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 to expand the current Section 100 (Highly Specialised Drugs Program), Authority Required (Written) PBS listing for onasemnogene abeparvovec (ONA) for the treatment of spinal muscular atrophy (SMA) to include paediatric patients weighing up to 21 kg.

1.2 Listing was requested on the basis of a cost-comparison approach versus ONA, when used in paediatric patients less than 9 months of age with (i) Type I SMA or with pre-symptomatic SMA with 1-2 copies of the *SMN2* gene, or (ii) pre-symptomatic SMA with three copies of the *SMN*2 gene (i.e. the current PBS listing for ONA). Table 1 provides a summary of the key components of the submission.

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

Component	Description
Population	Paediatric patients weighing up to 21kg with (i) Type I SMA or pre-symptomatic SMA with 1-2 copies of the survival motor neuron 2 (*SMN2*) gene and (ii) Pre-symptomatic SMA with 3 copies of the *SMN2* gene.
Intervention	Onasemnogene abeparvovec (ONA), administered as a single intravenous infusion through a venous catheter delivered over 60 minutes. 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.
Comparator	Paediatric patients less than 9 months of age with (i) Type I SMA or pre-symptomatic SMA with 1-2 copies of the *SMN2* gene and (ii) Pre-symptomatic SMA with 3 copies of the *SMN2* gene currently treated with ONA (administered as above).
Outcomes	Motor milestone development and safety.
Clinical claim	Treatment of paediatric patients weighing up to 21kg with (i) Type I SMA or pre-symptomatic SMA with 1-2 copies of the *SMN2* gene and (ii) Pre-symptomatic SMA with 3 copies of the *SMN2* gene is non–inferior to treatment of paediatric patients less than 9 months of age with (i) Type I SMA or pre-symptomatic SMA with 1-2 copies of the *SMN2* gene and (ii) Pre-symptomatic SMA with 3 copies of the *SMN2* gene with respect to development milestones and safety.

Source: Table 1.1, p3 of the submission.
SMA= spinal muscular atrophy

1.3 The submission proposed to remove the 9-month age limit and replace it with a weight limit of up to 21kg, and described the circumstances in which patients ineligible for ONA under the current listing may benefit from the proposed expanded listing (see Table 2).

Table 2: Proposed circumstances for patients who could benefit from the proposed restriction change

Category name	Description of population
Patient choice	When diagnosed at birth with Type I or pre-symptomatic SMA (1-3 *SMN2* copies), the patient (or caregiver) has selected not to be treated with ONA. They are now 9 months or older and wish to be treated with ONA.
High AAV9 at birth	High levels of anti-AAV9 antibody (>1:50) is a contraindication for the use of ONA. These antibodies are highest in early infancy and may decline over time. A patient with high AAV9 which continues beyond 9 months currently cannot access ONA.
Migrated to Australia after birth	Patients originally born outside Australia and were not diagnosed with SMA at birth who were subsequently diagnosed with Type I or pre-symptomatic SMA (1-3 *SMN2* copies), and are 9 months or older and wish to be treated with ONA. Without an extension to this age, these children will not have access to ONA.
NBS missed patients	NBS for SMA is offered nationally to all newborns in Australia, with participation rates exceeding 99% of all live births (Woodcock 2025)[1]. For the small group of patients who were not diagnosed with SMA via NBS at birth, either because parents opt out of testing or babies are born at home, if these children are then diagnosed with SMA, after 9 months of age, they do not have access to ONA.
Patients with a point mutation	These are patients with a point mutation that are not detected by NBS (<5% of cases; Schwartz et al. 2024). These patients would become eligible for ONA if they developed symptoms before 6 months of age and classified as SMA Type 1 but diagnosed after 9 months.

Source: Table 4.1, p99 of the submission; p2 of the submission, *p1* Pre-Sub-Committee Response (*PSCR).*
AAV9= adeno-associated virus serotype 9; kg= kilogram; NBS= newborn bloodspot screening; ONA= onasemnogene abeparvovec; SMA= spinal muscular atrophy; SMN2=survival motor neuron 2 gene

1.4 It was unclear how many (treatment naïve) patients would initiate treatment with ONA due to the circumstances described above by the submission. Given sequential use of ONA is allowed following treatment with disease modifying treatments (DMTs), patients with SMA currently treated with nusinersen or RIS would likely initially form the majority of the requested PBS population treated under the extended listing. That is, most patients under the requested extended listing (who are older than 9 months but below the 21 kg weight limit) would already be treated with a DMT before switching to ONA.

1.5 Based on weight-for-age data from the World Health Organisation (WHO)[2], a weight of 21kg corresponds to the weight of an average 6-year-old child, though a weight limit of 21kg "may occasionally include patients up to 9 years of age" (TGA Clinical Evaluation Report).

2 Background

Registration status

2.1 ONA was TGA registered 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 pre-symptomatic

[1] Woodcock, IR., et al, (2025), 'Cost-Effectiveness of Newborn Screening for Spinal Muscular Atrophy in Australian Hospitals', Neurology and Therapy, 14(3), 1007–1022. https://doi.org/10.1007/s40120-025-00744-8

[2] World Health Organisation weight-for-age data; 50th percentile: https://www.who.int/tools/growth-reference-data-for-5to19-years/indicators/weight-for-age-5to10-years

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

2.2 It was noted that this indication for patients "less than 9 months" was supported by clinical study data and was proposed based on advice from the Advisory Committee on Medicines (ACM) (ACM Minutes, December 2020 meeting). At the time, the ACM agreed that an indication of up to 2 years of age (as originally proposed by the sponsor) was not supported due to a lack of clinical study data, and increased risk of gene therapy toxicities in older and larger children (ACM Minutes, December 2020 meeting). Further, the ACM advised that the indication should specify 1-3 copies of SMN2, as this reflected the experience from the studies (ACM Minutes, December 2020 meeting).

2.3 An application was lodged to the TGA on 31 October 2024 to remove the conditions of 'less than 9 months of age' and '1 to 3 copies of the *SMN2* gene' from the current TGA indication. The proposed indication was:

> "ZOLGENSMA (onasemnogene abeparvovec) is indicated for the treatment of paediatric patients with symptomatic or pre-symptomatic spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene."

2.4 At the time of PBAC consideration the TGA Delegate's Overview and ACM advice were available. The pre-PBAC response noted that ACM considered that ONA has a positive benefit-risk profile for the indication (TGA ACM Minutes):

> "ZOLGENSMA is indicated for the treatment of:
> Patients with 5q spinal muscular atrophy (SMA) with bi-allelic pathogenic variants in the SMN1 gene with 3 or fewer copies of the SMN2 gene.
> Therapy may only be administered to patients up to the age of nine years and who weigh less than or equal to 21kg."

2.5 Although an expansion from an age limit of 9 months of age to a weight limit of 21kg was requested, the submission noted that the sponsor would align the proposed PBS restriction with the TGA indication recommended by the Delegate. The PSCR noted that the intention for the indication when first submitted to the TGA was an age limit of up to 2 years. The pre-PBAC further clarified that the sponsor is willing to accept an upper age restriction of 36 months for ONA treatment in Type I and pre-symptomatic SMA patients with 1–3 SMN2 copies and noted that this is within the ACM proposed indication.

2.6 The pre-PBAC response noted that there are still negotiations occurring with the TGA Delegate regarding either the removal of SMN2 copy number (or addition of 4 SMN2 copy number) and as to the inclusion of age or weight in the TGA indication.

Previous PBAC consideration

2.7 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 Public Summary Document [PSD], September 2021 PBAC meeting). 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 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). 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 SMN2 copies 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). At its July 2023 meeting the PBAC recommended amendment to the current listing of ONA to include pre-symptomatic treatment in patients aged up to 9 months with SMA and SMN2 gene copy number of 3. The PBAC was satisfied that extension of the listing would be adequately cost-effective with a price reduction for use in the proposed population (paragraph 7.1, ONA PSD, July 2023 PBAC meeting).

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	№.of Rpts	Available brands
Onasemnogene abeparvovec (Type I SMA or pre-symptomatic SMA with 1-2 *SMN2* copies)					
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 $[redacted] effective price	1	1	0	ZOLGENSMA
Onasemnogene abeparvovec (Pre-symptomatic SMA with 3 copies of *SMN2*)					
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 $[redacted] effective price	1	1	0	ZOLGENSMA

Source: Tables 1.10 & 1.11, p19 of the submission.
SMA= spinal muscular atrophy; *SMN2*= survival motor neuron 2 gene

Category / Program: Section 100 – Highly Specialised Drugs Program
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (in writing only via post/HPOS upload)
Indication: Spinal Muscular Atrophy
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
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
The treatment must be given concomitantly with best supportive care for this condition
Treatment criteria:
Must be treated by a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA; or in consultation with a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA
AND
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
Patient must be undergoing treatment with this pharmaceutical benefit once only in a lifetime
AND
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 weigh no heavier than 21kg
AND
Patient must have symptomatic Type I SMA; OR
Patient must have pre-symptomatic SMA with 1-2 copies of the *SMN2* gene

Treatment Phase: Use occurring after treatment with at least one disease modifying therapy for this condition (i.e. switching from nusinersen/risdiplam to onasemnogene abeparvovec)
Clinical criteria:
The treatment must be given concomitantly with best supportive care for this condition
AND
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.
Treatment criteria:
Patient must be undergoing treatment with this pharmaceutical benefit following prior PBS-subsidised treatment with at least one other disease modifying therapy for this condition
AND
Must be treated by a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA; or in consultation with a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA
AND
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
Patient must be undergoing treatment with this pharmaceutical benefit once only in a lifetime
AND
Patient must be undergoing treatment with this pharmaceutical benefit with the intent that treatment with the replaced disease modifying agent is/has ceased
Population criteria:
Patient must weigh no heavier than 21kg
AND
Patient must have symptomatic Type I SMA; OR
Patient must have pre-symptomatic SMA with 1-2 copies of the *SMN2* gene

Source: Table 1.12, pp20-21 of the submission.
kg= kilogram; SMA= spinal muscular atrophy; SMN= survival of motor neurone; PBS= Pharmaceutical Benefits Scheme

Category / Program: Section 100 – Highly Specialised Drugs Program
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (in writing only via post/HPOS upload)
Indication: Spinal Muscular Atrophy
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
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
The treatment must be given concomitantly with best supportive care for this condition
Treatment criteria:

Must be treated by a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA; or in consultation with a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA
AND
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
Patient must be undergoing treatment with this pharmaceutical benefit once only in a lifetime
AND
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 weigh no heavier than 21kg
AND
Patient must have pre-symptomatic SMA with 3 copies of the *SMN2* gene
Treatment Phase: Use occurring after treatment with at least one disease modifying therapy for this condition (i.e. switching from nusinersen/risdiplam to onasemnogene abeparvovec)
Clinical criteria:
The treatment must be given concomitantly with best supportive care for this condition
AND
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.
Treatment criteria:
Patient must be undergoing treatment with this pharmaceutical benefit following prior PBS-subsidised treatment with at least one other disease modifying therapy for this condition
AND
Must be treated by a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA; or in consultation with a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA
AND
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
Patient must be undergoing treatment with this pharmaceutical benefit once only in a lifetime
AND
Patient must be undergoing treatment with this pharmaceutical benefit with the intent that treatment with the replaced disease modifying agent is/has ceased
Population criteria:
Patient must weigh no heavier than 21kg
AND
Patient must have pre-symptomatic SMA with 3 copies of the *SMN2* gene

Source: Table 1.13, pp21-22 of the submission.
kg= kilogram; SMA=spinal muscular atrophy; SMN= survival of motor neurone; PBS= Pharmaceutical Benefits Scheme

3.1 Restriction wording was proposed for paediatric patients weighing up to 21kg with (i) Type I SMA or pre-symptomatic SMA with 1-2 copies of the *SMN2* gene and (ii) pre-symptomatic SMA with three copies of the *SMN2* gene. Appropriately, no continuation criteria or grandfathering criteria were requested.

3.2 The requested restriction was based on the current Section 100 PBS listing for ONA, with the following key modifications:

- The removal of the condition that the "patient must be no older than 9 months of age"; and
- The addition of the condition that the "patient must weigh no heavier than 21kg".

3.3 Currently, eligibility for DMTs in symptomatic SMA (with the SMA type being determined by age of symptom onset – see Table 3) and pre-symptomatic SMA with 1-3 SMN2 copies are determined by age and not weight (see Figure 1). The ESC agreed with the evaluation that the proposed change from age to weight for ONA could cause confusion. The PSCR and pre-PBAC response stated that an age-based restriction would be acceptable to the sponsor.

3.4 The ESC agreed with the evaluation that consideration should be given to using an upper limit based on age for initiation of ONA (for example, 36 months as with the pre-symptomatic listings for NUSI and RIS) rather than weight. This approach would ensure consistency between different DMTs listed on the PBS and also addresses the issue of the uncertain cost-effectiveness of pre-symptomatic treatment in patients aged 36 months and older but weighing less than 21kg who are DMT naïve (which was not addressed in the submission). The pre-PBAC response confirmed that inclusion of an upper limit of 36 months would be acceptable to the sponsor, noting that it is within the ACM recommended indication and aligns with age restrictions in the current listings for other disease-modifying treatments for which cost-effectiveness has been accepted.

3.5 Patients in the pivotal clinical trial (SMART) were required to have a symptomatic SMA diagnosis (including SMA Type II and Type III), which was broader than the requested restriction in which only patients with symptomatic SMA Type I would be eligible for ONA. Input from clinical experts indicated that it would be preferable for the listing for patients with symptomatic SMA to not be limited to Type I, so as not to exclude patients with onset of symptoms at >6 months of age (see also paragraph 6.3). The current listings for nusinersen and risdiplam include symptomatic patients with Type I-IIIa SMA and the cost-effectiveness of DMTs has been established in these patients.

3.6 Patients with a pre-symptomatic SMA diagnosis were excluded from SMART but not excluded from the requested PBS population. Therefore, the safety and effectiveness of ONA in pre-symptomatic patients older than nine months who weigh less than 21 kg has not been investigated.

