

7.06 ONASEMNOGENE ABEPARVOVEC, Solution for injection, Customised based on patient weight, Zolgensma[®], Novartis Pharmaceuticals Australia Pty Ltd.

1 Purpose of submission

- 1.1 The Standard Re-entry resubmission requested an extension to the Section 100 (Highly Specialised Drugs Program), Authority Required (Written) listing for onasemnogene abeparvovec (ONA) for the pre-symptomatic treatment of babies with spinal muscular atrophy (SMA) and 3 copies of the Survival Motor Neuron 2 (*SMN2*) gene.
- 1.2 Listing was requested on the basis of a cost-minimisation approach versus ONA administered in a different population (pre-symptomatic treatment of patients with SMA and 1-2 copies of the *SMN2* gene). Table 1 provides a summary of the key components of the resubmission.

Table 1: Key components of the clinical issue addressed by the resubmission (as stated in the resubmission)

Component	Description
Population	Paediatric patients less than 9 months of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (<i>SMN1</i>) gene and 3 copies of the <i>SMN2</i> gene.
Intervention	Onasemnogene abeparvovec (ONA), administered as a single intravenous infusion through a venous catheter delivered over 60 minutes. The recommended dose is 1.1×10^{14} vector genomes per kilogram (vg/kg) of body weight, to be individually made up by the sponsor for each patient.
Comparator	Paediatric patients less than 9 months of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (<i>SMN1</i>) gene and 2 copies of the <i>SMN2</i> gene treated with onasemnogene abeparvovec (administered as above).
Outcomes	Milestone developments (e.g. standing and walking).
Clinical claim	Pre-symptomatic treatment of patients with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (<i>SMN1</i>) gene and 3 copies of the <i>SMN2</i> gene with onasemnogene abeparvovec is non-inferior to the pre-symptomatic treatment of babies with 2 copies of the <i>SMN2</i> gene with respect to developmental milestones and safety.

Source: Table 1.1, p27 of the resubmission.

ONA= Onasemnogene abeparvovec; SMA=spinal muscular atrophy; SMN=survival motor neuron

- 1.3 The resubmission's clinical claim was that pre-symptomatic treatment of patients with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (*SMN1*) gene and 3 copies of the *SMN2* gene with onasemnogene abeparvovec is non-inferior to the pre-symptomatic treatment of babies with 2 copies of the *SMN2* gene with respect to developmental milestones and safety.
- 1.4 The resubmission was based on the following key assumptions, some of which were not well supported, as noted below:
- The pre-symptomatic treatment of patients aged <9 months with 3 copies of

SMN2 would lead to better outcomes than treating patients aged <9 months with 1-2 copies of *SMN2* and the value is comparable, if not better.

This may not be supported and was inconsistent with the view held previously by PBAC that overall, “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” (paragraph 7.6, onasemnogene abeparvovec Public Summary Document (PSD), November 2022 PBAC meeting).

- When NBS is in place in Australia many babies will be diagnosed prior to symptom development.
- The provided epidemiology is robust and NBS has not identified any extra patients that would not have previously been treated with available disease modifying treatments (DMTs).

It was unclear on what basis this assumption was made.

- SMA is a disease of irreversible motor neuron loss. Waiting for symptoms to appear means allowing motor neuron loss to occur and letting irreparable damage happen. International guidelines recommend the immediate treatment of all babies identified as having SMA.
- There is a current inequity in Australia where babies identified through NBS with 1-2 *SMN2* copies can access immediate treatment and thereby expect the outcomes presented in the clinical trials, while babies with 3 *SMN2* copies experience motor neuron loss and outcomes which represent a life of disability.
- The SPR1NT study provides outcomes data where children are walking and thriving when natural history data has these children living with disability, respiratory and feeding issues and a life-limiting condition.

However, comparisons made against natural history data by the resubmission do not reflect current clinical practice.

- ONA provides a once-off treatment with an up-front cost that is overshadowed by the cost of treating these children for a lifetime on other available DMTs.

However, there is a lack of long-term follow up data for patients treated with ONA, including the incidence of subsequent therapy after ONA treatment. In addition, patients with 3 *SMN2* copies may develop symptoms later in life, which would mean, on average, fewer doses of RIS /NUSI throughout their lifetime than those with 1-2 *SMN2* copies.

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 ONA was recommended for the treatment of SMA in patients aged less than 9 months, with Type I SMA or pre-symptomatic patients with 1-2 copies of the *SMN2* gene at the September 2021 PBAC meeting. This recommendation was on a cost-minimisation basis to the least costly disease-modifying therapy for this condition, which was RIS, and in the context of an outcomes-based RSA (paragraph 9.1, ONA PSD, September 2021 PBAC meeting).
- 2.3 ONA was not recommended for listing at the November 2022 meeting for the pre-symptomatic treatment of patients with SMA and 3 copies of the *SMN2* gene. The target population for the resubmission remains unchanged.
- 2.4 Table 2 shows key matters of concern from the November 2022 submission and how the resubmission addresses these.

Table 2: Summary of key matters of concern

Matter of concern	How the resubmission addresses it
Clinical	
<p>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 (paragraph 7.1, ONA PSD, November 2022 PBAC meeting)</p> <p>The PBAC acknowledged that substantial new clinical data, were unlikely to be forthcoming given the rarity of the condition (paragraph 7.5, ONA PSD, November 2022 PBAC meeting).</p>	<p>The incremental benefit of pre-symptomatic treatment compared to symptomatic treatment with DMTs for SMA patients with 3 copies of <i>SMN2</i> remained unaddressed.</p>
Economic	
<p>Overall, the PBAC considered that the economic model presented in the submission was not suitable to support decision-making (paragraph 7.9, ONA PSD, November 2022 PBAC meeting).</p> <p>The PBAC considered that a comparison between the cost and clinical benefits for treating patients with 1-2 copies of <i>SMN2</i> 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 <i>SMN2</i> 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 (paragraph 7.10, ONA PSD, November 2022 PBAC meeting).</p>	<p>The resubmission presented a comparison between 2 and 3 <i>SMN2</i> copy patients in the SPR1NT study for the clinical evaluation and a cost-minimisation analysis comparing 2 and 3 <i>SMN2</i> copy patients treated with ONA was presented for the economic evaluation. The resubmission claimed that this was in response to the PBAC comments. This was inconsistent with the view held previously by PBAC that “the incremental benefit of pre symptomatic treatment with ONA compared to symptomatic treatment with disease modifying therapies for patients with 3 <i>SMN2</i> copies would be less than that for patients with 1-2 <i>SMN2</i> copies” (paragraph 7.6, ONA PSD, November 2022 PBAC meeting).</p>
<p>The PBAC considered that there were 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 <i>SMN2</i> copies (paragraph 7.8, ONA PSD, November 2022 PBAC meeting).</p>	<p>The resubmission provided a cost-minimisation approach against risdiplam based on an 11-year time horizon.</p>
Financial	
<p>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 (paragraph 7.11, ONA PSD, November 2022 PBAC meeting).</p>	<p>Partially addressed with a discontinuation rate (5%) applied to nusinersen and risdiplam by the resubmission, though this did not consider treatment switching. However, the resubmission continued to assume patients treated with ONA would have otherwise been treated (with nusinersen, risdiplam or ONA) and that patients treated with ONA would not require subsequent treatment.</p>
<p>The PBAC considered that the number of patients with 3 <i>SMN2</i> 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 (paragraph 7.11, ONA PSD, November 2022 PBAC meeting).</p>	<p>The number of patients with 3 copies of <i>SMN2</i> remained somewhat uncertain.</p>

Source: Compiled during the evaluation based on onasemnogene abeparvovec PSD, November 2022 PBAC meeting and Table 1.12, p51 of the resubmission.

DMT = disease modifying treatment; ONA = onasemnogene abeparvovec; PSD = public summary document; SMA = spinal muscular atrophy; *SMN2* = survival motor neuron 2

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

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
Onasemnogene abeparvovec					
onasemnogene abeparvovec 1.1 x 10 ¹⁴ vg/kg, liquid in vial, each finished pack customised based on patient weight	\$2,527,773.87 published price \$█ effective price	1	1	0	Zolgensma

Category / Program: Section 100 Highly Specialised Drugs Program (Public hospital code only)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type: <input checked="" type="checkbox"/> Authority Required (in writing only via post/HPOS upload)
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 (<i>SMN1</i>) gene; or
The condition must have genetic confirmation of deletion of one copy of the <i>SMN1</i> gene in addition to a pathogenic/likely pathogenic variant in the remaining single copy of the <i>SMN1</i> 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 2 3 copies of the survival motor neuron 2 (<i>SMN2</i>) gene
AND
Clinical criteria:
The treatment must not be a PBS-subsidised benefit where the condition has progressed to a point where invasive permanent assisted ventilation (i.e. ventilation via tracheostomy tube for at least 16 hours per day) is required in the absence of potentially reversible causes
AND
Clinical criteria:
The treatment must be given concomitantly with best supportive care for this condition
AND
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:
Must be treated in a treatment centre that is each of: (i) recognised in the management of SMA, (ii) accredited in the use of this gene technology by the relevant authority, (iii) will(has) source(d) this product from an accredited supplier, as specified in the administrative notes to this listing
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
AND
Population criteria:
Patient must have symptomatic Type 1 SMA; or
Patient must have presymptomatic SMA

Source: Table1.17, pp57-59 of the resubmission.

Bold text reflects change from the current listing.

