

Addendums to these minutes have been included at the end of the document.

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

1 Purpose of submission

- 1.1 The submission requested listing for onasemnogene abeparvovec (ONA) for the treatment of spinal muscular atrophy (SMA) Type I in patients under 2 years of age.
- 1.2 Listing was requested on the basis of cost-effectiveness analyses versus nusinersen (NUSI) and best supportive care (BSC).

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

Component	Description
Population	Paediatric patients less than 2 years of age with SMA with bi-allelic mutations in the SMN1 gene
Intervention	ONA is administered as a single (once off) intravenous infusion through a venous catheter delivered over 60 minutes. The recommended dose is 1.1×10^{14} vector genomes per kilogram (vg/kg) of body weight, to be individually made up by the sponsor for each patient. To manage possible liver function abnormalities, all patients should receive a course of oral prednisolone (1mg/kg) as described in the product information.
Comparator	<ul style="list-style-type: none"> • NUSI intrathecal injections and • best supportive care
Outcomes	<ul style="list-style-type: none"> • Time to death or permanent ventilation • Improvement in motor milestones (independent sitting and walking measured by the Bayley scales), including CHOP-INTEND score • Safety (primary endpoint of START trial)
Clinical claim	<ul style="list-style-type: none"> • In patients with Type I SMA, ONA is more effective than NUSI at reducing mortality; • In patients with Type I SMA, ONA is more effective than placebo / natural history at reducing mortality and increasing motor development

Source: Table 1.2, p23 of the submission, draft PI.

CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; NUSI = nusinersen; ONA = onasemnogene abeparvovec; SMA = spinal muscular atrophy; SMN = survival motor neuron;

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

2 Background

Registration status

- 2.1 The submission was made under the TGA/PBAC Parallel Process for the following indication:

Treatment of paediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene.

- 2.2 At the time of PBAC consideration, the Delegate’s Overview was available, however the Delegate has sought the advice of the Advisory Committee on Medicines (ACM) on a number of issues including the proposed indication (maximum age; number of SMN2 copies, symptomatic only or also presymptomatic) and the ACM advice was not available at the time of PBAC consideration.

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

3 Requested listing

- 3.1 The submission requested the following listing:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
ONASEMNOGENE ABEPARVOVEC liquid in vial 1.1 x 10 ¹⁴ vg/kg	1	0	\$ [REDACTED] #	Zolgensma®, Novartis Pharmaceuticals Pty Ltd
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners			
Episodicity:	Once off treatment			
Severity:	Type 1			
Condition:	Spinal muscular atrophy			
PBS Indication:	Treatment of spinal muscular atrophy in patients under the age of 2 years			
Treatment phase:	Initial/once-off			
Restriction:	<input checked="" type="checkbox"/> Authority Required - In Writing			
Treatment criteria:	Must be treated by a specialist medical practitioner experienced in the diagnosis and management of spinal muscular atrophy associated with a neuromuscular clinic which is certified to provide gene-replacement therapy.			
Clinical criteria:	The condition must be 5q homozygous deletion, mutation of, or compound heterozygous mutation in the SMN1 gene AND The treatment must be concomitantly with standard supportive care for this condition AND Patients must have AAV ₉ antibody titres < 50 and the test must be no more than 2 months old.			

Price is based on average exchange rate at January 2020 for \$USD [REDACTED] ex GST

- 3.2 The PBAC noted the requested restriction allows for use in a broader population than was included in the clinical trials, and does not deal with the potential for concomitant or sequential use of other SMA therapies. The PBAC deferred further consideration of the PBS restriction wording pending the advice of the ACM and the outcome of its recommendation for a decision support analysis for SMA.

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

4 Population and disease

- 4.1 SMA is a rare autosomal recessive progressive neuromuscular disease caused by mutations or deletions in the SMN1 gene on chromosome 5q. Alterations to this gene result in deficiency of SMN protein, which in turn, results in loss of motor function and respiratory failure. Patients with SMA typically develop weak muscles, and may have

trouble walking and breathing. SMA is classified into types (0, I, II, III and IV) and subtypes (a, b, c) based on age of onset and maximal motor function achieved.

4.2 There is a clinical spectrum of disease with earlier age of onset associated with lower numbers of SMN2 gene copies and increased severity of symptoms (see Table 2).

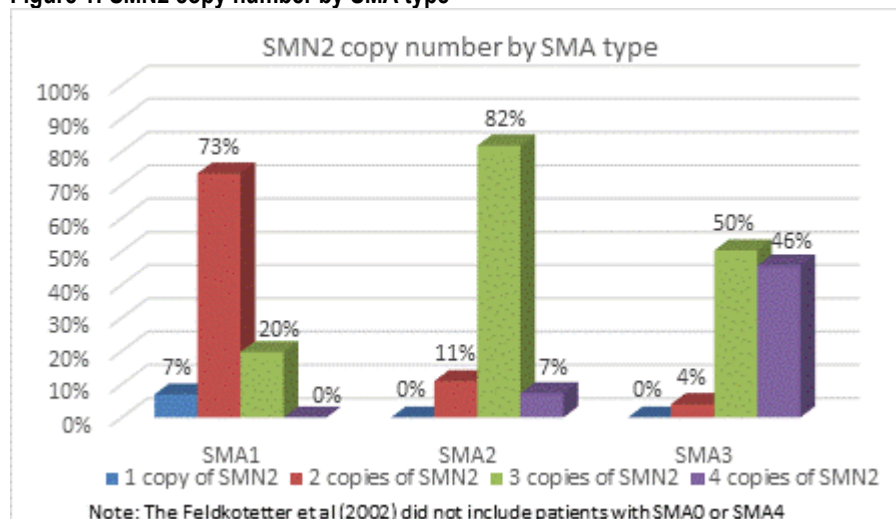
Table 2: Classification of SMA based on age of symptom onset, motor function and life expectancy

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

Source: Table 1.1, p24 of the submission.

Bold = predominant SMN2 copy number that defines the SMA type, the other copy numbers represent a small percentage of the designated SMA type. SMA= spinal muscular atrophy; SMN2 = survival motor neuron 2 gene.

Figure 1: SMN2 copy number by SMA type



Source: reconstructed during evaluation from Feldkotter et al. (2002).

4.3 Figure 1 illustrates the imperfect relationship between SMN2 copy number and SMA phenotype. For SMA Type I, while the majority of patients (80%) had ≤ 2 copies of the SMN2 gene, 20% had 3 copies of SMN2. Patients with 3 copies of the SMN2 gene could also manifest as either Type III or IV SMA.

4.4 ONA is a once per life-time gene replacement therapy consisting of a non-replicating recombinant adeno-associated viral (AAV₉) vector containing the human SMN gene under control of the chicken beta-actin promoter. It is designed to deliver a copy of the gene encoding the human SMN protein.

5 Comparator

5.1 The submission nominated NUSI as the main comparator, but a comparison versus natural history as proxy for BSC was also made.

- 5.2 The resubmission also nominated risdiplam and branaplam, both small molecule therapies, to be near market comparators.
- 5.3 The PBAC considered these comparators appropriate.

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician presented clinical case studies and discussed the natural history of the disease and how the therapy would be used in practice, including advocating for it to be available to pre-symptomatic infants with up to 3 copies of the SMN2 gene.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (12) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with ONA including the improvement in quality of life for the child and parents, and the prospect of not needing ongoing treatment.
- 6.3 The PBAC noted the advice received from Spinal Muscular Atrophy Australia (SMAA) that families using Spinraza [NUSI] for their child and then transitioning to Zolgensma have seen improvements in breathing, swallowing and better core strength. Parents of children with SMA also reported improvements in swallowing and breathing in their child after treatment with ONA following initial treatment with NUSI.
- 6.4 The PBAC noted advice from both SMAA and the Victorian Clinical Genetics Services that a once-off treatment is more desirable for patients than ongoing lumbar injections. A parent of a child with SMA type 1 who received treatment with NUSI described the fear and trauma associated with intrathecal injections and the need for sedation to enable administration of NUSI.
- 6.5 The PBAC also noted support for ONA to be available for all Types of SMA and for pre-symptomatic patients, with one parent of a recipient of ONA pre-symptomatically through a trial noting *“in the two years since the infusion, our daughter is still pre-symptomatic and ... our daughter running around each and every day gives us no doubt that Zolgensma should be accessible to all those that wish to receive it”*.
- 6.6 The PBAC noted that some individuals perceived ONA as a *“cure”* that could reverse SMA. However, this is not supported by the evidence in the submission.

Clinical studies

- 6.7 Details of the studies presented in the submission, or identified in the evaluation (italicised), are provided in the table below.

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Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
ONA		
START (Completed)	Phase I Gene Transfer Clinical Trial for Spinal Muscular Atrophy Type 1 Delivering AVXS-101. CSR. (Study AVXS-CL-101) Mendell JR, Al-Zidy S, Shell R et al. Single-dose gene-replacement therapy for spinal muscular atrophy.	August 2018 The New England Journal of Medicine 2017; 377 (18): 1713-1722.
START LT (Interim)	A Long-term Follow-up Safety Study of Patients in the AVXS-101-CL-101 Gene Replacement Therapy Clinical Trial for Spinal Muscular Atrophy Delivering ACXS-101. Protocol. (Study AVXS-101-LT-001)	January 2020.
STR1VE US (Completed)	Phase 3, Open-label, Single-arm, Single-dose Gene Replacement Therapy Clinical Trial for Patients with Spinal Muscular Atrophy Type 1 with One or Two SMN2 Copies Delivering AVXS-101 by Intravenous Infusion. CSR. (Study AVXS-101-CL-303)	March 2020
STR1VE EU (Interim)	Phase 3, Open-label, Single-arm, Single-dose Gene Replacement Therapy Clinical Trial for Patients with Spinal Muscular Atrophy Type 1 with One or Two SMN2 Copies Delivering AVXS-101 by Intravenous Infusion. Protocol. (Study AVXS-101-CL-302)	November 2019
SPR1NT (Interim)	A Global Study of a Single, One-Time Dose of AVXS-101 Delivered to Infants with Genetically Diagnosed and Pre-symptomatic Spinal Muscular Atrophy with Multiple Copies of SMN2. Protocol. (Study AVXS-101-CL-304) Strauss KA, Farrar MA, Swoboda KJ et al. Onasemnogene abeparvovec in pre-symptomatic spinal muscular atrophy: SPR1NT study update as of 31 Dec 2019	November 2019 2020 Muscular Dystrophy Association (MDA) Clinical and Scientific Conference, Virtual Poster Session.
NUSI		
ENDEAR	Finkel RS, Mercuri E, Darras BT et al. NUSI versus sham control in infantile-onset spinal muscular atrophy.	The New England Journal of Medicine 2017; 377: 1723-1732.
NURTURE	De Vivo D, Bertini E, Swoboda K et al. NUSI initiated in infants during the pre-symptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study.	Neuromuscular Disorders 2019; 29: 842-856.
SHINE	Castro D, Finkel RS, Farrar MA et al. NUSI in infantile-onset spinal muscular atrophy: Results from longer-term treatment from the open-label SHINE extension study. [Conference presentation, data presented only for patients who started treatment in the ENDEAR trial]	American Academy of Neurology Annual Meeting 2020.
EAP	Aragon-Gawinska K, Seferian AM, Daron A et al. NUSI in patients older than 7 months with spinal muscular atrophy type 1.	Neurology 2018; 91: e1312-e1318.
EAP AUS	Farrar MA, Teoh HL, Carey KA et al. NUSI for SMA: Expanded access programme.	J Neurology Neurosurgery Psychiatry 2018; 89: 937-942.
CS3A	Finkel RS, Chiriboga CA, Vajsar J, et al. Treatment of infantile-onset spinal muscular atrophy with NUSI: a phase 2, open-label, dose-escalation study.	The Lancet 2016; 388:3017-3026.
Natural history		
NeuroNEXT	Kolb SJ, Coffey CS, Yankey JW et al. Baseline results of the NeuroNEXT spinal muscular atrophy infant biomarker study. Kolb SJ, Coffey CS, Yankey JW et al. Natural history of infantile-onset spinal muscular atrophy.	Annals of Clinical and Translational Neurology 2016; 3(2): 132-145. Annals of Neurology 2017; 82: 883-891.
PNCR	Finkel RS, McDermott MP, Kaufmann P et al. Observational study of spinal muscular atrophy type I and implications for clinical trials.	Neurology 2014; 83: 910-917.