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 (see Table 3). Patients with SMA typically develop weak muscles and may have trouble walking and breathing (paragraph 4.1, onasemnogene abeparvovec PSD, November 2022 PBAC meeting). While patients 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 (paragraph 4.2, onasemnogene abeparvovec PSD, November 2022 PBAC meeting). Treatment for patients with SMA is most effective when initiated early, ideally before symptoms present. Early identification of patients with SMA through NBS can facilitate diagnosis and treatment initiation in those with clinically silent or pre-symptomatic SMA, which prevents the irreversible loss of motor neurons (Woodcock 2025).

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

Type	Age at symptom onset	Maximum motor function	Life expectancy	Likely *SMN2* copy number
0	Foetal	Nil	Days-weeks	1
1	<6 months	Never sits	< 2 years	1, **2**, 3
2	6-18 months	Never walks	20-40 years	2, **3,** 4
3	1.5-10 years	Walks, regression	Normal	**3, 4,** 5
4	>35 years	Slow decline	Normal	**4, 5**

Source: Table 1.2, p4 of the submission.
SMA= spinal muscular atrophy; *SMN2*= survival motor neuron 2 gene
Note: This was also most recently presented in the onasemnogene abeparvovec PSD, July 2023 PBAC meeting,
Bold indicates predominant *SMN2* copy number that defines the SMA type, the other copy numbers represent a small percentage of the designated SMA type.

4.2 There were inconsistencies between classifications of SMA in recent submissions considered by the PBAC with regards to the age of symptom onset and likely *SMN2* copy numbers in each SMA type. An alternate classification of SMA was previously presented in the NUSI submission at the July 2023 PBAC meeting (Table 3, nusinersen PSD, July 2023 PBAC meeting) where the age of symptom onset for SMA Type III and IV were 1.5-18 years and >18 years respectively, and range of *SMN2* copy numbers for SMA Type III was 2-4 copies, and the RIS submission at the July 2024 PBAC meeting (Table 2, risdiplam PSD, July 2024 PBAC meeting) where it was considered that patients with SMA Type II typically have an *SMN2* copy number of three whereas previous descriptions stated that patients with an *SMN2* copy number of three were commonly classified as having either SMA Type II or III (IIIa or IIIb).

4.3 ONA is a once per life-time gene replacement therapy consisting of a non-replicating recombinant 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

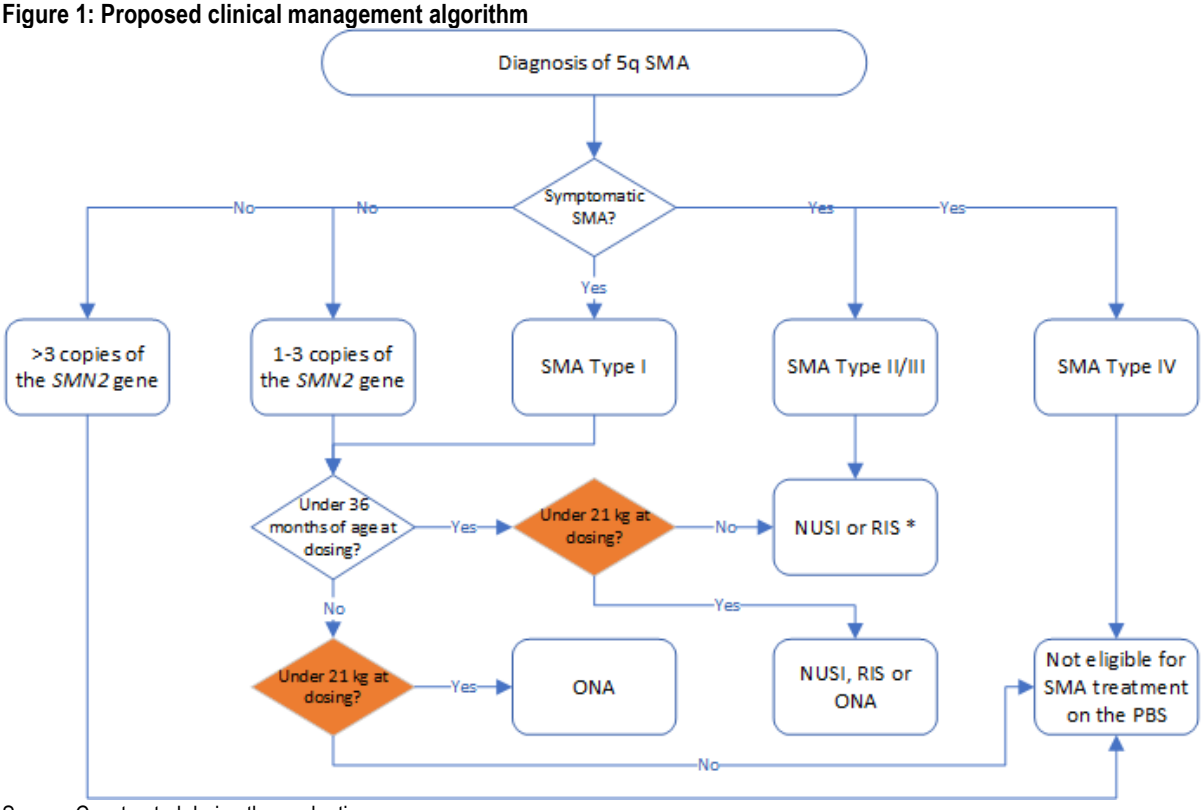
human SMN protein. All patients should receive oral prednisolone (1mg/kg) to manage possible liver function abnormalities, started one day prior to treatment, and for at least 30 days post-treatment. The ESC considered that further information regarding Australian treatment protocols for monitoring and discontinuation of corticosteroids for patients treated with ONA and the costs of these treatments, would be informative. The PBAC noted that information provided by clinical experts suggested that for patients in Australia liver function is monitored closely and patients do not continue corticosteroids for as long as patients in the SMART trial.

4.4 ONA is currently PBS listed for the treatment of SMA in patients aged no older than 9 months who were diagnosed with:

- Type 1 SMA or pre-symptomatic SMA with 1-2 copies of the *SMN2* gene. This was recommended 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 risk sharing arrangement (RSA) (paragraph 9.1, onasemnogene abeparvovec PSD, November 2020 PBAC meeting with May 2021 Addendum and September 2021 Addendum); and
- pre-symptomatic SMA with three copies of the *SMN2* gene. This was recommended as "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" (paragraph 7.1, onasemnogene abeparvovec PSD, July 2023 PBAC meeting).

4.5 The submission inappropriately did not present a clinical management algorithm for the intended use of ONA. This was constructed during the evaluation (see Figure 1). The severity of SMA and eligibility of treatment options for SMA are currently aligned by age.

Figure 1: Proposed clinical management algorithm



Source: Constructed during the evaluation
NUSI= nusinersen; ONA= onasemnogene abeparvovec; RIS= risdiplam; SMA= spinal muscular atrophy; *SMN2*= survival motor neuron; WHO = World Health Organisation
* For patients with SMA Type I: it is extremely unlikely to have a patient under 36 months of age who weighs more than 21 kg (see the WHO weight-for-age charts: https://www.who.int/tools/child-growth-standards/standards/weight-for-age).
Orange shading depicts the addition of the weight restriction, as proposed by the submission.

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

5 Comparator

5.1 The submission nominated ONA when used in paediatric patients less than 9 months of age with (i) Type I SMA or with pre-symptomatic SMA with 1-2 copies of the *SMN2* gene, or (ii) pre-symptomatic SMA with three copies of the *SMN2* gene, as the main comparator (i.e. ONA under the current PBS listings).

5.2 The submission aimed to demonstrate that ONA, when used in paediatric patients weighing up to 21kg is non-inferior in terms of effectiveness and safety, compared with ONA when used in patients less than 9 months of age. However, the nominated comparator may not be appropriate. Instead:

- In patients older than 9 months but younger than 18 years with Type I SMA, NUSI or RIS are PBS listed DMTs which are used and as such would be the most appropriate comparator.

- In patients older than 9 months but younger than 36 months with pre-symptomatic SMA with i) 1-2 copies or ii) three copies of the *SMN2* gene, NUSI or RIS are PBS listed DMTs which are used and as such would be the most appropriate comparator.
- In pre-symptomatic SMA patients with 1-3 copies of the *SMN2* gene weighing less than 21kg and aged 36 months or older at initiation of DMT, no PBS subsidised treatment is currently available (symptomatic patients would be eligible for NUSI or RIS). Therefore, at the age of 36 months and beyond, the comparator for pre-symptomatic SMA patients with 1-3 copies of the SMN2 gene should be 'watchful waiting and treat as symptoms appear'. The pre-PBAC response confirmed that it was acceptable to the sponsor to exclude pre-symptomatic patients aged >36 months from the proposed listing, in which case watchful waiting was no longer a relevant comparator.

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 the National Paediatric Medicines Forum (NPMF) via the Consumer Comments facility on the PBS website. The NPMF supported the extension of the ONA existing listing to include patients weighing up to 21 kg, on the basis that it would improve equitable access and provide the best outcomes for patients with SMA. The NPMF noted that it is critical to enable access to gene therapy for SMA patients so that it can be administered within the pre-symptomatic therapeutic window, preventing irreversible motor neuron degeneration.

6.3 The PBAC also noted that additional clinical input was received prior to the PBAC meeting from three clinicians with extensive experience in treating patients with SMA. Input from clinicians suggested that access to ONA for patients with symptomatic Type II and III SMA was important and should be considered in the listing (see also paragraph 3.5). The clinicians also expressed that it was critical to review the current eligibility criteria for nusinersen and risdiplam treatment in children who have had previous ONA and have a suboptimal response. Clinicians noted restrictions for subsequent treatment with nusinersen or risdiplam following ONA require a regression in a developmental state, which can be a major and very late and irreversible change. Clinicians indicated that patients may have neurophysiological and molecular assessments in children that indicate disease activity but they are not

eligible additional DMT which is likely to be of benefit to them. In addition the criteria for subsequent treatment do not include regression in respiratory or bulbar function, which can be a major source of morbidity. Clinicians noted the following scenarios where patients treated with ONA experienced suboptimal treatment response or treatment failure but were not eligible for treatment with risdiplam or nusinersen under the current restrictions:

- Children who have developed and maintained the ability to walk independently, however their walking distance is limited due to weakness, falls and fatigue.
- Children who make initial gains in a motor milestone but have a much slower than expected gain in function or do not continue to gain motor function (i.e. plateau).
- Children who have deterioration in the ability to swallow (i.e. are feeding independently and then subsequently required gastrostomy support).
- Children who require ongoing nocturnal non-invasive ventilation, despite being treated in the neonatal period.

In addition, clinicians noted that the current wording of the restrictions does not allow access to subsequent NUSI/RIS in patients previously treated with ONA outside the PBS (e.g. under special access programs or clinical trials).

Clinicians also noted concerns that the PBS Highly Specialised Drugs Program number is only open during business hours (Monday to Friday 8am – 5pm) which causes unnecessary delays in getting approval to commence treatment. In addition, it can take up to 6 days to receive supply from the US. Clinicians noted that these delays in treatment are significant as disease progression can be rapid and delays can have a long-term impact on outcomes.

Clinical studies

6.4 Table 4 summarises the submission's proposed changes (using age and weight restrictions) and the evidence presented for each population. As outlined in Table 4, no clinical evidence for the pre-symptomatic SMA population was presented by the submission. Further, the commentary considered the clinical claim and economic evaluation presented by the submission may not be appropriate given the comparator used was not appropriate.

Table 4: Summary of proposed changes by the submission and evidence presented

	Patient populations						
	9 months old or younger AND less than 21kg [a]		Older than 9 months but less than 36 months AND less than 21kg [a]		36 months old or older AND less than 21kg [b]		Symptomatic type II/III
	Symptomatic type I	Pre-symptomatic, 1-3 SMN2 copies	Symptomatic type I	Pre-symptomatic, 1-3 SMN2 copies	Symptomatic type I	Pre-symptomatic, 1-3 SMN2 copies	
Current PBS listed DMT options	NUSI, ONA, RIS	NUSI, ONA, RIS	NUSI, RIS	NUSI, RIS	NUSI, RIS	None (unless previously initiated when younger than 36 months)	NUSI, RIS
DMT options under the proposed restriction	NUSI, RIS, ONA	NUSI, RIS, ONA	NUSI, RIS, ONA [c]	NUSI, RIS, ONA [c]	NUSI, RIS ONA [c]	Excluded in PSCR/pre-PBAC response	NUSI, RIS
Clinical evidence for ONA presented	START, STR1VE-US, STR1VE-EU	SPR1NT	SMART [d]	Nil	SMART [d]	Nil	SMART [d]
Economic evaluation for ONA presented	CUA ONA vs NUSI (base case) and BSC; then CMA ONA vs NUSI; then CMA ONA vs RIS [e]	1-2 copies: CMA ONA vs NUSI; then CMA ONA vs RIS [e] 3 copies: CMA ONA vs NUSI; then CMA ONA vs ONA [f]	CMA ONA vs ONA [g]	CMA ONA vs ONA [g]	CMA ONA vs ONA [g]	Excluded in PSCR/pre-PBAC response	Not requested

Source: Constructed during the evaluation.

BSC = best supportive care; CMA = cost minimisation approach; CUA = cost utility analysis; DMT= disease modifying therapy; NUSI= nusinersen; ONA= onasemnogene abeparvovec; RIS= risdiplam; SMA= spinal muscular atrophy; *SMN2*= survival motor neuron 2 gene

a It is extremely unlikely to have a patient under 36 months of age who weighs more than 21kg (see the WHO weight-for-age charts: https://www.who.int/tools/child-growth-standards/standards/weight-for-age).

b In the SMART study and in the first TGA evaluator assessment, the upper limit of 21kg in SMA patients was correlated to an age of approximately nine years.

c Includes provision for patients previously treated with NUSI and RIS to switch to ONA.

d Only a small subset of patients (33%; 8/24) enrolled in SMART had SMA Type I, while 46% (11/24) had SMA Type II and 21% (5/24) had SMA Type III. No pre-symptomatic patients were enrolled in SMART. The majority of patients (21/24, 87.5%) in SMART had previously been treated with NUSI or RIS prior to initiating ONA. The age of enrolled patients ranged from 1.51-9.13 years.

e This was recommended on a cost-minimisation basis to the least costly DMT for this condition (RIS) (paragraph 9.1, onasemnogene abeparvovec PSD, November 2020 PBAC meeting with May 2021 Addendum and September 2021 Addendum)

f This was recommended as "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" (paragraph 7.1, onasemnogene abeparvovec PSD, July 2023 PBAC meeting), even though ESC considered the cost minimisation approach presented may not be appropriate.

g Only CMA against ONA presented in submission, but ONA is not currently PBS listed in this patient population and instead, a comparison against NUSI or RIS should have been made (for SMA Type I patients under 21kg, and pre-symptomatic SMA patients with 1-3 *SMN2* copies under the age of 36 months and under 21kg).