3.1 The resubmission proposed a SPA with an effective price equivalent to the current effective price for ONA for pre-symptomatic treatment of SMA patients with 1-2 *SMN2* copies. The proposed effective price (\$**1**) was lower than the requested price in the previous (November 2022) submission where an effective price of \$**1** (with no special pricing arrangement (SPA)) was proposed. This represented a **1**% reduction from the requested price in the previous submission.

3.2 No continuation criteria or grandfathering criteria were requested. The requested restriction was based on ONA’s current PBS restriction, with the exception of the following modification:

- “The condition must be presymptomatic SMA, with genetic confirmation that there are 1 to 3 copies of the survival motor neuron 2 (*SMN2*) gene”.

The Secretariat advised that the addition of a criterion specific to patients with 3 *SMN2* gene copies would have the advantage of facilitating ease in future utilisation analysis.

3.3 Under the proposed restriction, patients aged less than 9 months diagnosed with 3 copies of *SMN2* prior to symptom development would be eligible for treatment with ONA. Patients who develop symptoms between the ages of >6 and <9 months (Type II SMA) (assuming they did not receive pre-symptomatic treatment) would remain ineligible for PBS-subsidised ONA treatment based on the proposed listing but, would be able access other DMTs (i.e. NUSI and RIS). The PBAC considered patients aged <9 months, with symptomatic SMA and 3 copies *SMN2* should also be eligible for treatment with ONA, though there are likely to be few (if any) patients who would meet these criteria once NBS is implemented.

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 numbers of *SMN2* gene copies and increased

severity of symptoms. Patients with SMA typically develop weak muscles and may have trouble walking and breathing (See Table 3).

Table 3: Classification of SMA based on age of symptom onset, motor function and life expectancy

Type	Age at symptom onset	Maximum motor function without treatment	Life expectancy without treatment	Likely <i>SMN2</i> copy number
0	Foetal	Nil	Days-weeks	1
I	<6 months	Never sits	< 2 years	1, 2, 3
II	6-18 months	Never walks	20-40 years	2, 3, 4
III	1.5-10 years	Walks, regression	Normal	3, 4, 5
IV	>35 years	Slow decline	Normal	4, 5

Source: Table 2, paragraph 4.2, onasemnogene abeparvovec, PSD, November 2022 PBAC meeting.

Bold = predominant *SMN2* copy number that defines the SMA type, the other copy numbers represent a small percentage of the designated SMA type.

SMA= spinal muscular atrophy; *SMN2* = survival motor neuron 2 gene.

- 4.2 Previously, 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 previously 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 (paragraph 7.6, ONA PSD, November 2022 PBAC meeting).
- 4.3 Newborn bloodspot screening (NBS) for SMA will identify and diagnose patients with SMA for treatment prior to symptom development. The resubmission claimed that by the July 2023 PBAC meeting, it is estimated that all announced programs will be in progress (assuming the South Australia program begins at the beginning of July 2023). It is therefore likely that, once NBS for the detection of SMA is implemented across Australia, all patients with SMA will be detected soon after birth and eligibility for the proposed ONA listing will be able to be determined.
- 4.4 ONA is a once per life-time gene replacement therapy consisting of a non-replicating recombinant adeno-associated viral (AAV9) 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. The resubmission claimed that there is no need for any additional therapy once gene therapy has been provided as no child who has received onasemnogene abeparvovec has lost a developmental milestone while on therapy. This claim may not be adequately supported. In the pivotal SPR1NT study, four (4/25) patients (all with 2 *SMN2* copies) received subsequent treatment (with NUSI or RIS) following treatment with ONA prior to or during the longer-term follow-up study. NUSI (for Type I SMA or pre-symptomatic SMA) and RIS (for Type I SMA) are currently PBS listed for treatment occurring after ONA therapy.

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

5 Comparator

- 5.1 The resubmission nominated itself (ONA) as the main comparator, but in a population with a different *SMN2* copy genotype (1-2 copies or 2 copies of *SMN2* vs 3 copies of *SMN2*). Only data from patients with 2 *SMN2* copies were presented in the resubmission's clinical evaluation. This differed from the previous submission which nominated 'usual care or watchful waiting and treat as symptoms appear'. The resubmission claimed that this change was based on the PBAC PSD (paragraph 7.10, ONA PSD, November 2022 PBAC meeting) which "suggested that a comparison of cost and clinical benefit of the presymptomatic treatment of 1-2 copies of *SMN2* and those with 3 copies of *SMN2* would be useful". The PBAC agreed with the evaluation and the ESC that ONA in patients with 1-2 copies of *SMN2* was not the appropriate comparator. The PBAC comments were in the context that such a comparison would be more informative for establishing the cost effectiveness in the expanded population (to include the proposed pre-symptomatic 3 *SMN2* patients in addition to the currently subsidised pre-symptomatic 1-2 *SMN2* population) given the limitations of the available evidence. That is, the PBAC was interested in the incremental benefit of pre-symptomatic treatment of 3 *SMN2* copies compared to the incremental benefit of pre-symptomatic treatment of 1-2 *SMN2* copies (given the incremental clinical benefit was expected to be lower in the 3 *SMN2* copies population due to better baseline outcomes), rather than the incremental benefit between pre-symptomatic treatment in patients with 3 copies of *SMN2* and in patients with 1-2 copies of *SMN2*.
- 5.2 The Pre-Sub-Committee Response (PSCR) stated the "request for a comparison of incremental cost-effectiveness between 1-2 *SMN2* copy babies and 3 *SMN2* copy babies could not be accommodated because no model for 1 to 2 *SMN2* copy babies which was accepted by the PBAC exists to provide a comparison". The ESC noted that an economic model was presented in consideration of nusinersen for patients with 1-2 copies *SMN2*, however the submission for ONA made no attempt at quantifying the costs or modelling the benefits of pre-symptomatic treatment of patients with 3 copies *SMN2*, but instead started from the assumption that the value was comparable.
- 5.3 The PSCR also stated that this comparator "provides the PBAC with a comparison and data which is contained within the same clinical conditions, with the same underlying principles for recruitment and measurement of outcomes and removes the issues with using either the natural history data or the available data for treatment with DMTs that proved not previously useful to decision making".
- 5.4 The PBAC agreed with the evaluation and the ESC that usual care or watchful waiting and treat as symptoms appear remained the appropriate comparator.
- 5.5 The resubmission appropriately nominated NUSI and RIS as near market comparators. This remained unchanged from the previous submission. Neither NUSI nor RIS are currently PBS listed for pre-symptomatic treatment of SMA patients with 3 *SMN2* copies, but a submission for NUSI will be considered by the PBAC at the July 2023 PBAC meeting. A submission to expand the PBS listing for RIS to include pre-symptomatic

treatment for the same population (based on a cost minimisation analysis versus ONA) was on the agenda for the March 2023 meeting but this indication was withdrawn by the sponsor.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (6), health care professionals (1) and organisations (1) via the Consumer Comments facility on the PBS website. Input from consumers noted the efficacy of early treatment with ONA and the negative, permanent impact on outcomes for babies who do not have access to pre-symptomatic treatment. The comments also noted the impact on the parents of these children who currently cannot access treatment until symptoms occur.

6.3 The PBAC noted that consumer comments on the previous submission 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.

6.4 The PBAC noted the advice received from the National Paediatric Medicines Forum (NPMF) in support of PBS listing of ONA for patients with SMA who have 3 copies of *SMN2* in addition to its advice regarding the previous submission. The NPMF considered that this expanded listing would improve equitable access and best outcomes for all stakeholders, while reducing anguish for families of recently diagnosed babies. The NPMF noted that currently approximately 30% of newborns with a SMA diagnosis and 3 *SMN2* copies are not eligible for genetic therapy. By the time signs of irreversible motor neuron degeneration manifest and they become eligible for genetic therapy, it can be too late to save the death of many more motor neurons, leading to the potential for a lifetime of neurodisability. The range of presentations are intermediate in half (onset in first three years and ability to sit but not walk), severe for 15% (inability to sit), and 'mild' for one third (falls and mobility problems in childhood). The NPMF also referred to Australian data (Kariyawasam et al, 2023) demonstrating significant functional differences from pre-

symptomatic treatment, with all children with 3 *SMN2* copies achieving walking status when treated pre-symptomatically, whereas walking was rarely achieved in those treated after symptom onset.

- 6.5 The PBAC noted advice from Spinal Muscular Atrophy Australia on the previous submission strongly supported expanding the current PBS listing of ONA to include the pre-symptomatic treatment of patients genetically diagnosed with SMA who have 3 *SMN2* 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 *SMN2* 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

- 6.6 The resubmission was based on five studies. Three were single arm intervention studies involving pre-symptomatic treatment of SMA patients with 2 and 3 *SMN2* copies (SPR1NT (ONA), NURTURE (NUSI) and RAINBOWFISH (RIS)), one study was a longer term follow-up study involving SPR1NT (LT-002) and one study was an Australian cohort study of SMA patients comparing an incident population diagnosed through newborn screening with a cohort of patients treated after clinical referral (referred to as the Sydney Children Hospital Network (SCHN) study (Kariyawasam et al, 2023)).
- 6.7 Four of the five studies (SPR1NT, LT-002, NURTURE and RAINBOWFISH) identified by the resubmission were previously presented and considered by the PBAC during the last application for ONA at the November 2022 meeting and were limited in terms of long-term follow-up data and comparability (paragraph 6.46, ONA PSD, November 2022 PBAC meeting). The resubmission identified one new study (the SCHN study) and presented new data for ONA from the longer-term follow up study of SPR1NT (LT-002, new data cut of 23 May 2022; previously 23 May 2021). No new efficacy data for NUSI or RIS were presented.
- 6.8 It was not possible to make statistical direct or indirect comparisons with the data from the clinical studies given the nature of the single arm, non-comparative studies. The lack of a control group also did not allow for any incremental benefit to be estimated.
- 6.9 Details of the studies presented in the resubmission are provided in Table 4.