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Trial ID	Protocol title/ Publication title	Publication citation
Farrar 2013	Farrar MA, Vuvic S, Johnston HM et al. Pathophysiological insights derived by natural history and motor function of spinal muscular atrophy.	The Journal of Paediatrics 2013; 162: 155-159.
Chung 2004	Chung BHY, Wong VCN, and Ip P. Spinal Muscular Atrophy: Survival pattern and functional status.	Pediatrics 2004; 114(5); e548.
Zerres 1995	Zerres K and Rudnik-Schoneborn S. Natural history in proximal spinal muscular atrophy.	Arch Neurol 1995, 52: 518-523.
Oskouri 2007	Oskouri M, Levy G, Garland CJ et al. The changing natural history of spinal muscular atrophy type I.	Neurology 2007; 69: 1931-1936.
Ge 2012	Ge X, Bai J, Lu Y et al. The natural history of infant spinal muscular atrophy in China: A study of 237 patients.	Journal of Child Neurology 2012; 27(4): 471-477.
Gregoretti 2013	Gregoretti C, Ottonello G, Beatrice M et al. Survival of patients with spinal muscular atrophy type I.	Pediatrics 2013; 131(5): e1509-e1514.
Indirect comparisons		
Precisionheor	Indirect comparison of AVXS-101 and NUSI. Technical report. Version 5.	May 2020.
Dabbous 2019	Dabbous O, Maru B, Jansen JP et al. Survival, motor function, and motor milestones: Comparison of AVXS-101 relative to NUSI for the treatment of infants with spinal muscular atrophy type 1.	Adv Ther 2019; 36: 1164-1176.

Source: pp56-69 of the submission plus the additional citations sourced during the evaluation.

Note: only main trial citations have been included in this table.

6.8 The key features of these studies (including the extra studies identified during the evaluation) are summarised in the table below. Studies relied on by the submission in the modelled economic evaluation are highlighted in red throughout the clinical data tables, whereas green highlight represents studies conducted in pre-symptomatic patients, otherwise the evidence base is in symptomatic patients.

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Table 4: Key features of the studies presented (including extras identified during the evaluation)

Study	N	Design/ duration	Risk of bias	Patient population	Outcomes*	Use in modelled evaluation
ONA						
START	15	OL, NC, 2 years	High#	Type I SMA; 2 SMN2 copies	Safety*, EFS (≥16 hrs/day; ≥14 days), OS, Motor milestones (Bayley scale), CHOP INTEND	Yes
START-LT [^]	15 ^b	OL extension of START, NC, 15 yrs planned (at Dec 2019 data cut, mean (range): age: 4.8 (4.3-5.6) years, time since treatment: 4.5 (4.1-5.2) years	High#	Type I SMA; 2 SMN2 copies	EFS (≥16 hrs/day; ≥14 days); Motor milestones (Bayley scale)	Yes
STR1VE-US	22	OL, NC, up to 18 mths of age	High#	Type I SMA; 1 or 2 SMN2 copies	EFS* (≥16 hrs/day; ≥14 days), OS, Motor milestones* (Bayley scale)	Yes
STR1VE-EU [^]	33	OL, NC, up to 18 months of age (Dec 2019 data cut: mean(range) follow up: 10.62 (1.8-15.4) mths	High#	Type I SMA; 1 or 2 SMN2 copies	EFS (≥16 hrs/day; ≥14 days), OS Motor milestones* (WHO MGRS)	-
SPR1NT [^]	29	OL, NC, up to 18 months of age (Dec 2019 data cut: patient mean age: 11.2mth (2 SMN2 copies) 9.7mth (3 SMN2 copies)	High#	Age <6 weeks SMN1 deletion/mutation 2 or 3 SMN2 copies Pre-symptomatic	EFS ^a , OS, Motor milestones* (Bayley scale)	-
NUSI						
ENDEAR	121	R, DB, MC, 13 mths	Low	Type I SMA; 2 SMN2 copies	EFS* (≥ 16 hrs/day, > 21 days), OS, Motor milestones* (HINE)	Yes
NURTURE [^]	25	OL, NC, 5 years planned (March 2019 data cut: infants at median age 34.8 mths)	High#	Age <6 weeks SMN1 deletion/mutation 2 or 3 SMN2 copies Pre-symptomatic	EFS* (≥6 hrs/day, ≥ 7 days; ≥ 16 hrs/day, > 21 days), OS, Motor milestones (WHO, HINE), CHOP INTEND	-
SHINE/ ENDEAR [^]	324	OL, NC, extension trial Up to 5 years (latest data cut: 3.4 years since 1 st dose in ENDEAR for NUSI)	High#	Type I (n=105) and Type II SMA patients from ENDEAR, CHERISH, CS3A or CS12, but only results for ENDEAR patients are reported in submission	EFS (≥16 hrs/day, > 21 days), OS, CHOP INTEND, Motor milestones (HINE)	Yes
EAP [^]	32	OL, NC, followed for 6 mth at last data cut	High#	Type I SMA	Motor milestones (HINE), CHOP INTEND	-
EAP AU [^]	16	OL, NC, followed for 5.1mths at last data cut.	High#	Type I SMA	EFS (>16 hrs/day), OS	-
CS3A [^]	20	OL, NC, 32 mths	High#	Type I SMA	Motor milestones (HINE), CHOP INTEND, EFS (≥16 hrs/day, ≥ 14 days), OS	-
Natural history						

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Study	N	Design/ duration	Risk of bias	Patient population	Outcomes*	Use in modelled evaluation
PNCr	79	Enrolled between 2005-2009	-	Type I (n=34) and II SMA, USA	EFS (≥ 16 hrs/day, ≥ 14 days), OS, CHOP INTEND	Yes
NeuroNEXT	53	Enrolled between Nov 2012 to Sept 2014	-	SMA ^a (n=26) and healthy infants, USA	EFS ^a , OS, CHOP INTEND	Yes
Farrar 2013	70	Enrolled 1995-2010,	-	Type I, II and III SMA, Australia	OS	-
Chung 2004	83	Enrolled Sept 2002,	-	Type I, II and III SMA Hong Kong	OS	-
Zerres 1995	445	Enrolled since 1985	-	Type I, II, III and IV SMA, Germany	OS	-
Oskouri 2007	143	Registry data from 1986-2006	-	Type I SMA, USA	OS, EFS	-
Ge 2012	237	Enrolled 2003-2008	-	Type I, II and III SMA, China	OS	Yes
Gregoretti 2013	194	Followed up 1992-2010	-	Type I SMA, Italy	OS	Yes

Source: constructed during the evaluation from source reports and publications. Italics indicate data extracted during the evaluation. CHOP INTEND, Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders; DB, double-blind, EFS, event-free survival (survival without permanent ventilation); FU, follow up, HINE, Hammersmith Infant Neurological Examination; NC, non-comparative single arm study, hrs, hours, MGRS, Multicentre Growth Reference Study; Mths, months, MC, multi-centre; R, randomised: SMA, spinal muscular atrophy; Yrs, years, OL, open label; OS, overall survival, WHO, World Health Organisation.

* primary outcome; ^ Study is still ongoing; # Considered to be high risk of bias being open-label studies.

^a the number of hours per day of ventilation, and the number of consecutive days of ventilation, were not defined.

^b All 15 patient who enrolled in START were recruited to START-LT, but results only reported for 13 patients, as 2 patients had discontinued.

6.9 All studies, with the exception of the ENDEAR RCT, were open label, non-comparative single arm studies (including Phase I studies). For ONA, the included studies had also enrolled small numbers of patients (N<35 in any one study). Common efficacy outcomes across the studies include overall survival (OS), event free survival (EFS) or survival without permanent ventilation and motor function assessments, however definitions of these outcomes differed across the studies.

6.10 Overall the risk of bias in the ENDEAR study was low. All other studies were considered to be at a high risk of bias due to their study design, being small, single arm, non-comparative studies.

6.11 The Pre-Sub-Committee Response (PSCR) argued that the nature of the disease being rare and having a high mortality rate, meant that “single arm trials are the ethical and appropriate design for this group”. However, the PBAC noted comparative studies against active comparators would be possible.

6.12 The PBAC noted there were some important study differences.

For studies conducted in symptomatic SMA Type I patients

- **Baseline age:** The ages at start of treatment in the ONA studies (3.4, 3.7 and 4.1 months in START Cohort 2, STR1VE-US and STR1VE-EU, respectively) were lower compared to the NUSI studies (5.4 and 6.0 months for ENDEAR NUSI and control

groups, respectively, and 4.6 months for CS3A approved dose subgroup). The median age at first NUSI injection was even older in the EAP studies, 21.3 months and 20.0 months in EAP and EAP-AU, respectively.

- **Disease duration:** Mean disease duration (where reported) was shorter in the ONA studies (2 months in START and 1.8 months in STR1VE-US) compared to NUSI (3.6 months and 3.8 months for NUSI and control arms, respectively, in ENDEAR).
- **Ventilatory support:** All ONA studies excluded patients needing invasive ventilatory support or non-invasive ventilatory support (for ≥ 16 hours/day in START, ≥ 6 hours/day in the STR1VE studies, and for any duration in SPR1NT), whereas these exclusion criteria did not apply in the NUSI studies. No patient in STR1VE-US reported the need for ventilatory support at baseline compared to 17% of START, 27.3% of STR1VE-EU and 26.3% and 14.3% of the ENDEAR NUSI and control groups respectively.
- **Nutritional support:** Patients with swallowing difficulties were excluded from START unless they received surgery for placement of a gastrostomy or nasogastric tube⁷, so the proportion of patients requiring nutritional support was higher for START (41.7%) compared to other ONA and NUSI studies (e.g., 0% and 30.3% in STR1VE-US and STR1VE-EU and 8.8% and 12.2% for ENDEAR NUSI and control group respectively).
- **CHOP-INTEND (Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders):** Higher baseline mean CHOP-INTEND scores indicating better motor function for those enrolled in the ONA studies (i.e., STR1VE-US 32 and START 28) compared to the NUSI studies (ENDEAR 26.6 and 28.4 for NUSI and placebo arms respectively and 26.7 and 17.3 in SHINE for previous NUSI and control arm patients respectively). Two of the 12 (17%) patients in START cohort 2 also had baseline scores above the range expected for symptomatic Type I patients (i.e., above 40).

Differences across the natural history studies

- The key differences were the time period and country of conduct, with the data periods spanning 4 decades and studies conducted across Asia, Europe, US and Australia.
- 6.13 In contrast, the SPR1NT (ONA) and NURTURE (NUSI) studies were conducted in pre-symptomatic patients and included patients who were younger and healthier than patients in the symptomatic studies. This was evident in their generally higher baseline CHOP intend scores (>40 , indicating a lack of SMA symptoms).
- 6.14 The dosages of ONA used in Cohort 1 and Cohort 3 of START were lower and higher than the PI recommended dose respectively. Therefore, only results from Cohort 2 of START are directly relevant to the submission. Use of prednisolone pre- and post-treatment in the ONA studies was consistent with the recommendations in the PI. Median follow up in the ONA studies (up 2 years) was generally longer than the NUSI

studies (less than 12 months), however for both ONA and NUSI, patients were rolled over into long term follow up studies, with the long term study for ONA, START-LT planning to follow patients for 15 years, and the long term follow up study for NUSI, SHINE, planning to follow patients up to 5 years. As SHINE enrolled patients from other trials of NUSI, the only results presented in the submission were for patients who were originally enrolled in ENDEAR. The PSCR noted that from the single-arm ONA trials, all children in the original Phase 1 study are still alive at a mean age of 4.8 years (START-LT) – noting the life expectancy of patients with Type I SMA is “considered to be 2 years of age”. The PBAC noted that only 13 of the 15 patients from START are reflected in the OS results for START-LT however, SHINE OS results included data from 81 patients treated with NUSI.

Comparative effectiveness

- 6.15 Efficacy outcome results were summarised during the evaluation and are presented by outcome for: i) OS, ii) EFS or survival without need for permanent ventilation, iii) motor functioning, iv) feeding and ventilatory support outcomes and v) safety. These outcomes were reported in most of the included studies, although their definitions and measurements including scales used and time points differed.
- 6.16 Quality of life (QoL) was not measured in the included studies.

Overall Survival (OS)

- 6.17 OS outcomes in the ONA and NUSI studies are summarised in the table below, survival as reported in natural history studies is summarised in Figure 2.