Text in underline indicate changes to DMT options, as proposed by the submission.

6.5 The submission was based on one single-arm study: SMART. The SMART study was a phase 3, open-label study evaluating the efficacy and safety of ONA in patients with symptomatic SMA who weighed between 8.5 to 21 kg, with any *SMN2* copy number. The submission noted that patients enrolled in SMART were older (at least 9 months

of age) and heavier than those enrolled in studies previously considered by the PBAC (SPR1NT, START, STR1VE-US, STR1VE-EU, and LT-002); these studies were used by the submission as side-by-side comparisons. Patients enrolled in SPR1NT, START, STR1VE-US, and STR1VE-EU were aged 6 months or under[3] at dosing and had varying disease types (pre-symptomatic disease with 2-3 SMN2 copies (SPR1NT) and SMA Type I (START, STRIVE-US, STR1VE-EU)). The LT-002 study is an on-going extension study which includes patients from SPR1NT and STR1VE (US and EU); latest data cut: 23 May 2022.

6.6 Details of the studies presented in the submission are provided in Table 5.

Table 5: Studies and associated reports presented in the submission

Study	Protocol title/ Publication title	Publication citation
SMART (NCT04851873)	COAV101A12306. A Phase IIIb, open-label, single-arm, single-dose, multicenter study to evaluate the safety, tolerability and efficacy of gene replacement therapy with intravenous OAV101 (AVXS-101) in pediatric patients with spinal muscular atrophy (SMA)	November 2023
	McMillan, H. J., et al. Safety and Efficacy of IV Onasemnogene Abeparvovec for Pediatric Patients With Spinal Muscular Atrophy: The Phase 3b SMART Study. https://doi.org/10.1212/WNL.0000000000210268	*Neurology* 2025; 104(2): e210268
	Lavrov, A., et al. Design and Rationale of SMART, a Phase IIIb Study Evaluating Intravenous Onasemnogene Abeparvovec in Spinal Muscular Atrophy.	*Neurology* 2022; 98(18 SUPPL)
SPR1NT (NCT03505099)	Strauss, K.A., et al. Onasemnogene abeparvovec for presymptomatic infants with two copies of SMN2 at risk for spinal muscular atrophy Type I: the Phase III SPR1NT trial. DOI: 10.1038/s41591-022-01866-4	*Nature Medicine* 2022; 28(7):1381-1389
	Strauss, K.A., et al. Onasemnogene abeparvovec for presymptomatic infants with three copies of SMN2 at risk for spinal muscular atrophy: the Phase III SPR1NT trial. DOI: 10.1038/s41591-022-01867-3	*Nature Medicine* 2022; 28(7):1390-1397
START (NCT02122952)	Mendell, J.R., et al. Five-Year Extension Results of the Phase 1 START Trial of Onasemnogene Abeparvovec in Spinal Muscular Atrophy. DOI:10.1001/jamaneurol.2021.1272	*JAMA Neurology* 2021; 78(7): 834-841
STRIVE US (NCT03306277)	Day, J.W., 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. https://doi.org/10.1016/S1474-4422(21)00001-6	*The Lancet Neurology* 2021; 20(4): 284-293
STRIVE EU (NCT03461289)	Mercuri, E., et al. Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy Type I (STR1VE-EU): an open-label, single-arm, multicentre, phase 3 trial DOI: 10.1016/S1474-4422(21)00251-9	*The Lancet Neurology* 2021; 20(10): 832-841
LT-002 (NCT04042025)	Stevens, M. K., et al. Onasemnogene Abeparvovec-xioi: Gene Therapy for Spinal Muscular Atrophy. DOI: 10.1177/1060028020914274	*Annals of Pharmacotherapy* 2020; 54(10):1001-1009

Source: Table 2.3, p27 of the submission.
Blue shading represents studies previously presented and considered at the PBAC.

6.7 The key features of the studies are summarised in Table 6.

[3] For START: The first nine patients were enrolled under previous version(s) of the protocol, which allowed an age range of 9 months or younger (p23, START CSR).

Table 6: Key features of the included studies

Study, n (SMN2 copy number)	Design/duration	Bias	Treatment	Population	Outcome(s)
SMART n=5 (2 copies); 18 (3 copies); 1 (≥4 copies)	MC, NC, SA, OL 12mths	High	ONA IV 1.1 x 10^{14} vg/kg	Patients weighing ≥8.5 kg and ≤21 kg, Symptomatic patients – SMA Type I-III with any copy of SMN2.	1°: safety 2°: motor milestones
SPR1NT n=14 (2 copies); 15 (3 copies)	MC, NC, SA, OL up to 24mths of age	High	ONA IV 1.1 x 10^{14} vg/kg	Pre-symptomatic patients – 2 and 3 copy SMN2; aged ≤6wks	1°: motor milestone – sitting (for 2 copies, 18 mths); standing (for 3 copies, 24 mths) 2°: motor milestones, EFS
START [a] N=15 (2 copies)	NC, OL 2 yrs	High	ONA IV 6.7 × 10^{13} vg/kg or 1.1 × 10^{14} vg/kg	Symptomatic patients – SMA Type I (2 SMN2 copies); aged ≤6mths	1°: safety 2°: motor milestones, EFS
STR1VE-US N=22 (1-2 copies)	MC, NC, SA, OL up to 18mths of age	High	ONA IV 1.1 x 10^{14} vg/kg	Symptomatic patients – SMA Type I (1-2 copies of SMN2); aged <6mths	1°: motor milestone – sitting (age 18mths), EFS (age 14mths) 2°: motor milestones, OS
STR1VE-EU N=33 (1-2 copies)	MC, NC, SA, OL up to 18mths of age	High	ONA IV 1.1 x 10^{14} vg/kg	Symptomatic patients – SMA Type I (1-2 copies of SMN2); aged <6mths	1°: motor milestone – sitting (age 18mths) 2°: EFS, OS Other: motor milestones
LT-002^ (SPR1NT) n=12 (2 copies); 13 (3 copies)	MC, OB, OL extension 15 yrs May 2022 data cut: median age (range): 43.7 (35.9, 50.5) mths for 2 copies and 40.1 (34.4, 46.0) for 3 copies; time since treatment (range): 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	Extension study of SPR1NT	1°: motor milestone (24mths) 2°: motor milestones, EFS
LT-002^ (STR1VE-US, STR1VE-EU) n=12; 24	MC, OB, OL extension 15 yrs May 2022 data cut: median age (range): 54.0 (47.8, 57.2) for STRIVE-US and 46.1 (40.4-50.1) for STRIVE-EU; time since treatment (range): 49.0 (12.6-52.3) mths for STRIVE-US and 41.9 (36.6-44.8) mths for STRIVE-EU.	High	As in STR1VE	Extension study of STR1VE-US and STR1VE-EU	1°: motor milestone (24mths) 2°: motor milestones, EFS

Source: Table 2.5, p29 of the resubmission; Table 4, p15&16 of the ONA PSD, November 2022 PBAC meeting; Tables 3-3 & 3-4, pp31 & 32 of the LT-002 CSR.

1°= primary outcome; 2°= secondary outcome; EFS= event free survival (survival without permanent ventilation); IV= intravenous; MC= multi-centre; mths= months NC= non-comparative single arm study; OB= observational; OL= open label; ONA= onasemnogene abeparvovec; OS= overall survival; SA= single arm; SMA= spinal muscular atrophy; *SMN2*= survival motor neuron 2; wks= weeks; yr= year

^ ongoing extension study; latest data cutoff: 23 May 2022. Results from SPR1NT were presented at the July 2023 PBAC meeting (May 2022 data cut); results from STR1VE-US and STR1VE-EU were presented at the November 2022 PBAC meeting (May 2021 data cut).

a 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 (LT-001), but results reported for 13 patients (3 low dose and 10 therapeutic dose), as 2 discontinued.
Blue shading represents studies previously presented and considered at the PBAC.
Italics indicates text adding during the evaluation.

6.8 All of the included studies were single arm, open label studies of ONA for the treatment of pre-symptomatic or symptomatic SMA and had small patient numbers (no study enrolled more than 33 patients). The lack of a comparator arm and small numbers of patients enrolled led to high levels of bias. This was consistent with the high risk of bias noted for the studies (SPR1NT, START, STR1VE-US, STR1VE-EU, and LT-002) previously considered by the PBAC (paragraph 6.15, onasemnogene abeparvovec PSD, November 2022 PBAC meeting and paragraph 6.10, onasemnogene abeparvovec PSD, July 2023 PBAC meeting). No hypothesis testing was performed in SMART.

6.9 The submission nominated ONA (in patients less than 9 months of age) as the comparator, represented by the SPR1NT, START, STR1VE-US and STR1VE-EU studies, only side-by-side comparisons were presented by the submission on the outcome of overall survival and event free survival with no non-inferiority margin nominated, and no statistical testing or any objective method of assessing non-inferiority were presented. However, the submission appeared to largely rely on the comparison of patients within the various weight categories of SMART, i.e. 8.5-13 kg (subgroup 1); >13-17 kg (subgroup 2); and >17-21 kg (subgroup 3), based on the outcome of change from baseline in Hammersmith Functional Motor Scale—Expanded (HFMSE) total score and Revised Upper Limb Module (RULM) total score, and the achievement of developmental milestones to support its clinical claim. This was inappropriate as it was not consistent with the nominated comparator (ONA in patients less than 9 months of age) nor the more appropriate comparators of NUSI and RIS in patients with SMA Type I or pre-symptomatic SMA patients less than 36 months or watchful waiting in pre-symptomatic SMA patients aged 36 months or older.

6.10 The following key differences in disease characteristics between the included studies were observed during the evaluation that suggest that patients across the included studies may not be comparable:

- The included studies enrolled patients with different SMA types and patients enrolled ranged from having SMA Type I (START, STR1VE-US and STR1VE-EU; 33% of patients in SMART) and SMA Type II (46% of patients in SMART), SMA Type III (21% of patients in SMART), and pre-symptomatic SMA (SPR1NT); and
- Patients enrolled in SPR1NT, START, STR1VE-US and STR1VE-EU were treatment naïve, whereas the 87.5% (21/24) of patients in SMART received previous treatment with DMT.

6.11 In the SMART study, only 33% (8/24) of patients enrolled were classified as having SMA Type I. Subgroup 1 enrolled the highest percentage of Type I children (42.9%; 3/7) compared to subgroup 2 (37.5%; 3/8) and subgroup 3 (22.2%; 2/9) and as such was the most aligned with the population requested by the submission. Although

symptomatic patients with SMA Type II and Type III were not eligible for ONA under the proposed restriction, the PBAC considered that they should be included in the restrictions for ONA. Additionally, pre-symptomatic patients were excluded from SMART, but not from the requested PBS population, representing an applicability issue.

6.12 When comparing between weight brackets, patients in subgroup 1 scored the lowest at baseline in HFMSE, RULM and developmental motor milestone assessments, followed by subgroup 2 then subgroup 3; that is, that children in heavier weight brackets had better motor function at baseline. Results from SMART may carry a high degree of bias given weight, age, and attainment of motor milestones are generally correlated. Patients in the heaviest subgroup (subgroup 3) were older, with a higher proportion having less severe disease (SMA Type III), and higher motor function at baseline. As such, the results of any comparison between the subgroups in the SMART study should be interpreted with caution. The ESC noted that some patients in the SMART study had already reached all milestones when enrolled.

6.13 Efficacy in SMART was based on HFMSE and RULM measures. It was noted that the HFMSE was devised for use in children with SMA Type II and Type III, and while the validity and reliability of HFMSE in SMA Type II and Type III patients have been established[4], this assessment may not be suitable for patients with SMA Type I (i.e. non-sitters) given the severity of disease (and the potential for a floor effect). Comparatively, while the RULM is limited to the upper limbs only, the ESC have previously noted that consumer preferences tended to be around maintenance of upper limb function (e.g. for basic self-care, using devices, steering a wheelchair) and that, for many non-ambulant patients, mobility in terms of transfer movements in and out of chairs was clinically meaningful (paragraph 6.23, nusinersen PSD, November 2020 PBAC meeting).

6.14 The submission nominated a minimally clinically important difference (MCID) for the change in the HFMSE total score and RULM total score of at least three points and two points, respectively. These were consistent with values proposed by previous submissions for NUSI (at the November 2020, July 2021 and March 2022 PBAC meetings) for the treatment of adult patients, considered to be clinically meaningful (paragraph 6.22, nusinersen PSD, March 2022 PBAC meeting).

6.15 Patients enrolled in SMART represent a heavily pre-treated population; the majority of patients (21/24; 87.5%) had previous SMA treatment with DMT and further, 91% (19/21) of previously treated patients received NUSI for a median duration of 2.09 years (range: 0.17-4.81). It was unclear if prior treatment with other DMTs were treatment modifiers and in which direction (if any). The high proportion of prior DMT was aligned to the submission's claim that most patients eligible under the proposed

[4] Glanzman, AM., et al, (2011), 'Validation of the Expanded Hammersmith Functional Motor Scale in spinal muscular atrophy type II and III', Journal of Child Neurology, 26(12): pp1499-507. doi: 10.1177/0883073811420294.

extended listing (older than nine months of age and weighing below 21kg) would be expected to be treated with a DMT prior to switching to ONA.

