5.09 ONASEMNOGENE ABEPARVOVEC, 1 vial solution for intrathecal injection, 1.2 x 10^{14} vector genomes per mL, 3mL, OAV101 IT®, Novartis Pharmaceuticals Australia Pty Ltd.

1 Purpose of submission

1.1 The Category 2 submission requested Section 100 (Highly Specialised Drugs Program), Authority Required (Written) PBS listing for onasemnogene abeparvovec (ONA) intrathecal (IT) for the treatment of symptomatic spinal muscular atrophy (SMA) in patients at least 2 years of age but yet to turn 19 years old who have experienced at least two of the defined signs and symptoms of SMA Type I, II or IIIa prior to 3 years of age.

1.2 Listing was requested on the basis of a cost-minimisation approach versus risdiplam (RIS) and nusinersen (NUSI).

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

Component	Description
Population	Symptomatic patients with Types I, II and IIIa SMA, who are at least 2 years of age but yet to turn 19 years of age i.e. 2 years to < 19 years of age
Intervention	ONA, administered as a single-dose IT bolus injection over approximately 1 to 2 minutes. Recommended dose of ONA IT is 1.2 x 10^{14} vg in 3mL.
Comparator	Comparator 1: NUSI 12 mg intrathecally administered solution for injection every 4 months. Comparator 2: RIS orally administered powder for solution given daily administered at the fixed 5mg dose.
Outcomes	Change from baseline in HFMSE and RULM and safety (adverse events, serious adverse events, and adverse events of special interest).
Clinical claim	In symptomatic patients with Types I, II and IIIa SMA, who are 2 years to < 19 years of age, ONA IT is clinically non-inferior in terms of comparative effectiveness with a different but manageable safety profile compared to NUSI and RIS.

Source: Table 1.1, p3 of the submission.

HFMSE, Hammersmith Functional Motor Scale-Expanded; IT, intrathecal; NUSI, nusinersen; ONA, onasemnogene abeparvovec; RIS, risdiplam; RULM, Revised Upper Limb Module; SMA, spinal muscular atrophy.

2 Background

Registration status

2.1 The submission was lodged under the TGA-PBAC parallel process. The TGA delegate's overview was received prior to PBAC consideration. The delegate proposed the following preliminary therapeutic indication:

> "ITVISMA (onasemnogene abeparvovec) is indicated for the treatment of 5q spinal muscular atrophy (SMA) with biallelic mutations in the survival motor neuron 1 (SMN1) gene in patients 2 years of age and older."

2.2 The PBAC noted that the TGA delegate sought ACM's advice regarding whether it is justifiable to extrapolate clinical efficacy and safety to patients with SMA over the age of 18 and in patients who had achieved the motor milestone of walking (less severe phenotype than in the clinical studies) or had failed to achieve the motor milestone of sitting (more severe phenotype than in clinical studies).

Previous PBAC consideration

2.3 ONA IT has not previously been considered by the PBAC and is not PBS-listed for any condition. However, ONA intravenous (IV) is currently PBS listed for the treatment of SMA in patients aged no older than 9 months 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 (DMT) for this condition, which was RIS, and in the context of an outcomes-based risk sharing arrangement (RSA) (paragraph 9.1, onasemnogene abeparvovec Public Summary Document [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" and "the PBAC was satisfied that extension of the current listing would be adequately cost-effective with a price reduction for use in the proposed population" (paragraph 7.1, ONA PSD, July 2023 PBAC meeting).

2.4 Further, ONA IV received a positive recommendation at the November 2025 PBAC meeting, to expand the SMA population eligible for treatment to:

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

2.5 This was recommended "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" (paragraph 7.1,onasemnogene abeparvovec PSD, November 2025). This recommendation was based on a cost comparison which compared the proposed population with ONA in paediatric patients less than 9 months of age (paragraph 6.5,onasemnogene abeparvovec PSD, November 2025), which the PBAC considered 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" (paragraph 7.9, onasemnogene abeparvovec PSD, November 2025). At the time of the evaluation, the expanded listing of ONA was yet to be implemented through the PBS.

At the time of PBAC consideration, agreement to the listing arrangements for the expanded listing of ONA IV was under consideration[1].

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

[1] ONASEMNOGENE ABEPARVOVEC | Medicine Status Website, as at 3/6/2026

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
Onasemnogene abeparvovec					
Onasemnogene abeparvovec 1.2 x 10^{14} vg, 3mL of solution for intrathecal injection	$[redacted] published price $[redacted] effective price	1	1	0	ITVISMA

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
Patient must have experienced at least two of the defined signs and symptoms of SMA Type I, II or IIIa prior to 3 years of age
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 be at least 2 years of age but yet to turn 19 years old.
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, which has been stopped prior to treatment with this pharmaceutical benefit item
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 be at least 2 years of age but yet to turn 19 years old.

Source: Table 1.12, pp28-29 of the submission.
Grey shading indicates items on the requested restriction which differed to the current listing of ONA IV (PBS item 12950N [for treatment of Type I SMA or pre-symptomatic SMA with 1-2 copies of the *SMN2* gene] was used for this comparison).

3.1 The submission's requested restriction for ONA IT for use occurring after treatment with at least one DMT for this condition did not stipulate any signs and symptoms of SMA for treatment experienced patients, such that a pre-symptomatic patient pre-treated with RIS or NUSI would not be precluded from treatment with ONA IT. This was inconsistent with the stated requested population (symptomatic SMA Types I-IIIa). No evidence was presented for ONA IT for the pre-symptomatic population. The ESC considered that the majority of patients >2 years old in Australia would be treatment-experienced.

3.2 The submission proposed a special pricing arrangement (SPA) with an effective price of $[redacted]. This was higher than the current listing of ONA IV for patients 9 months of age and younger for symptomatic Type I SMA as well as the proposed price for ONA IV in patients with SMA Type I-IIIa, weighing up to 21kg (see paragraph 6.53).

3.3 The requested restriction was narrower than the proposed TGA indication. In the requested restriction:

- Patients must have yet to turn 19 years old;
- Patients must not have 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;
- Patients who are receiving treatment must be given treatment concomitantly with best supportive care for this condition; and

- For treatment naïve patients – must have experienced at least two of the defined signs and symptoms of SMA Type I, II or IIIa prior to 3 years of age.

3.4 The STRENGTH study may not be fully aligned with the target population of patients with symptomatic SMA Type I-IIIa (as per the restriction), given the STRENGTH study enrolled patients who had clinical symptom onset <18 months (SMA Type I-Type II; i.e. excluded SMA Type IIIa patients). Additionally, STRENGTH was restricted to patients who had at least four loading doses of NUSI or at least 3 months of treatment with RIS, and excluded patients who received NUSI within 4 months of baseline or RIS within 15 days of baseline (which were not stipulated in the requested restriction).

3.5 The STEER study may not be fully aligned with the target population of patients with symptomatic SMA Type I-IIIa (as per the restriction), given STEER was restricted to patients who had an onset of clinical signs and symptoms at ≥6 months of age (SMA Type II and beyond) and was restricted to patients who were able to sit independently but had never had the ability to walk independently, which would likely exclude patients with SMA Type I.

3.6 According to the draft TGA PI, patients previously treated with ONA (any route of administration) should not be treated with ONA IT. The existing listings include the treatment criterion "Patient must be undergoing treatment with this pharmaceutical benefit once only in a lifetime". The PBAC considered that, for clarity, the initial restrictions should specify that the patient must be untreated with ONA (any route of administration); and this should flow on to all existing SMA listings for ONA.

3.7 There are specific PBS-listings that allow patients to access NUSI/RISD following treatment with ONA under special circumstances (where they have a regression in developmental milestones). These listings do not specify the route of administration (IT or IV), however, they would need to be amended to allow retreatment with RIS/NUSI following ONA IT where a patient received ONA for Type II-IIIa SMA (for both RIS and NUSI) or for pre-symptomatic SMA (for RIS) where they have a regression in developmental milestones.

Treatment Phase	PBS item codes
Initial Treatment After receiving ONA for Type 1 SMA	12943F / risdiplam 750 microgram/mL powder for oral liquid, 80 mL 12959C / risdiplam 750 microgram/mL powder for oral liquid, 80 mL
Initial treatment After receiving ONA for Type 1 SMA, or pre-symptomatic SMA	12972R / nusinersen 12 mg/5 mL intrathecal injection, 5 mL vial

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 SMN gene located on chromosome 5q. Alterations to this gene result in deficiency of SMN protein, which in turn results in irreversible loss of motor neurons that control the movement of skeletal muscles, mainly affecting

those involved in breathing, swallowing, head and neck movement, walking, crawling and arm movement (Kolb & Kissel, 2011; De Sanctis 2016; James & Talbot, 2006). Without treatment, patients with SMA typically develop weak muscles and may have trouble walking and breathing (Clevland Clinic, 2024; National Institute of Neurological Disorders and Stroke, 2024). Patients with a later age of onset typically have better functional ability initially, however their condition also deteriorates over time and often results in disability, regardless of SMA type (Mercuri 2022; Lunn & Wang, 2008).

4.2 SMA has historically been classified into types (0, I, II, III and IV) and subtypes (a, b, c) based on age of onset and maximal motor function achieved (Table 2). 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.

Table 2: Classification of SMA based on age of symptom onset, motor function and life expectancy (without DMT)

Type	Age at symptom onset	Maximum motor function	Able to sit	Able to stand	Able to walk	Life expectancy	Likely *SMN2* copy number [b]
0	Foetal/prenatal	Nil	X	X	X	Days-weeks	1
I	<6 months	Never sits	X	X	X	<2 years	1, **2**, 3
II	6-18 months	Never walks	✓	X	X	20-40 years	2, **3,** 4
IIIa	18 months-3 years	Walks, regression	✓	✓	Assisted	Normal	3, 4, 5 [d]
IIIb [a]	>3 years	Walks, regression	✓	✓	Assisted	Normal	4, 5 [d]
IIIc [a]	>12 to ≤18 years	Walks, regression	✓	✓	Assisted	Normal	4, 5 [d]
4	*>18 years or* >35 years [c d]	Slow decline	✓	✓	✓	Normal	4, 5

Source: Table 1.2, p4 of the submission.

DMT, disease modifying therapy; SMA, spinal muscular atrophy; *SMN2*, survival motor neuron 2 gene

a The submission p(4) indicated that recent publications also distinguish between Type IIIb and IIIc SMA, with Type IIIc SMA being defined as when symptoms develop after 12 years but before 19 years of age.

b *SMN2* copies in the genome varies between 0 and 8. *SMN2* copy number does not define SMA Type, and there is some patient variability in *SMN2* copy number within SMA Type.

c A discrepancy in the age at symptom onset for patients with Type IV SMA between the ONA IV PSD from the July 2023 PBAC meeting *(>35 years)* and the RIS PSD from the March 2021 PBAC meeting *(>18 years)* was noted by the submission.

d 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 have been noted (paragraph 4.2, onasemnogene abeparvovec PSD, November 2025 PBAC). An alternate classification of SMA was presented in the NUSI submission at the July 2023 PBAC meeting, where the age of symptom onset for SMA Type IV (>18 years) and range of *SMN2* copy numbers for SMA Type III (2-4 copies) differed to that of those presented by the submission (>35 years; 3-5 copies respectively).

Values in bold indicate the predominant SMN2 copy number that defines the SMA type, the other copy numbers represent a small percentage of the designated SMA type.

Grey shading indicates the submission's requested population (SMA Type I-IIIa).

4.3 ONA is a once per life-time gene replacement therapy consisting of a non-replicating recombinant adeno-associated viral vector serotype 9 (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.

4.4 Although ONA IT and ONA IV share the same formulation, they differ in both their route of administration and dosing regimen. The systemic viral vector exposure associated with IT administration of ONA via the fixed dosing regimen (1.2×10^{14} vg) is lower than with weight based IV dosing (1.1×10^{14} vg/kg), which allows treatment with ONA IT in older children and adolescents living with SMA, regardless of weight. The ESC noted that input from clinical experts suggests that the IV route is likely to still be preferred, especially in patients who have previously received nusinersen, due to

the less invasive route of administration and the difficulties associated with IT administration in patients with scoliosis.

4.5 The Pre-Sub-Committee Response (PSCR) stated that ONA IT offers an important practical and clinical advantage over NUSI and RIS by reducing ongoing treatment burden, hospital and drug costs as well as risks to adherence and therefore outcomes, while also reducing cumulative costs and out-of-pocket burden for families over time. The pre-PBAC response stated that the PBS listing of ONA IT would ensure equitable access to gene therapy, particularly for older children, regional families, and those who may have missed earlier treatment pathways due to age, timing of diagnosis or historical PBS eligibility criteria. The PSCR and pre-PBAC response stated that the sponsor is aware of at least < 500 paediatric SMA patients in Australia that will be too old (19 years of age or older) to access OAV101 IT if the PBS listing is implemented after January 2027.

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

5 Comparator

5.1 The submission nominated RIS and NUSI as the main comparators. The main arguments provided in support of this nomination were that (i) the targeted population for ONA IT in the submission was the same as for RIS and NUSI, and (ii) RIS and NUSI are the DMTs that will be replaced in clinical practice.

5.2 The submission noted that based on PBS 100% Sample (PBS100) data[2], RIS and NUSI currently (in the previous 12 months to June 2025) hold market shares of 54% and 46%, respectively and therefore both are appropriate comparators. However, given the expansion of patients eligible to receive ONA IV to include symptomatic Type I, II and IIIa SMA patients weighing up to 21kg (recommended at the November 2025 PBAC meeting, see paragraph 2.3), it is expected that ONA IV would also replace RIS and NUSI in this population and may be replaced by ONA IT in clinical practice. As such, ONA IV may also represent a comparator in symptomatic Type I-IIIa SMA patients who are at least 2 years old and weigh up to 21 kg.

5.3 Table 3 summarises the age/weight restrictions for symptomatic treatment with DMTs for SMA currently listed on the PBS. The submission's requested restriction for ONA IT was largely aligned to the existing restrictions for NUSI and RIS for the treatment of SMA Type I-IIIa with respect to (the upper limit of) patient age (<19 years and ≤18 years, respectively).