Table 4: Studies and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
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 <i>SMN2</i> . Strauss et al. Onasemnogene abeparvovec for presymptomatic infants with three copies of <i>SMN2</i> at risk for spinal muscular atrophy: The Phase III SPR1NT trial.	October 2021. <i>Nature Medicine</i> 2022; 28(7):1390-1397.
	Strauss, K., et al. Onasemnogene Abeparvovec for Presymptomatic Infants with Spinal Muscular Atrophy and Two Copies of <i>SMN2</i> .	Conference abstract <i>Neurology</i> 2022; 98 (18 SUPPL)
	Strauss, K. A et al. Onasemnogene abeparvovec for presymptomatic infants with two copies of <i>SMN2</i> at risk for spinal muscular atrophy type 1: the Phase III SPR1NT trial.	<i>Nature Medicine</i> 2022; 28(7):1381-1389.
	Schultz, M et al. Genetic Replacement Therapy (GRT) Clinical Trial with AVXS-101 in Presymptomatic Spinal Muscular Atrophy (SMA): Design of the Phase III Trial and Baseline Demographic Data.	Conference abstract <i>Nervenheilkunde</i> 2019; 38(5):300.
LT-002 NCT04042025 (interim)	AVXS101/AV101. Summary of data from long-term follow-up studies	November 2022.
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.	<i>Neuromuscular Disorders</i> 2019; 29(11):842-856.
	Biogen. A Study of Multiple Doses of Nusinersen (ISIS 396443) Delivered to Infants With Genetically Diagnosed and Presymptomatic Spinal Muscular Atrophy. In: https://ClinicalTrials.gov/show/NCT02386553	NCT record 2015.
	Kirschner, J., et al. Impact of Nusinersen on Caregiver Experience and HRQoL in Presymptomatic SMA: NURTURE Study Results. https://doi.org/10.3233/JND-229001	Conference abstract <i>Journal of Neuromuscular Diseases</i> 2022;9, S113-S114
RIS		
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.
	A Study of Risdiplam in Infants With Genetically Diagnosed and Presymptomatic Spinal Muscular Atrophy.	NCT record 2019
	Servais, L., et al. POOLED SAFETY DATA FROM THE RISDIPLAM CLINICAL TRIAL DEVELOPMENT PROGRAMME. https://doi.org/10.1136/innp-2022-ABN.456	Conference abstract <i>Journal of Neurology, Neurosurgery and Psychiatry</i> 2022; 93(6),142
Servais, L., et al. RAINBOWFISH: Preliminary Efficacy and Safety Data in Risdiplam-Treated Infants with Presymptomatic Spinal Muscular Atrophy. https://doi.org/10.3233/JND-229001	Conference abstract <i>Journal of Neuromuscular Diseases</i> 2022; 9, S114-S115	
Cohort study		
SCHN	Kariyawasam et al. Newborn screening for spinal muscular atrophy in Australia: a non-randomised cohort study. DOI: https://doi.org/10.1016/S2352-4642(22)00342-X	<i>Lancet Child Adolesc</i> 2023; 7(3):159-170

Blue shading indicates items presented by the previous submission.

Source: Table 2.3, p67 of the resubmission.

NUSI=nusinersen; ONA=onasemnogene abeparvovec; RIS=risdiplam; SCHN= Sydney Children Hospital Network; SMA=spinal muscular atrophy; *SMN1*=survival motor neuron 1; *SMN2*=survival motor neuron 2

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

Table 5: Key features of the included evidence

Study, n	Design/duration	Bias	Treatment	Population	Outcome(s)
SPR1NT n=14 (2 copies); 15 (3 copies)	MC, NC, SA, OL up to 18&24 mths of age for 2SMN2 and 3SMN2 respectively	High	ONA IV 1.1 x 10 ¹⁴ vg/kg	Pre-symptomatic patients – 2 and 3 copy SMN2 aged ≤ 6 wks	1°: motor milestone – sitting (for 2 copies, 18 mths); standing (for 3 copies, 24 mths) 2°: motor milestones, EFS
LT-002 (SPR1NT) [^] n=12 (2 copies); 13 (3 copies)	MC, NC, SA, OB, OL extension 15 yrs May 2022 data cut: median (range) age: 43.7 (35.9, 50.5) mths for 2 copies and 40.1 (34.4, 46.0) for 3 copies; time since treatment: 43.2 (35.2, 50.2) mths for 2 copies and 39.6 (33.8, 44.8) mths for 3 copies.	High	As in SPR1NT	Pre-symptomatic patients – 2 and 3 copy SMN2. Extension study of SPR1NT	1°: motor milestone 2°: motor milestones, EFS
NURTURE [^] n=15 (2 copies); 10 (3 copies)	MC, NC, SA, OL, 5y March 2019 data cut: median (range) age 34.8 (25.7-45.4) mths; time in study was 33.9 (25.3-45.1) mths.	High	NUSI IC 12 mg	Pre-symptomatic patients – 2 and 3 copy SMN2 aged ≤ 6 wks	1°: EFS 2°: OS, motor milestones
RAINBOWFISH [#] n=7 (2 copies); 11 (>2 copies)	MC, NC, SA, OL 2 yrs / 3 yrs July 2021 data cut: median (range) treated for 8.7 (0.5-22.8) mths.	High	RIS oral target dose	Pre-symptomatic patients ≥2 copies of SMN2 aged ≤ 6 wks	1°: motor milestone - sitting (12 mths) ^a 2°: motor milestones, EFS
SCHN n=18 (3 copies); 13 (3 copies); 2 (4 copies)	NR cohort study of SMA babies comparing an incident population diagnosed through newborn screening (1/8/2018-1/8/2020) and an incident population diagnosed by clinical referral (1/8/2016 – 31/7/2018)	High	No treatment administered as part of study ^b	Symptomatic and pre-symptomatic diagnosed SMA patients	1°: motor milestone – highest motor attainment (24 mths) 2°: OS, changes in HINE-2 score, WeeFim, CHOP-INTEND

Blue shading represents studies previously presented and considered at the PBAC November 2022 meeting.

Source: Table 2.4, 2.5, 2.6 & 2.11, p67, 68, 72 & 85 of the resubmission; Table 4, p15 of the onasemnogene abeparvovec, PSD, November 2022 PBAC meeting; Table 3.3 & 3.4, p31 & 32 of the summary of long-term follow-up data; p4 of De Vivo et al 2019 (NURTURE); p1 of Finkel et al 2022 (RAINBOWFISH)

1° = primary outcome; 2°= secondary outcome; CHOP-INTEND=The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; EFS=event-free survival (survival without permanent ventilation); HINE-2=Hammersmith Infant Neurological Examination; IC=intrathecal; IV=intravenous; MC=multi-centre; mths = months NC=non-comparative single arm study; NR=non randomised; NUSI=nusinersen; OB=observational; OL=open label; ONA=onasemnogene abeparvovec; OS=overall survival; RIS=risediplam; SA=single arm; SMA=spinal muscular atrophy; SMN2=survival motor neuron 2; WeeFim= Functional Independence Measure for Children; wks=weeks; yr=year

[^] Ongoing study.

[#] Includes 7 patients with 3 SMN2 copies and 4 with ≥4 SMN2 copies

^a Primary efficacy population included patients with 2 copies of SMN2 and CMAP ≥1.5 mV at baseline.

^b No interventions were administered as part of the study, but patients were allowed to access treatment. Patients in the screening group received: NUSI; ONA; palliative care; or active surveillance. Patients in the comparator group received NUSI or palliative care.

Comparative effectiveness

Pre-symptomatic ONA in 3 copies of *SMN2* compared to pre-symptomatic ONA in 2 copies of *SMN2*

6.11 A comparison of developmental milestones achieved between patients with 3 copies of *SMN2* and patients with 2 copies of *SMN2* treated pre-symptomatically with ONA from the SPR1NT study is summarised in Table 6.