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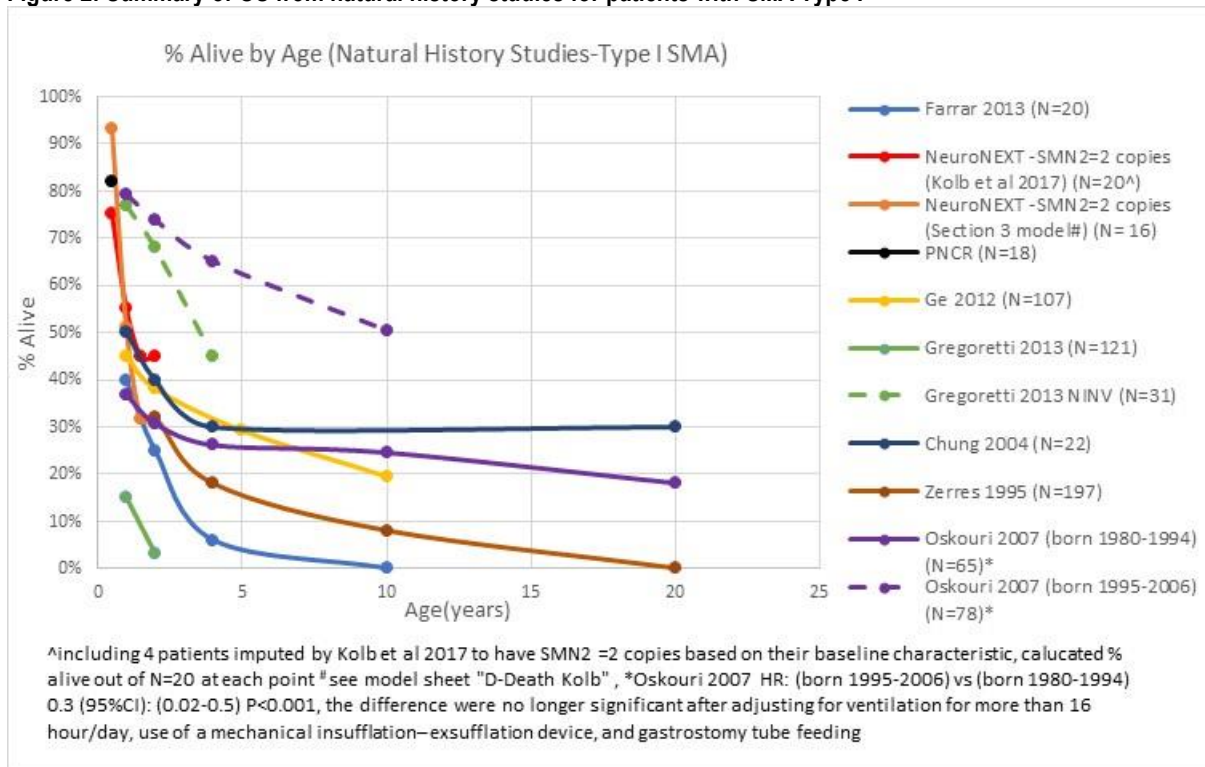
Table 5: OS (proportion alive) in ONA and NUSI studies

Study	ONA n/N (%)	Control n/N (%)	NUSI n/N (%)	HR (95%CI) p-value
ONA studies				
START (Cohort 2) ^a - 13.6 months of age - 20 months of age - 24 months post-dose ^b	12/12 (100.0%) 12/12 (100.0%) 12 ^b /12 (100.0%)	25% (PNCr)	-	p<0.0001 [§] - -
START-LT - Mean age at last data snapshot 4.8 years (range: 4.3-5.6)	13/13 ^f (100.0%)	-	-	-
STR1VE US - 10.5 months of age - 13.6 months of age - 18 months of age	21/22 (95.5%) 21/22 (95.5%) 21/22 (95.5%)	-	-	-
STR1VE EU: - 31/12/19 data cut (average age 10.62 months ^c)	32/33 (97.0%)	-	-	-
SPR1NT (pre-symptomatic) - 31/12/2019 data cut (mean age 11.2 months and 9.7 months ^d for 2 copies SMN2 and 3 copies SMN2, respectively)	29/29 (100.0%)	-	-	-
NUSI studies				
ENDEAR - Median follow-up 280 days (9.2mth) NUSI; 187 days (6.1mth) control	-	25/41 (61.0%)	67/81 (82.7%)	0.37 (0.18, 0.77)
SHINE/ENDEAR - 6 months in SHINE - 12 months in SHINE - 18 months in SHINE	-	[▲] 27 (65.9%) 23 (56.1%) 15 (56.1%)	[#] 68 (85.3%) 64 (81.6%) (77.5%)	-
NURTURE - Interim analysis data cut 29/03/19 (median 34.8 months of age)	-	-	25/25 (100.0%)	-
EAP-AU – 6 months follow up - SMN2=2 copies (median age at follow up: 25.8 months ^e) - SMN2=3 copies (median age at follow up: 33.7months ^e)	-	-	15/15 (100%) 17/17 (100%)	-
EAP-AU ((median treatment duration 5.1 months)	-	-	16/16 (100%)	-
CS3A (12 mg group) - Interim analysis data cut 26/01/16 (2-27 months follow-up)	-	-	13/16 (81.3%)	-

Source: constructed during the evaluation based on pp.110-167 of the submission, Data for SHINE from Figure 3 of NICE assessment report with digitised data from Nsn_ENDEAR_SHINE worksheet of Section 3 EXCEL model, and Finkel et al. 2016 publication for CS3A study

[§] Against PNCr # ENDEAR NUSI and SHINE NUSI [▲] ENDEAR control /SHINE NUSI; ^a In START, only results from Cohort 2 with the recommended ONA dose are reported here. Results from Cohort 1 with a lower than recommended ONA dose, are not reported here; ^b In START, at the final timepoint of 24 months post-dose, the age at the visit was mean (SD) of 27.9 (2.2) months, median 27.8 months, range 25.3 to 32.4 months; ^c At the time of the data cut, 30 of the 32 patients were ≥ 10.5 months of age, 18 were ≥ 14 months of age and 4 were ≥ 18 months of age. The 2 remaining patients had not yet reached 10.5 months of age; ^d Sourced from Strauss et al. (2020); ^e median age for the cohort; ^f 3 patients from Cohort 1 and 10 patients from Cohort 2.

Figure 2: Summary of OS from natural history studies for patients with SMA Type I



Source: Constructed during the evaluation from identified natural history studies. Note this graph summarises % alive at each time point and is not to be misinterpreted as Kaplan Meier data.
NINV=non-invasive nasal ventilation

6.18 Both ONA and NUSI studies reported much higher OS compared to natural history results reviewed during the evaluation for SMA Type I, with OS at 2 years of age ranging between 3% and 73.9% in the natural history studies with most reporting 30% to 40% survival (Oskouri 2007 – cohort born 1980-1994, Zerres 1995, Ge 2012, Chung 2004). Less than 45% of patients in NeuroNEXT were alive at 2 years of age.

6.19 The PBAC noted that the results are potentially biased against NUSI given patients had received treatment much later in ENDEAR than in the ONA studies, with earlier treatment potentially associated with greater benefit. In NURTURE, where patients had initiated NUSI treatment earlier (i.e., pre-symptomatic), 100% of the patients are still alive at a median of age of 34.8 months.

Event Free Survival (survival without permanent ventilation)

6.20 Event-free survival (EFS) (survival without permanent ventilation) outcomes are summarised in the table below for all ONA and NUSI studies and Figure 3, from natural history studies. Kaplan Meier curves comparing results from START, STR1VE-US and START-LT to PNCR and NeuroNEXT are presented in Figure 4 (Appendix 1) and Kaplan Meier curves from the NUSI trial ENDEAR and the extension study are presented in Figure 5 (Appendix 1).

Table 6: Survival without permanent ventilation† (event-free survival)

Proportion alive and without event	ONA n/N (%)	Control n/N (%)		NUSI n/N (%)	HR (95% CI) P-value
ONA studies					
START ^a - 13.6 months of age - 20 months of age - 24 months post-dose	12/12 (100%) 12/12 (100%) 12/12 (100%)	PNCr 5/23 (21.7%)	NeuroNext 6/16 (37.5%)	-	P<0.0001 [§]
START LT (Dec 2019 cut) (Cohort 2)	10/10 (100%)	-	-	-	-
STRIVE US - 10.5 months of age - 13.6 months of age* - 18 months of age	21/22 (95.5%) 20/22 (90.9%) 20/22 (90.9%)	-	-	-	-
STRIVE EU: - 31/12/19 data cut (average age 10.62 months ^b)	32/33 (97.0%)	-	-	-	-
SPR1NT (pre-symptomatic) - 31/12/19 data cut (mean age 11.2 months and 9.7 months for 2 copies SMN2 and 3 copies SMN2, respectively)	29/29 (100%)	-	-	-	-
NUSI studies					
ENDEAR* - Interim analysis data cut 15/06/16 (Median follow-up 9.2 months NUSI; 6.2 months control) - Median time to death or permanent ventilation ^d	- -	13/41 (31.7%) 22.6 weeks	-	49/81(60.5%) Not reached	0.53 (0.32, 0.89) P=0.005 -
SHINE/ENDEAR - At a median follow up of 9.2 months in SHINE - Median time (95%CI) to death or permanent ventilation	- -	^ - 22.6 weeks (13.6 – 31.3)	-	# 7/12 (58.3%) 73.0 weeks (36.3 –NA)	-
NURTURE* - Interim analysis data cut 29/03/19 (median 34.8 months of age) - Primary endpoint definition ^e - Exploratory endpoint definition ^f	-	-	-	21/25 (84%)* 25 ^g /25 (100%)	-
EAP – 6 months	-	-	-	30/33 (90.9%)	-
EAP AU (median treatment duration 5.1 months)	-	-	-	16/16 (100%)	-
CS3A (12 mg group) - Interim analysis data cut 26/01/2016 (2-27months follow-up)	-	-	-	11/16 (68.8%)	-

Source: constructed during the evaluation based on Sections 2.5 pp.110-167 of the submission, Figure 2.31 p151 of the submission based on De Vivo et al. 2019, and Finkel et al. 2016.

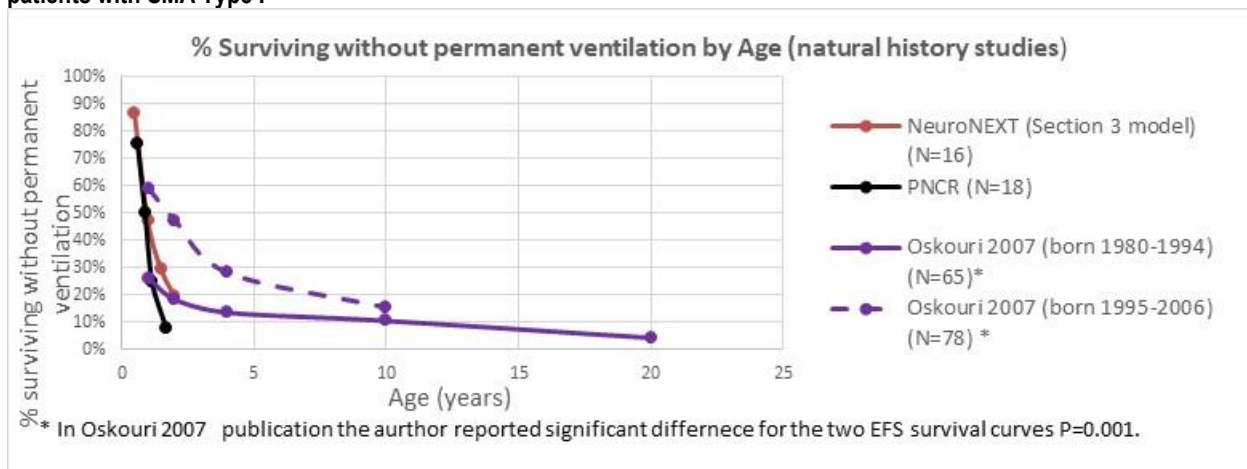
NA = not available; ONA =onasemnogene abeparvovec; SMA = spinal muscular atrophy.

* Primary endpoint of study. § Against PNCr and NeuroNEXT. † Permanent ventilation (unless otherwise specified) was defined as requirement of invasive ventilation ≥ 16 hours per day (including non-invasive ventilatory support) for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation. # ENDEAR NUSI and SHINE NUSI ^ ENDEAR control /SHINE NUSI

^a In START, only results from Cohort 2 with the recommended ONA dose are reported here. Results from Cohort 1 with a lower than recommended ONA dose, are not repeated here.

- ^b At the time of the data cut, 30 of the 32 patients were ≥ 10.5 months of age, 18 were ≥ 14 months of age and 4 were ≥ 18 months of age. The 2 remaining patients had not yet reached 10.5 months of age.
- ^c From De Vivo 2019, four patients utilised respiratory intervention for ≥ 6 hours per day continuously for ≥ 7 days during an acute reversible illness. At the time of the data cut, one infant continued to receive respiratory intervention for 10 hours per day, this infant received respiratory intervention for ≥ 6 hours per day for total of 644 days over the course of the study.
- ^d Permanent ventilation defined as tracheostomy or ≥ 16 hours of ventilatory support per day continuously for >21 days in the absence of an acute reversible event.
- ^e Permanent ventilation defined as respiratory intervention (invasive or non-invasive) for ≥ 6 hours per day continuously for ≥ 7 days or tracheostomy.
- ^f Permanent ventilation defined as ≥ 16 hours per day continuously for > 21 days in the absence of an acute reversible event or tracheostomy.