Table 3: Symptomatic treatment with DMTs on the PBS

Type	Age at symptom onset	ONA IT	ONA IV	NUSI [a]	RIS [a]
0	Prenatal	n/a	n/a	n/a	n/a

[2] The submission stated a patient was defined to be on therapy if they purchased a script in the previous 12 months (RIS or NUSI) or unlimited (ONA IV), but did not appear to account for the market share of ONA IV (currently listed for patients aged no older than 9 months with SMA Type I and pre-symptomatic SMA with 1-3 copies of the *SMN2* gene). The PBS100 data was based on patients with SMA Type I-IIIa and did not appear to be restricted by age (this was not clearly stated by the submission).

I	<6 months	2 to <19 years	<21 kg [b]	≤18 years	≤18 years
II	6-18 months	2 to <19 years	<21 kg [b]	≤18 years	≤18 years
IIIa	18 months to 3 years	2 to <19 years	<21 kg [b]	≤18 years	≤18 years
IIIb	>3 years	n/a	n/a	<19 years	<19 years
IIIc	>12 to ≤18 years	n/a	n/a	<19 years	<19 years
IV	>18 years	n/a	n/a	n/a	n/a

Source: Amended during the evaluation from Table 2, p10 of the ONA PSD, November 2022 PBAC meeting.
DMT, disease modifying therapy; IT, intrathecal; IV, intravenous; n/a, not available; NUSI, nusinersen; ONA, onasemnogene abeparvovec; RIS, risdiplam; SMA, spinal muscular atrophy; *SMN2*, survival motor neuron 2 gene
a Type I/II/IIIa: 18 years or under; Type IIIb/IIIc: before 19th birthday. Note that adults (at least 19 years) with symptom onset prior to their 19th birthday but never claimed PBS subsidy for a disease modifying treatment during childhood, may also be eligible. Patient must have SMA where the onset of signs/symptoms (at least one) of SMA first occurred prior to their 19th birthday (SMA symptom onset after this age will be considered Type IV SMA, which is not PBS-subsidised).
b A weight limit of up to 21kg was recommended at the November 2025 PBAC meeting but has not yet been listed on the PBS (currently restricted to ≤9 months of age for Type I SMA and n/a for Type II and IIIa SMA). In the SMART study, the upper limit of 21kg in SMA patients was correlated to an age of approximately nine years.
Note: Listings for NUSI and RIS occurring after ONA therapy in patients with Type I SMA are also available.
Grey shading indicates categories in which changes are being proposed by the submission.

5.4 In the context of the cost-minimisation approach taken by the submission, a further consideration for PBAC is that, under Section 101(3B) of the National Health Act 1953, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect.

5.5 For the requested population, the following PBS-listed medicines are alternative therapies because they could be replaced in practice: RIS, NUSI and ONA IV in patients with symptomatic SMA Type I-IIIa who are aged at least two years and weigh up to 21kg.

5.6 The PSCR argued that "ONA IV is not PBS-listed for the requested population, nor is the progression of the listing guaranteed, and therefore it is not an appropriate comparator. However, if the listing is progressed, any overlap would constitute a very small proportion of the population". The pre-PBAC response suggested that the weighted price for ONA IT could account for this small proportion of the population if the listing is progressed.

5.7 The ESC considered that NUSI and RIS were appropriate clinical comparators, but that ONA IV would also be a relevant comparator in symptomatic Type I-IIIa SMA patients who are at least 2 years old and weigh up to 21 kg and should be considered as a relevant alternative therapy in relation to the cost-minimisation approach. The pre-PBAC response argued that "indication-based pricing is an established feature of PBS listings and provides a robust mechanism to align price with value across different patient populations".

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 inputs

6.2 The PBAC noted and welcomed the input from individuals (28), health care professionals (4) and organisations (4) via the Office of Health Technology Assessment Consultation Hub. The input from health professionals described an unmet need for additional treatment options for children and adolescents with SMA after infancy. Both healthcare professionals and consumers noted current treatment with intrathecal nusinersen can impose a substantial burden, including repeated lumbar punctures, frequent travel, and ongoing healthcare use. Contributors noted that ONA IT, may reduce treatment burden for patients, families and healthcare services, while potentially improving longevity, reducing disease progression, increasing functional capacity and independence, and improving quality of life. Contributors (mainly parents) also noted even small gains or maintenance of function may have meaningful impacts on participation, confidence, schooling, social engagement and future independence. Some concerns were raised by healthcare professionals and patients/parents regarding adverse events, risks and monitoring requirements for ONA IT, and adverse events associated with intrathecal administration, however intrathecal administration was considered by another contributor to be safer than systemic administration.

6.3 Contributors raised concerns that access to treatment with ONA may be limited by eligibility criteria relating to age, timing of diagnosis, disease classification, and existing PBS restrictions. It was noted some children were diagnosed before newborn screening was introduced, or after infancy, and may therefore have missed earlier access pathways despite ongoing clinical need. It was also noted equitable access would be important to minimise barriers to treatment and consumers expressed hope access could be extended beyond children, with one adult consumer concerned that age-based restrictions may prevent access.

6.4 SMA Australia noted its support for the proposed listing, stating that over the past five years access to ONA IV and Newborn Bloodspot Screening have changed the trajectory for children with SMA. However, many children were diagnosed later or were ineligible for gene-replacement therapy under the current age-restricted listing. The inputs stated that PBS listing of ONA IT would provide children aged 2–18 with genuine choice, flexibility, and individualised care.

6.5 Neurological Alliance Australia (NAA) also supported the proposed listing of ONA IT, stating that this one-time gene therapy has the potential to address an important unmet need for older children and young people with SMA. NAA requested that the PBAC consider the broader system benefits that may arise from improved treatment choice and reduced treatment burden, including fewer repeated treatment visits for some families, reduced travel pressures, less disruption to education and family life,

and potential impacts on health service capacity particularly given the persistent inequities in access to specialist care for people living outside metropolitan areas.

6.6 The National Paediatric Medicines Forum (NPMF) also supported the proposed listing of ONA IT to enable equitable access for older patients who may otherwise miss out on treatment with ONA due to age restrictions.

6.7 Additional input from Paul Fennessy Advisory outlined practical problems encountered by the public hospital system when the PBS listing of ONA IV was first implemented, including hospital funding and procurement issues. This input suggested that a means of communication with jurisdictions be established to ensure that jurisdictions are aware of what is/will be considered by PBAC that likely impacts public hospital service delivery and budgets to ensure provider hospitals are prepared to support timely patient access once PBS listing occurs.

Clinical studies

6.8 The evidence for ONA IT was based on two studies: STRENGTH (single arm study of ONA IT) and STEER (RCT of ONA IT versus sham). As no head-to-head trials comparing ONA IT and RIS or NUSI were identified, the submission took the following approach to support the claim of non-inferiority:

- In treatment experienced patients: an unanchored matching-adjusted indirect comparison (MAIC) was conducted using data from STRENGTH and the placebo arm of patients enrolled in the SAPPHIRE study (RCT of apitegromab versus placebo), who were on background RIS or NUSI treatment; and
- In treatment naïve patients: an anchored indirect treatment comparison (ITC) was conducted using the Bucher methodology (using placebo as the common comparator). The ITC was based on the following trials: STEER, SUNFISH part 2 (herein referred to as SUNFISH; RCT of RIS versus placebo) and CHERISH (RCT of NUSI versus sham). Additional sensitivity analyses including MAIC and multilevel network meta-regression (ML-NMR) to account for differences in trial design and patient characteristics, were also presented by the submission to support the clinical claim.

6.9 The PBAC has previously considered CHERISH and SUNFISH, most recently at the March 2021 PBAC meeting (submission for RIS for the treatment of SMA Types II & IIIa in patients aged ≤18 years [population 1]) and the March 2023 PBAC meeting (resubmission for RIS for the treatment SMA in adults with symptom onset prior to 19 years of age [population 1]), respectively. The PBAC has not considered results from SAPPHIRE previously.

6.10 Details of the studies presented in the submission are provided in Table 4.

Table 4: Studies and associated reports presented in the submission

Study/Trial ID	Protocol title/ Publication title	Publication citation
STRENGTH (NCT05386680)	Phase IIIb, open-label, single-arm, multi-centre study to evaluate the safety, tolerability and efficacy of OAV101 administered intrathecally (1.2x10^14 vector genomes) to participants 2 to <18 years of age with spinal muscular atrophy (SMA) who have discontinued treatment with NUSI (Spinraza®) or RIS (Evrysdi®). Kwon JM., et al. Intrathecal onasemnogene abeparvovec for treatment-experienced patients with spinal muscular atrophy: a phase 3b, open-label trial. doi: 10.1038/s41591-025-04119-2.	Clinical Study Report; 11 March 2025 *Nature Medicine* 2026; 32(2): 481-487.
STEER (NCT05089656)	A Randomized, Sham-controlled, Double-blind Study to Evaluate the Efficacy and Safety of Intrathecal OAV101 in Type 2 Spinal Muscular Atrophy (SMA) Patients Who Are ≥ 2 to < 18 Years of Age, Treatment Naive, Sitting, and Never Ambulatory. Proud CM, et al. Intrathecal onasemnogene abeparvovec in treatment-naive patients with spinal muscular atrophy: a phase 3, randomized controlled trial. doi: 10.1038/s41591-025-04103-w	Clinical Study Report; 13 March 2024 *Nature Medicine* 2025; 32(2): 488-493.
SUNFISH (NCT02908685)	Mercuri, E., et al. Safety and efficacy of once-daily RIS in type 2 and non-ambulant type 3 spinal muscular atrophy (SUNFISH part 2): a phase 3, double-blind, randomised, placebo-controlled trial.	*The Lancet Neurology* 2022; 21(1): 42-52.
CHERISH (NCT02292537)	Mercuri, E., et al. Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy.	New England Journal of Medicine 2018; 378(7): 625-635p.
	Gemeinsamer Bundesausschuss (G-BA), 2020. Modul 4A.2 Nusinersen: Nutzenbewertung gemäß § 35a SGB V. [online]. Available at: https://www.g-ba.de/downloads/92-975-4210/2020-12-01_Modul4A.2_Nusinersen.pdf	IQWiG assessment, 21 February 2019
SAPPHIRE (NCT05156320)	Crawford, T. O., et al. Safety and efficacy of apitegromab in non-ambulatory type 2 or type 3 spinal muscular atrophy (SAPPHIRE): a phase 3, double-blind, randomised, placebo-controlled trial.	*The Lancet Neurology* 2025; 24(9): 727-739.

Source: Table 2.3, pp34-36 of the submission.
IQWiG, Institute for Quality and Efficiency in Health Care; NUSI, nusinersen; OAV101, onasemnogene abeparvovec; RIS, risdiplam
Blue shading represents trials previously seen by the PBAC.

6.11 The key features of the included studies are summarised in Table 5. Common efficacy outcomes between the studies were the Hammersmith Functional Motor Scale Expanded (HFMSE) and Revised Upper Limb Module (RULM); the submission's claim of non-inferiority was based on change from baseline of the HFMSE and RULM score.

Table 5: Key features of the included evidence

Study, N	Design/duration	Bias [a]	Intervention(s)	Population	*Key outcome(s)*
STRENGTH N=27	MC, SA, OL, 12 months	High [b]	ONA IT	Treatment experienced SMA patients aged 2 to <18 years who were able to sit independently but had never walked independently	1°: Safety 2°: HFMSE, RULM, ACEND
STEER N=126	MC, R, DB,12 months [c]	Low	ONA IT vs sham	Treatment naïve SMA patients aged 2 to <18 years, onset at ≥6 months of age, and were able to sit independently but never walked independently	1°: HFMSE, 2°: RULM
SUNFISH N=180	MC, R, DB, until last patient completed 12 months of trt	Low	RIS vs placebo	SMA patients aged 2 to 25 years who had the ability to sit independently but were non-ambulant	1°: MFM32 2°: RULM, HFMSE, FVC, SMAIS, CGI-C
CHERISH N=126	MC, R, DB, 9-month trt period and 6-month follow-up	Low	NUSI vs sham	SMA patients aged 2 to 12 years with symptom onset >6 months of age who were able to sit independently but had never walked independently	1°: HFMSE 2°: WHO motor milestones, RULM
SAPPHIRE [d] N=188	MC, R, DB, 12 months	Low	SKR-015 + NUSI/RIS vs Placebo + NUSI/RIS	Patients aged 2-21 years with non-ambulatory Type II or Type III SMA, who had received NUSI or RIS	1°: HFMSE 2°: RULM, WHO motor milestones

Source: Table 2.9, p59 of the submission.
1°, primary outcome; 2°, secondary outcome; CGI-C, Clinical Global Impression of Change; DB, double-blind; FVC, Forced Vital Capacity; HFMSE, Hammersmith Functional Motor Scale Expanded; MFM32, Motor Function Measure 32; MC, multi centre; OL, open label; ONA, onasemnogene abeparvovec; RULM, revised upper limb module; R, randomised; SA, single arm; SKR-015, apitegromab; SMA, spinal muscular atrophy; SMAIS, Spinal Muscular Atrophy Independence Scale; trt, treatment
a Refers to within-trial bias
b Considered as high risk of bias due to single arm study design, short follow up (52 weeks) and small number of patients enrolled.
c Total duration of the trial was 64 weeks, but primary analysis was conducted at 52 weeks (end of Treatment and Follow-up Period 1).
d Only data from the placebo arm of SAPPHIRE are used for the indirect treatment comparison of ONA IT in the treatment experienced patient population.
Blue shading represents trials previously seen by the PBAC.

6.12 The submission only assessed the risk of bias within the individual studies (see Table 5), however, the submission relied upon ITCs (unanchored and anchored, see paragraph 6.8) to inform the comparative efficacy of ONA IT versus RIS and NUSI. The clinical evidence presented by the submission was prone to a higher risk of bias due to differences in trial design and baseline characteristics of patients enrolled, and the limitations of population-adjusted methodologies from strong assumptions (which were not satisfied) and loss of statistical power.