Table 6: Summary of developmental milestone results in SPR1NT

Outcome	3 <i>SMN2</i> copies (n=15)† 'Cohort 2'		2 <i>SMN2</i> copies (n=14)‡ 'Cohort 1'	
	WHO-MGRS	BSID	WHO-MGRS	BSID
Achieved sitting without support n (%)	14 (93.3)	14 (93.3)	14 (100)	14 (100)
Median age (months) at earliest achievement (95%CI)	8.80 (7.1, 8.8)	7.60 (6.9, 8.6)	9.00 (7.6, 11.1)	8.85 (7.2, 9.2)
Achieved within 99 th percentile of normal development, n (%)	10 (66.7)	11 (73.3)	10 (71.4)	11 (78.6)
Achieved standing with assistance n (%)	14 (93.3)	14 (93.3)	14 (100)	14 (100)
Median age (months) at earliest achievement (95%CI)	9.30 (9.05, 10.64)	9.25 (8.7, 10.6)	12.95 (11.1, 15.3)	13.70 (10.4, 15.7)
Achieved within 99 th percentile of normal development, n (%)	11 (73.3)	11 (73.3)	5 (35.7)	6 (42.9)
Achieved crawling n (%)	14 (93.3)	14 (93.3)	10 (71.4)	9 (64.3)
Median age (months) at earliest achievement (95%CI)	10.75 (9.75, 12.37)	10.75 (9.8, 11.8)	13.40 (10.5, 14.9)	14.40 (10.5, 14.9)
Achieved within 99 th percentile of normal development, n (%)	13 (86.7)	14 (93.3)	5 (35.7)	4 (28.6)
Achieved walking with assistance n (%)	14 (93.3)	14 (93.3)	12 (85.7)	11 (78.6)
Median age (months) at earliest achievement (95%CI)	12.30 (11.04, 13.46)	12.20 (10.9, 13.0)	14.90 (13.3, 16.4)	12.50 (11.8, 15.2)
Achieved within 99 th percentile of normal development, n (%)	12 (80.0)	13 (86.7)	5 (35.7)	6 (42.9)
Achieved standing alone n (%)	15 (100)	15 (100)	10 (71.4)	11 (78.6)
Median age (months) at earliest achievement (95%CI)	13.30 (12.97, 15.46)	12.60 (12.2, 14.7)	16.40 (14.6, 18.0)	15.30 (13.4, 17.1)
Achieved within 99 th percentile of normal development, n (%)	13 (86.7)	14 (93.3)	5 (35.7)	7 (50.0)
Achieved walking alone n (%)	14 (93.3) ^a	14 (93.3) ^a	10 (71.4)	9 (64.3)
Median age (months) at earliest achievement (95%CI)	14.05 (13.02, 15.37)	14.10 (13.2, 16.1)	16.40 (14.4, 17.9)	17.50 (14.3, 18.3)
Achieved within 99 th percentile of normal development, n (%)	13 (86.7)	11 (73.3)	6 (42.9)	5 (35.7)

Blue shading represents results previously presented and considered at the PBAC November 2022 meeting.

Source: Tables 2.19-2.25, pp102-106 of the resubmission.

BSID=Bayley Scale for Infant Development; *SMN2*=survival motor neuron 2; WHO-MGRS=World Health Organisation Multicentre Growth Reference Study

† Measured up to and including the 24 months of age visit; ‡ Measured up to and including the 18 months of age visit

^a One patient did not have any recorded video footage for central review confirmation of being able to walk alone and was not formally counted as achieving this milestone prior to reaching 24 months of age. However, at the age 24 month visit, the clinical evaluator observed by video that the patient was able to stand and walk alone.

6.12 Overall, compared to patients with 2 copies of *SMN2*, a larger proportion of patients with 3 copies of *SMN2* enrolled in the SPR1NT study achieved more advanced developmental milestones and these were consistently achieved within a shorter

median time. A larger proportion of patients with 3 copies of *SMN2* also achieved their relevant developmental milestones within the upper bound of normal development according to the WHO-MGRS. Walking for 14 children and standing for one child represented the highest achieved milestones for patients with 3 copies of *SMN2* enrolled in SPR1NT.

- 6.13 A total of 25 patients (12 with 2*SMN2* copies; 13 with 3*SMN2* copies) from SPR1NT rolled over into LT-002. At the time of the latest data cut-off (23 May 2022, median age 40.1 months), all patients in both cohorts had achieved and maintained the highest developmental milestone of walking alone. Longer-term results, including whether patients will regress, were unknown.
- 6.14 The PBAC has previously 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” (paragraph 7.6, ONA PSD, November 2022 PBAC meeting). Given this, better outcomes in patients with 3 copies of *SMN2* compared to patients with 2 copies of *SMN2* would likely be observed even in the absence of treatment, and it was not possible to accurately distinguish the treatment effect of pre-symptomatic treatment with a DMT from any natural development of the patient in the absence of an appropriate control group.
- 6.15 Based on the results from SPR1NT, no conclusion could be drawn with regards to the magnitude of incremental benefit (if any) for pre-symptomatic ONA treatment compared to symptomatic initiation of treatment in either patients with 3 copies of *SMN2* or in patients with 2 copies of *SMN2*, therefore a comparison of the incremental benefit of pre-symptomatic treatment in patients with 3 copies of *SMN2* with pre-symptomatic treatment in patients with 2 copies of *SMN2* could not be conducted.

Near market comparators

- 6.16 Table 7 presents comparisons between ONA and the nominated near market comparators, NUSI and RIS, for the pre-symptomatic treatment of SMA patients, based on the outcome of developmental motor milestones. These comparisons have been presented in multiple submissions including the evaluation of the previous submission (discussed at the November 2022 PBAC meeting).

Table 7: Summary of developmental milestone results in the clinical studies

Outcome	SPR1NT (ONA)		Control [^]	NURTURE (NUSI) [#]		RAINBOWFISH(RIS) [*]	
	2SMN2 [†]	3SMN2 [‡]	≥2SMN2	2SMN2	3SMN2	2SMN2	>2SMN2
Achieved ability to stand unsupported, n/N (%)							
BSID ^a	11/14 (78.6)	15/15 (100)	19/81 (23.5)	—	—	—	—
% achieved within window	7/14 (50.0)	14/15 (93.3)	—	—	—	—	—
WHO-MGRS ^b	10/14 (71.4)	15/15 (100)	—	12/15 (80)	10/10 (100)	—	—
% achieved within window	5/14 (35.7)	13/15 (86.7)	—	4/15 (27)	10/10 (100)	—	—
HINE-2 ^c	—	—	—	—	—	2/4 (50)	3/3 (100)
% achieved within window	—	—	—	—	—	1/4 (25)	3/3 (100)
Achieved ability to walk unsupported, n/N (%)							
BSID ^d	9/14 (64.3)	14/15 ^e (93.3)	17/81 (21)	—	—	—	—
% achieved within window	5/14 (35.7)	11/15 (73.3)	—	—	—	—	—
WHO-MGRS ^f	10/14 (71.4)	14/15 ^e (93.3)	—	12/15 (88)	10/10 (100)	—	—
Median age (months) at earliest achievement (95%CI)	16.40 (14.4, 17.9)	14.05 (13.0, 15.4)	—	20.4 (15.5, 29.7)	12.3 (11.2, 14.9)	—	—
% achieved within window	6/14 (42.9)	13/15 (86.7)	—	6/15 (40)	10/10 (100)	—	—
HINE-2 ^g	—	—	—	—	—	1/4 (25)	3/3 (100)
% achieved within window	—	—	—	—	—	1/4 (25)	3/3 (100)

Blue shading represents results previously presented and considered at the PBAC November 2022 meeting.

Source: Tables 2.30-2.32, pp114-116 of the resubmission; De Vivo et al 2019 (NURTURE); Finkel et al 2022 (RAINBOWFISH).

BSID=Bayley Scale for Infant Development; HINE-2=Hammersmith Infant Neurological Examination-2; MGRS=Multicentre Growth Reference Study, NUSI=nusinersen; ONA=onasemnogene abeparovvec; RIS=risdiplam; SMN2=survival motor neuron 2; WHO=World Health Organisation; NR=not reported; PNCR= Paediatric Neuromuscular Clinical Research Network for SMA

† Measured up to and including the 24 months of age visit; ‡ Measured up to and including the 18 months of age visit; ^ comparison with PNCR population, the PNCR was a natural history study (2014) of the disease which was used for comparisons to the study populations in SPR1NT. The “population matched” control cohort for the ability to sit without support was those with 2SMN2 copies while those with 3SMN2 copies were matched for the ability to stand and walk unsupported; # Measured at 24 months of age; * In RAINBOWFISH the preliminary exploratory analysis at the July 2021 data cut was for 7 patients treated with RIS for ≥12 months; in the >2SMN2 group: two patients had 3 SMN2 copies and one patient had atypical 3-4SMN2 copies.

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

e One patient did not have any recorded video footage for central review confirmation of being able to walk alone and was not formally counted as achieving this milestone prior to reaching 24 months of age. However, at the age 24 month visit, the clinical evaluator observed by video that the patient was able to stand and walk alone.

f 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.

g HINE-2: “walking independently”.

6.17 The ‘control group’ presented in Table 7 was based on a natural history study (the Paediatric Neuromuscular Clinical Research study; Finkel et al, 2014). The PBAC previously noted that such studies would not reflect a scenario where patients are

treated with DMTs pre-symptomatically or soon after symptoms appear, and hence, would not reflect current clinical practice (paragraph 4.6. & 7.5, ONA PSD, November 2022 PBAC meeting). Further, the developmental milestones assessed were measured using different scales at different timepoints.

- 6.18 Only SPR1NT and NURTURE reported similar outcomes which allowed for some level of naïve comparisons (WHO milestone ability to sit without support, ability to stand unsupported and ability to walk unsupported). While the patients were assessed at different timepoints which made the comparisons more difficult, the median age at which patients with 3 copies of *SMN2* achieved ability to sit in NURTURE was lower (6.4 months) than in SPR1NT (8.8 months), and a similar trend was observed in the median age at which patients achieved ability to walk unsupported (12.3 months in NURTURE and 14.05 months in SPR1NT), though the clinical significance of these differences was unclear. Of the patients with 3 copies of the *SMN2* gene, a higher proportion of patients treated with NUSI (compared to those treated with ONA) were found to have consistently achieved these milestones within the normal window.
- 6.19 All patients from SPR1NT enrolled in LT-002 (n=25) were alive at the latest data cut-off (May 2022). Similar results were observed for NURTURE (n=25; March 2019 data cut) and RAINBOWFISH (n=18; July 2021 data cut). None of the patients from SPR1NT in LT-002 required ventilatory support (invasive or non-invasive). While none of the patients enrolled in NURTURE required permanent ventilation (defined as ≥ 16 h/day continuously for > 21 days in the absence of an acute reversible event or tracheostomy), four patients (all with two *SMN2* copies) utilised respiratory support. This was not reported for RIS in RAINBOWFISH.