6.16 In addition, only three patients (3/24; 21.5%) in SMART were treatment naïve and it was unclear what SMA diagnosis these patients had (though this was likely to be Type II or Type III), the comparative efficacy of ONA in the treatment naïve SMA Type I population (above the age of nine months and below 21kg) was unclear.

6.17 The evaluation considered a more informative comparison would have been between SMA Type I patients in SMART and SMA Type I patients treated with NUSI in ENDEAR (CS3B; NCT02193074) and/or CS3A (NCT01839656), using longer-term results from the SHINE extension study (NCT02594124)[5] i.e. a treatment switching comparison of ONA versus NUSI, of patients pre-treated with NUSI. It was noted during the evaluation, that a long-term comparative efficacy and safety study of RIS and NUSI (using results from SHINE) in patients with SMA Type I was performed using matching adjusted indirect comparison (MAIC)[6]. The use of (an unanchored) MAIC was also previously presented to PBAC in their consideration of ONA versus NUSI in patients with Type I SMA (aged less than two years, as originally proposed for ONA) (paragraph 6.36, onasemnogene abeparvovec PSD, November 2020 PBAC meeting). The PSCR provided a side-by-side comparison of OS and EFS between the SMART trial for ONA and the ENDEAR and FIREFISH trials for NUSI and RIS. The PSCR also noted that a comparison of motor function outcomes was not possible because the instruments used to assess motor function in the SMART trial were different to those used in ENDEAR and FIREFISH; SMART measured these outcomes using HFSME, RULM and measured attainment of motor milestones using WHO-MGRS criteria, whereas ENDEAR and FIREFISH used HINE-2 and CHOP-INTEND scales.

Comparative effectiveness

6.18 Table 7 summarises overall survival and event free survival across the included studies.

[5] https://clinicaltrials.gov/study/NCT02594124?tab=results

[6] Kokaliaris, C., et al, (2024), 'Long-Term Comparative Efficacy and Safety of Risdiplam and Nusinersen in Children with Type 1 Spinal Muscular Atrophy', Advances in Therapy, 41(6): pp2414-2434. doi: 10.1007/s12325-024-02845-6.

Table 7: Overall survival and event free survival in the included studies (Safety Set)

Study	Overall survival n/N (%)	Event free survival n/N (%)
SMART	24/24 (100)	24/24 (100)
SPR1NT	29/29 (100)	29/29 (100)
START	15/15 (100)	15/15 (100)
STRIVE-US	21/22 (95.5) [a]	20/22 (90.9) [a]
STRIVE-EU	32/33 (97.0) [b]	32/33 (97.0)
LT-002	81/81 (100) [c]	80/81 (98.8) [c]
ENDEAR	67/80 (84)	49/80 (61)
FIREFISH (part 1) FIREFISH (part 2)	19/21 (90) 38/41 (93)	19/21 (90) 34/41 (83)

Source: Table 2.18, p53 of the submission; p60 of the STRIVE-US CSR; p33 of the LT-002 CSR, PSCR Table 2

a One patient died at age 7.8 months due to respiratory failure that was not considered related to ONA and one patient discontinued (withdrew consent) at 11.9 months of age; this patient also required permanent ventilation prior to withdrawal of consent (Study Day 176, age 11 months).

b One patient discontinued from the study on Day 53 at the age of 6.9 months due to SAEs of hypoxic-ischaemic encephalopathy and respiratory distress that resulted in death.

c All patients were alive, and 80 patients were free of permanent ventilation at data cut off (23 May 2022) – one patient from STR1VE-AP reached permanent ventilation status during the study.

6.19 All patients in the SMART, SPR1NT and START studies survived and were event free, while one death was reported in each of the STR1VE-US and STR1VE-EU studies. The submission claimed that these data indicate there is no difference in overall survival and event free survival in older, heavier babies treated with ONA compared to those treated at <6 months of age. As discussed in paragraph 6.10, patients across the included studies were not comparable in terms of disease severity (both symptomatic and pre-symptomatic; range from SMA Type I to III) and prior SMA treatment (treatment naïve versus heavily pre-treated), and the results were limited by the short follow-up period (of 52 weeks) in SMART. Overall, the side-by-side comparisons presented by the submission were unlikely to be meaningful and may not be informative for PBAC decision making. The PSCR stated "historically, a certain level of pragmatism has been applied by the PBAC when evaluating submissions for rare diseases such as SMA where only single arm trials are available. In previous submissions, naïve comparisons were accepted to determine effectiveness of treatments. Such decisions recognise the inherent challenges, including the lack of traditional comparative data, and lower standard of evidence available to assist decision-making in rare diseases."

6.20 Table 8 summarises the change from baseline in HFMSE total score and RULM total score, by subgroups and for the overall population in SMART.

Table 8: Change from baseline in HFMSE total score and RULM total score (Full analysis set)

Timepoint	Statistics	Subgroup 1 8.5-13 kg N=7	Subgroup 2 >13-17 kg N=8	Subgroup 3 >17-21 kg N=9	Overall 8.5-21 kg N=24
HFMSE					
Baseline	n	5	6	9	20
	Mean (SD)	19.4 (13.96)	29.2 (22.78)	32.6 (19.05)	28.3 (18.98)
	Median	20.0	29.5	39.0	29.5
	Min-Max	6-40	0-55	4-51	0-55
Change from baseline at Week 52	n	5	6	7	18
	Mean (SD)	3.0 (5.24)	3.7 (5.75)	4.3 (4.07)	3.7 (4.73)
	Median	3.0	4.0	5.0	4.0
Change from baseline at Week 52 (mixed model) [a]	n	5	6	7	18
	LS Mean	3.51	3.60	4.23	3.78
	95% CI	-1.05-8.07	-0.52-7.72	0.78-7.67	1.44-6.11
RULM					
Baseline	n	4	6	8	18
	Mean (SD)	16.3 (10.56)	23.2 (11.58)	24.0 (10.86)	22.0 (10.86)
	Median	14.0	24.0	26.5	22.0
	Min-Max	7-30	4.35	8-37	4-37
Change from baseline at Week 52	n	3	6	8	17
	Mean (SD)	6.0 (3.46)	0.3 (1.63)	1.8 (4.71)	2.0 (4.02)
	Median	4.0	0.5	2.5	2.0
Change from baseline at Week 52 (mixed model) [b]	n	3	6	8	17
	LS Mean	6.00	0.42	1.90	2.77
	95% CI	1.69,10.30	-2.99,3.83	-1.05,4.86	0.70,4.85

Source: Table 2.19 & 2.20, pp54 & 55 of the submission.

kg= kilogram; HFMSE= Hammersmith Functional Motor Score Expanded; LS Mean= least square mean; RULM= Revised Upper Limb Module SD= standard deviation.

Note: At each time point, only patients with data at both baseline and that timepoint were included.

For HFMSE, patients with 24 months of age or older at baseline were considered.

For RULM, patients with 30 months of age or older at baseline were considered.

A total score is not derived if any item score is missing or 'cannot test' at baseline or post-baseline visit.

All data collected after the intake of prohibited concomitant medication with the intent to treat SMA is excluded

a The model included the change from baseline as the dependent variable, fixed effect of weight bracket, visit, a covariate of baseline HFMSE value, and interactions of weight bracket*visit. A mixed model of repeated measures was applied using unstructured covariance matrix.

b The model included the change from baseline as the dependent variable, fixed effect of weight bracket, visit, a covariate of baseline RULM value, and interactions of weight bracket*visit. A mixed model of repeated measures is applied using unstructured covariance matrix.

6.21 The submission noted that the mean change from baseline in HFMSE score at 52 weeks was at least 3 points in each weight group, which met the nominated MCID of ≥3-point improvement. Patients in subgroup 3 reported the most improvement in total HFMSE score at Week 52 (median 5.0-point improvement), compared to subgroup 2 (median 4.0-point improvement) and subgroup 1 (median 3.0-point improvement). Sensitivity analysis was conducted wherein missing item scores and "cannot test" assessments were imputed by a score of zero. This analysis included 22 patients (an additional two patients in subgroup 2, representing 25% of patients in subgroup 2 (n=8)). In subgroup 2, the median change from baseline in HFMSE score at Week 26 and Week 52 of 3.5 and 4.0-point improvement, was adjusted to 0.5 and 1.5 respectively, and would not have met the submission's nominated MCID. This highlights the lack of robustness of the data due to small sample sizes.

6.22 Notably, there may be some misclassification in SMART, as subgroup 1 included patient(s) with weight >13kg and subgroup 2 included patient(s) with weight >17kg, further confounding any comparison between subgroups in SMART.

6.23 Results from the mixed model approach (see Table 8) met the submission's nominated MCID of ≥3-point improvement. The least squares mean change from baseline in HFMSE total score at Week 52 was 3.51 (95%CI: -1.05-8.07), 3.60 (95%CI: -0.52-7.72) and 4.23 (95%CI: 0.78-7.67) for subgroup 1, subgroup 2 and subgroup 3, respectively. However, the confidence intervals were large and included values which were lower than the nominated MCID of '3'.

6.24 The mean (SD) increase in RULM total score overall was 2.0 (4.02) at Week 52, which met the nominated MCID of ≥2-point improvement. Patients in subgroup 1 reported the most improvement in RULM score from baseline (median 4.0-point improvement) compared to subgroup 2 (median 0.5-point improvement) and subgroup 3 (median 2.5-point improvement). The reported median increase in RULM total score for subgroup 2 (0.5-point improvement) did not meet the submission's nominated MCID. Sensitivity analysis was conducted wherein missing item scores and "cannot test" assessments were imputed by a score of zero. This analysis included 21 patients (an additional one patient (25%) in subgroup 1 (at Week 52), two patients (25%) in subgroup 2 and one patient (11%) in subgroup 3). While the results were more favourable across the subgroups, subgroup 2 (median 1.5-point improvement) still did not meet the MCID of ≥2-point improvement.

6.25 Results from mixed model approach (see Table 8) met the submission's nominated MCID of ≥2-point improvement for subgroup 1, but not subgroup 2 or subgroup 3. The least squares mean change from baseline in RULM total score at Week 52 was 6.00 (95%CI: 1.69-10.30), 0.42 (95%CI: -2.99, 3.83) and 1.90 (95%CI: -1.05, 4.86) for subgroup 1, subgroup 2 and subgroup 3, respectively. Similar to the results of the sensitivity analyses for the change from baseline in HFMSE total score, the confidence intervals were large and included '0' or included values which were lower than the nominated MCID of '2', suggesting uncertainty.

6.26 The submission did not present subgroup analysis for the intended PBS population of SMA Type I patients, and it was unclear what proportion of SMA Type I patients met the submission's nominated MCID for the change from baseline in total HFMSE or total RULM score.

6.27 The submission presented the proportion of patients demonstrating developmental milestones at baseline and post baseline in SMART. Of note, six patients (two in subgroup 2 and four in subgroup 3) had already achieved the highest milestone assessed in the study (Walking alone) at baseline; for these patients achieving new milestones as per the checklist was not possible. Based on natural history data, the majority of patients with Type III SMA would achieve and retain the ability to walk. Therefore, it was plausible that a proportion of these patients would have retained the ability to walk without treatment with ONA.

6.28 Developmental motor milestones data presented by the submission and extracted during the evaluation indicated that for patients with SMA Type I enrolled in SMART (n=8):

- Two patients (25.0%) experienced a decline in the highest developmental motor milestone achieved during the study; and
- The six remaining patients (75.0%) experienced no change in the highest developmental motor milestone achieved during the study (up to 52 weeks of follow-up).

Comparative harms

6.29 The submission provided an overview of treatment-emergent adverse events (TEAEs) in the included studies. Almost all patients across the included studies experienced TEAEs (100% in all studies, except for 97% in STR1VE-EU). Patients enrolled in SMART experienced more TEAEs related to ONA when compared to the other included studies (100% in SMART compared to 27%-73% in the remaining studies), however, the number of serious TEAEs related to ONA *(29%)* were comparable to those reported in START *(27%)*. No TEAEs led to study discontinuation or death in SMART, SPR1NT and START, however two patients in STRIVE-US discontinued due to TEAEs, with one death reported. Similarly, one patient in STRIVE-EU discontinued and one death was reported.

6.30 An overview of TEAEs by weight bracket in the SMART study is summarised in Table 9. All patients experienced at least one TEAE and TEAE related to ONA during the study. Serious adverse events (SAEs) were reported in 62.5% of patients, including 29.2% who had SAEs considered related to study medication. Subgroup 1 reported fewer severe adverse events (AEs), SAEs and SAEs related to ONA than the heavier two subgroups. No deaths, and no AEs leading to discontinuation from the study were reported.

Table 9: Overview of treatment-emergent adverse events by weight bracket (Safety Set)

	Subgroup 1 8.5-13 kg N=7 n (%)	Subgroup 2 >13-17 kg N=8 n (%)	Subgroup 3 >17-21 kg N=9 n (%)	Overall N=24 n (%)
Any TEAEs	7 (100.0)	8 (100.0)	9 (100.0)	24 (100.0)
Any TEAEs related to ONA	7 (100.0)	8 (100.0)	9 (100.0)	24 (100.0)
Any severe TEAEs	1 (14.3)	4 (50.0)	3 (33.3)	8 (33.3)
Any serious TEAEs	3 (42.9)	7 (87.5)	5 (55.6)	15 (62.5)
Serious TEAEs related to ONA	1 (14.3)	4 (50.0)	2 (22.2)	7 (29.2)
TEAEs leading to study discontinuation	0	0	0	0
TEAEs leading to death	0	0	0	0
TEAEs of special interest	7 (100.0)	7 (87.5)	9 (100.0)	23 (95.8)

Source: Table 2.30, p69 of the submission.
kg= kilogram; ONA= onasemnogene abeparvovec; TEAEs= treatment-emergent adverse events

6.31 The most frequently reported AEs overall (>20% of patients) in SMART were vomiting (79.2%), pyrexia (41.7%), COVID-19 (37.5%), nausea and upper respiratory tract infection (33.3% each), hypertransaminasaemia, platelet count decreased, and

thrombocytopenia (29.2% each), transaminases increased (25.0%), and nasopharyngitis (20.8%). There were no clear differences in the type of AEs reported between the weight groups. The type of AEs reported were consistent with the known safety profile of ONA (TGA Clinical Evaluation Report, March 2025).