6.13 While STRENGTH and SAPPHIRE enrolled broadly similar treatment experienced SMA populations, including non-ambulatory patients who were able to sit independently, the submission noted differences relating to SMA Type, age, ethnicity and baseline motor function (as assessed using the HFMSE and RULM) between the STRENGTH study and the control arm of SAPPHIRE, which contributed to population heterogeneity between the two studies. The unanchored MAIC presented by the submission only adjusted for four out of the possible 18 identified prognostic factors (PFs) and treatment effect modifiers (TEMs) in the submission's base case, which did not satisfy the strong assumption of conditionally constant absolute effects requiring

that all TEMs and PFs are accounted for and the absolute treatment effects across variables are constant. As such, the results of the MAIC in treatment experienced patients should be considered uncertain and associated with a high risk of bias in an unknown direction. Moreover, as a result of the adjustments, only 14 patients in STRENGTH (representing 51.8% [14/27] of the cohort) were used to inform the comparison, further eroding the already small sample size. The PSCR stated that the MAIC adjusted for the most clinically relevant available baseline differences between STRENGTH and SAPPHIRE, including baseline HFMSE, baseline RULM, age at SMA onset and age at screening.

6.14 For the treatment naive population, all trials (STEER, SUNFISH and CHERISH) enrolled treatment naïve patients who were non-ambulatory but able to sit independently. However, the submission noted differences in age, SMA Type, ethnicity, baseline motor function (HFMSE and RULM score) and *SMN2* copy number, which may impact the transitivity assumption. Further, the submission noted that responses were larger for the sham arm in STEER than the placebo/sham arm in SUNFISH and CHERISH (discussed further in paragraph 6.30) likely reflecting between-trial heterogeneity in baseline characteristics and poor transitivity. As such, the anchored Bucher indirect comparison may be inappropriate. Population-adjusted ITCs conducted by the submission to adjust for these differences could not fully adjust for these factors (between one and three PFs and TEMs were accounted for, out of the possible 18 across the multiple MAICs conducted; while the ML-NMR adjusted for four [3]). As such, the evaluation considered that the results of the ITCs in the treatment naïve population presented by the submission should be interpreted with a high degree of caution.

6.15 The dosage and utilisation of RIS and NUSI in children 2-12 years from the control arm of SAPPHIRE was not reported and as such, the applicability of the control arm of SAPPHIRE to Australian clinical practice was uncertain.

6.16 The submission described a number of possible minimal clinically important differences (MCIDs) for the change from baseline in HFMSE and RULM score. For the outcome of change from baseline in HFMSE score, a 1.46 to 2.38-point threshold was applied by the submission as the non-inferiority margin for the treatment naïve population. This was based on a study by Coratti (2024) which estimated a clinically meaningful improvement of 1.46 points in Type II SMA and 2.38 points in Type III SMA for HFMSE using an anchor-method based on standard error. However, different results were observed for improvement (as proposed in the submission) compared to deterioration and when using a different methodology. Further, Coratti 2024 concluded that these results emphasize that the interpretation of a single MCID value obtained in large cohorts with different functional status needs to be made with

[3] MAIC: Adjustments performed by the submission varied with each outcome (change from baseline in HFMSE score and change from baseline in RULM score)and each treatment (RIS or NUSI), but were limited to age at screening and baseline HFMSE score for comparison against RIS; and limited to age at screening, highest motor milestone ever achieved and baseline HFMSE score for comparison against NUSI.
ML-NMR: Adjusted for age at screening, baseline HFMSE score, *SMN2* copy number, and baseline RULM score

caution. While it was claimed that a threshold of 1.46 to 2.38 was applied for HFMSE, the submission never explicitly stated when the margin of 1.46 (as opposed to 2.38 for HFMSE) should be applied, and there were no outcomes for which non-inferiority could be concluded using the margin of 2.38 but not using 1.46. The PBAC have not previously considered a non-inferiority margin of 1.46 (or 2.38) for the outcome of change from baseline in HFMSE score, and the evaluation considered the reliability and validity of this value as a non-inferiority margin was uncertain.

6.17 The submission considered a 2-point change from baseline in RULM score to be clinically meaningful, noting that this was 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 (paragraph 6.22, NUSI PSD, March 2022 PBAC meeting). The ESC previously considered that the importance of this outcome (and the relevance of changes in this score) in terms of clinically meaningful benefits for adult patients with SMA was unclear (paragraph 6.23, NUSI PSD, November 2020 PBAC meeting). A 2-point change in baseline RULM was applied by the submission as the non-inferiority margin for the treatment naïve population.

6.18 The submission noted that no MCID specific to treatment experienced SMA patients has been established in the published literature, and so the same treatment naïve non-inferiority thresholds were used as proxy benchmarks to contextualise interpretation of motor function outcomes in the ITC.

Comparative effectiveness

STRENGTH and STEER results

6.19 Table 6 summarises the motor function outcomes reported in STRENGTH (at Week 52) and STEER (at end of Follow-up Period 1; up to 52 weeks).

Table 6: Summary of motor function outcomes in STRENGTH and STEER (FAS population)

Timepoint	Statistics	CFB in HFMSE		CFB in RULM	
STRENGTH ONA IT (N=27)					
Baseline	n	26		24	
	Mean (SD)	24.31 (14.04)		24.60 (7.44)	
	Median (range)	23.25 (2.0 - 46.5)		25.00 (7.5 - 36.0)	
Week 52	n	21		21	
	Mean (SD)	22.67 (14.80)		23.95 (7.64)	
	Median (range)	20.00 (1.0 - 46.0)		26.00 (5.0 - 37.0)	
Change from baseline at Week 52 [a]	n	21		21	
	Mean (SD)	0.17 (2.88)		0.29 (2.85)	
	Median (range)	0.00 (-5.5 - 7.5)		0.50 (-6.0 - 6.0)	
	LS mean change (SE [95% CI])	1.05 (0.61 [-0.21, 2.32])		0.59 (0.55, [-0.56, 1.73])	
STEER (N=126)		**ONA IT (N=75)**	**Sham (N=51)**	**ONA IT (N=75)**	**Sham (N=51)**
Baseline	n	75	51	75	51
	Mean (SD)	17.97 (10.11)	18.17 (9.76)	16.52 (6.74)	17.42 (6.35)
	Median (range)	16.50 (1.0 - 41.0)	19.00 (2.0 - 42.5)	16.67 (4.0 - 31.7)	17.67 (4.3 - 31.0)
End of Follow-up period 1	n	74	50	74	50
	Mean (SD)	20.49 (11.36)	19.05 (10.13)	19.09 (6.71)	18.53 (6.12)
	Median (range)	18.00 (2.0 - 50.5)	20.75 (2.5 - 41.5)	18.75 (3.5 - 35.0)	19.00 (4.5 - 31.5)
Change from baseline at end of Follow-up Period 1	n	74	50	74	50
	Mean (SD)	2.38 (3.83)	0.56 (3.87)	2.41 (3.44)	0.91 (3.25)
	Median (range)	2.00 (-5.5 - 15)	1.00 (-8.5 - 10.5)	2.00 (-4.7 - 12.3)	0.83 (-7.0 - 8.2)
	LS mean change (SE [95% CI])	2.39 (0.44 [1.52, 3.26])	0.51 (0.53 [-0.55,1.56])	2.44 (0.38 [1.69, 3.19])	0.92 (0.46 [0.00, 1.83])
	Treatment difference (SE [95% CI]) [b]	**1.88 (0.69) [0.51, 3.25]); p=0.0074** [c]		1.52 (0.60 [0.34, 2.71]); p=0.0122 [c]	

Source: Table 2.18 & 2.20, p87 & 89 of the submission; Table 11-1 & 11-3, pp 60, 61 & 62 of the STRENGTH CSR; Tables 11-1, 11-3 & 11-5, pp 68, 69, 72, 74 & 75 of the STEER CSR

CFB, change from baseline; CI, confidence interval; CSR = clinical study report; FAS, full set analysis; HFMSE, Hammersmith Functional Motor Scale Expanded; IT, intrathecal; LS, least square; ONA, onasemnogene abeparvovec; RULM, Revised Upper Limb Module; SD, standard deviation; SE, standard error

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

In STRENGTH, a total score is not derived if any item score is missing or "cannot test" at baseline or post-baseline visit.

In STRENGTH, for RULM, assessment was performed for patients starting at 30 months of age.

In STEER, baseline is defined as the average of all non-missing assessments prior to the first administration of study treatment during Treatment Period 1, assuming all assessments have complete and valid total scores available. If two of the assessments have a complete and valid total score available, then the baseline HFMSE or RULM total score is defined as average of the two available assessment scores. If just one of the assessments has a complete and valid total score available, then the baseline HFMSE or RULM total score is defined as the single total score available.

In STEER, the end of Follow-up Period 1 assessment is defined as the average of the week 48 and week 52 assessments, assuming both assessments have total scores available. If just one (and not both) of the assessments collected at these two visits has a total score available, then the end of Follow-up Period 1 assessment is defined as the single assessment total score collected at week 48 or week 52.

Maximum total score is 66 for HFMSE and 37 for RULM.

a Analysis using a mixed model with repeated measurement. The model included fixed factors of baseline age stratum, visit and baseline HFMSE/RULM total score as covariate. A mixed model of repeated measures was applied using unstructured covariance matrix.

b The efficacy endpoint variable is analysed using a linear mixed effects repeated measures model with the observed change from Baseline in HFMSE or RULM total score at all post-baseline visits as the dependent variable. The fixed effects include treatment, visit, treatment by visit interaction, strata and baseline HFMSE or RULM total score as covariate. An unstructured covariance matrix is used.

c Two-sided p-values.

Bold values represent statistically significant results.

6.20 In STRENGTH, the least square (LS) mean change from baseline in HFMSE score was 1.05 points (95% CI, -0.21 to 2.32); the LS mean change from baseline in RULM score was 0.59 points (95% CI, -0.56 to 1.73). The submission claimed that ONA IT demonstrated stabilisation, with no evidence of deterioration of motor function over

the 52-week study period, and considered these findings to be clinically meaningful in the context of progressive neuromuscular disease. However, the observed range (-5.5 to 7.5 for HFMSE and -6.0 to 6.0 for RULM) indicated that some patient(s) experienced deterioration, and the lower 95% CI for the LS mean change for both HFMSE and RULM were less than 0 (i.e. included worsening). As such, the evaluation considered it was unclear that the results from STRENGTH supported the claim that ONA IT in treatment experienced patients demonstrated stabilisation of motor function.

6.21 In Treatment Period 1 of STEER, treatment with ONA IT demonstrated a statistically significant improvement in motor function (measured by change from baseline in HFMSE total score) compared to sham procedure, with a treatment difference of 1.88 points (95% CI: 0.51 to 3.25; p=0.0074). Improvement in upper limb function, assessed using the RULM, was also numerically greater in patients treated with ONA IT, with a treatment difference of 1.52 points, which the submission claimed was statistically significant (95% CI: 0.34 to 2.71; p=0.0122). However, p-values for secondary outcomes did not pass the respective thresholds for statistical significance after adjusting for multiple testing, and as such, a statistically significant difference between ONA IT and sham for RULM could not be concluded. Notably, the point estimate of 1.52 points was lower than the MCID of 2 points as proposed by the submission.

Indirect treatment comparison – treatment experienced

6.22 The baseline characteristics of the control arm in SAPPHIRE and STRENGTH before and after adjustment for the MAIC is presented in Table 7. There were inconsistencies in the baseline characteristics of STRENGTH as reported in the submission compared to the STRENGTH clinical study report (CSR). These are listed as footnotes in Table 7. The PSCR argued that "these minor discrepancies are not expected to materially affect the general ITC direction" and the overall evidence interpretation is unchanged. The submission stated that the use of RIS or NUSI at treatment initiation and duration was also adjusted for in the MAIC given that usage was included as an adjustment factor in the mixed model repeated measures (MMRM) model in the SAPPHIRE trial, despite not being identified as a potential PF or TEM.

Table 7: Baseline characteristics of treatment experienced patients (and MAIC adjustments)

Baseline characteristics	SAPPHIRE [a]	STRENGTH	
	Control N=50	ONA IT N=27 [b]	Adjusted (MAIC) N=14 [c]
Age at screening, mean (range), years	8 (2)	7.3 (3.35) [d]	8.0 (2.92)
Age at spinal muscular atrophy onset, mean (SD), years	1 (0.50)	0.8 (0.38)	1.0 (0.30)
SMN-targeted therapy at randomisation, %			
RIS	20	22.2 [e]	20.0
NUSI	80	77.8	80.0
Years on RIS prior to study drug exposure, mean (SD)	3 (2)	0.7 (1.54) [f]	0.6 (1.28)
Years on NUSI prior to study drug exposure, mean (SD)	6 (2)	3.4 (2.07) [g]	3.4 (1.95)
Scoliosis at treatment initiation, %			
No	30	77.8 [h]	68.5
Yes	70	22.2 [h]	31.5
Baseline HFMSE score, mean (SD)	27.8 (10.6)	24.31 (14.04)	27.8 (12.34)
Baseline RULM score, mean (SD)	27.3 (5.8)	24.60 (7.44)	27.3 (5.07)

Source: Table 2.31, p99 of the submission.