Figure 3: Summary of EFS (% surviving without permanent ventilation by age) from natural history studies for patients with SMA Type I



Source: constructed during the evaluation from data from PNCR study (were as reported in START CSR and p33 of resubmission) and Oskouri (2007) publication.

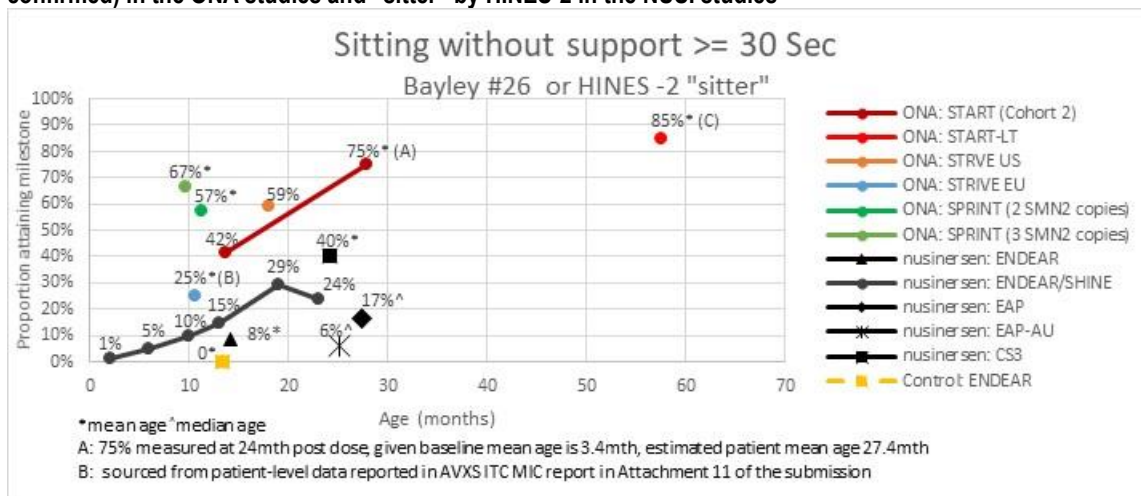
Note this graph summarises % alive at each time point and is not to be misinterpreted as Kaplan Meier data.

6.21 The PBAC noted that while the reported proportions of patients alive without permanent ventilation were consistently lower in the NUSI studies compared to ONA studies, the results were difficult to compare due to the differences across the studies and the high risk of bias in the ONA studies.

Motor functioning

6.22 Figure 6 and Table 7 summarise proportions of patients attaining independent sitting without support and of patients walking without assistance, respectively. The submission also presented a table comparing results for individual patients in Cohort 2 of START to the PNCR natural history cohort, see Table 8 (Appendix 1).

Figure 6: summary of proportion of patients sitting without support (≥ 30 sec as defined by Bayley #26 video confirmed) in the ONA studies and “sitter” by HINES-2 in the NUSI studies



Source: constructed during the evaluation.

Table 7: Walking without assistance

Treatment	Outcomes	ONA n/N (%)	Control n/N (%)	NUSI n/N (%)
WALKING WITHOUT ASSISTANCE (BAYLEY SCALES)				
ONA	START ^a - 13.6 months of age - 24 months post-dose	2/12 (13.3%) 2/12 (13.3%)	-	-
	START-LT - Mean age 4.8 years	2/13 (15.4%)	-	-
	SPR1NT (pre-symptomatic) - 2 copies SMN2; 31/12/19 data cut (mean age 11.2 mths) - 3 copies SMN2; 31/12/19 data cut (mean age 9.7 mths)	2/14 (16.7%) 2/15 (16.7%)	- -	- -
	NURTURE - Interim analysis data cut-off 29/03/19 (median 34.8 months of age)	-	-	22/25 (88.0%)
NUSI	SHINE/ENDEAR - At 2.08 years - At 3.4 years	-	0 0	0 (0.0%) 1/58 (1.7%)

Source: constructed during the evaluation based on pp.110-167 of the submission, Castro et al. 2020 and Finkel et al. 2016.

HINE = Hammersmith Infant Neurological Examination; MGRS = Multicentre Growth Reference Study; ONA = onasemnogene abeparovvec; SMA = spinal muscular atrophy; SMN = survival motor neuron; WHO = World Health Organisation.

* primary outcome of the study

^a In START, only results from Cohort 2 with the recommended ONA dose are reported here. Results from Cohort 1 with a lower than recommended ONA dose, are excluded. It is noted that no patients in Cohort 1 achieved the sitting unassisted milestone.

6.23 The PBAC noted both ONA and NUSI improved motor functioning. However, neither treatment was able to cure SMA, with patients in the trials remaining significantly disabled.

Long term motor outcomes

6.24 Results from longer term extension studies for ONA (START-LT) and NUSI (SHINE) are summarised in Tables 9 and 10 (Appendix 1).

- 6.25 Individual patient results for highest development milestone achievement in START-LT showed that all patients (10/10) from Cohort 2 of START who received the PI proposed dose of ONA maintained all previously attained milestones, with 3 patients gaining new milestones ('stands with assistance' from previous sit alone for either ≥ 15 or 30 sec). However, for one patient, this may have been due to concomitant NUSI.
- 6.26 The PBAC noted use of concomitant NUSI was high in START-LT, with 7/13 (54%) and 4/10 (40%) patients from the overall and the START Cohort 2 populations receiving concomitant therapy respectively, with the majority started post START but prior to enrolment in START-LT (therapy was initiated independent of the sponsor in each case). The Pre-PBAC response stated that some patients receiving NUSI after ONA in the START-LT-001 trial, did so not due to loss of motor function, but due to a perceived potential additional benefit and because funding for NUSI remained available to them.
- 6.27 For patients who began NUSI in ENDEAR and continued in SHINE, additional improvements in total and specific Hammersmith Infant Neurological Examination (HINE)-2 motor milestones, such as head control and sitting alone were observed; in those who received sham control in ENDEAR and began NUSI in SHINE, new improvements in total HINE-2 motor milestones were also observed. The highest milestone attained in this group at 3.4 years after first dose of NUSI include 1/58 (2%) that could walk alone, 4/58 (7%) that could walk with assistance, 1/58 (2%) that could stand alone, 11/58 (19%) that could stand with assistance and 37/58 (64%) that could sit without support (see Table 10, Appendix 1).

CHOP-INTEND

- 6.28 The PBAC noted that all the changes from baseline in CHOP-INTEND scores for ONA and NUSI had met the prespecified MCID of 3.4-5.0 points, so were clinically meaningful changes. For NUSI, in the ENDEAR trial, significantly more patients randomised to NUSI treatment had at least 4 point improvement from baseline compared to patients in the Sham control arm (71.2% versus 2.7%, $p < 0.001$).
- 6.29 Natural history studies, by comparison, illustrate that patients with SMA normally report a decline in CHOP-INTEND over time, with a mean rate of decline estimated to be 1.27 points/year (95% CI: 0.21-2.33, $p = 0.02$) from the PNCR study, for all SMA Type I and II patients. For the subgroup of Type IB patients, the mean rate of decline in the CHOP-INTEND scale was 1.83 points/year (95% CI: 0.32-3.35, $p = 0.02$). Data from NeuroNEXT also illustrate accelerating decline in CHOP-INTEND scores over time (data reported up to 24 months of age).
- 6.30 Results of CHOP-INTEND from longer term follow up were available from SHINE for NUSI. For patients who began NUSI in ENDEAR and continued in SHINE, additional improvements in total and specific general motor function were observed; in those who received sham control in ENDEAR and began NUSI in SHINE, new improvements were also observed, albeit at a much slower rate. Mean CHOP-INTEND score for

patients who received NUSI in ENDEAR and in SHINE was 43.7 (SD:13.03) at Day 1,538 in SHINE. The achievement and maintenance of scores greater than 40 points have been considered to be clinically meaningful because patients with SMA type 1 rarely achieve and never maintain this level of motor function¹.

Feeding support

- 6.31 In general, use of feeding support increased over study follow up. In START, 5/12 (41%) infants in Cohort 2 were using non-oral feeding support at baseline and increasing to 50% by the end of the study. In STR1VE-US the increase was from 0% at baseline to 31.8% anytime during study. In STR1VE-EU the proportion requiring feeding support remained relatively stable at 30%. In SPR1NT, where treatment with ONA was started pre-symptomatically, no patients required feeding support.
- 6.32 The ability to thrive at 18 months of age was a co-secondary endpoint in STR1VE-US defined as the ability to tolerate thin liquids, not requiring nutrition through mechanical support, and maintaining weight consistent with age. Using the combined definition of maintaining the ability to thrive at 18 months of age, 9/22 patients (40.9%) met all three criteria of maintaining ability to thrive (co-secondary endpoint, $p < 0.0001$) at 18 months of age. In the START ability to thrive subgroup ($n=7$), only including patients who did not require non-oral nutrition prior to ONA administration, 5/7 (71.4%) were considered to have attained this by 24 months post dose.
- 6.33 Feeding support outcomes were not measured in the NUSI studies, hence no comparisons could be made.

Ventilatory support

- 6.34 In general, use of ventilatory support also increased over study follow up. In START ventilatory support increased from 16.7% at baseline to 50% at 24 months post dose and for the 10 patients from Cohort 2 who continued to START-LT, to 40% during START-LT follow up. In STR1VE-US the increase was from 0% at baseline to 4/22 patients (18.2%) by 18 months. The STR1VE-EU study had a much higher baseline use of ventilatory support (9/33, 27.3%), and this had increased to 54.5% at any time during follow up at the last data cut. By comparison, in SPR1NT (the pre-symptomatic study), no patient had so far required ventilatory support during follow up.
- 6.35 Baseline ventilatory support was much higher in the NUSI studies compared to the ONA studies. With 21/80 (26.3%) and 6/41 (14.6%) on ventilatory support in the NUSI and sham control arms of ENDEAR respectively at baseline. Among infants not receiving ventilatory support at baseline, significantly fewer patients in the NUSI arm of the trial required ventilation support compared to sham control, (i.e., 44/59 (75%)

¹ Finkel, Richard S., et al. "Observational study of spinal muscular atrophy type I and implications for clinical trials." *Neurology* 83.9 (2014): 810-817.

versus 34/35 (97.12%), $p=0.021$). In EAP, ventilatory support remained above 50% over the 6 months follow up.

Indirect comparisons ONA versus NUSI

6.36 Three unanchored indirect comparisons were presented in the submission: i) a naïve indirect comparison using pooled individual patient data (IPD) from START and STR1VE-US compared with results reported in ENDEAR/SHINE for NUSI, ii) a naïve indirect comparison comparing START with ENDEAR (as published by Dabbous et al 2019) and iii) an unanchored matching adjusted indirect comparison (MAIC) that attempted to adjust for cross trial differences using IPD data for START and STR1VE-US, matching to reported aggregate baseline characteristics of ENDEAR/SHINE for NUSI. Results from the MAIC are presented below.

Results of the MAIC

- 6.37 For the base case analysis which pooled patients from START and STR1VE-US, the effective sample size (ESS) after weighting was 24.6, compared to a total patient population of 34. For START alone, the ESS was 11.8, compared to 12 total patients. For STR1VE-US, reweighting produced an ESS of 16.4 for 22 patients.
- 6.38 The submission provided a reweighted OS KM curve for ONA and the reconstructed published OS KM curve from SHINE. The ESC noted a Cox proportional hazards model was fit to the data; using pooled and weighted patient-level data from START and STR1VE-US, ONA was numerically superior to NUSI in terms of OS, though the result was not statistically significant (HR: ONA vs NUSI: 0.35; 95% CI: 0.09-1.32).
- 6.39 The submission provided a reweighted KM curve for ONA and the reconstructed published KM curve from SHINE. A Cox proportional hazards model was fitted to the data; using pooled and weighted patient-level data from START and STR1VE-US, ONA was statistically superior to NUSI in terms of EFS (HR (ONA vs NUSI): 0.19, 95% CI: 0.07-0.54).
- 6.40 Table 11 summarises results of the applicant's MAIC of for ONA versus NUSI for motor milestone achievements, using pooled and weighted patient-level data from START and STR1VE-US versus aggregate data reported in SHINE/ENDEAR.