SCHN study (Kariyawasam et al 2023) – SMA treatment before and after implementation of SMA screening

- 6.20 The SCHN study was a study of pre-symptomatic treatment of SMA (identified through NBS between 1 August 2018 to 1 August 2020; screening group) and patients who were identified via referral between 1 August 2016 and 31 July 2018 and treated after symptom onset (comparator group) in Australia. However, actual treatments received by patients with 3 copies of *SMN2* in the screening group (patients identified by NBS and primarily treated pre-symptomatically) were unknown therefore it was unclear any of the results would be applicable to the resubmission, and the comparator arm has similar applicability issues as other natural history studies, with longer delay between symptom onset and treatment (difference between median age at treatment and median age at ‘symptom onset’ was 28.5 weeks) than would be expected with patients identified through NBS.
- 6.21 In the SCHN study, by the two-year follow-up, 14 (93%) of 15 patients in the screening group and 16 (89%) of 18 patients in the comparator group were alive. With regard to WHO motor milestones, of the screening group, 11 (79%) of 14 patients were walking independently or with assistance compared with one (6%) of 16 patients in the comparator group (79% vs 6%; $\chi^2=16.27$; $p<0.0001$). In this comparator group, at a

median chronological age of 2.84 years, the highest motor milestone attained by most patients was sitting ability, observed in nine (56%) patients.

- 6.22 The resubmission claimed that based on the SCHN study, it is the impact of when treatment was accessed that has the most impact on outcome and not the *SMN2* copy number itself and that having 3 *SMN2* copies was not protective of poorer outcomes. The evaluation considered this was not a reasonable conclusion. While the age of treatment may have a larger impact, the SCHN study found *SMN2* copy number was also a significant predictor of HINE-2 and WHO motor scores where those with 3 *SMN2* copies on average, had more favourable scores than those with 2 *SMN2* copies. Even though patients with 3 copies of *SMN2* in the screening group attained more advanced motor milestones than patients with 3 copies of *SMN2* in the comparator group, it should be noted that patients in the comparator group were significantly worse off at baseline.
- 6.23 Overall, the SCHN study was confounded and prone to selection bias. Patients enrolled in the comparator group were worse off at baseline compared to the screening group, with lower motor function (indicated by significantly lower HINE-2 and CHOP-INTEND scores) and at least half of the patients expressing the severe SMA Type I phenotype (non-sitters). As such, comparisons made between the screening and comparator groups were likely biased in favour of the screening group, and it was difficult to draw any meaningful comparisons from the study.

Comparative harms

- 6.24 An overview of adverse events (AEs) reported in SPR1NT is presented in Table 8.

Table 8: Adverse events reported in SPR1NT by patient cohort

Safety outcome, n (%)	Cohort 2 (3 <i>SMN2</i> copies) (n=15)	Cohort 2 (2 <i>SMN2</i> copies) (n=14)
Any TEAE	15 (100)	14 (100)
TEAEs related to study treatment	8 (53.3)	10 (71.4)
TEAEs of Grade 3 severity or higher	3 (20.0)	4 (28.6)
Serious TEAEs	3 (20.0)	5 (35.7)
Serious TEAEs related to study treatment	0	0
TEAEs leading to study discontinuation	0	0
Deaths	0	0

Blue shading represents results previously presented and considered at the PBAC November 2022 meeting.

Source: Table 2.33, p117 of the resubmission.

TEAE=treatment-emergent adverse event; *SMN2*=survival motor neuron 2

Notes: For each category, patients are included only once, even if they experienced multiple events in that category.

TEAEs were considered treatment related if they were classified by the investigator as possibly, probably, or definitely related to study treatment.

- 6.25 Overall, the safety profile of ONA for the pre-symptomatic treatment of patients with 3 copies of *SMN2* appeared to be generally consistent with patients with 2 copies of *SMN2*, but it was difficult to make a formal conclusion based on the small numbers of patients in each cohort.
- 6.26 An overview of AEs reported in the included clinical studies (SPR1NT, NURTURE and RAINBOWFISH) with different DMTs is presented in Table 9. The SCHN study did not report any safety outcomes.

Table 9: Adverse events reported in the included clinical studies – total populations

Outcome, n (%)	SPR1NT (ONA)		NURTURE (NUSI)		RAINBOWFISH (RIS)	
	2SMN2 copies (n=14)	3SMN2 copies (n=15)	2SMN2 copies (n=15)	3SMN2 copies (n=10)	2SMN2 copies (n=7)	>2SMN2 copies ^a (n=11)
Any AE	14 (100)	15 (100)	15 (100)	10 (100)	5 (71)	9 (82)
AE related to study treatment	10 (71)	8 (53)	4 (27)	4 (40)	0	2 (18)
AE of Grade 3 severity or higher	4 (29)	3 (20)	–	–	1 (14) ^a	1 (9) ^a
Serious AE	5 (36)	3 (20)	9 (60)	3 (30)	0	0
Severe AE	–	–	5 (33)	0	–	–
Serious AE related to study treatment	0	0	0	0	0	0
AE leading to study discontinuation	0	0	0	0	0	0
AE leading to death	0	0	0	0	0	0

Blue shading represents results previously presented and considered at the PBAC November 2022 meeting.

Source: Table 2.33, p117 of the resubmission.

NUSI=nusinersen; ONA=onasemnogene abeparovvec; RIS=risdiplam; TEAE=treatment-emergent adverse event; SMN2=survival motor neuron 2

Note: For each category, patients are included only once, even if they experienced multiple events in that category.

Note 2: TEAEs were considered treatment related if they were classified by the investigator as possibly, probably, or definitely related to study treatment.

^a includes 7 patients with 3 SMN2 copies and 4 with ≥ 4 SMN2 copies.

^a Corrected during the evaluation. These were previously listed as not available “-”.

6.27 In its consideration of ONA at the November 2020 meeting, the PBAC did not accept the claim of superior safety for ONA versus NUSI, noting that safety data presented for ONA and NUSI 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 (paragraph 7.6 ONA PSD, November 2020 PBAC meeting). The PBAC has also noted that it was difficult to conclude ONA and NUSI were non-inferior in terms of safety based on available evidence (paragraph 6.51, ONA PSD, September 2021 meeting). At the November 2022 meeting, the PBAC further 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 (paragraph 7.7, ONA PSD, November 2022 PBAC meeting).

6.28 For the purpose of the economic evaluation (in which a cost-minimisation approach was provided), the resubmission further described that ONA had a different but non-inferior safety profile compared to RIS. In the March 2021 consideration of RIS in symptomatic SMA, the PBAC considered that the conclusion that RIS has a favourable safety profile compared to NUSI in some patients was reasonable (paragraph 7.8, risdiplam PSD, March 2021 PBAC meeting). Overall, it was difficult to make an informed conclusion with respect to the safety profile of ONA compared to RIS. The PBAC has previously considered that RIS had a more favourable safety profile than NUSI in some patients, whereas the PBAC rejected a superior safety claim of ONA compared to NUSI previously, preventing a transitivity argument for non-inferior safety between ONA and RIS.

Benefits/harms

- 6.29 The naïve indirect comparisons presented in the resubmission did not allow for a quantitative comparison of the benefits and harms of ONA and the nominated comparators (ONA (for pre-symptomatic treatment in patients with 2 copies of *SMN2*), NUSI or RIS). Accordingly, a benefits/harms table has not been presented.

Clinical claim

- 6.30 The resubmission described the pre-symptomatic treatment with ONA for patients with 3 copies of *SMN2* as non-inferior in terms of effectiveness compared with pre-symptomatic treatment with ONA for patients with 2 *SMN2* copies. The therapeutic conclusion presented in the resubmission was not supported because even though naïve comparisons of the absolute developmental outcomes in SPR1NT appeared to suggest that more patients with 3 copies of *SMN2* treated with ONA pre-symptomatically achieved developmental milestones within the normal timeframe compared to patients with 2 copies of *SMN2*, this was likely confounded by the differences in baseline attainment of milestones and the natural course of the disease between patients with 2 and 3 *SMN2* copies and it was difficult to make any meaningful or reliable comparisons between the two distinct populations.
- 6.31 Moreover, the nominated comparator (pre-symptomatic treatment with ONA in patients with 2 copies of *SMN2*) was inappropriate, with standard of care (symptomatic initiation with DMT) being the appropriate comparator.
- 6.32 A more informative comparison would have been a comparison of the incremental benefit of pre-symptomatic initiation of ONA in patients with 3 copies of *SMN2* compared to symptomatic initiation of DMTs, with the incremental benefit of pre-symptomatic initiation of ONA in patients with 1-2 copies of *SMN2* compared to symptomatic initiation of DMTs (see paragraph 5.1). The evaluation considered this could have been used to support an economic evaluation in the Southwest quadrant of the cost-effectiveness plane (i.e. less effective, less costly), which would be consistent with PBAC's previous consideration of pre-symptomatic ONA in patients with 3 copies of *SMN2* (see paragraph 3.4).
- 6.33 In its evaluation of the previous submission, the PBAC considered that, "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" (paragraph 7.5, ONA PSD, November 2022 PBAC meeting).
- 6.34 Overall, the ESC agreed with the evaluation that the incremental benefit of pre-symptomatic treatment with ONA in patients with 3 copies of *SMN2* compared to current standard of care (symptomatic initiation) remains uncertain, and the magnitude of incremental benefit of pre-symptomatic treatment with ONA in patients

with 3 copies of *SMN2* compared to current standard of care relative to the magnitude of incremental benefit of pre-symptomatic treatment with ONA in patients with 1-2 copies of *SMN2* compared to current standard of care was also not informed by the resubmission.