CFB, change from baseline; ESS, effective sample size; HFMSE, Hammersmith Functional Motor Scale Expanded; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; NUSI, nusinersen; ONA, onasemnogene abeparvovec; SD, standard deviation; SMN2, survival motor neuron 2; RIS, risdiplam; RULM, Revised Upper Limb Module

a Baseline characteristics are reported for patients for the placebo + nusinersen/risdiplam population aged 2-12 years.

b The unmatched and unadjusted analysis set N was 27 for the exploratory safety analysis, but was 26 and 24 for CFB in HFMSE and CFB in RULM analyses respectively due to missing baseline values respectively. However, after matching on eligibility criteria, the analyses sets had the same patients included.

c MAIC scenario (for both CFB in HFMSE and RULM score) adjusted for baseline HFMSE score, age at SMA onset, baseline RULM score, age at screening, SMN-targeted therapy at randomisation, per ESS stopping rule (ESS of at least 40% of the original sample size) (Table 7.5, p27 of the ONA IT DMT-experienced ITC report).

d Reported as 7.3 years by the submission but was 7.4 years in the CSR (Table 10-3, p52 of the STRENGTH CSR).

e Reported as 22.2% by the submission but was 14.8% in the CSR though 7.4% of patients had previously received both NUSI and RIS (Table 10-6, p56 of the STRENGTH CSR).

f Reported as 0.7 (1.54) by the submission but was 2.976 (2.024) in the CSR (Table 10-6, p57 of the STRENGTH CSR).

g Reported as 3.4 (2.07) by the submission but as 4.321 (1.070) in the CSR (Table 10-6, p57 of the STRENGTH CSR).

h Reported as 77.8% of patients not having scoliosis but the inverse was reported in the CSR (77.8% of patients had scoliosis at baseline; p70 of the STRENGTH CSR).

6.23 Results of the base case unanchored MAIC of ONA IT versus RIS or NUSI (informed by the control arm of SAPPHIRE) in treatment experienced patients are presented in Table 8. Results of the unadjusted ITC were extracted during the evaluation for comparison.

Table 8: Unadjusted ITC and base case unanchored MAIC of ONA IT vs RIS or NUSI in treatment experienced patients

	STRENGTH (ONA IT)	SAPPHIRE (RIS or NUSI)	ONA IT vs RIS/NUSI MD (95% CI)	p-value
Unadjusted ITC [a]				
CFB in HFMSE, mean (SE)	1.05 (0.57) [c]	-1.20 (0.66)	**2.25 (0.54, 3.96)**	0.010
CFB in RULM, mean (SE)	0.59 (0.49) [d]	0.10 (0.40)	0.49 (-0.74, 1.72)	0.436
Base case MAIC [b]				
CFB in HFMSE, mean (SE)	0.96 (0.923)	-1.20 (0.66)	2.16 (-0.06, 4.38)	0.057
CFB in RULM, mean (SE)	-0.16 (0.582)	0.10 (0.40)	-0.26 (-1.64, 1.12)	0.713

Source: Table 2.35, p104 of the submission; Table 7.1, Figures 7.1 & 7.2, pp24, 28-29 of the ONA IT DMT-experienced ITC report.
CFB, change from baseline; CI, confidence interval; HFMSE, Hammersmith Functional Motor Scale Expanded; IPD, individua patient data; IT, intrathecal; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; MD, mean difference; NUSI, nusinersen; ONA onasemnogene abeparvovec; PF; prognostic factor; RIS, risdiplam; RULM, Revised Upper Limb Module; SE, standard error; TEM, treatment effect modifier.
Note: MD > 0 implies that the indirect comparison favours ONA IT.
a Unadjusted ITC, equivalent to an unmatched and unadjusted ITC, without the application of MAIC weights.
b PFs and TEMs included for adjustment in the base case MAIC were baseline HFMSE score, age at spinal muscular atrophy onset, baseline RULM score, age at screening. SMN-targeted therapy at randomisation age at screening was adjusted for but was not a PF or TEM. The MAIC was based on the IPD of 14 patients in STRENGTH, (representing 51.8% [14/27] of the cohort).
c Reported as 0.57 by the submission but was 0.61 in the CSR (Table 11-2, p61 of the STRENGTH CSR).
d Reported as 0.49 by the submission but was 0.55 in the CSR (Table 11-4, p63 of the STRENGTH CSR).
Bold values represent statistically significant indirect treatment comparisons as indicated by 95% confidence intervals.

6.24 Results of the ITC supported the submission's claim of non-inferiority of ONA IT to RIS or NUSI in treatment experienced patients. For the outcome of HFMSE, the lower bound of the 95% CI (-0.06) did not exceed the threshold of 1.46 to 2.38 points. For RULM, the lower bound of the 95% CI (-1.64) was within the MCID of a 2-points.

6.25 However, as only four out of a possible 18 PF and TEMs were adjusted for (see paragraph 6.13), the key assumption for MAICs requiring that all PFs and TEMs are accounted for was not met and as such, the results of the MAIC in treatment experience patients should be interpreted with caution as it may be associated with a high risk of bias in an unknown direction.

Indirect treatment comparison – treatment naive

6.26 In treatment naïve patients, an anchored ITC (Bucher methodology) was conducted to compare ONA IT with RIS and NUSI. Results for the Bucher comparisons of ONA IT versus RIS conducted using summary level data only (i.e. not individual patient level data) are presented in Table 9.

Table 9: Base case Bucher indirect treatment comparison of ONA IT versus RIS in treatment naïve patients

Trial	ONA IT Mean CFB (95%CI)	Sham/placebo Mean CFB (95%CI)	RIS Mean CFB (95%CI)	MD
Change from baseline in HFMSE				
STEER [a]	2.39 (1.52, 3.26)	0.51 (-0.55, 1.56)	-	**1.88 (0.51, 3.25)**
SUNFISH [b]	-	0.37 (-0.54, 1.28)	0.95 (0.29, 1.61)	0.58 (-0.53, 1.69)
Indirect treatment comparison (ONA IT vs RIS)				1.30 (-0.45, 3.05)
Change from baseline in RULM				
STEER [a]	2.44 (1.69, 3.19)	0.92 (0.00, 1.83)	-	1.52 (0.34, 2.71)
SUNFISH [c]	-	0.02 (-0.83, 0.87)	1.61 (1.00, 2.22)	**1.59 (0.55, 2.62)**
Indirect treatment comparison (ONA IT vs RIS)				-0.07 (-1.64, 1.50)

Source: Table 2.36, p106 of the submission.
CFB, change from baseline; CI, confidence interval; HFMSE, Hammersmith Functional Motor Scale Expanded; IT, intrathecal; MD, mean difference; ONA, onasemnogene abeparvovec; RULM, Revised Upper Limb Module
Note: MD > 0 implies that the indirect comparison favours ONA IT.
a ONA IT n=74; sham n=50
b RIS n=119 and placebo n=58 (based on the relevant publication, Mercuri 2022)
c RIS n=120; placebo n=60 (based on the relevant publication, Mercuri 2022)
Bold values indicate statistical significance achieved (with respect to the trials' hierarchical testing

6.27 The estimated mean difference (MD) between ONA IT versus RIS was 1.30 (95% CI: -0.45, 3.05) and -0.07 (95%CI: -1.64, 1.50) for the change from baseline in HFMSE and RULM, respectively. The submission noted that the 95% CI included zero, indicating no statically significant difference between treatments. Results of the ITC met the submission's nominated non-inferiority threshold and supported the submission's claim of non-inferiority. For HFMSE, the lower bound of the 95% CI (–0.46) did not cross the thresholds derived in treatment-naïve Type II and III SMA populations (1.46 to 2.38 points) and for RULM, the lower bound (-1.64) did not exceed the threshold (of -2 points). However, it was unclear whether it was reasonable to conduct an indirect comparison in which results which were not statistically significantly different between ONA IT and sham (RULM) or RIS and placebo (HFMSE) were assumed to be different between arms.

6.28 For ONA IT versus NUSI in treatment naïve patients, the base case Bucher ITC presented by the submission used 12-month CHERISH data (as opposed to 15-month data, the primary analysis for CHERISH) and STEER individual patient data (IPD) that were re-analysed using an ANCOVA approach using the same baseline and Week 52 outcome definitions consistent with the CHERISH methodology. Results for the Bucher ITCs of ONA IT versus NUSI are presented in Table 10.

Table 10: Base case Bucher indirect treatment comparison of ONA IT versus NUSI in treatment naïve patients

Trial	ONA IT Mean CFB (SE)	Sham/placebo Mean CFB (SE)	NUSI Mean CFB Δ (SE)	MD
Change from baseline in HFSME				
STEER [a b]	3.02 (0.51)	0.41 (0.60)	-	**2.61 (1.06, 4.16)**
CHERISH [c]	-	0.24 (0.66)	3.35 (0.47)	**3.11 (1.51, 4.71)**
Indirect treatment comparison (ONA IT vs NUSI)				-0.50 (-2.72, 1.72)
Change from baseline in RULM				
STEER [a]	2.13 (0.41)	0.61 (0.49)	-	**1.51 (0.27, 2.76)**
CHERISH [c]	-	0.66 (0.45)	3.59 (0.32)	**2.94 (1.86, 4.01)**
Indirect treatment comparison (ONA IT vs NUSI)				-1.43 (-3.07, 0.22)

Source: Table 2.38, p109 of the submission.

CFB, change from baseline; CI, confidence interval; HFMSE, Hammersmith Functional Motor Scale Expanded; ITC, indirect treatment comparison; IT, intrathecal; MD, mean difference; NUSI, nusinersen; ONA, onasemnogene abeparvovec; RULM, Revised Upper Limb Module; SE, standard error

Note: MD > 0 implies that the indirect comparison favours ONA IT.

a Eight patients with missing HFMSE and RULM data at Week 52 were excluded from the FAS for the purposes of the ONA IT versus NUSI comparisons. N=118 in STEER; ONA IT n= 69; sham n= 49 (Table 7.17. p40 of the ONA IT DMT-naïve ITC report).

b The treatment effects for STEER were estimated using the ANCOVA as well as the baseline and week 52 outcome definitions specified in CHERISH (Table 7.16, p39 of the ONA IT DMT-naïve ITC report).

c NUSI n= 84; n=42 (Table E.19, p73 of the ONA IT DMT-naïve ITC report)

Bolded values indicate mean difference which does not include the null. Due to the reanalysis, statistical significance could not be claimed for STEER.

6.29 The submission noted the 95% CIs included zero for both the change from baseline in HFMSE and change from baseline in RULM, indicating no statistically significant difference between ONA IT and NUSI. However, the submission's claim of non-inferiority between ONA IT and NUSI was not supported by the results of the ITC, which exceeded the submission's nominated non-inferiority margin for change from baseline in HFMSE (1.46 to 2.38 points) and for change from baseline in RULM (-2 points). For both outcomes, point estimates of the ITC were in favour of NUSI.

6.30 The submission argued that responses were larger for the sham arm in STEER than the placebo arm in SUNFISH and the sham arm in CHERISH, which may bias against ONA IT. This was untrue for RULM for STEER compared to CHERISH, and may not be justified given the treatment effects being compared were based on differences between treatments within each trial (i.e. the higher response rate for sham in STEER was equally likely to have increased the response rate for ONA IT, assuming randomisation was appropriately achieved). Rather, these differences likely reflect between-trial heterogeneity in baseline characteristics, and potential transitivity issues.

6.31 Sensitivity analyses with population-adjusted ITCs (anchored MAICs and ML-NMR analyses) were conducted for the treatment naïve population, to assess the robustness of the base case Bucher results and to adjust for differences in trial design and patient characteristics. The results of the sensitivity analyses conducted for ONA IT versus RIS are summarised in Table 11. While results of the multiple ITCs conducted consistently met the submission's nominated non-inferiority margin for the outcome of change from baseline in HFMSE, the non-inferiority margin was exceeded for the outcome of change from baseline in RULM (2-point threshold) when conducted using the anchored MAIC and ML-NMR approaches. The confidence intervals with the anchored MAIC and ML-NMR were wider than the base case Bucher indirect comparison, likely reflecting the loss in sample size from STEER due to the matching.

Further, there were discrepancies between results reported between different sections of the submission (see footnotes of Table 11).

Table 11: Summary of indirect treatment comparisons for ONA IT versus RIS in treatment naïve patients

Analysis	Description	ITC MD (95%CI)	p-value
Change from baseline in HFMSE score			
Base case Bucher	Computed using summary level data	1.30 (-0.45, 3.05)	–
Anchored MAIC	Adjusted for age at screening and baseline HFMSE score	1.93 (-0.25, 4.10) [a]	0.0825
ML-NMR	Adjusted for age at screening, baseline HFMSE score, SMN2 copy number, and baseline RULM score	2.12 (-0.84, 5.09) [b]	–
Change from baseline in RULM score			
Base case Bucher	Computed using summary level data	-0.07 (-1.64, 1.50)	–
Bucher using MMRM methodology	Computed after calculating ONA IT versus sham treatment effects using SUNFISH methodology	-0.14 (-1.73, 1.44)	–
Anchored MAIC	Adjusted for age at screening	-1.46 (-3.38, 0.46)	0.1367
ML-NMR	Age at screening, SMN2 copy number, baseline RULM score, and baseline HFMSE score	0.04 (-2.47, 2.52) [c]	–

Source: Table 2.37, p107 of the submission.
CI, confidence interval; HFMSE, Hammersmith Functional Motor Scale Expanded; ITC, indirect treatment comparison; IT, intrathecal; MAIC, matching-adjusted indirect comparison; MD, mean difference; ML-NMR, multilevel network meta-regression; MMRM, mixed model repeated measures; ONA, onasemnogene abeparvovec; RIS, risdiplam; RULM, Revised Upper Limb Module
Note: MD > 0 implies that the indirect comparison favours ONA IT.
a Reported as 1.93 (-0.24, 4.1) in Figure 2.17, p108 of the submission.
b Reported as 2.12 (-0.95, 5.19) in Figure 2.17, p108 of the submission.
c Reported as -0.04 (-2.58, 2.5) in Figure 2.18, p108 of the submission.

6.32 The results of the sensitivity analyses conducted for ONA IT versus NUSI are summarised in Table 12. Across the multiple ITCs, the lower bound of the 95% CI exceeded the nominated non-inferiority thresholds for the change from baseline in HFMSE and RULM score and point estimates favoured NUSI. As for the comparison with RIS, the confidence intervals with the anchored MAIC and ML-NMR were wider than the base case Bucher indirect comparison, likely reflecting the loss in sample size from STEER due to the matching. The PSCR stated that the population-adjusted analyses were presented as supportive sensitivity analyses to test robustness; wider confidence intervals in these analyses are expected given the loss of effective sample size after matching.