Table 11: MAIC of motor milestone achievements, ONA versus NUSI – START and STR1VE-US versus SHINE/ENDEAR

Time on study	ONA START / STR1VE-US n/N (%)	NUSI SHINE/ENDEAR n/N (%)	RR (95% CrI)	RD (95% CrI)	NNT (95%CrI)
Independent sitting (Scenario A):					
START / STR1VE-US definition – sitting unassisted for ≥ 30 seconds - Bayley Scales Gross Motor Subset (#26)					
SHINE definition – stable sitting and pivoting (HINE-2)					
6 months	0.8/24.6 (3.3%)	3/65 (4.6%)	0.72 (0.07-7.95)	-0.01(-0.10-0.07)	-77.54(-9.98-13.44)
12 months	6.4/24.6 (26.2%)	7/48 (14.6%)	1.79 (0.69-4.66)	0.12(-0.08-0.32)	8.64(-11.82-3.16)
18 months	13.3/24.6 (54.1%)	9/31 (29%)	1.86(0.96-3.60)	0.25 (-0.00-0.50)	3.99(-320.69-1.98)
24 months	15.1/24.6 (61.3%)	4/17 (23.5%)	2.60 (1.05-6.49)	0.38 (0.10-0.66)	2.65 (1.52-10.13)
Independent sitting (Scenario B):					
START definition – sitting unassisted for ≥ 5 seconds - Bayley Scales Gross Motor Subset (#22)					
STR1VE US definition – sitting unassisted for ≥ 30 seconds - Bayley Scales Gross Motor Subset (#26)					
SHINE definition – stable sitting and pivoting (HINE-2)					
6 months	0.8/24.6 (3.3%)	3/65 (4.6%)	0.72 (0.07-7.95)	-0.01(-0.10-0.07)	-77.54 (-9.98-13.44)
12 months	6.4/24.6 (26.2%)	7/48 (14.6%)	1.79 (0.69-4.66)	0.12 (-0.08-0.32)	8.64 (-11.82-3.16)
18 months	13.5/24.6 (55%)	9/31 (29%)	1.90 (0.98-3.65)	0.26 (0.01-0.51)	3.85 (153.53-1.95)
24 months	16.1/24.6 (65.7%)	4/17(23.5%)	2.79 (1.13-6.89)	0.42 (0.15-0.70)	2.37 (1.44-6.86)
Independent walking					
6 months (on study)	0/24.6 (0%)	0/65 (0%)	-	-	-
12 month (on study)	0/24.6 (0%)	0/48 (0%)	-	-	-
18 months (on study)	0.2/24.6^ (0.7%)	0/31 (0%)	1.40 (0.04-54.50)	1.39 (0.04-50.16)	0.01 (-0.07-0.08)
24 months (on study)	0.6/24.6^ (2.5%)	0/17 (0%)	2.08 (0.06-76.33)	2.03 (0.06-67.02)	0.02 (-0.08-0.13)
Independent walking					
6 months of age	0/24.6 (0%)	0/81 (0%)	-	-	-
12 months of age	0/24.6 (0%)	0/81 (0%)	-	--	-
18 months of age	0.2/24.6^ (0.7%)	0/81 (0%)	1.73 (0.04-76.27)	0.01 (-0.05-0.06)	143.75 (-21.49-16.55)
24 months of age	0.6/24.6^ (2.5%)	0/81 (0%)	3.62 (0.17-77.18)	0.02 (-0.05-0.10)	40.33 (10.17, -20.51)

Source: Tables 2.64-2.67, pp203-206 of the submission, Tables 22-25, pp40-42 of PrecisionHEOR (2020) in Attachment 11 of submission. **Bold** indicates statistical significance (5% level). HINE = Hammersmith Infant Neurological Examination; ONA = onasemnogene abeparvovec

^ 18-month results for STR1VE-US were carried forward to the 24-month timepoint.

6.41 The PBAC noted the results of the MAIC favoured ONA but were unlikely to be robust because:

- The unanchored MAIC requires acceptance of the strong assumption that absolute outcomes can be predicted from the covariates; that is, it assumes that all effect modifiers and prognostic factors are accounted for. This is unlikely to be met.
- The MAIC was matched on just two baseline patient characteristics (CHOP-INTEND score and proportion with nutritional support) in the pooled analysis using both START and STR1VE-US IPD and on just one covariate (CHOP-INTEND) in sensitivity analysis using just START or just STR1VE-US IPD. Therefore, other observed cross study differences were not adjusted for, including age at treatment initiation (2 months later for NUSI in ENDEAR); disease duration (≤2 month for ONA versus 3.6 months for NUSI treated patients) and ventilator support at baseline (16.7% and

0% for ONA in START and STRIVE respectively and 26.3% for NUSI treated patients in ENDEAR).

- By matching ONA IPD to NUSI aggregate data, another implicit assumption is that the target population is closer to that represented in the NUSI study than in the ONA studies, and this is reflected in the estimates.

Comparative harms

6.42 Table 12 summarises the safety outcomes in the ONA and NUSI studies. Limited adverse events (AEs) data were available from the ongoing studies.

Table 12: Safety Outcomes in ONA and NUSI studies

	ONA studies				NUSI studies			
	START ^a	STR1VE US	STR1VE EU	SPR1NT	ENDEAR	SHINE/ENDEAR	NURTURE	CS3A
Any AE n/N (%)								
ONA	12/12 (100)	22/22 (100)	32/33 (97)	30/30 (100)	-	-	-	-
Control	-	-	-	-	40/41 (97.6)	22/22 (100) [^]	-	-
NUSI	-	-	-	-	77/80 (96.3)	58/60 (96.7) [*]	25/25 (100)	16/16 (100)
AEs related to treatment n/N (%)								
ONA	3/12 (25.0)	12/22 (54.5)	24/33 (72.7)	17/30 (56.7)	-	-	-	-
Control	-	-	-	-	NR	NR	-	-
NUSI	-	-	-	-	NR	NR	0/25 (0)	NR
Severe AEs n/N (%)								
ONA	10/12 (83.3)	10/22 (45.5)	NR	NR	-	-	-	-
Control	-	-	-	-	33/41 (80.5)	7/22 (31.8)	-	-
NUSI	-	-	-	-	45/80 (56.3)	19/60 (31.7)	5/25 (20.0)	NR
Serious AEs n/N (%)								
ONA	10/12 (83.3)	10/22 (45.5)	19/33 (57.6)	6/30 (20.0)	-	-	-	-
Control	-	-	-	-	39/41 (95.1)	14/22 (63.6)	-	-
NUSI	-	-	-	-	61/80 (76.3)	35/60 (53.8)	12/25 (48.0)	13/16 (81.3)
Treatment-related serious AEs n/N (%)								
ONA	1/12 (8.3)	3/22 (13.6)	NR	NR	-	-	-	-
Control	-	-	-	-	NR	0/22 (0.0)	-	-
NUSI	-	-	-	-	NR	0/60 (0.0)	0/25 (0.0)	NR
Discontinued due to AEs n/N (%)								
ONA	0/12 (0)	2/22 (9.1)	1/33 (3.1)	0/30 (0)	-	-	-	-
Control	-	-	-	-	16/41 (39.0)	1/22 (4.5)	-	-
NUSI	-	-	-	-	13/80 (16.3)	0/60 (0)	0/25 (0)	NR
Died n/N (%)								
ONA	0/12 (0)	1/22 (4.5) ^b	1/33 (3.1)	0/30 (0)	-	-	-	-
Control	-	-	-	-	16/41 (39.0) ^c	NR	-	-
NUSI	-	-	-	-	13/80 (16.3) ^d	NR	NR	3/16 (18.8) ^e

Source: Tables 2.38, 2.40; pp168-170 of the submission; pp.126-165 of the START CSR; Table 24, pp.83-84 of the STR1VE-US CSR; Castro et al. 2020; Finkel et al. (2016) publication

AE = adverse events; NR= not reported; ONA = onasemnogene abeparvovec; [^] ENDEAR control/SHINE NUSI; ^{*} ENDEAR NUSI and SHINE NUSI; ^a In START, only results from Cohort 2 with the recommended ONA dose are reported here. Results from Cohort 1 with a lower than recommended ONA dose, are excluded; ^b Assessed as not-related to treatment by the Investigator and Sponsor; ^c 12 patients died of respiratory disorder (which could plausibly be linked to SMA), 3 patients died of cardiac disorder, and 1 patient died of nervous-system disorder; ^d 7 patients died of respiratory disorder (which could plausibly be linked to SMA), the other patients died of cardiac disorder, general disorder and nervous-system disorder; ^e One patient died of SMA disease progression, two died from progression of disease secondary to a recent pulmonary infection.

6.43 With the exception of one patient in SPR1NT who did not report any treatment-emergent adverse events (TEAEs), all ONA treated patients reported at least one TEAE, with 25% and 54.5% of those events deemed to be related to ONA treatment in START and STR1VE-US, respectively. The most commonly reported TEAE were upper

respiratory tract infection, pyrexia and vomiting. The most frequently reported Grade 3 and 4 TEAEs for ONA patients in the START study were pneumonia (46.7%), atelectasis (20.0%), parainfluenza virus infection (20.0%), pneumonia respiratory syncytial viral (20%) and respiratory failure. The most common AEs in STR1VE-US were similar. There were no deaths in the ONA START and SPR1NT studies and one death in each of the STR1VE studies.

- 6.44 All NUSI patients in the NURTURE and CS3A studies experienced at least one TEAE, however three patients in ENDEAR did not report any TEAEs. The most commonly reported events in ENDEAR and NURTURE were upper respiratory tract infection, pyrexia, cough and nasopharyngitis. The most frequently reported serious adverse events in the ENDEAR study were respiratory failure and distress (25% and 26%, respectively), and pneumonia (24%). 32% of NUSI patients in NURTURE experienced an AE possibly related to the lumbar puncture procedure.
- 6.45 Thirteen (16.3%) and 16 (39%) patients in the NUSI and control groups of ENDEAR had died during the study respectively. Seven and 12 patients in the NUSI and control groups, respectively, died due to respiratory disorder, which could be linked to SMA. Three (18.8%) of NUSI 12 mg patients in CS3A died due to SMA disease progression and disease progression secondary to pulmonary infection.
- 6.46 The submission's superior safety claim was based on the claim of better survival for ONA, and the need for regular intrathecal injections (which is considered a more invasive procedure than intravenous infusion) to administer NUSI rather than the safety data from the trials. However, the PBAC noted that the safety data indicated ONA had a similar or greater proportion of patients with any AE, serious AEs, and treatment related serious AEs compared with NUSI. The PBAC also noted that the draft PI for ONA includes a black box safety warning² for the risk of acute serious liver injury.

Clinical claim

- 6.47 The submission described ONA as:
- superior in terms of effectiveness compared to BSC,
 - superior in terms of effectiveness (on survival outcomes) compared with NUSI and
 - superior in terms of safety compared with NUSI.
- 6.48 The PBAC accepted the results from the single arm studies support the claim of improved survival and motor functioning with ONA against BSC. However, the size of the benefit is uncertain, because of the lack of a comparator arm in the ONA studies and because the natural history studies may not adequately capture improvements in supportive care over time.

² <https://www.tga.gov.au/publication/boxed-warning-guidance>

- 6.49 The PBAC did not accept the claim that ONA is superior to NUSI in terms of effectiveness (on survival outcomes), noting this was not consistent with the evidence presented. In particular, the result of the MAIC (which, as described above is likely to favour ONA) did not show a statistically significant improvement in OS for ONA compared to NUSI and the confidence intervals were very wide due to the small sample size in ONA trials.
- 6.50 The PBAC did not accept the claim of superior safety for ONA versus NUSI, noting this was not consistent with the presented evidence (see Comparative Harms above).
- 6.51 However, the PBAC also noted the issues that affect the comparison of ONA versus NUSI (small single arm ONA trials, imbalanced study populations in the MAIC) make it difficult to conclude ONA and NUSI are non-inferior in terms of effectiveness and safety. Overall, having regard to the issues described above, the PBAC concluded that, on balance ONA would likely deliver similar clinical outcomes to NUSI in matched patients.

Economic analysis

- 6.52 The PBAC noted the submission presented two cost-utility analyses for the naïve comparisons of ONA vs NUSI (base case), and ONA vs BSC, using the same model structure but different parameters. The economic model was a Markov cohort model with six health states based on the level of motor functioning achieved: A (within a broad range of normal development), B (walks independently), C (sits unassisted ≥5 seconds), D (cannot sit independently), E (requires permanent assisted ventilation [PAV]) and Dead.
- 6.53 Tables 13 and 14 provide the results of the submission’s modelled economic evaluation for ONA vs NUSI and ONA vs BSC, respectively.