6.32 The most frequent SAEs in SMART were thrombocytopenia and vomiting (12.5% each), and COVID-19, gastroenteritis viral, and pneumonia (8.3% each). All other SAEs were reported in one patient each. The TGA Clinical Evaluation report noted there were no clear dose-trends observed for either SAEs or severe AEs.

6.33 The submission claimed that this suggests the increase in weight does not correlate to a higher number of AEs in ONA treated children. This claim was not adequately supported due to the lack of comparator arm, small sample size, and short study follow-up period of 52 weeks; further, AEs of special interest (AESIs) in the hepatoxicity and transient thrombocytopenia category were reported in the majority of patients in SMART. The TGA Clinical Evaluation Report also noted that compared to younger patients with SMA, older (and heavier) patients will likely experience more severe and prolonged transaminitis, as well as higher and more prolonged dosing of systemic corticosteroids (see paragraph 6.36), which carries with it additional risks such as diabetes mellitus, that may not be sufficiently captured with the available data with limited follow-up (see paragraph 6.39).

6.34 An overview of treatment-emergent AEs of special interest (AESIs) by weight bracket in SMART is summarised in Table 10.

Table 10: Overview of treatment-emergent adverse events of special interest by risk name and weight bracket (Safety Set)

	Subgroup 1 8.5-13 kg N=7 n (%)	Subgroup 2 >13-17 kg N=8 n (%)	Subgroup 3 >17-21 kg N=9 n (%)	Overall N=24 n (%)
Hepatotoxicity	6 (85.7)	5 (62.5)	9 (100.0)	20 (83.3)
Transient thrombocytopenia	4 (57.1)	6 (75.0)	7 (77.8)	17 (70.8)
Cardiac adverse events	0	2 (25.0)	1 (11.1)	3 (12.5)
Thrombotic microangiopathy	0	0	0	0
Dorsal root ganglion cell inflammation	0	0	0	0

Source: Table 2.33, p73 of the submission.
kg= kilogram

6.35 AESIs in the hepatotoxicity category were reported in 83.3% (20/24) of patients in SMART; most frequently reported preferred terms were hypertransaminasaemia and transaminases increased. All events were asymptomatic, and there were no cases of acute liver failure. Many patients had prolonged elevations in alanine aminotransferase (ALT)/aspartate aminotransferase (AST) post dosing. It was noted the current Product Information (p1) includes a boxed warning for hepatoxicity.

6.36 Hepatotoxicity events were managed by use of prednisolone (or equivalent), which was given prophylactically from Day -1. The mean total number of days of prednisolone administration in SMART was 218 (range: 80 - 444 days). By the end of the study (Week 52), six patients (25.0%) were still receiving prednisolone. 21 patients (87.5%) received a daily dose that was above 1 mg/kg prednisolone (or equivalent) at

least once during the study, and nine patients (37.5%) received a daily dose that was above 2 mg/kg. These higher doses of prednisolone, and the longer duration of prednisolone administration compared to the protocol guidance, were based on Investigator's judgment (more than half of all patients had ALT >10x the upper limit of normal (ULN)). The PBAC noted that input from clinicians suggested that in Australian practice patients are likely to be treated with prednisolone for a shorter duration and at a lower dose than was used in the trials, which may reduce the impact of AEs related to prolonged corticosteroid use.

6.37 The submission claimed that because subgroup 2 spent the highest number of days receiving prophylactic prednisolone and had the highest mean total cumulative dose of prophylactic prednisolone, these indicated that increased weight does not correspond to increased prednisolone exposure. This was in direct contradiction to the findings from the TGA (TGA Clinical Evaluation Report) and Periodic Safety Update Report (PSUR; p5140); see paragraph 6.39. Moreover, given the small number of patients and misclassification of patients in subgroup 1 and 2 (see paragraph 6.22), any claims based on comparing the subgroups were highly uncertain and may not be reliable.

6.38 AESIs in the transient thrombocytopenia category were reported in 70.8% (17/24) of patients; the most frequent preferred terms were platelet count decreased and thrombocytopenia. Events that were considered related to study treatment by the investigator were reported in 58.3% (14/24) of patients (the preferred terms were thrombocytopenia, platelet count decreased, and platelet count abnormal).

6.39 The submission provided an updated PSUR for ONA which covered the reporting interval from 24 May 2023 to 23 May 2024. The PSUR found that the overall benefit-risk profile of ONA remains favourable. Notably, there were signals related to "higher frequency of aminotransaminase elevations and platelet count decreases"– these were based on the safety findings from the SMART study and reflected the new aspects of known identified risks of hepatotoxicity and thrombocytopenia associated with ONA (p45 of the PSUR). The core data sheet (CDS) was updated to reflect the key safety findings from the SMART study:

- Hepatoxicity: The incidence of hepatoxicity was reported in 83.3% patients in SMART, compared to 35.4% patients in five earlier clinical studies (SPR1NT, START, STR1VE-US, STR1VE-EU and STR1VE-AP[7]). Elevations in ALT values were >3xULN in 87.5%, 10xULN in 58.3%, and >20xULN in 20.8% of patients in SMART, compared to >3xULN in 19.2%, >10xULN in 4.0%, and >20xULN in 4.0% of patients in the earlier clinical studies (p5139 of the PSUR);
- Transient thrombocytopenia: Incidence of thrombocytopenia was reported in 70.8% of patients in SMART and 87.5% of patients had a platelet count value below

[7] STR1VE-AP only enrolled two patients; therefore, this comparison should be similar to that of the submission's included studies.

lower limit of normal (LLN). Comparatively, the incidence of thrombocytopenia was 22.2% in the five earlier clinical studies, and platelet count values below 75x109/L (i.e. the laboratory criteria for thrombocytopenia) were observed in 5.1% of patients (p5140 of the PSUR).

6.40 The TGA evaluator noted that in heavier patients treated with ONA:

- There was a second peak in AST and/or ALT 4 to 6 weeks post-infusion with ONA.
- Incidence of transaminitis was correlated with both age and weight.
- Higher doses of systemic corticosteroids are required; and for longer, based on age and weight.

The TGA evaluator concluded that "based on the totality of the clinical data presented in support of this application, the benefit-risk balance is positive for children with SMA aged up to 2 years of age to receive OAV101 [ONA] treatment, albeit management of transaminitis and hepatoxicity; as well as the side-effects from systemic corticosteroid usage would be expected to have a more negative impact on health compared to children aged < 9 months-old. In older, heavier children, unless SMA is identified earlier and treated promptly, preferably pre-symptomatically, the most realistic goal of treatment with OAV101 [ONA] is to maintain motor function rather than achieve major improvements in function. In older, heavier children, there is also an expectation that treatment of transaminitis will be more protracted and more invasive; as well as development of more severe and serious sequelae from long-term corticosteroid use; which may require additional management/intervention" (TGA Clinical Evaluation Report). The ACM expressed concern that hepatic toxicity appears more frequently in individuals with greater body mass, and that toxicity may not always be reversible. As such, the ACM advised to restrict the weight limit to up to 21 kilograms and that the upper weight limit should be included in the wording of the indication.

Benefits/harms

6.41 A benefits and harms table is not presented as the submission made a claim of non-inferiority.

Clinical claim

6.42 The submission described ONA for the treatment of paediatric patients weighing up to 21kg as non-inferior in terms of effectiveness compared with ONA for the treatment of paediatric patients less than 9 months of age with (i) Type I SMA or pre-symptomatic SMA with 1-2 copies of the *SMN2* gene and (ii) Pre-symptomatic SMA with three copies of the *SMN2* gene. The Commentary considered the therapeutic conclusion presented in the submission was not adequately supported by the evidence presented in the submission because:

- The results of SMART were limited by the study design and small number of patients enrolled which introduced a high risk of bias, and were likely confounded as:
  - weight, age and attainment of motor milestones are generally correlated;
  - differences exist between the subgroups at baseline, where patients in the heaviest subgroup (subgroup 3) were older, a higher proportion had less severe disease, and better motor function;
  - the vast majority (21/24; 87.5%) of patients enrolled were pre-treated with NUSI or RIS, and it was unclear if prior treatment with other DMTs were treatment modifiers and in which direction (if any);
- The SMART study did not enrol any patients with pre-symptomatic SMA, and only eight (33%; 8/24) patients enrolled in SMART were diagnosed with SMA Type I; and
- Although overall survival and event free survival in the SMART study was comparable between the included studies (nominated comparator represented by the SPR1NT, START, STR1VE-US and STR1VE-EU studies), key differences between the patient population (with respect to disease severity and previous SMA treatment) across the included studies and the short duration of follow-up in SMART (of 52 weeks) made it difficult to draw meaningful or reliable comparisons.

6.43 The submission described ONA for the treatment of paediatric patients weighing up to 21kg as non-inferior in terms of safety compared with ONA for the treatment of paediatric patients less than 9 months of age with (i) Type I SMA or pre-symptomatic SMA with 1-2 copies of the *SMN2* gene and (ii) Pre-symptomatic SMA with three copies of the *SMN2* gene. The ESC considered the therapeutic conclusion presented in the submission was not supported and was not consistent with TGA Clinical Evaluation Report and the findings in the PSUR. Hepatoxicity was found to have occurred in majority of patients enrolled in SMART, but the same was not observed in earlier clinical studies (SPR1NT, START, STR1VE-US, STR1VE-EU and STR1VE-AP); this was also the case for the incidence of thrombocytopenia.

6.44 The submission did not present any evidence on the safety and efficacy of ONA in patients older than nine months but weighing less than 21 kg with pre-symptomatic SMA with 1-3 copies of SMN2 and as such, it was unclear on what basis a claim of non-inferior efficacy or safety in this extended population could be supported.

6.45 The efficacy of ONA compared to NUSI or RIS (the appropriate comparator/s) in patients with Type I SMA or patients younger than 36 months with pre-symptomatic SMA with 1-3 copies of the SMN2 gene, weighing less than 21kg, was not considered by the submission and remains uncertain. It was noted in their previous consideration of ONA versus NUSI in patients (less than two years of age) with SMA Type I, "the PBAC concluded that, on balance ONA would likely deliver similar clinical outcomes to NUSI

in matched patients" (paragraph 7.1, onasemnogene abeparvovec PSD, November 2020 PBAC meeting).

6.46 Regarding evidence on comparative safety of ONA versus NUSI or RIS the PBAC previously:

- did not accept the claim of superior safety for ONA versus NUSI (paragraph 6.50, onasemnogene abeparvovec PSD, November 2020 PBAC meeting), noting this was not consistent with the presented evidence, where safety data indicated ONA had a similar or greater proportion of patients with any AE, SAEs, and treatment related SAEs compared with NUSI (paragraph 6.46, onasemnogene abeparvovec PSD, November 2020 PBAC meeting); and
- found that it was difficult to make an informed conclusion with respect to the safety profile of ONA compared to RIS (paragraph 6.28, onasemnogene abeparvovec PSD, July 2023 PBAC meeting). 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 (as above), preventing a transitivity argument for non-inferior safety between ONA and RIS (paragraph 6.28, onasemnogene abeparvovec PSD, July 2023 PBAC meeting).

6.47 The PBAC considered that although the evidence available was limited, the effectiveness of ONA in patients older than 9 months appears similar to that in patients younger than 9 months based on supportive data from the SMART trial. The PBAC considered the claim of non-inferior comparative effectiveness for ONA compared with NUSI/RIS was not well supported, particularly for non-symptomatic patients >36 months (but < 21 kg).

6.48 The PBAC considered that the claim of non-inferior safety compared with NUSI/RIS was uncertain (as per paragraph 6.46) but noted the ACM advice that ONA appears safe in patients up to 21 kg and 9 years of age.

6.49 Although the clinical claims were based on very limited supportive data, the PBAC noted that this was consistent with other considerations for SMA as a rare disease.

Economic analysis

6.50 The submission presented a cost comparison which compared ONA in paediatric patients with bi-allelic mutations in the *SMN1* gene weighing up to 21kg (the proposed population) with ONA in paediatric patients less than 9 months of age (as currently listed on the PBS). The approach was not consistent with the relevant comparators (NUSI and RIS). However, ONA was recommended based on it being no more costly than RIS, over a period of 11 years with costs discounted at 5% annually (paragraph 9.2, onasemnogene abeparvovec PSD, November 2020 PBAC meeting with May 2021 Addendum and September 2021 Addendum). As such, ONA is likely to be cost saving compared to NUSI or RIS, given ONA is a once in a lifetime treatment whereas NUSI or RIS are lifelong treatments.

6.51 Table 11 provides a summary of the key assumptions of the cost comparison.

Table 11: Key components and assumptions of the cost comparison

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on evidence presented in Section 2, ONA for patients weighing up to 21kg is clinically non-inferior in terms of efficacy to ONA for patients less than 9 months of age for Type I and pre-symptomatic 1-2 and three SMN2 copy babies.
Therapeutic claim: safety	Based on evidence presented in Section 2, ONA for patients weighing up to 21kg has a non-inferior safety profile to ONA for patients less than 9 months of age for Type I and pre-symptomatic 1-2 and three SMN2 copy babies.
Evidence base	Comparisons of developmental milestones achieved and safety profile in patients weighing up to 21kg and patients less than 9 months of age.
Equi-effective doses	ONA dosed once per lifetime for patients weighing up to 21kg is equivalent to ONA dosed once per lifetime for patients less than 9 months of age. This was consistent with the draft Product Information.
Direct medicine costs	The direct medicine cost of ONA for patients weighing up to 21kg was equivalent to ONA for patients less than 9 months of age over a lifetime horizon. Discounting was not considered.
Other costs or cost offsets	None; no difference in MBS costs between patients weighing up to 21kg and patients less than 9 months of age was assumed by the submission. No adverse event costs were included. This may not be reasonable given the likely inferior safety of ONA in older (and heavier) patients compared to younger patients, where a higher incidence of hepatoxicity and thrombocytopenia were reported. The cost of subsequent therapy was not considered; however, the submission proposed any subsequent DMT for SMA for the expanded population to be captured by the existing outcomes-based RSA.