Table 12: Summary of indirect treatment comparisons for ONA IT versus NUSI in treatment naïve patients

Analysis	Description	ITC MD (95%CI)	p-value
Change from baseline in HFMSE score			
Base case Bucher	Computed after calculating ONA IT versus sham treatment effects using CHERISH methodology (including ANCOVA)	-0.50 (-2.72, 1.72)	–
Anchored MAIC	Adjusted for age at screening, highest motor milestone ever achieved prior to treatment initiation, and baseline HFMSE score	-0.13 (-2.93, 2.66)	0.9252
ML-NMR	Adjusted for age at screening, baseline HFMSE score, SMN2 copy number, and baseline RULM score	-0.36 (-3.11, 2.36)	–
Change from baseline in RULM score			
Base case Bucher	Computed after calculating ONA IT versus sham treatment effects using CHERISH methodology (including ANCOVA)	-1.43 (-3.07, 0.22)	–
Anchored MAIC	Adjusted for age at screening and highest motor milestone ever achieved prior to treatment initiation	-1.15 (-3.32, 1.01)	0.2975
ML-NMR	Age at screening, SMN2 copy number, baseline RULM score, and baseline HFMSE score	-1.51 (-3.58, 0.52)	–

Source: Table 2.39, p107 of the submission.
Note: MD > 0 implies that the indirect comparison favours ONA IT.

Comparative harms

6.33 In the STRENGTH study, all patients experienced at least one adverse event (AE) during the 52-week follow-up period. The most frequently reported AEs (>20% of patients) were nasopharyngitis (55.6% [15/27]), pyrexia (51.9% [14/27]), vomiting (48.1% [13/27]), headache (29.6% [8/27]), and abdominal pain upper (22.2% [6/27]). 13 patients (48.1%) experienced AEs considered related to study treatment, most commonly vomiting (22.2% [6/27]), headache (14.8% [4/27]), and pyrexia (11.1% [3/27]). Overall, the STRENGTH CSR concluded that the safety profile in terms of type and severity of AEs was consistent with previous observations from ONA clinical studies.

6.34 For STEER, the submission claimed that the safety profile of ONA IT was comparable to sham, with similar incidences of AEs (97.3% [73/75] versus 90.2% [46/51] for ONA IT and sham, respectively) and serious AE (SAE) (28.0% [21/75] versus 33.3% [17/51] for ONA IT and sham, respectively). However, a higher proportion of patients treated with ONA IT compared to sham experienced AEs related to study treatment (34.7% [26/75] versus 11.8% [6/51]) and SAEs related to study treatment (10.7% [8/75] versus 2.0% [1/51]), respectively. The most frequent AEs reported in the ONA IT versus sham arms were upper respiratory tract infection (34.7% [26/75] versus 29.4% [15/51]), pyrexia (25.3% [19/71] versus 23.5% [12/51]), and vomiting (20.0% [15/75] versus 11.8% [6/51]), respectively. The most frequent AEs (>5%) that were considered related to study treatment by the investigators were headache (8.0% [6/75] versus 0%), vomiting (6.7% [5/75] versus 0%), and nausea (5.3% [4/75] versus 0%), for ONA IT and sham, respectively. The STEER CSR concluded that overall, the safety profile of ONA IT was consistent with the known safety profile of ONA IV in SMA patients, in terms of type of AEs and SAEs

6.35 The submission claimed that the lower frequency of hepatotoxicity observed with ONA IT compared to ONA IV was consistent with the lower systemic exposure associated with IT administration via a fixed dosing regimen compared with weight-based IV dosing, but did not provide data to support this claim. Table 13 summarises hepatotoxicity events reported for STRENGTH and STEER (ONA IT), which are compared side by side against the SMART, STR1VE-US and STR1VE-EU studies for ONA IV, extracted during the evaluation. Compared to ONA IV, a lower proportion of patients treated with ONA IT in STRENGTH and STEER experienced hepatotoxicity. It was noted the current product information (PI) for ONA IV includes a boxed warning for hepatoxicity, while this was not included in the draft PI for ONA IT. The ESC noted that, based on these comparisons, hepatotoxicity events do appear to be reduced for ONA IT compared to ONA IV.

Table 13: Hepatotoxicity by preferred term across ONA studies (Safety Set; FAS for STRENGTH)

	STRENGTH (N=27)	STEER		SMART (N=24)	STR1VE-US (N=22)	STR1VE-EU (N=33)
		ONA IT (N=75)	Sham (N=51)			
Hepatotoxicity – any event [a]	4 (14.8)	7 (9.3)	5 (9.8)	20 (83.3)	7 (31.8)	18 (54.6)
AE severity						
Mild	3 (11.1)	6 (8.0)	4 (7.8)	11 (45.8)	NR	NR

Moderate	1 (3.7)	1 (1.3)	1 (2.0)	5 (20.8)	NR	NR
Severe	0	0	0	4 (16.7)	NR	NR
Treatment-related AEs	2 (7.4)	5 (6.7)	1 (2.0)	20 (83.3)	NR	NR
SAEs	0	1 (1.3)	0	5 (20.8)	NR	NR

Source: Constructed during the evaluation based on Table 12-5, p77 of the STRENGTH CSR; Table 14.3.1-13, pp2358-2364 of the STEER CSR; Table 12-5, p75 of the SMART CSR; Table 31, p92-93 of the STR1VE-US CSR; Table 12-6, p104 of the STR1VE-EU CSR
AE, adverse event; SAE, serious adverse event; IT, intrathecal; ONA, onasemnogene abeparvovec
a Refers to number of patients experiencing at least one event (patients may experience multiple hepatotoxicity events)
Note: SMART enrolled symptomatic patients (SMA Type I-III) patients weighing ≥8.5 kg and ≤21 kg, with any copy of *SMN2*. The STR1VE-US and STR1VE-EU studies enrolled symptomatic patients (SMA Type I) with 1-2 copies of *SMN2*, aged <6mths.

6.36 The submission presented safety outcomes separately for each of the included studies but did not provide any discussion regarding comparative harms. A side-by-side comparison was conducted during the evaluation, though no comparative statistics were calculated. Across the included studies, AEs were reported for the majority of patients (range: 87-100%), however a higher proportion of patients treated with ONA IT (48.1% [13/27] in STRENGTH and 34.7% [26/75] in STEER) were observed to have experienced any AE related to treatment compared to other treatments (11.8% [6/51] for the sham arm of STEER; and ranged between 10-18% in the remaining trials for RIS and NUSI). Additionally, a higher proportion of patients treated with ONA IT (14.8% [4/27] in STRENGTH and 28.0% [21/75] in STEER) experienced SAE(s) compared to those treated with RIS (20% [24/120]) or NUSI (17% [14/84]). Across the included studies, no deaths were reported, and no AE leading to study withdrawal were reported, except for STEER, where one patient in each of the ONA IT (1.3% [1/75]) and sham (2.0% [1/51]) arms withdrew.

6.37 The PSCR provided ITCs of safety outcomes between ONA IT versus RIS and NUSI (Tables 3-5) as requested in the evaluation.

6.38 While no comparison between the safety of ONA IT and ONA IV was provided in the submission (therefore no transitive comparison could be made), the evaluation considered the safety of ONA IV relative to RIS or NUSI may be informative. Regarding the comparative safety of ONA IV versus RIS or NUSI:

- The PBAC previously did not accept the claim of superior safety for ONA IV versus NUSI (paragraph 6.50, ONA 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, ONA PSD, November 2020 PBAC meeting);
- The PBAC previously found that it was difficult to make an informed conclusion with respect to the safety profile of ONA IV compared to RIS (paragraph 6.28, ONA 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 IV compared to NUSI (as above), preventing a transitivity argument for non-inferior safety between ONA and RIS (paragraph 6.28, ONA PSD, July 2023 PBAC meeting); and

- In addition to the above, the PBAC most recently considered that the claim of non-inferior comparative safety of ONA IV to RIS/NUSI was uncertain (paragraph 7.8, onasemnogene abeparvovec PSD, November 2025).

Benefits/harms

6.39 A benefits and harms table was not presented as the submission made a claim of non-inferiority for efficacy and a different but manageable safety profile.

Clinical claim

6.40 The submission described ONA IT as non-inferior in terms of effectiveness compared with RIS and NUSI in treatment experienced SMA patients. The evaluation considered this conclusion may not be adequately supported by the evidence presented. The results of the ITC met the submission's nominated non-inferiority margin and supported the submission's claim of non-inferiority for the outcomes of change from baseline in HFMSE score and change from baseline in RULM score. However, the clinical evidence presented was associated with a high level of uncertainty because while the base case MAIC of ONA IT versus RIS or NUSI appeared to balance some relevant characteristics, only four out of the possible 18 treatment effect modifying factors identified were adjusted for, suggesting that the strong assumption of all PF and TEMs were accounted for was not satisfied for the unanchored MAIC, resulting in the results of the MAIC possibly being biased in an unclear direction.

6.41 The submission described ONA IT as non-inferior in terms of effectiveness compared with RIS and NUSI in treatment naïve SMA patients. The evaluation considered that the therapeutic conclusion presented in the submission may not be adequately supported by the evidence presented in the submission because:

- The base case Bucher ITCs had differences in key characteristics (see paragraph 6.13) and differences in sham/placebo response across the included trials (see paragraph 6.30) which suggested a lack of transitivity;
- Non-inferiority of ONA IT vs RIS was not supported using population-adjusted methods (anchored MAIC and the ML-NMR, for the outcome of change from baseline in RULM score); and
- Results of the Bucher comparison and population-adjusted ITCs of ONA IT versus NUSI for both HFMSE and RULM exceeded the nominated non-inferiority thresholds for both outcomes and non-inferiority could not be claimed, with point estimates consistently in favour of NUSI.

6.42 Overall, the results of the ITCs presented by the submission were considered uncertain and the evaluation considered they should be interpreted with a high degree of caution due to transitivity issues, incomplete matching of all identified PFs and TEMs and uncertainty associated with the reporting of results by the submission. However, the evaluation noted that in a previous submission for ONA IV in SMA Type I patients where the PBAC noted it was difficult to determine ONA IV and NUSI are non-inferior in terms of effectiveness (paragraph 6.51 & 7.5, ONA PSD, November 2020 PBAC meeting), the PBAC ultimately concluded that "on balance ONA would likely deliver

similar clinical outcomes to NUSI in matched patients" (paragraph 7.1, ONA PSD, November 2020 PBAC meeting).

6.43 The submission described ONA IT as 'different, with a manageable safety profile' in terms of safety compared to RIS or NUSI. The evaluation considered this may be reasonable, though it was noted that compared to RIS or NUSI treatment arms, a higher proportion of patients treated with ONA IT in STRENGTH and STEER reported AEs related to treatment and SAEs.

6.44 The PSCR stated that the submission presented the best comparative evidence available, using clinically relevant motor-function outcomes (HFMSE and RULM) and population-adjusted and comparative methods where feasible. The ESC noted that the evidence for ONA IT was limited as it was based on indirect treatment comparisons from small trials, including one single-arm trial. However, the ESC considered that the level of evidence presented for ONA IT was similar to ONA IV and to other SMA treatments and was reasonable for a rare condition. On balance, the ESC considered that the evidence likely supported the claim of non-inferior efficacy and safety compared with NUSI and RIS and that it would also be likely to provide similar outcomes to ONA IV.

6.45 The PBAC considered that the claim of non-inferior comparative effectiveness was uncertain, but concluded that, as for ONA IV in the younger population, ONA IT would likely deliver similar clinical outcomes to NUSI or RIS in matched patients. The PBAC also considered that ONA IT is likely to deliver similar clinical outcomes to ONA IV in matched patients.

6.46 The PBAC considered that the claim of non-inferior comparative safety of ONA IT to RIS/NUSI is uncertain but accepted the claim based on the limited supportive data available.

Economic analysis

6.47 The submission presented a cost-minimisation approach comparing ONA IT (the proposed treatment) with RIS and NUSI (as currently listed on the PBS) for the treatment of symptomatic patients with Type I, II and IIIa SMA aged 2 to <19 years of age. The cost-minimisation approach was based on the submission's clinical claim that treatment with ONA IT is non-inferior in terms of comparative effectiveness, with a different but manageable safety profile, to RIS and NUSI for the treatment of symptomatic patients with Type I, II and IIIa SMA aged 2 to <19 years of age.

6.48 The submission compared a once-per-lifetime treatment, ONA IT, against RIS and NUSI over a time horizon of 11 years, with costs discounted at 3.5% annually. The submission noted that the time horizon of 11 years was aligned with the approach used for a previous submission of ONA IV (cost-minimised against RIS), recommended by the PBAC (paragraph 9.2, ONA PSD, November 2020 PBAC meeting with May 2021 Addendum and September 2021 Addendum) – where costs were discounted at 5% annually. The ESC considered the submission's discounting of 3.5% was not appropriate and was not aligned with the PBAC guidelines which state that costs that

occur or extend beyond one year should be discounted at a "uniform, annual (compounding) rate of 5% per year". Table 14 provides a summary of the cost-minimisation approach.

Table 14: Key components and assumptions of the cost-minimisation approach

Component	Claim or assumption
Therapeutic claim: effectiveness	ONA IT is clinically non-inferior to RIS and NUSI in symptomatic patients with Types I, II and IIIa SMA aged 2 to <19 years of age. This may not be adequately supported by the evidence presented in Section 2.
Therapeutic claim: safety	ONA IT has a different but manageable safety profile to RIS and NUSI in symptomatic patients with Types I, II and IIIa SMA aged 2 to <19 years of age.
Evidence base	Comparisons of motor milestones achieved and safety profile in symptomatic patients with Types I, II and IIIa SMA aged 2 to <19 years of age.
Equi-effective doses	ONA IT dosed once per lifetime is equivalent to RIS administered at a dose of 5 mg daily and NUSI administered at a dose of 12 mg (maintenance dosing), over 11 years.
Direct medicine costs	The direct medicine cost of ONA IT is equivalent to RIS and NUSI for symptomatic patients with Types I, II and IIIa SMA aged 2 to <19 years of age over a time horizon of 11 years with costs discounted at 3.5%.
Other costs or cost offsets	Only the cost of administering ONA IT was included, with the cost of administering NUSI IT excluded which was biased against ONA IT. MBS item 14245 (IV infusion) was used, though MBS item 18216 (IT infusion) may be more appropriate for ONA IT given the different route of administration. Assumed no other differences in the proposed MBS costs or healthcare utilisation for ONA IT compared to RIS and NUSI. No adverse event costs included. The cost of subsequent therapy was not considered.