Table 13: Results of the economic evaluation – ONA vs NUSI (submission base case)

Step and component	ONA	NSN	Increment
Modelled analysis over 20 years			
Costs (20 years)	\$ [redacted]	\$2,817,445	\$ [redacted]
QALYs (20 years)	5.85	3.38	2.47
Incremental cost/QALY			\$ [redacted] ¹
Modelled analysis over lifetime (base case)			
Costs (lifetime)	\$ [redacted]	\$3,330,222	\$ [redacted]
QALYs (lifetime)	7.71	4.36	3.35
Incremental cost/QALY			\$ [redacted] ²
Incremental cost / Life Years gained			\$ [redacted] ³
Incremental cost/extra QALY gained (base case in submission)			\$ [redacted] ²

Source: compiled during the evaluation. NSN = NUSI; ONA = onasemnogene abeparovvec.

The redacted values correspond to the following ranges:

¹ \$155,000 to < \$255,000

² \$45,000 to < \$55,000

³ \$35,000 to < \$45,000

Table 14: Results of the economic evaluation – ONA vs BSC

Step and component	ONA	BSC	Increment
Modelled analysis over 20 years			
Costs (20 years)	\$ [redacted]	\$157,180	\$ [redacted]
QALYs (20 years)	5.85	0.21	5.64
Incremental cost/QALY			\$ [redacted] ¹
Modelled analysis over lifetime			
Costs (lifetime)	\$ [redacted]	\$157,180	\$ [redacted]
QALYs (lifetime)	7.71	0.21	7.49
Incremental cost/QALY			\$ [redacted] ²
Incremental cost / Life Years gained			\$ [redacted] ³
Incremental cost/extra QALY gained			\$ [redacted] ²

Source: compiled during the evaluation. BSC = best supportive care; ONA = onasemnogene abeparvovec.

The redacted values correspond to the following ranges:

¹ \$555,000 to < \$655,000

² \$355,000 to < \$455,000

³ \$255,000 to < \$355,000

6.54 The evaluation noted that much of the data included in the model could not be verified. By structuring the model to track motor milestones, the submission implicitly applied any naïve differences between ONA and NUSI from the trials, which significantly favoured ONA. Due to the lack of available data, key parameters such as overall survival by health state, extrapolation of motor function milestones and values for health state utilities were driven by assumptions, most of which favoured ONA. The PBAC considered that the modelled results are therefore highly uncertain and the incremental cost-effectiveness ratios (ICERs) presented were likely to be substantially underestimated. The PBAC noted the evaluation and ESC identified a number of other issues with the cost-effectiveness analysis for ONA versus NUSI and agreed these issues would need to be addressed in any future submission that continues to assert clinical superiority for ONA over NUSI.

Estimated PBS usage & financial implications

- 6.55 This submission was not considered by DUSC. The submission used an epidemiological approach to estimate the financial impact of listing ONA on the PBS.
- 6.56 The key inputs applied in the financial analysis are presented below.

*Public Summary Document – November 2020 PBAC Meeting with May 2021 Addendum
and September 2021 Addendum*

Table 15: Key inputs applied in the financial analysis

Data	Value	Source	Comment
SMA population			
Australian population	-	ABS pop projections 3222.0 Series B – Persons aged 0	Reasonable.
SMA incidence in Australia	1 / 10,000 live births	SMA Australia Fact Sheet	This may be under or over estimated. Other sources indicate that incidence may be 8.5 (Lally et al 2017) or 11.9 (Verhaart et al 2017) per 100,000.
SMA patients diagnosed as Type 1	60%	SMA Australia Fact Sheet	The lower end of the SMA Australia estimate was used in the base case. The upper estimate of 70% is tested in sensitivity analyses.
Proportion of newborns and infants in whom AAV ₉ was detected	6.0%	Combined ONA trials	Based on those screened in the clinical trial program.
Proportion with SMA Type 1 who are treated with NUSI and survive to age 24 months	50%	ENDEAR	Cannot be confirmed. The ENDEAR trial plus SHINE extension indicated overall survival at 24 months for those treated with NUSI to be at 78%. The submission is referring to EFS, which was 48% at 24 months for NUSI in ENDEAR.
Proportion with SMA Type 1 who are treated with NUSI and survive to age 12 months	61%	ENDEAR/SHINE	Cannot be confirmed. The ENDEAR trial plus SHINE extension indicated overall survival at 12 months for those treated with NUSI to be at 83%. The submission is referring to EFS, which was approx 69% for NUSI at 1 year.
NUSI continuation after 36 months	90%	Assumption	While it is reasonable to assume discontinuation, this figure is uncertain. Not consistent with the base case economic model, which assumed zero NSN discontinuation.
Patients not seeking treatment	2 patients /year	Assumption	

Source: compiled during the evaluation. BSC = best supportive care; ONA = onasemnogene abeparovvec, NSN=NUSI.

6.57 The submission’s estimated use and financial impact of listing is presented below.

Table 16: The estimated use and financial impact of listing

Estimates	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
ONA costs						
Australian live births	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
SMA population	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
SMA Type 1	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
NUSI patients - 24 months	█ ²					
NUSI patients - 12 months	█ ²					
Patients already treated	-█ ²					
Patients not seeking treatment	-█ ²					
Total prevalent patients	█ ²					
Total available patients	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
AAV ₉ positive patients	-█ ²	-█ ²	-█ ²	-█ ²	-█ ²	-█ ²
Total eligible patients	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Patients not seeking treatment	-█ ²	-█ ²	-█ ²	-█ ²	-█ ²	-█ ²
Treated patients	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
MTOP patients*	█ ²					
AVXS MAP patients**	█ ²					
Total ONA patients (scripts)	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
MTOP ONA costs	█ ³					
Total ONA costs – PBS	█ ⁴	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵
Concomitant PBS medicines	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶
Total PBS cost of listing ONA	█ ⁴	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵
NSN cost offsets						
NSN - initiating patient	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
NSN - initiating scripts	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
PBS costs - initiating scripts	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
NSN - continuing patient	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
NSN - continuing scripts	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
PBS costs - continuing scripts	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ³	█ ³
Total NSN cost offsets – PBS	█ ³	█ ³	█ ³	█ ⁷	█ ⁷	█ ⁷
Net PBS cost of listing ONA	█ ⁵	█ ⁸	█ ⁸	█ ⁸	█ ⁸	█ ⁸

* MTOP: Medical Treatment Overseas Program patients (N=<500) were included in the total patients (N=<500) in Year 1; ** The Market Access Program (MAP) patients (N=<500) did not contribute to the PBS drug costs but were included for the MBS costs associated with treatment

SMA=spinal muscular atrophy; Source: Table 4.5, 4.7 of the submission and calculated during the evaluation.

The redacted values correspond to the following ranges:

¹ 300,000 to < 400,000

² < 500

³ \$10 million to < \$20 million

⁴ \$60 million to < \$70 million

⁵ \$50 million to < \$60 million

⁶ \$0 to < \$10 million

⁷ \$20 million to < \$30 million

⁸ \$30 million to < \$40 million

6.58 The pre-PBAC response noted that “since lodgement of the original submission, children with Type 1 SMA have continued to be treated with ONA under various early access routes in Australia and an additional six children have now been treated”. [REDACTED]

6.59 The net cost to the PBS of listing ONA was estimated by the submission to be over \$30 million to < \$40 million in Year 6, and \$200 million to < \$300 million in the first 6 years of listing. This included a net PBS offset for NUSI of \$100 million to < \$200 million over six years, based on the published price for NUSI, and included the cost for patients treated through the Medical Treatment Overseas Program.

6.60 The PBAC noted the submission’s assumption ONA will replace NUSI is not consistent with the requested PBS restriction and has a large impact on the cost to the PBS.

6.61 The PBAC noted the submission’s estimates do not account for the recent MSAC support for public funding of reproductive carrier testing to detect cystic fibrosis, SMA and fragile X syndrome pathogenic variants in women early in pregnancy or intending to become pregnant, and in their reproductive partners as needed (MSAC 1573).

Quality Use of Medicines

6.62 No quality use of medicines information was presented in the submission.

Financial Management – Risk Sharing Arrangements

6.63 The PBAC noted the submission listed a number of options for structuring payments for ONA, including payments by instalment, a pay-for-performance model or a more traditional PBS-type agreement with ‘list versus effective’ pricing rebates and expenditure caps.

6.64 The PBAC advised the usual practice of paying the full price³ for each prescription up front may not be appropriate for ONA. The PBAC considered an instalment and performance based payment arrangement may be an appropriate means of managing the risk to the payer that ONA will not deliver the long term improvements in function predicted by the submission, particularly in the context of the available short duration of follow up of a small number of patients. The Pre-PBAC response noted that the price in the submission is influenced by the exchange rate at the time, and that the upfront payment for ONA should be taken into the context of it being a once only payment while treatment with NUSI involves ongoing costs.

³ With or without a Special Pricing Arrangement rebate.

- 6.65 In the event ONA is recommended for subsidy, the PBAC considered it appropriate for long-term data on the effectiveness and safety of ONA to be captured in a registry as a way to better inform the cost-effectiveness of treatment with ONA in the longer term. The PBAC noted a registry may form part of the TGA Risk Management Plan (RMP). The PBAC requested the applicant provide further information on this matter to allow the PBAC to consider whether the RMP data could be used for an instalment based payment arrangement and/or for monitoring and reviewing cost-effectiveness, or whether it would need to be supplemented with further data elements (see additional comments in PBAC outcome regarding potential need for a disease-based registry).

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

7 PBAC Outcome

- 7.1 The PBAC deferred making a decision on the request for PBS listing of onasemnogene abeparvovec (ONA) (Zolgensma®) in patients less than 2 years of age with confirmed Type I SMA (based on genotype and phenotype) to allow the TGA to confirm the indication for the therapy and work to be progressed on a Decision Support Analysis as described below. However, as set out above, the PBAC had a number of concerns with the current subsidy proposal for ONA. Most importantly, the PBAC did not accept the submission's claim that ONA is superior in terms of effectiveness and safety compared to NUSI. Overall, having considered all the available evidence, the PBAC concluded that, on balance ONA would likely deliver similar clinical outcomes to NUSI in matched patients (see Clinical Claim above).
- 7.2 The PBAC recognised the high clinical need for effective treatments to treat Type I SMA and noted that ONA is a new in class therapy, which will expand the options available for patients and their families. The PBAC noted the consumer comments describing the perceived quality of life improvements for patients and their families and indicating that patients value the once off treatment for ONA which avoids the trauma associated with ongoing intrathecal injections of NUSI. In the absence of substantial new clinical data, which is unlikely to be forthcoming, and in the context of the high clinical need for effective treatments for SMA, the PBAC considered a simple "frame of reference" cost-comparison with NUSI may provide a way forward.
- 7.3 The PBAC considered that without a TGA decision on the key aspects of the indication viz: patient age at time of treatment; number of copies of the survival motor neuron 2 (SMN2) gene; defined SMA type and symptomatic versus pre-symptomatic status, it would be premature for PBAC to recommend PBS eligibility criteria.
- 7.4 The PBAC noted that evidence for ONA consisted of small single arm studies (N<35 in each study). The PBAC considered the claim of improved survival and motor functioning with ONA compared with BSC was reasonable, however, the size of the benefit is uncertain because of the lack of a comparator arm in the ONA studies and

because the natural history studies may not adequately capture improvements in supportive care over time.