- 6.35 The resubmission described the pre-symptomatic treatment with ONA for patients with 3 *SMN2* copies as non-inferior in terms of safety compared with pre-symptomatic treatment with ONA for patients with 2 *SMN2* copies. For the purpose of the economic evaluation (in which a cost-minimisation analysis was provided), the resubmission further described ONA as non-inferior in terms of safety compared with RIS. It was difficult to draw a conclusion regarding relative safety given the small sample size and the single arm nature of the included studies. A transitivity argument for non-inferior safety between ONA and RIS (using NUSI) could not be made (see paragraph 6.28).
- 6.36 The ESC considered that the clinical claim of 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.
- 6.37 The PBAC considered that the efficacy and safety claims made in the submission were not directly relevant to the requested change to the listing of ONA.

Economic analysis

- 6.38 The resubmission presented a cost-minimisation approach which compared ONA for pre-symptomatic patients with 3 copies of *SMN2* (the proposed population) with ONA for pre-symptomatic patients with 1-2 copies of *SMN2* (as currently listed on the PBS) over a time horizon of two years based on the follow up of SPR1NT (see Table 10). The ESC noted that this comparison was based on the assumption that the incremental benefit of pre-symptomatic treatment of SMA patients with 3 copies *SMN2* was comparable to the incremental benefit of pre-symptomatic treatment of SMA patients with 1-2 copies *SMN2*.
- 6.39 The ESC considered the cost minimisation approach presented may not be appropriate as the claim of comparable benefit was not supported by the evidence presented, and given the PBAC has previously considered 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 (paragraph 7.6, ONA PSD, November 2022 PBAC meeting).

Table 10: Key components and assumptions of the cost-minimisation approach

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on evidence presented in SPR1NT, effectiveness was assumed to be non-inferior to ONA for patients with 1-2 copies of <i>SMN2</i> [†] . This may not be reasonable (see paragraph 6.30). Additionally, the SPR1NT study did not include patients with 1 copy of <i>SMN2</i> (who would likely have more severe disease).
Therapeutic claim: safety	Based on evidence presented in Section 2, safety is assumed to be non-inferior to ONA for patients with 1-2 copies of <i>SMN2</i> . It was difficult to draw a conclusion regarding relative safety given the small sample size and the single arm nature of the included studies.
Evidence base	Crude comparisons of developmental milestones achieved in patients with 3 <i>SMN2</i> copies and 2 <i>SMN2</i> copies within the SPR1NT study.
Equi-effective doses	ONA dosed once per lifetime is equivalent to ONA dosed once per lifetime
Direct medicine costs	The direct medicine cost of ONA was sourced from the PBS. The direct medicine cost of ONA was equivalent to ONA over a 2-year time horizon. Discounting was not considered.
Other costs or cost offsets	Cost to MBS of specialist appointments Cost to MBS of physiotherapy appointments Healthcare resource utilisation was based on attainment of motor milestones in SPR1NT. In the base case, no difference in MBS costs between patients with 2 copies of <i>SMN2</i> and 3 copies of <i>SMN2</i> was assumed. The cost of subsequent therapy was not considered.

Source: Table 3.1, p133 of the resubmission.

ONA=onasemnogene abeparvovec

[†] The resubmission claimed that the clinical data showed 3 *SMN2* copy patients having superior outcomes. The resubmission noted that it understood the bias in the design of the data may not allow a claim of superiority and as such were willing to accept a non-inferior pricing strategy.

6.40 Healthcare resource utilisation for the 1-2 copies of *SMN2* and the 3 copies of *SMN2* populations was estimated using motor milestone outcomes from the SPR1NT study (sitting without support and walking without support) as a proxy for healthcare intervention requirements. All treated patients were able to sit without support and walk without support at two-year follow-up. Although more patients with 3 copies of *SMN2* achieved the ability to walk within the WHO specified threshold for normal development (and as such healthcare costs were likely to be lower), the resubmission assumed equal resource utilisation for all children who achieve the ability to walk independently and thus the price of ONA for the proposed and currently subsidised populations was equal. Table 11 presents the results of the cost minimisation approach.

Table 11: Results of the cost-minimisation approach

Component	ONA published price (AEMP)		ONA effective price	
	3 <i>SMN2</i> copies	1-2 <i>SMN2</i> copies	3 <i>SMN2</i> copies	1-2 <i>SMN2</i> copies
Cost per dose	\$2,527,773.87	\$2,527,773.87	\$	\$
Total number of doses (lifetime)	1	1	1	1
Total healthcare cost (per year)	\$630.60 ^a	\$630.60 ^a	\$630.60 ^a	\$630.60 ^a
Total cost over 2 years	\$2,529,035.07	\$2,529,035.07	\$	\$

Source: Table3.6, p135 of the resubmission.

AEMP=approved ex-manufacturer price; ONA=onasemnogene abeparvovec; SMN= survival of motor neuron

^a Calculated by the resubmission

Drug cost/patient/course

6.41 The cost of ONA based on the effective price (AEMP/DPMQ) is \$ [REDACTED] per patient (administered only once in a lifetime).

Table 12: Drug cost per patient for proposed and comparator drugs

	ONA Trial dose and duration	ONA economics	ONA Financial estimates	Comparator ^a Trial dose and duration	Comparator ^a Financial estimates
Dose		1.1x10 ¹⁴ vg/kg		ONA: 1.1x10 ¹⁴ vg/kg NUSI: 12mg at days 0, 14, 28 and 63, then every 4 months thereafter RIS: by age and weight to target exposure (maximum 5mg/day)	ONA: 1.1x10 ¹⁴ vg/kg NUSI: 12mg at days 0, 14, 28 and 63, then every 4 months thereafter RIS: by age and weight to target exposure (maximum 5mg/day)
Duration		Once-off injection		On-going	6 years
Cost		\$ [REDACTED] /patient		-	NUSI: \$74,096/dose RIS: \$8,180.70/60mg
Cost/patient (maintenance)		-		ONA: \$ [REDACTED] (once off) NUSI: \$222,288/year ^d RIS: \$249,000/year ^e	ONA: \$ [REDACTED] (once off) NUSI: \$222,288/year ^d RIS: \$249,000/year ^e

NUS = nusinersen; ONA = onasemnogene abeparvovec; PI = product information; RIS = risdiplam

^a Comparators listed here are for symptomatic initiation which were used as offsets in financial estimates. The comparator nominated in the base case for ONA was ONA. RIS was included as a near-market comparator in the cost minimisation approach.

^b 0.2 mg/kg in 2 months and <2 years of age, 0.25 mg/kg in ≥2 years and <20 kg, 5mg in >2 years and ≥20kg. WHO weight-for-age tables used to inform dosage over time.

^c RIS withdrew the request for pre-symptomatic treatment in patients with 3 copies of *SMN2* at the March 2023 PBAC meeting therefore the cost of RIS for the pre-symptomatic treatment of patients 3 copies of *SMN2* was unknown.

^d Assume 3 doses per year and no discontinuation. 5% discontinuation assumed in financial estimates.

^e Assume 365.25 days, 5mg dose (12 doses per bottle) and no discontinuation, though 5% discontinuation assumed in financial estimates
Source: Table 1.15, p56, Table 4.22, p152 and Table 4.26, p155 of the resubmission.

Estimated PBS usage & financial implications

6.42 This resubmission was not considered by DUSC. The resubmission utilised an epidemiological approach to estimate the financial impact of listing ONA for the pre-symptomatic treatment of SMA patients with 3 *SMN2* copies on the PBS.

6.43 The data sources, parameters and assumptions used to estimate the financial impact are summarised in Table 13. The estimated expected treatments that would be substituted for by ONA (symptomatic initiation of NUSI, RIS and ONA) was based on SMA phenotype and age of symptom onset (see Table 14).