Source: Table 3.2, pp121-122 of the submission.
DMT, disease modifying treatment; IT, intrathecal administration; IV, intravenous; MBS, Medicare Benefits Schedule; NUSI, nusinersen; ONA, onasemnogene abeparvovec; PBAC, Pharmaceutical Benefits Advisory Committee; PSD, public summary document; RIS, risdiplam; SMA, spinal muscular atrophy

6.49 For the cost-minimisation approach of ONA IT against RIS, the equi-effective doses were: ONA IT administered once per lifetime = RIS administered at a dose of 5 mg daily over 11 years. The use of the maximum dosage for RIS may have resulted in the cost of RIS being overestimated. According to the dosing regimen of RIS (see Table 15), the maximum dose of 5 mg per day is recommended for patients who are 2 years of age and older weighing 20 kg or more. Based on the WHO weight-for-age data[4], a weight of 20 kg approximately corresponds to the weight of an average six-year-old child (i.e. a patient would be expected to reach the maximum dosing of RIS by the age of six). Based on the submission's PBS100[5] data of symptomatic Type I-IIIa SMA patients aged between 2 and 18 years and treated with RIS or NUSI, 23/133 (17%) of patients were aged between two and six years as of June 2025.

Table 15: Dosing regimen of RIS by age and body weight

Age [a] and body weight	Recommended Daily Dose
< 2 months of age	0.15 mg/kg
2 months to less than 2 years of age	0.20 mg/kg
2 years of age and older weighing less than 20 kg	0.25 mg/kg
2 years of age and older weighing 20 kg or more	5 mg

Source: Table 1, p2 of the RIS product information.
Kg, kilograms; mg. milligrams

[4] 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
[5] PBS 100% sample

a Based on corrected age for preterm infants.

6.50 For the cost-minimisation approach of ONA IT versus NUSI, the equi-effective doses were: ONA IT administered once per lifetime = NUSI administered at a dose of 12 mg at maintenance dosing over 11 years. It was reasonable to use maintenance dosing for NUSI consistent with the PBAC guidelines and was conservative to exclude the administration cost for NUSI. It was unclear why the submission assumed only 2 doses of NUSI in year 1 as maintenance dosing (i.e., three administrations per year) is the relevant NUSI steady state dosing regimen. This correction was performed during the evaluation; the resulting weighted price is presented in Table 16.

6.51 Results of the submission's cost minimisation approach using the relevant published and effective prices (calculated by the submission by applying a [redacted]% reduction to the published AEMP) of RIS and NUSI are presented in Table 16. The submission calculated a weighted price for ONA IT based on the market share of RIS (54%) and NUSI (46%) in the proposed PBS population, using the PBS100 dataset (June 2025). The evaluation noted that based on this PBS100 data for the 2-18 age group, the market share would be 50% [67/133] for RIS and 50% (66/133) for NUSI. However, using a weighted approach may not be reasonable, as under Section 101(3B) of the *National Health Act 1953*, the PBAC cannot recommend listing a therapy that is substantially more costly than an alternative therapy unless it is satisfied that the therapy provides, for some patients, a significant improvement in efficacy and/or reduction in toxicity. The ESC considered that ONA IV should be considered as a relevant alternative therapy in relation to the cost-minimisation approach.

Table 16: Results of the cost-minimisation approach for ONA IT (base case)

Component	ONA IT published AEMP		ONA IT effective AEMP	
	RIS	NUSI	RIS	NUSI
Total number of bottles or vials over 11 years	334.81 [a]	32 [b]	334.81 [a]	32 [b]
Cost per bottle or vial	$10,841.89	$104,500	$[redacted]	$[redacted]
Cost per dose of ONA IT	$3,074,618	$2,816,141	[redacted]	$[redacted]
Total number of doses of ONA IT (11 years)	1	1	1	1
Market share [c]	54%	46%	54%	46%
Weighted price for ONA IT	$2,955,719		$[redacted]	
Weighted price for ONA IT assuming 3 doses of NUSI per year [d]	$3,003,789		$[redacted]	

Source: Table 3.3, p124 of the submission; Sheets 'RISD 5mg dose_Discounting'& 'NUSI_Discounting' of the submission's cost minimisation approach.

AEMP, approved ex-manufacturer price; IT, intrathecal; NUSI, nusinersen; ONA, onasemnogene abeparvovec; RIS, risdiplam.

a Assuming a dose of 5 mg per day, which equates to 30.44 bottles per year.

b Assuming maintenance dosing only (i.e. 2 doses in year 1, and 3 doses per year thereafter), as used by the submission.

c This submission (p124) claimed this was based on PBS100 dataset for treatment of symptomatic paediatric SMA patients unable to walk independently up to 18 years of age, however, using the PBS100 data provided in the financial model, this was based on patients with SMA Type I-IIIa and did not appear to be restricted by age (54% [93/173] for RIS and 46% [80/173] for NUSI). Based on this PBS100 data for the 2-18 age group, the market share would be 50% [67/133] for RIS and 50% (66/133) for NUSI.

d Assuming steady state dosing only for NUSI (i.e. 3 doses per year; 33 doses over 11 years), conducted during the evaluation.

6.52 The resulting effective AEMP of ONA IT against RIS of $[redacted] was likely overestimated given the maximum dose of RIS (of 5 mg per day) was used, as well as the application of a 3.5% discount rate. The resulting effective AEMP of ONA IT against NUSI of $[redacted] may also be overestimated due to the application of a 3.5% discount rate. The weighted cost was also likely overestimated as a higher proportion of RIS use was

assumed because the estimated split was based on the number of scripts for all patients up to 18 years of age rather than aged 2-18 years.

6.53 As discussed in paragraph 5.2, ONA IV may also be a comparator for ONA IT, given the positive recommendation for ONA IV for the treatment of Type I-IIIa SMA in patients weighing up to 21kg at the November 2025 PBAC meeting. The requested effective price of $[redacted] for ONA IT was higher than the current listings of ONA IV for SMA Type I patients no older than 9 months of age which has an effective price of $[redacted], and the proposed price for ONA IV for SMA patients weighing under 21kg (paragraph 6.53, onasemnogene abeparvovec PSD, November 2025). This represented a difference of $[redacted] between ONA IT and ONA IV. The submission did not provide a justification for the price premium of more than $[redacted] for ONA IT compared to ONA IV in symptomatic treatment of SMA Type I, II or IIIa patients.

6.54 The higher cost for ONA IT versus ONA IV when using RIS as the comparator was likely due to the following assumptions, which differed between the cost-minimisation approaches used (i.e. ONA IV versus RIS; and ONA IT versus RIS):

- The cost minimisation approach for ONA IT assumed the maximum dose of RIS across the 11-year time horizon, whereas the cost minimisation approach for ONA IV used a lower dose of RIS calculated for the first five years[6] before assuming the maximum recommended dosage of RIS.
- The cost minimisation approach for ONA IT used a 3.5% discount rate whereas a 5% discount rate was used in the approach for ONA IV.
- The difference in the cost of ONA administration ($101.90 versus $114.30 used by the submission [100% benefit]) though MBS item 14245[7] was used for both cost-minimisation approaches.

6.55 Sensitivity analyses conducted during the evaluation found that assuming a 5% discount rate for ONA IT versus NUSI resulted in an ONA IT effective price of $[redacted], while the multivariate sensitivity analyses (ONA IT versus RIS) assuming a 5% discount rate and reduced dosing of RIS in 17% of patients resulted in an effective price of $[redacted] for ONA IT. The PSCR and pre-PBAC response stated that sensitivity analyses provided by the evaluator for the comparison with RIS/NUSI do not materially change the weighted base case price estimate.

[6] Calculated based on the World Health Organisation weight-for-age data; https://www.who.int/tools/growth-reference-data-for-5to19-years/indicators/weight-for-age-5to10-years

[7] Description: "IMMUNOMODULATING AGENT, administration of, by intravenous infusion for at least 2 hours duration - payable once only on the same day and where the agent is provided under section 100 of the Pharmaceutical Benefits Scheme"

Drug cost/patient

Table 17: Drug cost per patient for proposed and comparator drugs

	ONA IT			Comparator [a] Trial dose and duration	Comparator [a] economics	Comparator [a] Financial estimates
	Study dose and duration	Economics	Financial estimates			
Dose	1.2 x 10^{14} vg			ONA IV: 1.1x10^{14} vg/kg RIS: by age and weight to target exposure (maximum 5mg/day) NUSI: 12 mg at days 0, 14, 28 and 63, then every 4 months thereafter	RIS: maximum dosing (5mg daily) Total over 11 years 20,088.75 mg NUSI: maintenance dosing, every 4 months	RIS: maximum dosing 5 mg/day NUSI: maintenance dosing, every 4 months
Duration	Once-off injection			Once-off injection (ONA IV); on-going (RIS and NUSI)	11 years	6 years
Cost	$[redacted]/patient			ONA IV: $[redacted]/patient	RIS: $[redacted]/60mg [d] NUSI: $[redacted]/dose [d]	
Cost/patient/yr	-			ONA IV: - RIS: $[redacted]/year [b] NUSI: $[redacted]/year [c]	RIS: $[redacted] [e] NUSI $[redacted] [e]	RIS: $[redacted]/year [f] NUSI: $[redacted]/year [c]

Source: Constructed during the evaluation

IT, intrathecal; IV, intravenous; NUSI, nusinersen; ONA, onasemnogene abeparvovec; RIS, risdiplam

a RIS and NUSI were comparators nominated by the submission, while ONA IV may also be a comparator for ONA IT, given the positive recommendation for ONA IV for the treatment of Type I-IIIa SMA in patients weighing up to 21kg at the November 2025 PBAC meeting.

b Assume 365.25 days, 5 mg dose (12 doses per bottle) and 30.44 bottle per year and no discontinuation

c Assume 3 doses per year and no discontinuation.

d Effective prices as noted/estimated in the submission (but were not applied in the submission's financials; this was performed during the evaluation).

e As presented by the submission in their cost-minimisation approach of ONA IT versus RIS and ONA IT versus NUSI, with a 3.5% discount rate (and considering dose administration of ONA IT only), divided by the time-horizon of 11 years.

f Based on 10.83 scripts required per year and 2.81 bottles dispensed per script, as used by the submission in their financial estimates

Estimated PBS usage & financial implications

6.56 This submission was not considered by DUSC. The submission used a market share approach to estimate the financial impact of PBS-listing ONA IT for the treatment of Type I, II or IIIa SMA for patients aged 2 to <19 years. The submission:

1. Extracted the number of scripts dispensed for 2025 from item codes for the target population to estimate the existing market and growth in the market*;*
2. Applied a proportion applicable to ONA IT, which excluded patients 19 years and older or with a high AAV9 titre;
3. Applied a proportion affected by the PBS-listing of ONA IT (the 'switch rate');
4. Calculated incremental affected scripts per year, compared to the previous year; and
5. Converted these annual incremental affected scripts to equivalent ONA IT patients by dividing by the number of scripts per patient per year for each treatment.

6.57 Table 18 summaries the key inputs relied on in the financial estimates.

Table 18: Key inputs for financial estimates

Parameter	Value & source	Comment
Existing Market	1,152 scripts in 2025 (full calendar year) were dispensed for RIS and NUSI in the target population of symptomatic patients with Type I, II and IIIa SMA where the patient initiated prior to the age of <19. The submission assumed the same number of scripts for 2026 and applied growth rates from 2027 onwards. Source: Services Australia, PBS dispensing data for the following item codes (see table below) Drug / Item code / Schedule / Type RIS / 12606L / Public / Continuing RIS / 12609P / Private / Continuing RIS / 12610Q / Private / Initiating RIS / 12614X / Public / Initiating NUSI / 11378W / Public / Continuing NUSI / 11476B / Private / Continuing NUSI / 11363C / Public / Initiating NUSI / 11472T / Private / Initiating	This may be slightly underestimated given the submission assumed the number of patients in 2025 was the same for 2026. However, the existing market may also be overestimated by the inclusion of pre-symptomatic patients. The submission (p130) acknowledged that for all of the continuing codes, pre-symptomatic SMA patients with 2 copies of SMN2 were allowed within the restriction, and these patients were not explicitly excluded from the calculation of eligible scripts for ONA IT. The submission assumed that this included an insignificant number of patients (there were four initiation scripts for item code 13655Q for RIS between 2021-2025, all occurring in 2025). The national implementation of NBS for SMA (in 2024) would likely increase pre-symptomatic treatment of SMA now and in the future.
% Growth Rate	RIS initiating (12614X; public): 20% applied for 2027-2030; 10% for 2031 equalling to 3 patients initiating per year NUSI initiating (11363C; public): negative growth, -50% applied for 2027 and 2028, and -100% for 2029, such that from 2029 onwards, there were 0 initiations for NUSI. RIS and NUSI continuing (12606L & 11378W; public): Annual growth for scripts was calculated to be previous year initiation scripts multiplied by annual scripts per patient, divided by half to account for an even distribution of patients initiating throughout the year. Source: Services Australia data (appeared to be for 2023 – 2025).	The submission's application of annual growth of continuing scripts, in which the previous year initiation scripts were multiplied by annual scripts per patient and divided by half, may not be appropriate. The submission applied this such that in the year a patient initiates treatment, continuing scripts were not counted for that year, and every patient initiating would only count half the continuing scripts due to the formula relying on previous year scripts as base. As such, this likely underestimated the market. These were tested as part of the sensitivity analyses conducted during the evaluation.
Proportion of patients younger than 19 years	RIS: 61% ([redacted]) NUSI: 71% ([redacted]) Source: PBS100 data for patients on treatment (in the 12 months to June 2025) which included each patient's date of birth. Calculated based on the number of patients younger than 18 years as of 1 January 2027 (the submission's [p132] expected PBS launch date of ONA IT) out of patients on treatment for RIS (93 patients) and NUSI (80 patients). All these patients would also be over 2 years of age by 1 January 2027.	While the source was reasonable and provided a snapshot for the current demographic of patients in the existing market, the submission's application of this proportion consistently over the six years may overestimate the eligible population in later years as patients who would be 18 years old in 2027 would not be eligible for ONA IT in 2028 onwards, i.e. they would only be eligible for uptake in the first year but the financial estimates assumed the patients would continue to be eligible across the six years.