Source: Table 3.1, p96 of the submission.

DMT= disease modifying treatment; kg= kilogram; MBS= Medicare Benefits Schedule; ONA= onasemnogene abeparvovec; PBS= Pharmaceutical Benefits Scheme; SMA = spinal muscular atrophy; *SMN2*= survival motor neuron 2; RSA = risk sharing arrangement

6.52 Table 12 and Table 13 present the results of the cost comparisons for patients with i) Type I SMA and pre-symptomatic SMA with 1-2 copies of the *SMN2* gene and ii) pre-symptomatic SMA with three copies of the *SMN2* gene, respectively. The submission assumed there were no differences in the proposed MBS costs or healthcare utilisation due to the extension to 21kg in the current indication. This may not be reasonable as a higher incidence of hepatoxicity and thrombocytopenia were reported in older (and heavier) patients. The ESC considered that inclusion of additional costs for treatment or prevention of AEs may be reasonable but noted that these costs are likely to be minimal relative to the cost of treatment with ONA.

Table 12: Results of the cost comparison (Type I SMA or pre-symptomatic SMA with 1-2 *SMN2* copies)

	ONA published price (AEMP)		ONA effective price	
Component	**Up to 21 kg**	**≤9 months of age**	**Up to 21 kg**	**≤9 months of age**
Cost per dose	$2,527,773.87	$2,527,773.87	$[redacted]	$[redacted]
Total number of doses (lifetime)	1	1	1	1
Total medicine cost per lifetime	$2,527,773.87	$2,527,773.87	$[redacted]	$[redacted]

Source: Table 3.2, p97 of the submission.

AEMP= approved ex-manufacturer price; ONA= onasemnogene abeparvovec; SMA= spinal muscular atrophy; *SMN2*= survival of motor neuron 2

Table 13: Results of the cost comparison (Pre-symptomatic SMA with 3 copies of *SMN2*)

	ONA published price (AEMP)		ONA effective price	
Component	**Up to 21 kg**	**≤9 months of age**	**Up to 21 kg**	**≤9 months of age**
Cost per dose	$2,527,773.87	$2,527,773.87	$	$
Total number of doses (lifetime)	1	1	1	1
Total medicine cost per lifetime	$2,527,773.87	$2,527,773.87	$	$

Source: Table 3.2, p97 of the submission.

AEMP= approved ex-manufacturer price; ONA= onasemnogene abeparvovec; SMA= spinal muscular atrophy; *SMN2*= survival of motor neuron 2

6.53 The sponsor proposed the same effective price for the listing of ONA for patients weighing up to 21kg as is currently agreed upon for each indication. The current listing of ONA for patients 9 months of age and younger has an effective price by way of a special pricing arrangement (SPA) for the two patient populations; i) Type I patients and pre-symptomatic SMA patients with 1-2 copies of the *SMN2* gene (effective price of $) and ii) pre-symptomatic SMA patients with three copies of the *SMN2* gene (effective price of $). The lower effective price for the pre-symptomatic treatment of patients with three copies of the SMN2 gene compared to pre-symptomatic treatment of patients with 1-2 copies, was reflective of the PBAC's consideration that "the smaller clinical benefit for patients with 3 SMN2 copies would require the price of ONA to be lower than for the current listing for it to be similarly cost-effective" (paragraph 7.10, onasemnogene abeparvovec PSD, November 2022 PBAC meeting).

6.54 The cost effectiveness of any DMT in the untreated pre-symptomatic SMA population aged >36 months has not been fully established due to uncertainty in the magnitude of incremental benefit compared to symptomatic treatment. The PSCR stated "maintaining the value in the same cost-minimisation boundaries as shown in the original submission against NUSI and RIS may mean that an age-limitation is appropriate". The ESC agreed with the PSCR and considered that if the same cost for ONA as in the current listings is accepted for the proposed expanded population, it would be reasonable to align the restriction for ONA with the age restrictions for other DMT (<36 months at treatment initiation) for pre-symptomatic patients with 1-3 copies of SMN2.

6.55 Cost minimisation approaches of ONA versus NUSI, and ONA versus RIS (the appropriate comparators) in the two proposed populations were performed during the evaluation. The PBAC noted that these analyses showed that ONA would be cost-neutral or cost-saving compared with NUSI or RIS (consistent with the CMA for ONA in patients <9 months of age).

Drug cost/patient/course

6.56 For SMA Type I patients and pre-symptomatic SMA patients with 1-2 copies of the *SMN2* gene, the cost of ONA is $ per patient (administered only once in a lifetime).

6.57 For pre-symptomatic SMA patients with three copies of the *SMN2* gene, the cost of ONA is $ per patient (administered only once in a lifetime).

Estimated PBS usage & financial implications

6.58 This submission was not considered by DUSC. The submission took the following steps in estimating the utilisation and financial impact of extending the PBS listing for ONA for the treatment of paediatric SMA patients weighing up to 21kg:

- Estimated the eligible population based on data from the sponsor's internal database;
- Implicitly estimated the uptake of ONA; and
- Applied relevant prices to estimate the cost of ONA (at published and effective prices), and the net cost for the PBS/RPBS and the Commonwealth health budget.

6.59 The submission did not apply any cost offsets for the expected treatments estimated to be substituted for by ONA. This approach overestimated the impact of listing as with exclusion of pre-symptomatic patients >36 months untreated with DMTs, all patients would otherwise be eligible for treatment with NUSI or RIS. Given RIS was recommended on a cost minimisation basis to NUSI (paragraph 7.1, risdiplam PSD, March 2021 meeting), and ONA was cost minimised against RIS (paragraph 9.1, onasemnogene abeparvovec PSD, September 2021 PBAC meeting) overall, the costs of expanding the listing of ONA in this population should be at least cost neutral, though upfront costs for ONA are higher. The outcomes-based RSA (see paragraph 6.67) would maintain this cost-neutrality, unless [redacted] and is not covered by the RSA.

6.60 The submission utilised information from the sponsor's internal patient tracking database (IPTD) and medical experts to estimate the number of paediatric SMA patients weighing up to 21kg likely to be treated with ONA. The pre-PBAC response noted that the IPTD has tracked all potential ONA patients, with < 500 not treated (< 500 declined, < 500 had a high anti-AAV9 titre, and < 500 were diagnosed after 9 months). The ESC noted that some Australian patients eligible for treatment may have already been treated with ONA via the SMART trial. The ESC also noted that the population identified with pre-symptomatic SMA is increasing over time as patients are identified via NBS.

6.61 Key inputs used to estimate the financial impact are summarised in Table 14.

Table 14: Key inputs for financial estimates

Data	Value & Source	Comment
Eligible population		
Total patients	Yr 1: [redacted][1] Yr 2: [redacted][1] Yr 3: [redacted][1] Yr 4: [redacted][1] Yr 5: [redacted][1] Yr 6: [redacted][1] Source: Based on the [redacted][1] patients identified as not treated with ONA in the sponsor's IPTD over a period of three years, it was estimated there may continue to be a similar number of patients in the future.	It was assumed there would be [redacted][1] patients over the six-year financial estimate period. It was unclear what proportion of patients were estimated to be treatment naïve versus pre-treated; and if pre-symptomatic – what proportion of patients would be younger than 36 months vs aged 36 months and older (and weighing less than 21 kg). In the submission it was assumed that all patients would be pre-symptomatic SMA patients with 2 copies or 3 copies of the SMN2 gene with a 50:50 split (though due to an odd number of patients being treated this was actually a 43:57 split).
Treatment utilisation		
Uptake rate	100% Source: Implicitly assumed by the submission.	The uptake rate of ONA was implicitly assumed by the submission to be equal to the total number of eligible patients.
Costs		
Proposed medicine	Published: $2,527,774 Effective: $[redacted] (SMA Type 1 and pre-symptomatic SMA with 1-2 copies of SMN2 gene); $[redacted] (Pre-symptomatic SMA with 3 copies of the SMN2 gene) Source: Requested price; the submission expected there will be an "even" distribution of patients that have 2 SMN2 copy numbers, and 3 SMN2 copy numbers by alternating the number of patients with 2 versus 3 SMN2 copies, commencing first with 3 SMN2 copies.	It appeared the submission assumed only pre-symptomatic patients (with 2 copies or 3 copies of the SMN2 gene) would receive treatment with ONA in their financial estimates (patients with symptomatic and pre-symptomatic SMA with 1 copy of the SMN2 gene were not mentioned). The submission assumed [redacted][1] patients (43%; [redacted]) had 2 *SMN2* copies and [redacted][1] patients (57%; [redacted]) had 3 *SMN2* copies. This was based on an assumption of a 50:50 split between 2 and 3 copies (with more in the 3 copies due to there being an odd number of patients) but the justification for 50:50 splits was not provided.
Comparator	None assumed by the submission.	No cost offsets were applied by the submission. This was inappropriate given NUSI/RIS would likely be substituted by ONA in prevalent patients. This overestimates the financial impact in patients who would have otherwise been treated with NUSI/RIS.

Source: Table 4.2, 4.4 & 4.5, pp100-101 of the submission.
IPTD= internal patient tracking database; MBS= Medicare Benefits Schedule; NUSI= nusinersen, ONA= onasemnogene abeparvovec; PBS= Pharmaceutical Benefits Scheme; RIS= risdiplam; SMA= spinal muscular atrophy; *SMN2*= survival of motor neuron 2; yr= year
The redacted values correspond to the following ranges:
[1] *< 500*

6.62 Table 15 presents the estimated net financial implications for the proposed listing of ONA for the pre-symptomatic treatment of SMA patients with two copies and three copies of the SMN2 gene over the first six years.

Table 15: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Patients with two *SMN2* copies	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Patients with three *SMN2* copies	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Total patients treated with ONA	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Total number of scripts dispensed	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Estimated financial impact of use for the PBS (not adjusted for co-pay)						
Total (eff)	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]
Estimation of changes in use and financial impact of other medicines (PBS)						
Total initiating patients (first year)	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Total continuing patients (second yr+)	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Total changes in number of scripts	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
PBS cost less co-pay						
Total (eff)	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Estimated financial implications for the PBS (not adjusted for co-pay)						
Net cost to PBS (eff) ($)	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]
Estimated financial implications for the health budget						
Net change in prescriptions	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Net MBS costs	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Net cost to Govt health budget (eff) ($)	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]

Source: Table 4.2, 4.4 & 4.5, pp100-101 of the submission.
eff= effective; govt= government; SMA= spinal muscular atrophy; MBS= Medicare Benefits Schedule; ONA= onasemnogene abeparvovec; PBS= Pharmaceutical Benefits Scheme; *SMN2*= survival of motor neuron 2; trt = treatment
The redacted values correspond to the following range:
[1] *< 500*
[2] *$0 to < $10 million*

6.63 The estimated net cost to the government budget of listing ONA on the PBS/RPBS at the proposed effective price was $0 to < $10 million in Year 1 and $0 to < $10 million in Year 6. The total cost for ONA (excluding offsets for NUSI or RIS) over the first 6 years of listing was estimated to be $10 million to < $20 million by the submission.

6.64 The financial estimates presented by the submission were uncertain and unreliable due to the following:

- The number of additional patients to be treated with ONA under the expanded restriction (based on IPTD) remains somewhat uncertain.
- It was unclear how many pre-symptomatic patients who are aged >36 months and weighing less than 21kg and previously untreated with DMTs were included in the estimates – these patients should not be included in the financial estimates given the revisions to the proposed restrictions.
- The submission assumed an even 50:50 split between patients with two *SMN2* copies and patients with three *SMN2* copies, but this was uncertain. If the proportion of patients with three *SMN2* copies is higher than proposed (which would be plausible given it is likely that older patients are being treated compared to the current ONA listing) then the financial estimates may be overestimated.
- The submission inappropriately did not consider a range of inputs in the financial estimates, such as comparators likely to be substituted (which would overestimate

the financial impact), other concomitant PBS medicine use (prednisolone in conjunction with ONA, as per the Product Information), patient copayments, MBS costs and the management of AEs. While not adjusting for the cost of other concomitant PBS medicine use, patient copayments, MBS items and AEs may underestimate the financial impact of ONA, the impact was likely to be limited given the relative low cost of these inputs in comparison to ONA.

6.65 Overall, the listing of ONA in the proposed expanded population was likely to be at least budget neutral in the longer term (beyond the 6 year forecast in the estimates), as these patients would otherwise have been eligible for nusinersen or RIS.

Financial Management – Risk Sharing Arrangements

6.66 The PBAC have previously noted the need to balance the requirement for access to subsequent treatments where they are needed, with the high cost of funding these treatments in addition to the full up-front cost of ONA, and therefore considered any access to subsequent DMTs needed to be accounted for in the RSA (paragraph 9.6, onasemnogene abeparvovec PSD, November 2020 PBAC meeting with May 2021 Addendum and September 2021 Addendum).

6.67 The sponsor proposed for this expanded population to be covered by the existing outcomes-based RSA; the sponsor did not request for the RSA to be modified. A current RSA is in place for ONA, for SMA Type I and pre-symptomatic patients with 1-3 copies of the *SMN2* gene, whereby:

- [redacted]
- [redacted]
- [redacted]

6.68 The use of nusinersen (for Type I SMA or pre-symptomatic SMA) and RIS (for Type I SMA) following ONA therapy are captured under PBS item codes: 12959C, 12943F, and 12972R, which have been accessed six, six and one time(s) respectively during the 2021-2022 and 2022-2023 financial years[8]. The PBAC noted that input from clinicians indicated that the circumstances allowing for addition of a DMT following ONA should be reviewed (see also paragraph 6.3).

