 copies of *SMN2* compared to ≥3 copies of *SMN2*. The PBAC noted that on average patients with 3

copies of SMN2 would have less severe disease than patients with 1-2 copies. Further, the PBAC noted that based on natural history data, the majority of type IIIa and IIIb SMA patients, who are likely to have 3 or more copies of SMN2, retained the ability to walk after 10 years. Therefore, a proportion of patients treated pre-symptomatically with ONA would have achieved the ability to walk without treatment. The PBAC considered that there was a small proportion of patients for whom the added benefit of pre-symptomatic treatment was highly uncertain and noted it would not be possible to identify these patients. Overall, the PBAC considered that the incremental benefit of pre-symptomatic treatment with ONA compared to symptomatic treatment with disease modifying therapies for patients with 3 *SMN2* copies would be less than that for patients with 1-2 *SMN2* copies.

7.7 The PBAC recalled it previously noted that safety data presented for ONA and nusinersen indicated that ONA had a similar or greater proportion of patients with any AE, serious AEs, and treatment related serious AEs, and a black box safety warning for the risk of acute serious liver injury (para 7.6 ONA PSD, November 2020 PBAC meeting). The PBAC considered that the claim of non-inferior comparative safety for pre-symptomatic treatment with ONA compared with watchful waiting was not reasonable, where some patients (albeit a small proportion) may not require symptomatic treatment with DMTs.

7.8 The PBAC considered the results of the modelled economic evaluation lacked face validity, noting the requested price for ONA was substantially higher than that for patients with 1-2 *SMN2* copies, yet the benefit would, on average, be less than for patients with 1-2 *SMN2* copies. The PBAC noted that the ICER was claimed to be dominant i.e., that pre-symptomatic treatment with ONA is less costly and more effective than treatment with disease modifying therapies after the onset of symptoms, primarily because a once-off, upfront cost of ONA was compared with ongoing treatment with nusinersen over 30 years. The PBAC considered that there are insufficient clinical data to support use of a 30-year time horizon and noted that an 11 year horizon was used for the economic evaluation for ONA for patients with 1-2 *SMN2* copies. The PBAC also considered that limiting symptomatic treatment in the status quo arm to NUSI was unlikely to adequately represent outcomes and costs in clinical practice.

7.9 Further, the PBAC considered that due to the very limited clinical evidence for the comparison there was substantial uncertainty with the inputs and assumptions applied in the model with respect to utilisation of subsequent treatments, motor milestone regression, utility values, and the incremental benefit modelled in terms of motor milestones obtained and survival. The PBAC noted that many of the assumptions and inputs to the model favoured pre-symptomatic treatment with ONA. Overall, the PBAC considered that the economic model presented in the submission was not suitable to support decision-making.

7.10 The PBAC considered that further adjustments to the model would be unlikely to result in more robust economic analyses given the limitations of the available evidence. The PBAC considered that a comparison between the cost and clinical benefits for treating patients with 1-2 copies of *SMN2* with ONA (as currently subsidised) and patients with 3 copies (proposed) would be more informative for establishing the cost-effectiveness in the expanded population. The PBAC noted that the smaller clinical benefit for patients with 3 *SNM2* copies (as per para 7.6) would require the price of ONA to be lower than for the current listing for it to be similarly cost-effective. The PBAC noted that the price may need to be substantially lower, referring to the economic analysis it considered for pre-symptomatic treatment with nusinersen where the addition of patients with 3 *SMN2* copies to the base case for patients with 1-2 *SMN2* copies increased the ICER/QALY by 141% (Table 14, nusinersen PSD, July 2020 PBAC meeting).

7.11 The PBAC noted that the net cost to the PBS of listing ONA was estimated by the submission to be $10 million to < $20 million in Year 6, and $100 million to < $200 million in the first 6 years of listing. This included cost-offsets for symptomatic treatment with nusinersen/risdiplam totalling $80 million to < $90 million over the first 6 years of listings. The PBAC considered it was uncertain whether these cost savings would be realised as the financial estimates assumed that patients treated with ONA would have otherwise been treated with nusinersen or risdiplam, that patients treated with ONA would not require subsequent treatment and that there would be no discontinuation of treatment with either nusinersen or risdiplam. The net cost for ONA (without offsets for nusinersen and risdiplam) was estimated to be $30 million to < $40 million - $40 million to < $50 million in each year, with a total cost of $200 million to < $300 million over the first 6 years of listing. The PBAC considered that the number of patients with 3 *SMN2* copies who would be treated pre-symptomatically with ONA was uncertain, noting this could increase with the expansion of newborn bloodspot screening but may also be reduced in the long term due to the introduction of reproductive genetic carrier screening.

7.12 The PBAC considered a resubmission for ONA should present a revised approach to demonstrating the cost effectiveness of pre-symptomatic treatment of patients with 3 copies SMN2 which addresses the issues outlined in paragraph 7.10.

7.13 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Not recommended

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers

applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

Zolgensma® has demonstrated significant impact on the lives of SMA babies with 3 SMN2 copies and has the potential to fundamentally change the quality of life of these Australians, with a single dose treatment. Novartis appreciates that the PBAC has recognised this clinical benefit. With newborn screening becoming more available in Australia, Novartis will continue to work with PBAC in the hope that this treatment will be available to all diagnosed presymptomatic SMA babies