<table>
<tr><th>Parameter</th><th>Value & source</th><th>Comment</th></tr>
<tr><td>% Treatment Uptake Rate</td><td>Yr 1: [redacted]%
Yr 2: [redacted]%
Yr 3: [redacted]%
Yr 4-6: [redacted]%
The submission assumed the switch rate only applied to continuing scripts.
Source: Calculated using both the switch to ONA and the switch from NUSI to RIS as clinical analogues. In both cases, the less invasive administration of the new products resulted in approximately [redacted]% of patients on treatment with the new medicine. The switch rate increase to 90% was assumed to be gradual, as patients become familiar with the patient experience overseas in countries such as the United States where ONA IT had FDA approval in December 2025.</td><td>The submission described that based on data from May 2022 to June 2025, there were [redacted][1] patients with symptomatic Type I SMA or pre-symptomatic SMA with 1-3 copies of the SMN2 gene on the PBS, with [redacted]% ([redacted][1]/[redacted][1]) treated with ONA IV. The remaining [redacted][1] patients not treated with ONA IV were treated with RIS: [redacted][1] was ten years old and [redacted][1] was 19-25 years old (and thus would never have been eligible for ONA IV). That is, a [redacted]% ([redacted][1]/[redacted][1]) switch rate may be more applicable, though a rate of [redacted]% was reasonable.

An uptake rate of 95% from Year 4 was tested in the sensitivity analyses conducted during the evaluation. Alternate values starting from 50% in year 1 and 75% in year 2 were tested during the evaluation.</td></tr>
<tr><td colspan="3">Costs</td></tr>
<tr><td>Affected medicines</td><td>Published prices:<table><tr><td>Drug</td><td>Public</td><td>Private</td><td>Weighted</td></tr><tr><td>RIS</td><td>$30,465.71</td><td>$30,603.06</td><td>$30,467.74</td></tr><tr><td>NUSI</td><td>$104,500.00</td><td>$104,548.88</td><td>$104,500.72</td></tr></table>Source: For RIS, this was based on the AEMP of $10,841.89 (public) and $10,890.77 (private), multiplied by 2.81 (the average number of units dispensed per script calculated by the submission). The price used by the submission matches the published AEMP for the PBS item codes: 12606L, 12609P, 12610Q, 12614X, 11378W, 11476B, 11363C, 11472T.</td><td>Revised financial estimates using the effective price of RIS and NUSI were performed during the evaluation.

The submission did not consider the impact of listing ONA IV for symptomatic SMA Type I-IIIa, weighing up to 21kg (recommended at the November 2025 PBAC meeting). Once available, a proportion of patients who would have been treated with RIS or NUSI would likely have already switched to ONA IV and therefore these patients would no longer be eligible for ONA IT. By not considering substitution of RIS and NUSI by ONA IV, the financial estimates may overestimate the use of ONA IT.</td></tr>
<tr><td>MBS Impacts</td><td>The submission (p141) provided a comparison of the MBS services required by patients treated with ONA IT and NUSI (see table below):<table><tr><td>Service</td><td>MBS item</td><td>MBS cost</td><td>No. req</td></tr><tr><td>ONA</td><td></td><td></td><td></td></tr><tr><td>Pre-treatment consult</td><td>104</td><td>$101.30</td><td>1</td></tr><tr><td>IV administration (1 hr)</td><td>14245</td><td>$114.30</td><td>1</td></tr><tr><td>Post-treatment follow-up consult: first year</td><td>104</td><td>$101.30</td><td>6</td></tr><tr><td>Liver Function Test</td><td>66512</td><td>$17.70</td><td>8</td></tr><tr><td>Cardiac Troponin Test</td><td>66518</td><td>$20.05</td><td>6</td></tr><tr><td>Full Blood Count Test</td><td>65070</td><td>$17.35</td><td>8</td></tr><tr><td>Creatinine Test</td><td>66500</td><td>$9.70</td><td>1</td></tr><tr><td>NUSI</td><td></td><td></td><td></td></tr><tr><td>Intrathecal infusion (2 hrs: 1hr + 15 mins x 4) – per episode of treatment incl. anaesthetic if needed</td><td>18216 + 4 x 18219</td><td>$281.15</td><td>1+4</td></tr></table></td><td>MBS items used were reasonable and the 80% MBS benefit was correctly applied, however, the use of MBS item 14245 may not be appropriate given the IT route of administration for ONA IT. The use of MBS item 18216 or 18219 (as used by the submission for NUSI) may be more appropriate. However, given the small difference in cost between MBS 14245 and MBS 18216 relative to the cost of ONA IT, this was unlikely to have a tangible impact on the overall financial estimates. This was tested for sensitivity during the evaluation.

It was noted that these were also used in a previous submission for ONA IV (considered at the July 2023 PBAC meeting) and were considered to be reasonable.</td></tr>
</table>

Source: Tables 4.1, 4.2, 4.6, 4.9, 4.13, 4.18, 4.20, pp128, 130, 133, 135, 137, 138, 140 & 141 of the submission.
AEMP, approved ex-manufacturer price; CMA, cost-minimisation approach; DPMQ, Dispensed Price for Maximum Quantity; FDA, Food and Drug Administration; NBS, newborn bloodspot screening; mg, milligram; IT, intrathecal; IV, intravenous; MBS, Medicare benefits schedule; NUSI, nusinersen; ONA, onasemnogene abeparvovec; PBS, pharmaceutical benefits schedule; RIS, risdiplam; SMA, spinal muscular atrophy; *SMN2*, survival motor neuron 2 gene

The redacted values correspond to the following ranges:
[1] < 500

6.58 Table 19 presents the estimated net financial implications for the proposed listing of ONA IT for the treatment of Type I, II or IIIa SMA in patients aged 2 to <19 years. The net cost to the PBS and to the health budget using the effective price of RIS and NUSI are presented in Table 19.

6.59 The PSCR provided revised financial estimates with some structural changes and the worksheets were provided with the pre-PBAC response (see also 6.61). The revised patient numbers, scripts and costs from the revised worksheet are shown in Table 19, in the shaded cells.

Table 19: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimation of use and financial impact of the proposed medicine (PBS)						
No. pt treated with RIS w/o ONA IT [a]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
No. pt treated with NUSI w/o ONA IT [b]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
No. pts switching from RIS	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
No. pts switching from NUSI	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Total patients treated with ONA [c]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Total patients treated with ONA (PSCR revised)	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
PBS cost less co-pay						
Total (eff) ($)	–	–	–	[redacted][6]	[redacted][4]	[redacted][4]
Total (eff, PSCR revised) ($)	–	–	–	[redacted][5]	[redacted][3]	[redacted][3]
Estimation of changes in use and financial impact of other medicines (PBS)						
Changes in number of scripts						
Item 12606L: RIS, cont public	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]
Item 12609P: RIS, cont private	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	[redacted][1]
Item 11378W: NUSI cont public	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]
Total	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]
Total (PSCR revised)	-[redacted][1]	-[redacted][1]	-[redacted][2]	-[redacted][2]	-[redacted][2]	-[redacted][2]
PBS cost less co-pay (eff)						
RIS [d]	-$[redacted][3]	-$[redacted][3]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]
NUSI [e]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]
Total (eff)	-$[redacted][3]	-$[redacted][4]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]
Total (eff, PSCR revised)	-$[redacted][3]	-$[redacted][4]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]
Estimated financial implications for the PBS						
Net cost to PBS (eff) ($)	[redacted][7]	–	[redacted][7]	[redacted][4]	[redacted][4]	[redacted][4]
Net cost to PBS (eff, PSCR revised) ($)	[redacted][8]	$[redacted][8]	$[redacted]56	$[redacted][10]	-$[redacted][5]	-$[redacted][5]
Estimated financial implications for the health budget						
Net MBS costs ($)	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Net cost to Govt health budget (eff) ($)	[redacted][7]	[redacted][8]	[redacted][7]	[redacted][4]	[redacted][4]	[redacted][4]
Net cost to Govt health budget (eff, PSCR revised) ($)	[redacted][8]	$[redacted][8]	$[redacted][6]	$[redacted][3]	-$[redacted][4]	-$[redacted][4]

Source: Tables 4.3-4.8, 4.10-4.12, 4.15-4.17, 4.21 & 4.22, pp 131-139, 141 & 142 of the submission.

AAV9, adeno-associated virus serotype 9; AHI, administration, handling and infrastructure; eff, effective; IT, intrathecal;; MBS, Medicare benefits schedule; NUSI, nusinersen; ONA, onasemnogene abeparvovec; PBS, pharmaceutical benefits schedule; RIS, risdiplam; w/o, without

a Calculated during the evaluation for continuing patients in the market, by the number of RIS scripts / annual scripts for RIS (10.83).

b Calculated during the evaluation for continuing patients in the market, by the number of NUSI scripts / annual scripts for NUSI (3).

c The number of ONA patients was determined by: Applying the proportion applicable to the indication (55% [61% under 19 years * 90% with eligible AAV9 status] for RIS and 64% [71% under 19 years * 90% with eligible AAV9 status] for NUSI) and the switch rate ([redacted]%-[redacted]% for Yr1-Yr6) to the estimated continuing scripts for RIS and NUSI in the market. The resultant script numbers to be replaced by ONA were then converted to the patient numbers by dividing this by the annual scripts per patient (10.83 for RIS and 3 for NUSI). The estimated number of patients treated with ONA IT was based on incremental difference between the current year and previous year, due to ONA IT being a once-in-a-lifetime treatment (and no subsequent DMT use assumed after ONA IT treatment).

d Effective price of $[redacted] was used. The effective price (private) was calculated by adding a $40 AHI fee and $8.88 dispensing fee.

e Effective price of $[redacted] was used. The effective price (private) was calculated by adding a $40 AHI fee and $8.88 dispensing fee

The redacted values correspond to the following ranges:

[1] *< 500*

[2] *500 to < 5,000*

[3] *$0 to < $10 million*

[4] *$10 million to < $20 million*

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

[6] *$30 million to < $40 million*

[7] *$40 million to < $50 million*

[8] $50 million to < $60 million
[9] $70 million to < $80 million

6.60 The net financial impact of PBS-listing ONA IT in the proposed population was estimated to become cost saving to the PBS from year 5 onwards as switches to ONA IT plateau and previous years savings of displaced RIS and NUSI use accrue. That is, while the total estimated financial impact of ONA IT over the six-year period would be a net cost given ONA IT is paid upfront, it may be cost saving annually if offsets are greater than the number of patients receiving ONA IT in a given year. The net financial impact of PBS-listing ONA IT was estimated to cost $100 million to < $200 million to the PBS, over the six-year period (revised to $100 million to < $200 million in the PSCR).

6.61 There were a number of uncertainties associated with the submission's assumptions which led to the financial estimates being uncertain as they could both lead to the under and overestimation of the financial estimates. Key uncertainties include:

- The proportion of patients younger than 19 years as of 1 January 2027 (the submission's expected PBS launch date of ONA IT) was estimated by the submission using PBS100 data for patients on treatment with RIS and NUSI (in the 12 months to June 2025). While the source was reasonable, the submission's application of this proportion consistently over the six years may overestimate the eligible population in later years as patients who would be 18 years old in 2027 would not be eligible for ONA IT in 2028 onwards, i.e. they would only be eligible for uptake in the first year but the model assumed the patients would continue to be eligible across the six years. This was revised in the estimates provided in the PSCR.
- The submission's estimation of annual growth of continuing scripts, in which the previous year initiation scripts (as a proxy for number of initiating patients) were multiplied by annual scripts per patient and divided by half, may not be appropriate. This likely underestimated the number of patients treated with RIS and consequently, eligible to switch to ONA IT. This was revised in the PSCR by applying a linear forecast for RIS and exponential smoothing for NUSI.
- The switch rate applied by the submission may be underestimated given the submission described that < 500 of the remaining < 500 patients not treated with ONA IV are ten years old and 19-25 years old respectively and thus would never have been eligible for ONA IV. As such, a [redacted]% (< 500/< 500) switch rate (as opposed to a [redacted]% [< 500/< 500] switch rate) may be more applicable. Additionally, it was unclear if the rate of gradual uptake used by the submission was reasonable. This may be higher if patients are already aware or familiar with ONA albeit administered as IV. Uptake was unchanged in the PSCR revised estimates.
- The lack of consideration that some patients treated with RIS or NUSI may switch to ONA IV, given the PBAC's positive recommendation for ONA IV for symptomatic Type I-IIIa SMA in patients weighing up to 21kg at the November 2025 meeting, may have overestimated the number of patients treated with ONA IT. This was unchanged in the PSCR revised estimates.

6.62 The listing of ONA IT should be cost saving compared to RIS and NUSI over the longer term (11 years or more) so long as subsequent DMTs are not utilised after receiving ONA IT (as assumed in the submission's financial estimates) and the patient remains alive.

Financial Management – Risk Sharing Arrangements

6.63 The submission did not propose an RSA. An outcomes-based RSA applies for ONA IV, whereby a [redacted]. In the case of ONA IV 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, ONA PSD, November 2020 PBAC meeting with May 2021 Addendum and September 2021 Addendum).

6.64 The PSCR acknowledged the PBAC's prior considerations regarding uncertainty and the role of RSAs for high-cost, one-time gene therapies such as ONA IV; but argued that these considerations are not applicable to ONA IT. The PSCR stated that ONA IT is a once-off treatment intended to replace, rather than sequence with, DMTs, and the submission does not assume subsequent DMT use. The PSCR proposed that any future request for PBS listing of DMTs after ONA IT would require the respective sponsors of NUSI and RIS to demonstrate the clinical and economic value of subsequent use.