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

[8] https://medicarestatistics.humanservices.gov.au/SASStoredProcess/guest?_PROGRAM=SBIP%3A%2F%2FMETASERVER%2FShared+Data%2Fsasdata%2Fprod%2FVEA0032%2FSAS.StoredProcess%2Fstatistics%2Fpbs_item_standard_report&itemlst=%2712959C%27%2C%2712943F%27%2C%2712972R%27&ITEMCNT=3&LIST=12959C%2C12943F%2C12972R&VAR=SERVICES&RPT_FMT=7&start_dt=202007&end_dt=202506 (Items processed up until June 2025)

7 PBAC Outcome

7.1 The PBAC recommended expanding the current listing of onasemnogene abeparvovec (ONA) which requires patients to be less than 9 months of age to include treatment of SMA patients with:

- Symptomatic Type I-IIIa SMA, weighing up to 21 kg.
- Pre-symptomatic SMA with 1-3 copies *SMN2,* weighing up to 21 kg, where treatment with DMTs was initiated prior to 36 months of age.
- Pre-symptomatic SMA with 1-3 copies *SMN2,* up to 36 months of age, where patients are untreated with DMTs.

Expanding the listings was on the basis that there may be a clinical need for a small number of patients who have not received ONA prior to 9 months of age, however the PBAC noted that earlier initiation of disease-modifying treatment remains the preferred approach. The PBAC considered that although the evidence available was limited, the efficacy and safety of ONA in patients older than 9 months appears similar to that in patients younger than 9 months. The PBAC considered that ONA would be acceptably cost-effective in the older population at the same cost per patient as in the younger population, with the same outcomes-based RSA conditions applied.

7.2 The PBAC noted that input from clinical experts indicated that it would be preferable for the listing for patients with symptomatic SMA to not be limited to Type I, so as not to exclude patients with onset of symptoms at >6 months of age. The current listings for NUSI and RIS include symptomatic patients with Type I-IIIa SMA and the PBAC considered that aligning the listing for ONA with these listings would be reasonable as cost-effectiveness of DMTs has been established in these patients and their inclusion is consistent with the patient population in the SMART trial.

7.3 The PBAC considered that the inclusion of an age limit of 36 months was appropriate for the listing in patients with pre-symptomatic SMA who had not received prior DMT, consistent with the existing listings for NUSI and RIS. The PBAC noted that these patients were likely to have a less severe disease and were less likely to benefit from treatment to the same extent, but would be eligible for other disease modifying treatment where symptoms become apparent. The PBAC considered that a restriction in weight (up to 21 kg) was sufficient for patients with symptomatic SMA noting that the existing listings for nusinersen and risdiplam in symptomatic patients allow treatment initiation in patients up to 18 years. The PBAC also considered that the restriction in weight (up to 21 kg) was sufficient for pre-symptomatic patients who have initiated treatment with nusinersen or risdiplam prior to 36 months, nothing that these patients would otherwise be eligible for ongoing nusinersen or risdiplam.

7.4 The PBAC considered that these changes to the restrictions for ONA would align with other DMTs, while maintaining consistency with the anticipated updated TGA indication for ONA. The PBAC noted that earlier treatment of SMA prevents the irreversible loss of motor neurons and given the increased safety concerns for ONA in

older patients, considered that early treatment remains the preferred approach. The PBAC considered that the extension of the listings for ONA would address potential equity issues for the small number of patients who have not received ONA at an earlier age.

7.5 The PBAC considered that NUSI and RIS were the relevant comparators for the revised population as per paragraph 7.3 as they are the treatments that would be replaced in practice. However, the PBAC noted that there were limited data to inform a comparison of RIS/NUSI to ONA in the specific population requested and the PBAC considered that the submission's approach to compare the safety and efficacy of ONA in older/heavier populations with ONA in younger/lighter patients was acceptable in the context of a rare disease.

7.6 The submission presented the results of the SMART trial to support the clinical claim that ONA in paediatric patients weighing up to 21 kg is non-inferior in terms of effectiveness compared with ONA in paediatric patients less than 9 months of age. The SMART study was a phase 3, single arm, open-label study evaluating the efficacy and safety of ONA in patients with symptomatic SMA who weighed between 8.5 kg to 21 kg. The PBAC noted that no evidence was presented for patients >9 months of age with pre-symptomatic SMA. The submission presented side-by-side comparisons of EFS and OS for patients in the SMART study with those enrolled in ONA studies previously considered by the PBAC (SPR1NT, START, STR1VE-US, STR1VE-EU, and LT-002). The PBAC noted that these comparisons were not meaningful as the patient populations were not comparable in terms of age, previous treatments, whether or not patients were symptomatic, and SMA Type for symptomatic patients.

7.7 The submission also presented a comparison of results for patients within the various weight categories of SMART, i.e.8.5-13 kg (subgroup 1); >13-17 kg (subgroup 2); and >17-21 kg (subgroup 3), based on the outcome of change from baseline in Hammersmith Functional Motor Scale—Expanded (HFMSE) total score and Revised Upper Limb Module (RULM) total score, and the achievement of developmental milestones. The PBAC noted that all patients met the MCID for HFMSE of a ≥3-point improvement, while only subgroup 1 met the MCID for RULM of ≥2-point improvement. The PBAC considered that although the evidence available was limited, the efficacy and safety of ONA in patients older than 9 months appears similar to that in patients younger than 9 months based on supportive data from the SMART trial. The PBAC considered the claim of non-inferior comparative effectiveness for ONA compared with NUSI/RIS was not well supported, particularly for non-symptomatic patients >36 months (but < 21 kg). However, the PBAC noted that this was consistent with other considerations for SMA as a rare disease with limited data to inform clinical claims.

7.8 The PBAC noted that there were limited additional data to inform the claim of non-inferior safety. The PBAC recalled it previously did not accept the claim of superior safety for ONA vs NUSI (paragraph 6.46, onasemnogene abeparvovec PSD, November 2020 PBAC meeting) and found that it was difficult to make an informed conclusion

with respect to the safety profile of ONA compared to RIS (paragraph 6.28, onasemnogene abeparvovec PSD, July 2023 PBAC meeting). The PBAC noted that the TGA evaluator stated that in patients > 9 months management of transaminitis and hepatoxicity, as well as the side-effects from systemic corticosteroid usage, would be expected to have a more negative impact on health compared to children aged < 9 months, and the PBAC considered that this supported the preferred clinical place of ONA treatment in younger patients. The PBAC considered that the claim of non-inferior comparative safety to RIS/NUSI was uncertain but noted the ACM advice that ONA appears safe in patients up to 21 kg and 9 years of age.

7.9 The PBAC noted that the submission presented a cost comparison and proposed the same price per patient (for a single dose) in the expanded population as for patients aged <9 months. The PBAC considered that the approach presented was reasonable as ONA in patients <9 months was cost-minimised to RIS and at the proposed cost ONA would therefore be expected to be cost-neutral.

7.10 The PBAC noted that the sponsor proposed for this expanded population to be covered by the existing outcomes-based RSA. The PBAC noted that the existing outcomes-based RSA addressed uncertainty regarding the cost-neutrality of ONA to NUSI and RIS and considered that it would be reasonable for the expanded population to be included in this RSA.

7.11 The PBAC considered there was some uncertainty with respect to the number of patients >9 months likely to be treated with ONA, but considered that the estimated < 500 to < 500 patients per year was likely to be reasonable based on the number of known patients eligible for treatment. The PBAC noted that offsets from RIS/NUSI that would be replaced had not been accounted for in the financial estimates, which would overestimate the net cost of listing ONA in the expanded population. The PBAC noted that although any additional cost to the Government over the longer term would be minimal (as the additional patients would otherwise be treated with ongoing nusinersen or risdiplam) ONA was associated with additional costs in the 6 years of the financial estimates as ONA is associated with a once off upfront cost, whereas offsets are from the replacement of ongoing treatments.

7.12 The PBAC noted that its recommendation was based on a cost comparison and advised that, because ONA is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over RIS or NUSI, or not expected to address a high and urgent unmet clinical need given the presence of alternative therapies, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

7.13 The PBAC considered that the clinical input provided was informative as experts at the major centres treating SMA now have substantial experience with treating SMA with ONA. The PBAC noted the clinical input indicating that the conditions for subsequent treatment with NUSI or RIS following ONA are too restrictive as they require the patient to have had a regression in a developmental state, which can be a major and

irreversible change. Clinicians indicated that patients may have neurophysiological and molecular assessments that indicate disease activity but they are not eligible additional DMT which is likely to be of benefit to them. Clinician input suggested that the restrictions should allow subsequent DMT for patients with slower than expected gain in motor function, where patients do not continue to gain motor function and where patients experience regression in respiratory or bulbar function. The PBAC advised that the restrictions outlining the eligibility criteria for NUSI and RIS treatment in children who have had previous ONA and have a suboptimal response should be reviewed as suggested by clinicians. The PBAC also considered that it would be reasonable for patients treated with ONA funded under programs other than the PBS (e.g. clinical trials) to be eligible for subsequent DMTs where they have a suboptimal response. Due to the complexity of the restrictions and the interaction of these restrictions with the RSA for ONA the PBAC noted that additional clinical input and stakeholder consultation would be required regarding these flow-on changes to NUSI and RIS listings.

7.14 The PBAC noted that dosing is individualised and ONA is provided as a customised finished pack for each patient. The PBAC noted that the current ONA listings include customised packs for weight ranges from 2.6 kg to 13.5 kg and additional item codes would be required for the extended weight ranges (from 13.6 kg up to 21 kg). The PBAC noted input from clinicians regarding delays in approval to commence treatment and in receiving supply of ONA from overseas. The PBAC noted that Services Australia's current processes do not allow authority approval outside business hours and that process improvements should be considered in order to minimise or remove delays so that approvals can be acquired in a timely manner.

7.15 The PBAC noted that this submission is not eligible for an Independent as it is a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Current ONA listings include customised packs for weight ranges from 2.6 kg to 13.5 kg, with the appropriate dose individually made up by the sponsor for each patient. Additional item codes would be required for the extended weight ranges (i.e., from 13.6 kg up to 21 kg).
Amend existing listing as follows:

Type I-IIIa SMA or pre-symptomatic SMA (1-2 *SMN2* gene copies)

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
ONASEMNOGENE ABEPARVOVEC					
onasemnogene abeparvovec 20 trillion vector genomes/mL injection [2 x 5.5 mL vials] (&) onasemnogene abeparvovec 20 trillion vector genomes/mL injection [2 x 8.3 mL vials], 1 pack	12958B	1	1	0	Zolgensma
onasemnogene abeparvovec 20 trillion vector genomes/mL injection [2 x 5.5 mL vials] (&) onasemnogene abeparvovec 20 trillion vector genomes/mL injection [3 x 8.3 mL vials], 1 pack	12940C	1	1	0	
onasemnogene abeparvovec 20 trillion vector genomes/mL injection [2 x 5.5 mL vials] (&) onasemnogene abeparvovec 20 trillion vector genomes/mL injection [4 x 8.3 mL vials], 1 pack	12950N	1	1	0	
onasemnogene abeparvovec 20 trillion vector genomes/mL injection [2 x 5.5 mL vials] (&) onasemnogene abeparvovec 20 trillion vector genomes/mL injection [5 x 8.3 mL vials], 1 pack	12963G	1	1	0	
onasemnogene abeparvovec 20 trillion vector genomes/mL injection [2 x 5.5 mL vials] (&) onasemnogene abeparvovec 20 trillion vector genomes/mL injection [6 x 8.3 mL vials], 1 pack	12941D	1	1	0	
onasemnogene abeparvovec 20 trillion vector genomes/mL injection [2 x 5.5 mL vials] (&) onasemnogene abeparvovec 20 trillion vector genomes/mL injection [7 x 8.3 mL vials], 1 pack	12952Q	1	1	0	
onasemnogene abeparvovec 20 trillion vector genomes/mL injection [2 x 5.5 mL vials] (&) onasemnogene abeparvovec 20 trillion vector genomes/mL injection [8.3 mL vial], 1 pack	12955W	1	1	0	
onasemnogene abeparvovec 20 trillion vector genomes/mL injection [5.5 mL vial] (&) onasemnogene abeparvovec 20 trillion vector genomes/mL injection [2 x 8.3 mL vials], 1 pack	12951P	1	1	0	
onasemnogene abeparvovec 20 trillion vector genomes/mL injection [5.5 mL vial] (&) onasemnogene abeparvovec 20 trillion vector genomes/mL injection [3 x 8.3 mL vials], 1 pack	12977B	1	1	0	
onasemnogene abeparvovec 20 trillion vector genomes/mL injection [5.5 mL vial] (&) onasemnogene abeparvovec 20 trillion vector genomes/mL injection [4 x 8.3 mL vials], 1 pack	12942E	1	1	0	
onasemnogene abeparvovec 20 trillion vector genomes/mL injection [5.5 mL vial] (&) onasemnogene abeparvovec 20 trillion vector genomes/mL injection [5 x 8.3 mL vials], 1 pack	12976Y	1	1	0	
onasemnogene abeparvovec 20 trillion vector genomes/mL injection [5.5 mL vial] (&	12975X	1	1	0	

onasemnogene abeparvovec 20 trillion vector genomes/mL injection [6 x 8.3 mL vials], 1 pack					
onasemnogene abeparvovec 20 trillion vector genomes/mL injection [5.5 mL vial] (&) onasemnogene abeparvovec 20 trillion vector genomes/mL injection [7 x 8.3 mL vials], 1 pack	12956X	1	1	0	
onasemnogene abeparvovec 20 trillion vector genomes/mL injection [5.5 mL vial] (&) onasemnogene abeparvovec 20 trillion vector genomes/mL injection [8 x 8.3 mL vials], 1 pack	12964H	1	1	0	
onasemnogene abeparvovec 20 trillion vector genomes/mL injection, 2 x 8.3 mL vials	12957Y	1	1	0	
onasemnogene abeparvovec 20 trillion vector genomes/mL injection, 3 x 8.3 mL vials	12961E	1	1	0	
onasemnogene abeparvovec 20 trillion vector genomes/mL injection, 4 x 8.3 mL vials	12971Q	1	1	0	
onasemnogene abeparvovec 20 trillion vector genomes/mL injection, 5 x 8.3 mL vials	12962F	1	1	0	
onasemnogene abeparvovec 20 trillion vector genomes/mL injection, 6 x 8.3 mL vials	12973T	1	1	0	
onasemnogene abeparvovec 20 trillion vector genomes/mL injection, 7 x 8.3 mL vials	12954T	1	1	0	
onasemnogene abeparvovec 20 trillion vector genomes/mL injection, 8 x 8.3 mL vials	12974W	1	1	0	
onasemnogene abeparvovec 20 trillion vector genomes/mL injection, 9 x 8.3 mL vials	12949M	1	1	0	