- 7.5 The PBAC noted the main evidence supporting the clinical claim for ONA was an unanchored matching adjusted indirect comparison (MAIC) of ONA versus NUSI which was only able to adjust for two factors (baseline CHOP-INTEND score and proportion with nutritional support). The PBAC did not accept the claim that ONA is superior to NUSI in terms of effectiveness, noting the study populations in the MAIC remained imbalanced, with the results of the MAIC likely to be biased against NUSI. Further, the results of the MAIC did not show a statistically significant improvement in OS for ONA compared to NUSI and the confidence intervals were very wide due to the small sample size in ONA trials.
- 7.6 The PBAC did not accept the claim of superior safety for ONA versus NUSI, noting this was not consistent with the presented evidence, where safety data presented for ONA and NUSI indicated that ONA had a similar or greater proportion of patients with any AE, serious AEs, and treatment related serious AEs and noting the black box safety warning for the risk of acute serious liver injury.
- 7.7 Overall, the PBAC concluded that, on balance ONA would likely deliver similar clinical outcomes to NUSI in matched patients.
- 7.8 The PBAC considered the cost-effectiveness analysis presented in the submission was not suitable to support decision-making.
- 7.9 The PBAC noted that there are now a number of therapies available for the treatment of SMA internationally, one of which is currently registered and subsidised in Australia for a defined group of patients. Others are either in development, or being considered for registration by the TGA and for public subsidy by the PBAC. These therapies include NUSI (sponsored by Biogen), ONA and branaplam (sponsored by Novartis) and risdiplam (sponsored by Roche).
- 7.10 The PBAC further noted that up to now, PBAC has been presented with subsidy applications for therapies for SMA sequentially with evidence based on sub-populations and stages of treatment. Submissions for NUSI were considered at the November 2017, March 2018, July 2018, July 2019, November 2019 and July 2020 PBAC meetings, submissions for NUSI, and for ONA were considered at the November 2020 PBAC meeting, and further PBAC submissions are expected in 2021.
- 7.11 The PBAC noted that whilst this approach reasonably reflects the different timeframes in which these therapies and/or new clinical data have become available, it means that it has not been in a position to conduct an overall assessment of all available therapies across the whole of this comparatively rare disease for which direct treatments have only become available in the past 5-years.
- 7.12 The PBAC noted this submission-by-submission approach is further complicated because NUSI, ONA and risdiplam/branaplam have different mechanisms of action or

routes of administration. However, at present there is very little information on how these three types of therapies could best be, or are being, used in SMA patients in clinical practice, for example, as monotherapy, or sequential monotherapy (on failure of prior therapy), or concomitantly in all or certain patients.

- 7.13 The PBAC considered an overall and holistic approach to consideration of the entire treatment algorithm and the strength of all available evidence would better support its decision making, particularly given that only short-term clinical data are available but the claims from each sponsor make varying predictions about the benefits of each treatment into the future which cannot be reconciled by an assessment of individual submissions independently from each other.
- 7.14 The PBAC noted its ESC canvassed the potential for a decision support analysis encompassing all available therapies with the applicant and that the applicant Pre-PBAC Response was strongly opposed to such an approach. The applicant argued such an analysis would be premature ahead of PBAC consideration of risdiplam and that PBAC had recently made a decision on NUSI for pre-symptomatic treatment and therefore could make a decision on ONA. Finally, the applicant asserted that PBAC is the independent body best positioned to consider this as it is privy to unpublished data and the prices for each therapy.
- 7.15 However, for the reasons given above, the PBAC considered it was in the interests of patients and families, prescribers and payers for a decision support analysis for SMA treatment that takes into account all the currently available clinical data and informs a broader “whole of disease” economic and financial analyses.
- 7.16 Noting the responses of the companies to the approach proposed by its ESC, the PBAC requested the Department convene a stakeholder meeting including clinical experts, consumer representatives and relevant sponsors with the intention of progressing work towards a decision support analysis for SMA. The PBAC considered an appropriate starting point would be for the stakeholder meeting to consider the following issues for each of the two broad groups of patients, presymptomatic and symptomatic for whom treatment with one, or more, SMA therapies may be considered. The PBAC noted these issues are intended to be a starting point for discussion and further matters may arise.

Pre-symptomatic

- For diagnosis by genotype alone –
 - What SMN2 copy numbers should be eligible to initiate treatment
 - Should antenatal genetic diagnosis be confirmed by post-natal genetic testing
- First, second and subsequent line treatment options
- Criteria to determine when to move to second or subsequent options
- Concomitant therapy
- Therapy continuation rules
- When to stop therapy

Symptomatic

- Who should be treated: some patients can access now, some not.
 - First line treatment options (if not treated while presymptomatic)
 - Criteria to determine when to move to second or subsequent options
 - Concomitant therapy
 - Therapy continuation rules
 - When to stop therapy
- 7.17 The PBAC noted that the limited clinical data available may make it more difficult to conduct robust economic and financial analyses that reflect the preferred treatment algorithm(s). However, the PBAC considered this does not, of itself, justify continuing the current piecemeal approach.
- 7.18 The PBAC noted a disease-based registry, rather than therapy-based registries, may be appropriate for informing the cost-effectiveness of all SMA therapies.
- 7.19 The PBAC noted that the effective price requested for ONA is more than three times the price requested for voretigene naparvovec (VOR, Luxturna®) another single-dose gene therapy that is also sponsored by Novartis. The PBAC advised the Minister consider whether this price differential is justified, particularly as the TGA has advised the manufacturing methods for both therapies appear broadly similar, albeit more production batches may be needed to produce the sufficient product to treat the same number of patients with ONA compared to VOR (ONA is dosed at 1.1×10^{14} vector genomes per kg; VOR at 1.5×10^{11} vector genomes per eye).
- 7.20 The PBAC noted that the Japanese reimbursement price for ONA is ¥ [REDACTED]⁴ or approx. \$ [REDACTED] AUD, around \$ [REDACTED] less than the requested price to the PBS. The pre-PBAC response added that in Japan, this is a single up-front payment for all Types of SMA in patients under the age of 2 years old, whether they are symptomatic or pre-symptomatic, and not restricted by number of SMN2 gene copy numbers.
- 7.21 The PBAC noted that the estimated net cost to the PBS of listing ONA was estimated by the submission to be over \$30 million to < \$40 million in Year 6, and \$200 million to < \$300 million in the first 6 years of listing. This included a net PBS offset for NUSI of \$100 million to < \$200 million over six years, based on the published price for NUSI, which is unlikely to be realised. The PBAC also noted advice in the pre-PBAC response that [REDACTED].

Outcome:

Deferred

⁴ www.mhlw.go.jp/content/12404000/000629578.pdf

Addendum to the November 2020 PBAC Minutes:

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

8 PBAC Outcome

- 8.1 The PBAC maintained its deferral from the November 2020 meeting for PBS listing of onasemnogene abeparvovec (ONA) for spinal muscular atrophy (SMA) as a number of concerns with the subsidy proposal remained. The PBAC noted the proposed population was revised to patients aged less than 9 months, with 1-3 copies of the SMN2 gene, and that patients with 3 copies of SMN2 are currently not eligible for treatment with nusinersen (NUSI). The PBAC considered the request for inclusion of patients with 3 copies of SMN2 was not adequately supported, and at the requested price ONA was unlikely to be cost-effective in these patients. The PBAC considered that the cost-minimisation analysis for ONA versus NUSI should be revised to take into account discounting of costs in the forward years, and an analysis versus risdiplam (as a near market comparator) should also be presented. The PBAC considered that the proposal which was conditional on an upfront payment with no outcomes-based measures did not adequately address the uncertainties with the clinical evidence and associated cost-effectiveness.
- 8.2 The PBAC noted that there is a clinical need for treatments for SMA with less invasive routes of administration compared with NUSI. The PBAC recalled its March 2021 recommendation for the PBS listing of orally administered risdiplam for symptomatic patients, and noted that evidence in treatment of pre-symptomatic patients from the RAINBOWFISH trial is expected to be available in the near future. The PBAC noted ONA is a gene therapy intended for once-off use.
- 8.3 The PBAC noted the sponsor's deferral proposal was an effective price of \$ [REDACTED], and that this price was conditional on ONA being available to all SMA patients aged <9 months with no restriction on SMA Type and including patients with 1-3 SMN2 copies, paid for as a single, upfront payment with no outcome measures or expenditure caps.
- 8.4 The PBAC noted that following the November 2020 deferral, the sponsor received notice of the outcomes of the second ACM meeting, at which the indication for onasemnogene abeparvovec (ONA) was confirmed:

for the treatment of paediatric patients less than 9 months of age with symptomatic or pre-symptomatic spinal muscular atrophy with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene and 1 to 3 copies of the SMN2 gene.

- 8.5 The PBAC noted that the approved indication for ONA resulted in changes to the population proposed compared with that previously considered. Specifically, the population was reduced from patients aged less than 2 years to patients aged less than 9 months but was broadened from Type 1 SMA patients to include both symptomatic and pre-symptomatic patients with 1-3 copies of the SMN2 gene. The PBAC noted that the requested population was broader than the existing listings for NUSI in pre-symptomatic patients, where patients must have 1-2 copies of the SMN2 gene. The PBAC noted that the population with 3 copies of SMN2 would encompass patients with a later onset of symptoms and disease severity consistent with SMA types 2 or 3. The PBAC noted that NUSI is not the appropriate comparator for pre-symptomatic patients with 3 copies of SMN2. The PBAC considered that for these patients ONA may be substantially less cost-effective and a cost offset for reduced NUSI use should not be included in the financial estimates. The PBAC considered the request for inclusion of patients with 3 copies of SMN2 was not adequately supported.
- 8.6 The PBAC noted that the submission stated there are patients currently treated with NUSI who may wish to then be treated with ONA. The PBAC noted that there may also be patients treated with risdiplam who wish to then be treated with ONA. The sponsor reported that in Australia children are now required to wait 3 months after their NUSI dose to be treated with ONA to address potential safety concerns where ONA is dosed too soon after the last NUSI dose. The sponsor suggested that dosing of ONA following NUSI could be managed through additional restrictions for the ONA listing and flow-on changes to existing NUSI listings that would prevent patients receiving ongoing treatment with NUSI following ONA dosing.
- 8.7 The PBAC noted that the sponsor did not specifically propose any limitations on the use of other disease-modifying treatments following dosing with ONA, which the sponsor considered to be concomitant use. The sponsor suggested that restrictions could be added to the NUSI and risdiplam listings to limit the circumstances under which they could be used following treatment with ONA, however noted in the absence of guidelines these criteria would be hard to determine. The sponsor further acknowledged the comments from the December 2020 SMA stakeholder meeting that access to alternative treatments needed to be available if there came a time that there was a need. The sponsor considered that access to further treatment following ONA should be based on the loss of key objective clinical criteria and not whether a patient reaches a developmental milestone.
- 8.8 The PBAC noted no evidence was presented that supported additional benefit with NUSI or risdiplam following ONA dosing. The sponsor considered that the evidence in 4 children from the START-LT study, who were treated with ONA followed by NUSI, did not demonstrate any additional benefit from NUSI. The PBAC considered that

sequential (concomitant) therapy following ONA dosing may be reasonable in the circumstance of treatment failure, however such use was not considered in the economic analysis presented. The PBAC considered the evolving treatment algorithm for SMA medicines, including use of other SMA medicines following ONA dosing, will require further advice from clinical specialists to consider the most clinically appropriate sequencing criteria.

- 8.9 The PBAC noted that updated data from the START-LT and SPR1NT studies were provided. The additional data from START-LT (Type 1 patients) showed all patients are still alive with a mean age of 6.5 years for the low therapeutic dose and 5.3 years for the therapeutic dose. The additional data from the SPR1NT pre-symptomatic study showed all children are still alive at mean ages of 15.6 months and 15.3 months for 2 and 3 SMN2 copy children, respectively. The updated data from both studies also showed no patients requiring permanent ventilation. In the SPR1NT study, 71% of children within the standardised normal walking age with 2 SMN2 copies were walking without assistance and 100% of 3 SMN2 copy children. The PBAC noted the additional follow-up data for the trials, supporting ongoing efficacy of ONA up to around 7 years, however PBAC considered that the extent of attenuation of treatment effect beyond 7 years is unknown. The PBAC also noted that the evidence in the pre-symptomatic population was limited, including only 29 patients with pre-symptomatic SMA (14 with 2 SMNs copies and 15 with 3 SMN2 copies) and less than 2 years of follow up.
- 8.10 In the deferral proposal a cost-minimisation analysis was undertaken on the basis of the therapeutic conclusion that ONA is non-inferior to the main comparator, NUSI, when used in the requested indication. The PBAC recalled “overall, having considered all the available evidence, the PBAC concluded that, on balance ONA would likely deliver similar clinical outcomes to NUSI in matched patients” (paragraph 7.1, ONA Public Summary Document (PSD), November 2020 PBAC meeting).
- 8.11 The PBAC noted that the proposed equi-effective doses of ONA and NUSI were based on the recommended dosing regimens, including loading doses for NUSI. The cost-minimisation calculations presented included administration costs and were based on treatment over seven years which corresponds to the longest follow-up data currently available from the ONA trials. The PBAC considered that seven years was a reasonable duration for the basis of the cost-minimisation analysis. The PBAC noted that in the calculations presented the costs were not discounted at 5% per annum as recommended in the guidelines for preparing PBAC submissions. Applying discounting reduced the cost of NUSI relative to the cost of ONA. The PBAC further noted that the calculations did not take into account any potential impact from patients treated with ONA requiring additional SMA treatments. The PBAC considered a cost-minimisation analysis included in any revised proposal should discount costs as per the PBAC guidelines, and an analysis versus risdiplam should be presented based on the PBAC’s recommendation at the March 2021 PBAC meeting. The PBAC considered the need

for additional treatments following ONA could potentially be addressed through a performance based payment arrangement.