6.65 Given the high level of uncertainty and high upfront costs associated with ONA IT, the ESC considered it would be prudent to implement an RSA for ONA IT. The ESC considered that given that the clinical evidence suggests that some patients still have deterioration in motor outcomes after treatment with ONA IT (see paragraph 6.20), there are likely to be patients who will wish to access NUSI or RIS after receiving ONA IT. The ESC considered that an RSA for ONA IT would not be needed if the price of ONA IT was reduced to account for potential subsequent use of NUSI or RIS.

6.66 The pre-PBAC response stated that the population relevant to the requested listing comprises patients where treatment is initiated later in the disease course and motor function trajectories are inherently more variable, with periods of stabilisation, plateau and variability in motor function consistently observed across NUSI and RISD studies. The pre-PBAC response also noted that there are no published data which shows that the addition of NUSI or RISD adds any additional clinical benefit for patients post OAV101 IT treatment (or even post-ONA IV) nor that the addition would be cost effective. The pre-PBAC response maintained that any changes to restrictions or indications that occur due to the add-on of NUSI or RISD should be accounted for by the respective sponsor of the product being given the add-on indication.

6.67 The PBAC also provided the following advice with regard to the listings allowing use of NUSI and RIS following ONA at its November 2025 Meeting:

"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 [for] 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… 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" (Paragraph 7.13, onasemnogene abeparvovec PSD, November 2025). The PBAC noted that these issues remain unresolved and would apply also to the older population proposed in this submission.

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

7 PBAC Outcome

7.1 The PBAC recommended onasemnogene abeparvovec administered intrathecally (ONA IT) for the treatment of symptomatic spinal muscular atrophy (SMA) in patients at least 2 years of age who have experienced at least two of the defined signs and symptoms of SMA Type I, II or IIIa prior to 3 years of age. The PBAC recommended the listing of ONA IT, on the basis that it should be available only under special arrangements under Section 100. The PBAC noted that the submission requested a higher price for ONA IT than the cost-effective price for onasemnogene abeparvovec administered intravenously (ONA IV) for use in patients aged no older than 9 months and in patients weighing up to 21kg. However, the PBAC considered that the higher cost proposed for older patients compared with the cost of treating patients at a younger age was not justified. The PBAC considered that ONA IT would be acceptably cost-effective at the same cost per patient as ONA IV, with the same outcomes-based RSA conditions applied.

7.2 The PBAC noted the consumer comments that some children were diagnosed before newborn screening was introduced, or after infancy, and may therefore have missed earlier access pathways. The input from consumers described an unmet need for additional treatment options for children and adolescents with SMA diagnosed after infancy, noting that current treatment with intrathecal nusinersen or daily oral risdiplam can impose a substantial treatment burden for patients, families and healthcare services.

7.3 The PBAC considered that with the introduction of the Newborn Bloodspot Screening program the need for ONA IT in patients aged >2 years is likely to diminish as the majority of patients is expected to be treated with ONA IV when younger. The PBAC

acknowledged that there is a population of patients who missed the early treatment window for ONA IV due to their age and timing of diagnosis. The PBAC noted that the sponsor is aware of at least < 500 patients who may soon become ineligible for ONA IT due to their age. The PBAC considered that it would be appropriate for patients >19 years to be eligible for ONA IT where they were 18 years or younger at initiation of DMT (NUSI or RIS), consistent with the current eligibility criteria that allow for ongoing treatment with NUSI or RIS.

7.4 The PBAC noted that the submission's requested restriction for ONA IT for treatment experienced patients did not stipulate any signs or symptoms of SMA, and hence a pre-symptomatic patient pre-treated with RIS or NUSI would not be precluded from treatment with ONA IT. The PBAC considered that the restrictions should ensure that patients are symptomatic, consistent with the clinical evidence presented and the population described in the submission.

7.5 The PBAC noted that the existing listings include the treatment criterion "Patient must be undergoing treatment with this pharmaceutical benefit once only in a lifetime". The PBAC considered that, for clarity, the restrictions should specify that the patient must be untreated with ONA (any route of administration) and this should flow on to all existing SMA listings for ONA.

7.6 The submission nominated RIS and NUSI as the main comparators, however the PBAC also noted its previous recommendation for ONA IV in symptomatic Type I-IIIa SMA patients who weigh up to 21 kg was relevant for some patients aged 2 years and above. The PBAC noted that only clinical comparisons with NUSI and RIS were presented in the submission. The PBAC considered that for the purpose of the cost-minimisation approach, a comparison with ONA IV was relevant because, as a once off treatment, a patient may either be treated early (<2 years, with ONA IV) or later (>2 years, with ONA IT). The PBAC also recalled that the submission for ONA IV in November 2025 was based on a comparison of the safety and efficacy of ONA in older/heavier populations with ONA in younger/lighter patients, which was considered acceptable in the context of a rare disease (paragraph 7.5, ONA IV PSD, November 2025 PBAC Meeting).

7.7 The PBAC noted that the clinical data for ONA IT was based on two studies: STRENGTH (a single arm study in treatment-experienced patients) and STEER (an RCT of versus sham in treatment-naïve patients). As no direct evidence for ONA IT vs NUSI/RIS was available, the submission presented indirect treatment comparisons with RIS and NUSI, separately in treatment-experienced and treatment-naïve patients, using motor-function outcomes (HFMSE and RULM) and population-adjusted and comparative methods where feasible. The evaluation considered that results of the indirect treatment comparisons were uncertain due to transitivity issues, only four out of the possible 18 treatment effect modifying factors identified were adjusted for, and there was uncertainty associated with results reported in the submission that were inconsistent with values in the clinical study report. The ESC noted that the evidence for ONA IT was limited as it was based on indirect treatment comparisons from small trials, including one single-arm trial. However, the PBAC agreed with the ESC that the

level of evidence presented for ONA IT was similar to that for ONA IV and other SMA treatments, and was reasonable for a rare condition. On balance, the PBAC considered that the evidence likely supported the claim of non-inferior efficacy and safety compared with NUSI and RIS and that it would also be likely to provide similar outcomes to ONA IV which has also previously been accepted as non-inferior in safety and efficacy to NUSI and RIS in matched patients.

7.8 The submission described ONA IT as 'different, with a manageable safety profile' in terms of safety compared to RIS or NUSI. The PBAC noted that there were limited data to assess the relative safety of ONA IT compared with NUSI or RIS and considered that the claim of non-inferior comparative safety of ONA IV to RIS/NUSI is uncertain but was accepted based on the available data. Compared to ONA IV, a lower proportion of patients treated with ONA IT in STRENGTH and STEER experienced hepatotoxicity (see Table 13). The PBAC noted that ONA IT may have a lower frequency of hepatotoxicity compared to ONA IV, consistent with the lower systemic exposure associated with IT administration and fixed dosing regimen

7.9 The PBAC did not accept the equi-effective doses and the weighted cost-minimisation approach versus NUSI and RIS as proposed in the submission. The PBAC noted that based on the approach in the submission the requested effective price of $[redacted] for ONA IT was substantially higher than that for the current listings of ONA IV for SMA Type I patients no older than 9 months of age ($[redacted]), and the proposed price for ONA IV for symptomatic SMA patients weighing under 21kg ($[redacted]; paragraph 6.53, ONA IV PSD, November 2025 PBAC meeting). The PBAC considered that the additional cost of more than $[redacted] per patient for ONA IT compared to ONA IV in treatment of symptomatic SMA Type I, II or IIIa patients was not justified. The pre-PBAC response argued that indication-based pricing provides a robust mechanism to align price with value across different patient populations. However, the PBAC considered that, given the once-off nature of the gene therapy (both IV and IT ONA), a patient may either receive treatment early (i.e. under the existing listings and the November 2025 recommended listing) or later (i.e. under the proposed listing for this submission). As such, the different indications for ONA IV and ONA IT do not represent separate populations. Further, the PBAC noted that earlier initiation of disease-modifying treatment remains the preferred approach and the higher price proposed for the older population appears counterintuitive. The PBAC considered that ONA IT would be acceptably cost-effective at the same price per patient as ONA IV in treatment of symptomatic SMA Type I, II or IIIa patients. The PBAC noted that this was consistent with its November 2025 recommendation that ONA IV would be acceptably cost-effective in the older population (up to 21 kg) at the same cost per patient as in the younger population (≤9 months) (paragraph 7.1, ONA IV PSD, November 2025 PBAC Meeting).

7.10 The PBAC noted that the total estimated financial impact of ONA IT over the six-year period was $100 million to < $200 million. The additional net cost resulted from the upfront cost of ONA, however the listing of ONA IT should be cost saving due to offsets from RIS and NUSI over the longer term (11 years or more) so long as subsequent DMTs are not utilised after receiving ONA IT (as assumed in the submission's financial

estimates) and the patient remains alive. The PBAC noted that the changes to the financial estimates in the PSCR addressed some of the uncertainties identified in the evaluation (ongoing eligibility despite increasing age and the annual growth in scripts). However, the changes in the PSCR did not address uncertainty in the uptake rates or the impact of expected uptake of ONA IV (which if listed would reduce the number of eligible patients for ONA IT). The PBAC considered that the estimates otherwise appeared reasonable as they were based on the current utilisation of RIS/NUSI in the relevant age group. The PBAC considered that, over time, utilisation of ONA IT is likely to be minimal as patients are identified through Newborn Bloodspot Screening and receive earlier treatment with ONA IV.

7.11 The PBAC noted that there are specific PBS-listings that allow patients treated with ONA IV for Type I or pre-symptomatic SMA to access NUSI/RISD following treatment with ONA under special circumstances (where they have a suboptimal response and regression in developmental milestones). These listings do not specify the route of administration (IT or IV), however, they should be amended to allow retreatment with RIS/NUSI following ONA IT where a patient received ONA for Type II-IIIa SMA (for both RIS and NUSI) where they have regression in developmental milestones.

7.12 The PBAC noted that the cost-effectiveness of ONA (IV or IT) relied on offsets from treatment with NUSI/RIS for at least 11 years. The PBAC noted that the existing outcomes-based RSA addressed uncertainty regarding the cost-neutrality of ONA IV to NUSI and RIS and considered that it would be reasonable for the expanded population for ONA IT to also be included in this RSA, with the same conditions applied.

7.13 The PBAC recalled that at its November 2025 meeting it advised that the listings for treatments with NUSI/RIS after ONA IV should be reviewed to ensure that they remain clinically appropriate (paragraph 7.13, onasemnogene abeparvovec PSD, November 2025, see also paragraph 6.67). The PBAC acknowledged that clinicians and patients would like to access subsequent DMT where patients have a suboptimal response to ONA, but considered that given the very high cost of treatments for SMA, it would not be appropriate to allow subsequent treatment with NUSI/RIS after ONA IT under less stringent criteria without an RSA or changes in price to ensure that the cost-effectiveness of both ONA and NUSI/RIS are maintained. 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 any additional flow-on changes to NUSI and RIS listings.

7.14 The PBAC noted the flow-on restriction changes to:

- Items 12943F and 12959C (RIS) and item 12972R (NUSI) to allow subsequent treatment for patients with SMA Type 1-3a (with no other changes to the conditions for subsequent treatment).
- All ONA IV listings, to specify that the patient must be untreated with ONA (any route of administration).

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

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

Outcome:
Recommended

8 Recommended listing

Add new item:

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
ONASEMNOGENE ABEPARVOVEC					
Onasemnogene abeparvovec Single dose vial, 1.2 x 1014 vg in 3 mL of solution for intrathecal injection.	NEW	1	1	0	ITVISMA

Restriction Summary / Treatment of Concept		
Concept ID (for internal Dept. use)		**Category / Program:** ☒ Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)
		Prescriber type: ☒Medical Practitioners
		Restriction type: ☒Authority Required (FULL assessment - 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 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
		Episodicity: n/a
		Severity: n/a
		Condition: Spinal Muscular Atrophy
		Indication: Spinal Muscular Atrophy
		Treatment Phase: Use in a patient untreated with disease modifying therapies for this condition
		Clinical criteria:
		Patient must be untreated with onasemnogene abeparvovec (any route of administration)
		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 SMA Type I, II or IIIa prior to 3 years of age
		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 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 between the ages of 2 and 18 years inclusive
	AND
	Population criteria:
	Patient must have symptomatic Type 1, 2 or 3a SMA
	Prescribing Instructions: Defined signs and symptoms of type 1 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 2 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 3a 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: 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: In the relevant PBS Authority Application form, specify the following: (i) specification of SMA type (I, II or IIIa); and (ii) sign(s) and symptom(s) that the patient has experienced; and (iii) patient's age at the onset of sign(s) and symptom(s). 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. Quote the date, pathology provider name and any unique identifying serial number/code that links the genetic test result to the patient.
	Administrative Advice: An outcome on the authority application is not immediate, but will follow in due course. Electronic upload is encouraged to reduce processing time.
Restriction Summary [new] / Treatment of Concept: [new]	
Concept ID (for internal Dept. use)	**Category / Program:** ☒Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)
	Prescriber type: ☒ Medical Practitioners
	Restriction type: ☒Authority Required (FULL assessment in writing only via OPA/post/HPOS upload)
	Authority type: ☒ Complex Authority Required (CAR)
	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 at least 2 years of age.
	AND
	Population criteria:
	Patient must have been 18 years of age or younger at the time of initial treatment with disease modifying therapy for this condition.
	AND
	Population criteria:
	Patient must have symptomatic Type 1, 2 or 3a SMA
	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: (3) details of the proposed prescription(s); and (4) 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 Symptomatic Type 1, 2 or 3a SMA. State the age of the patient.
	Prescribing Instructions: Adhere to any Product Information or local treatment guidelines with respect to treatment-free ('wash out') periods prior to administering this benefit.
	Administrative Advice: An outcome on the authority application is not immediate, but will follow in due course. Electronic upload is encouraged to reduce processing time.

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 positive recommendation for ITVISMA for the treatment of paediatric patients with SMA. Novartis looks forward to working with the

Department to facilitate the listing and improve access for children living with SMA in Australia.