Category / Program: ☒ Section 100 – Highly Specialised Drugs Program – Public (Code HB)
Prescriber type: ☒ Medical Practitioners
Benefit type: ☒ Authority Required (in writing only via OPA/post/HPOS upload)
Authority type: ☒ Complex Authority Required (CAR)
Prescribing rule level:
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.
Administrative Advice: Other disease modifying therapies for this condition are: (i) nusinersen, (ii) risdiplam.
Administrative Advice: 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.
Administrative Advice: 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
Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. 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 authorisation under this restriction should be made using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos)* *Alternatively*, ~~A~~ applications for authority to prescribe can 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
Restriction Summary edit 12639 / Treatment of Concept: edit 12639
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~~/~~ and symptoms of ~~Type 1~~ SMA type I, II or IIIa ~~specified below~~ prior to 3 years of age; OR
The condition must be pre-symptomatic SMA, with genetic confirmation that there are 1 to 2 copies of the survival motor neuron 2 (*SMN2*) gene; AND
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
Treatment criteria:
Must be treated by a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA; or in consultation with a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA
AND
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~~ Patient must weigh 21 kg or less
AND
Population criteria:
Patient must have symptomatic Type 1, 2 or 3a SMA; OR
Patient must have pre-symptomatic SMA with 1-2 copies of the SMN2 gene and are no older than 36 months of age.
Prescribing Instructions: The authority application must be made *via the Online PBS Authorities System, or* in writing *via HPOS form upload or mail* and must include: (1) ~~a completed authority~~ *details of the proposed* prescription*(s)* ~~form~~; and (2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).
Prescribing Instructions: ~~Prescribing Instructions:~~ In the relevant PBS Authority Application form, specify the following: (i) the SMA type being treated: symptomatic Type 1, 2 or 3a SMA, or, pre-symptomatic SMA; (ii) for Type 1, 2 or 3a 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.
Prescribing Instructions: Defined signs and symptoms of type I SMA are: i) Onset before 6 months of age; and ii) Failure to meet or regression in ability to perform age-appropriate motor milestones; or iii) Proximal weakness; or iv) Hypotonia; or v) Absence of deep tendon reflexes; or vi) Failure to gain weight appropriate for age; or vii) Any active chronic neurogenic changes; or viii) A compound muscle action potential below normative values for an age-matched child.
Prescribing Instructions: Defined signs and symptoms of type II SMA are: i) Onset between 6 and 18 months; and ii) Failure to meet or regression in ability to perform age-appropriate motor milestones; or iii) Proximal weakness; or iv) Weakness in trunk righting/derotation; or

v) Hypotonia; or vi) Absence of deep tendon reflexes; or vii) Failure to gain weight appropriate for age; or viii) Any active chronic neurogenic changes; or ix) A compound muscle action potential below normative values for an age-matched child.
Prescribing Instructions: Defined signs and symptoms of type IIIa SMA are: i) Onset between 18 months and 3 years of age; and ii) Failure to meet or regression in ability to perform age-appropriate motor milestones; or iii) Proximal weakness; or iv) Hypotonia; or v) Absence of deep tendon reflexes; or vi) Failure to gain weight appropriate for age; or vii) Any active chronic neurogenic changes; or viii) A compound muscle action potential below normative values for an age-matched child.
Prescribing Instructions: An outcome on the authority application is not immediate, but will follow in due course. Electronic upload is encouraged to reduce processing time.
Restriction Summary: edit 15459 / Treatment of Concept: edit 15460
Indication: Spinal muscular atrophy (SMA)
Treatment Phase: Use occurring after treatment with at least one disease modifying therapy for this condition (i.e. switching from nusinersen/risdiplam to onasemnogene abeparvovec)
Clinical criteria:
The treatment must be given concomitantly with best supportive care for this condition
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
Treatment criteria:
Patient must be undergoing treatment with this pharmaceutical benefit following prior PBS-subsidised treatment with at least one other disease modifying therapy 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 of a recognised hospital in the management of SMA; or in consultation with a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA
AND
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 be undergoing treatment with this pharmaceutical benefit with the intent that treatment with the replaced disease modifying agent is/has ceased
	Population criteria:
	~~Patient must be no older than 9 months of age~~ Patient must weigh 21 kg or less
	AND
	Population criteria:
	Patient must have symptomatic Type 1, 2 or 3a SMA; OR
	Patient must have pre-symptomatic SMA with 1-2 copies of the SMN2 gene *where a disease-modifying therapy (DMT) was initiated prior to 36 months of age*
	Prescribing Instructions: The authority application must be made *via the Online PBS Authorities System, or* in writing *via HPOS form upload or mail* and must include: (1) ~~a completed authority~~ *details of the proposed* prescription*(s)* ~~form~~; and (2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).
	Prescribing Instructions: Do not resubmit previously submitted documentation concerning the diagnosis and type of SMA. Confirm that a previous PBS authority application has been approved for one of the following: (i) Symptomatic Type 1*, 2 or 3a* SMA; or (ii) Pre-symptomatic SMA with 1-2 copies of SMN2 gene. 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.
	Prescribing Instructions: Adhere to any Product Information or local treatment guidelines with respect to treatment-free ('wash out') periods prior to administering this benefit.
	Prescribing Instructions: An outcome on the authority application is not immediate, but will follow in due course. Electronic upload is encouraged to reduce processing time.

Pre-symptomatic SMA (3 *SMN2* gene copies)

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
ONASEMNOGENE ABEPARVOVEC					
onasemnogene abeparvovec 20 trillion vector genomes/mL injection [2 x 5.5 mL vials] (&) onasemnogene abeparvovec 20 trillion vector genomes/mL injection [2 x 8.3 mL vials], 1 pack	13669K	1	1	0	Zolgensma
13682D / onasemnogene abeparvovec 20 trillion vector genomes/mL injection [2 x 5.5 mL vials] (&) onasemnogene abeparvovec 20 trillion vector genomes/mL injection [3 x 8.3 mL vials], 1 pack	13682D	1	1	0	
onasemnogene abeparvovec 20 trillion vector genomes/mL injection [2 x 5.5 mL vials] (&) onasemnogene abeparvovec 20 trillion vector genomes/mL injection [4 x 8.3 mL vials], 1 pack	13683E	1	1	0	
onasemnogene abeparvovec 20 trillion vector genomes/mL injection [2 x 5.5 mL vials] (&)	13681C	1	1	0	

onasemnogene abeparvovec 20 trillion vector genomes/mL injection [5 x 8.3 mL vials], 1 pack					
onasemnogene abeparvovec 20 trillion vector genomes/mL injection [2 x 5.5 mL vials] (&) onasemnogene abeparvovec 20 trillion vector genomes/mL injection [6 x 8.3 mL vials], 1 pack	13679Y	1	1	0	
onasemnogene abeparvovec 20 trillion vector genomes/mL injection [2 x 5.5 mL vials] (&) onasemnogene abeparvovec 20 trillion vector genomes/mL injection [7 x 8.3 mL vials], 1 pack	13668J	1	1	0	
onasemnogene abeparvovec 20 trillion vector genomes/mL injection [2 x 5.5 mL vials] (&) onasemnogene abeparvovec 20 trillion vector genomes/mL injection [8.3 mL vial], 1 pack	13663D	1	1	0	
onasemnogene abeparvovec 20 trillion vector genomes/mL injection [5.5 mL vial] (&) onasemnogene abeparvovec 20 trillion vector genomes/mL injection [2 x 8.3 mL vials], 1 pack	13671M	1	1	0	
onasemnogene abeparvovec 20 trillion vector genomes/mL injection [5.5 mL vial] (&) onasemnogene abeparvovec 20 trillion vector genomes/mL injection [3 x 8.3 mL vials], 1 pack	13670L	1	1	0	
onasemnogene abeparvovec 20 trillion vector genomes/mL injection [5.5 mL vial] (&) onasemnogene abeparvovec 20 trillion vector genomes/mL injection [4 x 8.3 mL vials], 1 pack	13672N	1	1	0	
onasemnogene abeparvovec 20 trillion vector genomes/mL injection [5.5 mL vial] (&) onasemnogene abeparvovec 20 trillion vector genomes/mL injection [5 x 8.3 mL vials], 1 pack	13680B	1	1	0	
onasemnogene abeparvovec 20 trillion vector genomes/mL injection [5.5 mL vial] (&) onasemnogene abeparvovec 20 trillion vector genomes/mL injection [6 x 8.3 mL vials], 1 pack	13677W	1	1	0	
onasemnogene abeparvovec 20 trillion vector genomes/mL injection [5.5 mL vial] (&) onasemnogene abeparvovec 20 trillion vector genomes/mL injection [7 x 8.3 mL vials], 1 pack	13662C	1	1	0	
onasemnogene abeparvovec 20 trillion vector genomes/mL injection [5.5 mL vial] (&) onasemnogene abeparvovec 20 trillion vector genomes/mL injection [8 x 8.3 mL vials], 1 pack	13666G	1	1	0	
onasemnogene abeparvovec 20 trillion vector genomes/mL injection, 2 x 8.3 mL vials	13674Q	1	1	0	
onasemnogene abeparvovec 20 trillion vector genomes/mL injection, 3 x 8.3 mL vials	13678X	1	1	0	
onasemnogene abeparvovec 20 trillion vector genomes/mL injection, 4 x 8.3 mL vials	13665F	1	1	0	
onasemnogene abeparvovec 20 trillion vector genomes/mL injection, 5 x 8.3 mL vials	13667H	1	1	0	
onasemnogene abeparvovec 20 trillion vector genomes/mL injection, 6 x 8.3 mL vials	13664E	1	1	0	
onasemnogene abeparvovec 20 trillion vector genomes/mL injection, 7 x 8.3 mL vials	13675R	1	1	0	

onasemnogene abeparvovec 20 trillion vector genomes/mL injection, 8 x 8.3 mL vials	13673P	1	1	0	
onasemnogene abeparvovec 20 trillion vector genomes/mL injection, 9 x 8.3 mL vials	13676T	1	1	0	

Category / Program: ☒ Section 100 – Highly Specialised Drugs Program – Public (Code HB)

Prescriber type: ☒ Medical Practitioners

Benefit type: ☒ Authority Required (in writing only via OPA/post/HPOS upload)

Authority type: ☒ Complex Authority Required (CAR)

Prescribing rule level:

Administrative Advice:
No increase in the maximum quantity or number of units may be authorised.

Administrative Advice:
No increase in the maximum number of repeats may be authorised.

Administrative Advice:
Special Pricing Arrangements apply.

Administrative Advice:
Other disease modifying therapies for this condition are: (i) nusinersen, (ii) risdiplam.

Administrative Advice:
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.

Administrative Advice:
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

Administrative Advice:
Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. 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 authorisation under this restriction should be made using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos)

Alternatively, ~~A~~ applications for authority to prescribe can 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

Restriction Summary edit 15987 / Treatment of Concept: edit 16045

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:
The condition must be pre-symptomatic SMA, with genetic confirmation that there are 3 copies of the survival motor neuron 2 (*SMN2*) 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
Treatment criteria:
Must be treated by a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA; or in consultation with a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA
AND
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~~ Patient must weigh 21 kg or less
AND
Population criteria:
Patient must be under 36 months of age
~~**AND**~~
~~**Population criteria:**~~
~~Patient must have pre-symptomatic SMA with 3 copies of the SMN2 gene~~
Prescribing Instructions: The authority application must be made via the Online PBS Authorities System, or in writing via HPOS form upload or mail and must include: (1) details of the proposed prescription*(s)*; and (2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).
Prescribing Instructions: 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. Confirm that there is a genetic test finding that substantiates the number of SMN2 gene copies to be 3 and has been 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.
Prescribing Instructions: An outcome on the authority application is not immediate, but will follow in due course. Electronic upload is encouraged to reduce processing time.
Restriction Summary edit 15988 / Treatment of Concept: edit 15989
Indication: Spinal muscular atrophy (SMA)
Treatment Phase: Use occurring after treatment with at least one disease modifying therapy for this condition (i.e. switching from nusinersen/risdiplam to onasemnogene abeparvovec)
Clinical criteria:
The treatment must be given concomitantly with best supportive care for this condition
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
Treatment criteria:
Patient must be undergoing treatment with this pharmaceutical benefit following prior PBS-subsidised treatment with at least one other disease modifying therapy for this condition prior to 36 months of age
AND
Treatment criteria:
Must be treated by a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA; or in consultation with a specialist medical practitioner experienced in the diagnosis and management of SMA associated with a neuromuscular clinic of a recognised hospital in the management of SMA
AND
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 be undergoing treatment with this pharmaceutical benefit with the intent that treatment with the replaced disease modifying agent is/has ceased
Population criteria:
~~Patient must be no older than 9 months of age~~ Patient must weigh 21 kg or less
~~**AND**~~
~~**Population criteria:**~~

~~Patient must have pre-symptomatic SMA with 3 copies of the SMN2 gene~~
Prescribing Instructions: The authority application must be made *via the Online PBS Authorities System, or* in writing *via HPOS form upload or mail* and must include: (1) details of the proposed prescription*(s)*; and (2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).
Prescribing Instructions: Do not resubmit previously submitted documentation concerning the diagnosis and type of SMA. Confirm that a previous PBS authority application has been approved for pre-symptomatic SMA with 3 copies of SMN2 gene. 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.
Prescribing Instructions: Adhere to any Product Information or local treatment guidelines with respect to treatment-free ('wash out') periods prior to administering this benefit.
Prescribing Instructions: An outcome on the authority application is not immediate, but will follow in due course. Electronic upload is encouraged to reduce processing time.

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

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

10 Sponsor's Comment

Novartis welcomes the PBAC's decision to extend the listing of ONA to include paediatric patients weighing up to 21kg who have previously been unable to access treatment and the pragmatic approach to evaluating data for a rare disease. Novartis will work with the Department in the hope we can advance this listing.