Table 13: Key inputs for financial estimates

Data	Value and source	Comment
Eligible population		
Number of babies born with SMA each year	1 in 10,000 live births Source: SMA Australia	The incidence rate may be slightly overestimated. An incidence of 0.866 in 10,000 live births was reported from the state-wide pilot NBS program in NSW/ACT where 9 newborns with SMA were identified out of 103,903 newborns screened (Kariyawasam 2020).
Distribution of SMA phenotypes	Type I: 50.1% Type II: 29.3% Type III: 20.5% Source: Based on a study that analysed 375 SMA patients for their SMN2 copy number (Feldkotter 2002). The resubmission claimed these SMA phenotype data were used in a prior submission recommended by PBAC (Figure 1, ONA PSD, November 2020 PBAC Meeting with May 2021 Addendum and September 2021 Addendum). This appeared to be used to inform the population and disease, rather than financial estimates.	Inappropriately does not account for SMA Type IV, and patients with 3 SMN2 copies could have this phenotype. The estimates for Type I were previously assumed to be 60% based on an estimate by SMA Australia (Table 15, ONA PSD, November 2020 PBAC meeting). The resubmission erroneously assumed that there will be 30% Type II (for a total of 100.7% across all three SMA types) in the base case. This was corrected during evaluation. Sensitivity analyses increasing the number of Type I patients to 60% increased the offsets and decreased the net cost of listing by approximately 20%.
Proportion of each SMA Type who have 3 copies of SMN2 gene	Type I: 20% Type II: 82% Type III: 50% Source: As above, (Feldkotter 2002).	This was similar to previously observed figures (Type I: 20%; Type II: 78%; Type III: 49%).
Distribution of Type 3 sub-phenotypes	Type IIIa: 75% of Type 3 Type IIIb: 25% of Type 3 Source: Data from a cross-sectional study of patients with SMA in the Netherlands (N=180) (Wadman 2018).	Based on a small sample size. Out of the 24 Type III patients with 3 SMN2 copies, 18 (75%) had Type IIIa and 6 (25%) had IIIb SMA.
Treatment utilisation		
Treatment uptake rate	95% Source: Assumption.	In response to the suggestion that the previous rate of 90% was an underestimate of treatment uptake, was increased to 95% (Table 15, ONA PSD, November 2022 PBAC meeting).
Treatment discontinuation rate	5% Source: Assumption The resubmission claimed this was in response to the view that 0% treatment discontinuation was not a reasonable assumption for this population, therefore a ■■■% discontinuation rate after the first year of treatment was applied for symptomatic treatment with NUSI and RIS (paragraph 6.74, ONA PSD, November 2022 PBAC meeting).	While patients may discontinue treatment, this potentially underestimated the cost offset as it did not account for treatment switching. In consideration of the previous submission, it was noted that “in clinical studies patients did discontinue treatment with nusinersen and in practice patients could discontinue nusinersen and switch to risdiplam treatment” (paragraph 6.74, ONA PSD, November 2022 PBAC meeting).
Costs		
Drug costs	As per Table 12 for ONA, RIS and NUSI. Effective price for RIS and NUSI based on an estimated 32.46% discount from published price. \$19.34 for Prednisolone (2 units per ONA treatment)	The DPMQ of prednisolone was \$18.53 at the time of evaluation.

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Data	Value and source			No. services	Comment
	Service	MBS item	MBS cost		
MBS costs	ONA			MBS items used were reasonable and the 80% MBS benefit was correctly applied. It was noted that these were also used by the previous submission. However, post treatment follow up with a specialist visit for NUSI or RIS were not considered by the resubmission, which may slightly overestimate the financial impact of ONA. The use of MBS item 104 was consistent with MBS item used in the resubmission's economic evaluation. The MBS cost offsets specific to ONA treatment were incorrectly calculated based on the total SMA Type I patients (rather than the 90% of Type I patients who were estimated to be treated with ONA) by the resubmission which slightly overestimated the cost offsets.	
	Pre-treatment consultation	104	\$91.80		
	Intravenous administration (1 hr)	14245	\$103.55		
	Post-treatment follow-up consultation: first year	104	\$91.80		
	Liver Function Test	66512	\$17.70		
	Cardiac Troponin Test	66518	\$20.05		
	Full Blood Count Test	65070	\$16.95		
	Creatinine Test	66500	\$9.70		
	NUSI				
	Intrathecal infusion (2 hrs: 1hr + 15 mins x 4) – per episode of treatment incl. anaesthetic if needed	18216 + 4 x 18219	\$281.15		

Source: Tables 4.1, 4.8, 4.17, 4.22, 4.26, 4.43, 4.45, pp139, 140, 144, 148, 152, 155, p168 and p170 of the resubmission.

AAV9=adeno-associated virus serotype 9; DPMQ = dispensed price for maximum quantity; IV=intravenous; hr=hour, NBS = newborn bloodspot screening; SMA = spinal muscular atrophy; DPMQ=dispensed price of maximum quantity; MBS=Medicare Benefits Schedule; NUSI=nusinersen, ONA=onasemnogene abeparovvec; RIS=risdiplam; SMN= survival of motor neuron; yr=year

Table 14: Parameter values applied to calculate the patients expected to receive NUSI, RIS and ONA in the absence of the proposed listing

	Type I	Type II	Type IIIa	Type IIIb
Age at symptom onset	0-6 months	>6-18 months	>18-36 months	>36 months
Initiation of treatment	First year of life	Second year of life	Third year of life	Sixth year of life
Proportion of patients over 6 years ^a	20/87 (23%)	47/87 (54%)	15/87 (17%)	5/87 (6%)
Market share (analysis performed by Sponsor) ^b	ONA: 90% NUSI: 9% RIS: 1%	ONA: 0% NUSI: 86% RIS: 14%	ONA: 0% NUSI: 86% RIS: 14%	ONA: 0% NUSI: 86% RIS: 14%

Source: Table 4.11&4.14, pp152&154 of the resubmission, and calculated for ESC advice from financial estimates worksheet.

NUSI=nusinersen; ONA=onasemnogene abeparovvec; RIS= risdiplam

^a Numbers differ from table 15 due to rounding.

^b This analysis was not provided as part of the resubmission.

6.44 Table 15 presents the estimated net financial implications for the proposed listing of ONA for the pre-symptomatic treatment of SMA patients with 3 SMN2 copies over the first 6 years.

Table 15: Estimated use and financial implications (corrected during evaluation)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimation of use and financial impact of the proposed medicine (PBS)						
Incidence of SMA	1	1	1	1	1	1
Eligible ^a Type I pts who elect trt	1	1	1	1	1	1
Eligible ^a Type II pts who elect trt	1	1	1	1	1	1
Eligible ^a Type IIIa pts who elect trt	1	1	1	1	1	1
Eligible ^a Type IIIb pts who elect trt	1	1	1	1	1	1
Total patients treated with ONA	1	1	1	1	1	1
Total number of scripts	1	1	1	1	1	1
Total PBS cost less co-pay (eff)	5	5	5	5	5	5
Estimation of changes in use and financial impact of other medicines (PBS)						
Total initiating patients (first year)	1	1	1	1	1	1
Total continuing patients (second yr+)	1	1	1	1	1	1
Changes in number of scripts						
Nusinersen	1	1	1	1	1	1
Risdiplam	1	1	1	1	1	1
ONA	1	1	1	1	1	1
Prednisolone	1	1	1	1	1	1
Total	1	1	1	1	1	1
PBS cost less co-pay (eff)						
Nusinersen ^c (\$)	2	2	2	2	2	2
Risdiplam ^c (\$)	2	2	2	2	2	2
ONA ^b (\$)	2	2	2	2	2	2
Prednisolone ^a (\$)	3	3	3	3	3	3
Total (eff) (\$)	2	2	2	2	2	2
Estimated financial implications for the PBS						
Net cost to PBS (eff) (\$)	4	4	4	4	3	3
Estimated financial implications for the health budget						
Net MBS costs (\$)	3	3	2	2	2	2
Net cost to Govt health budget (eff) (\$)	4	4	4	4	3	3

Source: Tables 4.2-4.7, 4.9-4.10, 4.12-4.13, 4.15-4.16, 4.18-4.21, 4.23-4.25, 4.27-4.42, 4.46-4.48, pp142-144, 146-149, 151, 153, 155,157-161, 163, 165, 167, 170-171 of the resubmission.

eff=effective; govt=government; SMA = spinal muscular atrophy; MBS=Medicare Benefits Schedule; NUSI=nusinersen, ONA=onasemnogene abeparovvec; PBS=Pharmaceutical Benefits Scheme; pts=patients; RIS=riski; SMN= survival of motor neuron; trt = treatment

^a Patients who had 3 copies of SMN2 and had eligible AAV9 status (patients identified as AAV9+ were not eligible).

^a The price of prednisolone used by the resubmission (\$19.34) was higher than the price on the PBS (\$18.53) at time of evaluation. A co-payment of \$15.48 was also used even though it was assumed that 100% of patients treated with pre-symptomatic ONA were general patients, in which case patients would pay the full amount for prednisolone as it is under the co-payment threshold of \$30. This was not corrected during the evaluation due to the minor impact.

^b A co-payment of \$15.48 was used instead of \$30. This would overestimate the financial impact of listing ONA but was not corrected during the evaluation due to the minor impact.

^c The resubmission assumed the effective price of NUSI and RIS was a 32.46% discount from published price.

The redacted values correspond to the following ranges:

¹ <500

² net cost saving

³ \$0 to < \$10 million

⁴ \$10 million to < \$20 million

⁵ \$20 million to < \$30 million

- 6.45 The estimated net cost to the government budget of listing ONA on the PBS/RPBS at the proposed effective price was \$10 million to < \$20 million in Year 1, decreasing to \$0 to < \$10 million in Year 6. The total cost over the six-year period was \$70 million to < \$80 million. The decline over time was consistent with the difference in number of doses, as ONA was assumed to be a once off treatment (with no subsequent DMT) whereas NUSI and RIS are life-long therapies (with a 5% discontinuation rate assumed).
- 6.46 The ESC recalled that an 11-year time horizon was used for the cost-minimisation calculations for ONA for patients with 1-2 copies *SMN2*. The ESC considered that the time before ONA would be cost neutral in patients with 3 copies *SMN2* would be likely to be longer than for patients with 1-2 copies *SMN2*, as patients would begin treatment at a later timepoint. Assuming the initiation of treatment timepoints and proportion of patients in each SMA type in Table 14, on average it would take 12.2 years before ONA was cost-neutral in the 3 *SMN2* copies population.
- 6.47 There were some uncertainties with regards to the financial estimates:
- Should any patient with 3 copies of *SMN2* who would have developed Type IV SMA be treated pre-symptomatically with ONA (assumed to be 0% in the resubmission), the financial estimates would be underestimated as there would be no cost offsets associated with these patients (as patients with Type IV SMA are currently not eligible for any DMT treatment). The PSCR noted that the proportion of patients with Type 4 SMA and 3 copies *SMN2* is very small (~0.2% of SMA patients);
 - Potential underestimation of the costs by not considering the prevalent population, thereby potentially underestimating the number of eligible patients in year 1. The PSCR considered this would be less than 5 additional patients in year 1;
 - Uncertainty around the proportion of patients with 3 copies of *SMN2* in each SMA type, and the distribution of SMA type;
 - The assumption of 100% coverage for NBS for SMA, although it is not clear when this would be fully implemented Australia-wide. The PSCR considered the impact of any delays to expected timelines is likely to be small;
 - The use of a higher incidence than observed in the state-wide pilot NBS program in NSW/ACT (Kariyawasam 2020); and
 - Assuming treatment discontinuation for NUSI/RIS while not accounting for treatment switching.
- 6.48 Overall, the net cost of listing ONA for the proposed population was uncertain and is dependent on the duration being considered (which affects the amount of cost offsets) as well as assumptions around SMA incidence and the expected phenotypes of patients with 3 copies of *SMN2*. The introduction of reproductive genetic carrier

screening to assist family planning decisions may affect the expected incidence of SMA in the longer term.

- 6.49 Inappropriately the resubmission did not include the results of any sensitivity analyses around the financial estimates. The financial estimates were most sensitive to the distribution of SMA phenotypes assumed for the estimates (see Table 13).

Quality Use of Medicines

- 6.50 The previous commentary noted access issues for ONA including few centres where gene therapy is offered which may require patients to travel interstate to access ONA, and delays to NBS screening rollout may limit accessibility to ONA, as patients will not be eligible for ONA if identified after 9 months of age. In response, the resubmission noted that ONA will be available in the same number of states as NUSI (NSW, QLD, WA, VIC and SA). Further, the resubmission maintained the issues regarding the availability of NBS will be resolved by the end of July 2023 with the roll-out of NBS across Australia being complete.

Financial Management – Risk Sharing Arrangements

- 6.51 The resubmission proposed that the current outcomes-based RSA for ONA for SMA Type I and pre-symptomatic patients with 1 or 2 copies of the *SMN2* gene will apply to the proposed 3 *SMN2* population, whereby a full refund is provided to the Commonwealth to compensate if patients die within 2 years of treatment, or a refund equivalent to the difference between ONA and RIS or NUSI for Years 2-5. This remained unchanged from the previous submission. The PBAC considered, given the low number of expected deaths during the deed period, loss of motor milestones is the better measure of treatment failure for this population.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the amendment to the current listing of ONA to include the pre-symptomatic treatment in patients aged up to 9 months, genetically diagnosed SMA, who have a *SMN2* gene copy number of 3. The PBAC considered that pre-symptomatic treatment with ONA in patients with 3 copies of *SMN2* would provide an additional benefit for some patients compared with initiation of treatment upon development of symptoms. The PBAC noted there was remaining uncertainty regarding the cost-effectiveness of pre-symptomatic treatment with ONA in patients with 3 copies of *SMN2* due to the uncertain magnitude of incremental benefit compared to symptomatic treatment. However, the PBAC was satisfied that extension of the current listing would be adequately cost-effective with a price reduction for use in the proposed population.
- 7.2 The PBAC acknowledged that the current requirement for symptoms to develop prior to accessing subsidised treatment for SMA could have a significant burden on the

families of infants genetically diagnosed with 3 copies of *SMN2*. The PBAC also acknowledged there was a need for equitable access to treatment for all infants genetically diagnosed with SMA, noting that NBS programs will soon be introduced across Australia.

- 7.3 The PBAC noted the trajectory of the disease for individuals with 3 copies of *SMN2* in the absence of treatment is uncertain, and that a small proportion would achieve normal milestones in the absence of treatment. The PBAC noted that while the spectrum of disease for patients with 3 copies of *SMN2* is heterogenous and not as severe as for patients with 2 copies of *SMN2*, that it is both biologically plausible and likely, that if patients are treated with ONA earlier the loss of motor neurons will be reduced and a higher level of motor function may be maintained.
- 7.4 The resubmission nominated treatment with ONA in patients with 1-2 copies of the *SMN2* gene as the main comparator. The PBAC considered that usual care or watchful waiting and treat as symptoms appear remained the relevant comparator as previously accepted by the PBAC. The PBAC noted that, while the resubmission had nominated both risdiplam and nusinersen as near market comparators, at the time of PBAC consideration neither of these treatments were PBS listed for patients diagnosed with 3 copies of *SMN2* prior to the onset of symptoms.
- 7.5 The PBAC noted that the resubmission was based on small, single arm clinical studies, the majority of which have previously been considered by the PBAC. A comparison of developmental milestones achieved between patients with 3 copies of *SMN2* and patients with 2 copies of *SMN2* treated pre-symptomatically with ONA from the SPR1NT study was presented. Although naïve comparisons of the absolute developmental outcomes in SPR1NT appeared to suggest that more patients with 3 copies of *SMN2* treated with ONA pre-symptomatically achieved developmental milestones within the normal timeframe compared to patients with 2 copies of *SMN2*, this was likely confounded by the differences in baseline attainment of milestones and the natural course of the disease between patients with 2 and 3 *SMN2* copies. The PBAC considered that no conclusion could be drawn with regards to the magnitude of incremental benefit for pre-symptomatic ONA treatment compared to symptomatic initiation of treatment in either patients with 3 copies of *SMN2* or in patients with 2 copies of *SMN2*.
- 7.6 On balance, the PBAC was satisfied that ONA initiated pre-symptomatically for patients with 3 copies of *SMN2* was likely to provide a significant improvement in efficacy over initiation of treatment (ONA, nusinersen or risdiplam) in patients once symptomatic. The PBAC considered that while some patients with 3 copies of *SMN2* would not develop symptoms until years after birth, and their disease would be less severe on average, the estimated benefit of early intervention for patients treated pre-symptomatically compared to patients treated symptomatically outweighed the negative impact of treating the small proportion of patients who would not have developed symptoms.

- 7.7 The PBAC recalled it had previously 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 (para 7.7, ONA PSD, November 2022 PBAC meeting).
- 7.8 The PBAC recalled it previously considered that given the limitations of the evidence and the unsuitability of the economic model presented, 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, and the smaller clinical benefit for patients with 3 *SMN2* 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 (para 7.10 ONA PSD, November 2022 PBAC meeting). The PBAC noted the resubmission for ONA made no attempt at quantifying the costs or modelling the benefits of pre-symptomatic treatment of patients with 3 copies *SMN2*, but instead started from the assumption that the value was comparable, presenting a cost-minimisation approach with ONA for patients with 1-2 copies *SMN2*.
- 7.9 The PBAC noted the requested price for this listing was the same as the price for pre-symptomatic patients with 1-2 copies of *SMN2*. The PBAC recalled it previously advised at its November 2022 PBAC meeting that a lower price for pre-symptomatic treatment for a patient with 3 copies of *SMN2* would be required to ensure similar cost-effectiveness to that of treating patients with 1-2 copies. The PBAC considered that a price reduction of around 10% would be appropriate in this context for the population with pre-symptomatic SMA with 3 copies *SMN2*. The PBAC considered the current outcomes-based RSA for ONA for SMA Type I and pre-symptomatic patients with 1 or 2 copies of the *SMN2* gene should also apply to the proposed 3 copies *SMN2* population.
- 7.10 The PBAC noted that a submission for nusinersen in patients with 3 copies *SMN2* was considered at the July 2023 PBAC meeting and advised that in the event that nusinersen is recommended and proceeds to PBS listing in this patient population the dose relativities for the current listings for pre-symptomatic patients with 1-2 copies *SMN2* should apply to listings for patients with 3 copies *SMN2*.
- 7.11 The PBAC noted the resubmission had taken an epidemiological approach to estimate use of ONA and considered that the approach was generally reasonable. The PBAC noted patients with SMA Type IV had not been accounted for in the distribution of patients with 3 copies of *SMN2*, however considered this to be reasonable, noting this would be expected to be no more than one patient across the 6 years of forward estimates. The PBAC noted the cost over 6 years was estimated to be \$70 million to < \$80 million, assuming an effective price for RIS and ONA that is a 32.46% less than the published price. The PBAC noted that the cost of treatment with ONA is borne up front, but for patients treated in year 1, offsets from nusinersen and risdiplam would be expected to continue beyond the 6 years of the forward estimates. The PBAC

considered that overall, the additional cost of expanding the listing to patients with 3 copies *SMN2* would largely be limited to the cost of earlier initiation of SMA treatment.

- 7.12 The PBAC found that the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022 for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for ONA:
- a) Based on the available evidence the magnitude of benefit of initiating treatment with ONA pre-symptomatically was not able to be quantified, and therefore the criterion of having a substantial and clinically relevant improvement in efficacy compared to symptomatic initiation of SMA treatment was not met;
 - b) The treatment is not expected to address a high and urgent unmet clinical need; and
 - c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.
- 7.13 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

- 8.1 Restriction to be finalised.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.