- 8.12 The PBAC considered the proposal of a single, upfront payment with no outcome measures or expenditure caps was not adequately justified given the high up-front cost, the uncertainties inherent for gene therapies as an emerging technology, and the limited clinical data currently available with more evidence being collected for ONA and the comparator treatments. The PBAC considered that an outcomes based measure is likely to be required to provide confidence that the extent of benefit claimed for ONA is realised in clinical practice.
- 8.13 The PBAC would welcome a revised proposal addressing the patient population and restriction issues, as well as the uncertainties noted with the cost-minimisation analysis potentially with a performance based payment arrangement. The PBAC noted that it may be appropriate for any such arrangement to manage the likely risks over a five year time horizon consistent with the usual period of a Deed of Agreement rather than over the period for the cost-minimisation analysis.

Outcome:

Deferred

Second Addendum to the November 2020 PBAC Minutes:

**4.04 ONASEMNOGENE ABEPARVOVEC,
Solution for injection,
Various pack sizes (16.5-74.3 ml),
Zolgensma[®],
Novartis Pharmaceuticals Australia Pty Ltd**

9 PBAC Outcome

- 9.1 Following a revised proposal from the sponsor, the PBAC recommended the Section 100 (Highly Specialised Drugs Program) listing of onasemnogene abeparvovec (ONA) for the treatment of Spinal Muscular Atrophy (SMA) in patients aged less than 9 months, with Type 1 SMA or pre-symptomatic patients with 1-2 copies of the SMN2 gene. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of ONA would be acceptable if it were cost-minimised to the least costly disease-modifying therapy for this condition, which is risdiplam (RIS), and in the context of an outcomes-based risk sharing arrangement (RSA).
- 9.2 The PBAC considered nusinersen (NUSI) was an appropriate comparator, however considered RIS was also an alternative therapy. The PBAC's recommendation was based on ONA (at the individualised dose based on 1.1×10^{14} vector genomes per kilogram (vg/kg) of body weight) being no more costly than RIS at the recommended dose over a period of ■ years with costs discounted at 5% annually. The PBAC also considered that an outcomes-based RSA would be required to mitigate the financial risk to the Commonwealth associated with the significant upfront payment for ONA where the treatment fails, resulting in death, permanent ventilation or lack of efficacy.
- 9.3 The PBAC noted that the requested population was revised from its previous consideration to patients aged up to 9 months with Type 1 SMA, and pre-symptomatic patients with 1-2 copies of the SMN2 gene which reflects the existing PBS listings for NUSI in pre-symptomatic patients. The PBAC considered the patient population to be appropriate given that the basis for listing is a cost-minimisation analysis versus NUSI.
- 9.4 The PBAC considered it would be appropriate for patients receiving treatment with NUSI or RIS to be eligible for treatment with ONA, except where invasive permanent assisted ventilation is required in the absence of a potentially reversible cause. PBAC also noted that consultation with clinicians is required to ensure that the restrictions for ONA, RIS and NUSI accommodate an appropriate washout period prior to ONA dosing.

- 9.5 The PBAC noted that the sponsor proposed criteria to allow the use of other disease-modifying treatments following dosing with ONA, based on the loss of key objective clinical criteria. For a child who has been dosed on ONA, the proposed criteria for being able to access either RIS or NUSI were:
- the child must have demonstrated a loss of an already gained milestone (as per the WHO definition);
 - the loss of the milestone cannot be because of acute illness or non-compliance with standard of care therapy (for example, physiotherapy);
 - the milestone gain and loss must have been documented;
 - the milestone loss must have been observed for a period of 3 months; and
 - the milestone loss must be confirmed by both the requesting clinician and one other clinician.
- 9.6 The PBAC noted that the proposed criteria do not allow access to other disease-modifying treatments when a patient treated with ONA fails to reach a developmental milestone. The sponsor’s proposal stated “Novartis does not believe that the use of additional SMA treatments post-ONA treatment is required or that there is biological plausibility for their use that would lead to superior outcomes”. However, the PBAC considered that further consultation with clinicians was required to ensure that the proposed criteria for access to NUSI or RIS following ONA are clinically appropriate, and specifically that precluding access to other disease-modifying treatments following dosing with ONA could be reasonably implemented. The PBAC 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 disease-modifying treatments needed to be accounted for in the RSA.
- 9.7 The PBAC considered NUSI was an appropriate comparator, however considered RIS was also an alternative therapy. The PBAC recalled its previous conclusion that “on balance ONA would likely deliver similar clinical outcomes to NUSI in matched patients” (paragraph 7.1 above). The PBAC also recalled that RIS was recommended for listing on the basis of a cost-minimisation analysis versus NUSI (para 7.1 risdiplam PSD, March 2021 PBAC meeting). The PBAC noted that the cost of treatment with RIS was less than for NUSI reflecting that the cost-minimisation analysis for RIS versus NUSI assumed that all patients received the maximum RIS dose of 5 mg per day and excluded the costs for the NUSI loading doses and administration (para 7.9, risdiplam PSD, Mar 2021).
- 9.8 The PBAC did not accept the sponsor’s argument that NUSI was the only alternative treatment for pre-symptomatic patients, noting that patients who initiate treatment with NUSI under the pre-symptomatic listing would become eligible for treatment with RIS through the continuing treatment listing. The PBAC also did not accept that NUSI was the only alternative treatment for patients treated prior to 8 weeks of age,

noting that although the TGA indication, but not the PBS listing, precluded the use of RIS in patients under the age of 8 weeks, this was an insignificant period of time compared to treatment over the patients' lifetime. As such, the PBAC did not accept that there are two distinct populations with different eligibility for NUSI versus RIS and considered RIS is an alternative therapy for the entire patient population. 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 PBAC did not accept that ONA provides a significant improvement in efficacy or reduction in toxicity over RIS, and therefore there was no basis for ONA to be more costly than RIS.

- 9.9 The PBAC noted that the proposal's cost-minimisation calculations applied the maximum dose for RIS and this resulted in the cost of RIS being overestimated. The PBAC considered it would be appropriate for the first 5 years of the analysis to use the WHO reported median weight for age reference data and the recommended dose of RIS⁵ to estimate the cost. Beyond 5 years it would be reasonable to assume that patients are treated with the maximum RIS dose (5 mg).
- 9.10 The PBAC noted a full upfront payment for ONA was requested. In the cost-minimisation calculations presented, contrary to the PBAC's previous advice, costs were not discounted. The PBAC noted the arguments in the proposal that discounting of costs was not justified for a cost-minimisation analysis and that discounting would have been factored into the assessment of the cost-effectiveness of NUSI. The PBAC noted that discounting usually has no impact in a cost-minimisation analysis as the costs and outcomes for the proposed and comparator treatments are aligned in terms of timing, however this is not the case for the comparison of ONA and NUSI/RIS. The PBAC noted that discounting is applied in economic analyses to account for time preference and uncertainty in the future and there is nothing fundamentally different between applying discounting in a cost-minimisation analysis compared with a cost-effectiveness analysis. On this basis, the PBAC considered that it would be appropriate to apply discounting at 5% per annum in the cost-minimisation analysis for ONA. As there is no difference in outcomes over time for ONA compared with NUSI/RIS discounting of outcomes has no impact on the analysis and therefore is not required. Given the difference in the timing of the costs with 100% of the cost of ONA being up front versus ongoing costs for NUSI/RIS, discounting of the costs is appropriate.

⁵ <https://www.who.int/tools/growth-reference-data-for-5to19-years/indicators/weight-for-age-5to10-years>

For patients aged 2 months to <2 years the dosage is 0.2 mg/kg, for patients aged >2 years and <20 kg the dosage is 0.25 mg/kg per day and for patients >20 kg the dosage is 5 mg per day.

For example, based on a median weight of 8.9 kg for girls and 9.6 kg for boys at 1 year of age, the average dose of RIS would be approximately 1.85 mg per day.

- 9.11 The PBAC noted that evidence of ongoing treatment benefit is available for up to seven years after dosing with ONA and recalled it had previously considered that seven years was a reasonable duration for the basis of the cost-minimisation analysis (paragraph 8.11 above). The PBAC considered that a longer duration, of up to ■ years, would be acceptable for the analysis, provided (i) an outcomes-based RSA provided for a ■% rebate of the cost of ONA for all patients who were placed on invasive permanent ventilation, died or were subsequently treated with NUSI or RIS over at least five years post listing, consistent with the standard period of a PBS Deed (noting that the criteria for subsequent treatment are to be confirmed with clinical experts), and (ii) ONA clinical trial data with longer term follow-up are provided for consideration by the PBAC before the end of that five year term in order to determine if the ■ year duration, or a shorter duration, should be used for the cost-minimisation analysis to inform the ONA price for a subsequent Deed.
- 9.12 The PBAC noted that the proposal included an outcomes-based RSA seeking to address the uncertainties with the clinical evidence and associated cost-effectiveness, and provide confidence that the extent of benefit claimed for ONA is realised in clinical practice. Under the proposed RSA, for patients treated with ONA who die or are placed on invasive permanent assisted ventilation within two years of receiving treatment, ■% of the upfront cost of ONA would be rebated. For patients who lose a previously gained milestone within the first two years of receiving ONA treatment (consistent with the milestones defined in the proposed restriction, see para 9.5), ■% of the upfront cost of ONA would be rebated. The sponsor noted that data supporting this RSA would come from two sources: i) the RESTORE registry, with Australian clinicians managing patients treated with ONA being required to participate in the registry; and ii) Services Australia Authority approvals documentation for patients approved for subsequent use of NUSI and RIS.
- 9.13 The sponsor stated that the risks the RSA is designed to mitigate are low. Only two patients had died by end of the START and STRIVE-US studies and the interim analysis of STRIVE-EU (68/70, 97%). Both these patients died within a year of treatment (Day 53 and Day 171). The interim analysis of the SPR1NT trial (in pre-symptomatic patients) showed that all patients were still alive at 2.9 years median follow-up. At the five-year follow up for the START trial (Mendell et al, 2021) all patients were alive, irrespective of whether they had the low or the therapeutic dose. The data also shows that no child had lost any gained milestones within the five-year follow-up period. Data regarding loss of milestones is not available for the other studies. The PBAC considered that few patients would meet the criteria for loss of milestones within 2 years as the natural history data demonstrates that paediatric SMA patients typically fail to progress rather than regress.
- 9.14 The PBAC noted the applicant's proposed RSA did not address the risk of patients treated with ONA failing to meet developmental milestones to at least the same extent that would be expected for patients treated with NUSI or RIS. The PBAC

considered that further consultation with clinicians was required to ensure the restrictions for ONA and flow-on changes to the RIS and NUSI restrictions were clinically appropriate, and that any access to subsequent disease-modifying treatments needed to be accounted for in the RSA.

9.15 In summary, the PBAC considered that the outcomes-based RSA should encompass a ■■■% rebate for the cost of ONA, over at least 5 years post-listing, in the following circumstances following treatment with ONA:

- Where a patient has died;
- Where a patient is placed on invasive permanent ventilation; and
- Where a patient has subsequent PBS-subsidised treatment with NUSI or RIS.

The PBAC advised that the sponsor work with the Department to ensure that the required data to inform this arrangement would be appropriately collected.

9.16 As noted in paragraph 9.11, the PBAC considered that ONA clinical trial data with longer term follow-up should be provided for consideration by the PBAC to be able to occur prior to five years elapsing since the listing of ONA on the PBS, to determine if the 11 year duration, or a shorter duration, should be used for the cost-minimisation analysis to inform the ONA price for a subsequent Deed.

9.17 The PBAC noted that the proposal presented revised financial estimates that assumed < 500 patients will receive ONA in the first year and then around < 500 patients in each year following. The PBAC noted that the number of patients in year 1 is higher due to additional patients identified between ONA registration (February 2021) and anticipated PBS listing. The estimates assumed ■■■% uptake for eligible patients. The PBAC considered that cost-offsets from RIS were overestimated as they assume the maximum dose for RIS. The PBAC noted that listing of ONA would not be cost-neutral to the PBS within the 6 years of forecasts and the acceptance of a time horizon of up to ■■■ years for calculation of the cost-minimised price of ONA would further increase the time-frame for reaching cost-neutrality. The PBAC advised that a total cap on expenditure based on the proposed estimates may be appropriate to manage the total financial impact associated with the listing.

9.18 The PBAC recommended that onasemnogene abeparvovec should not be treated as interchangeable on an individual patient basis with any other drugs.

9.19 The PBAC noted the flow-on restriction changes required for RIS and NUSI as described in paragraph 9.5 and 9.6 which are likely to result in complex changes to restrictions and require additional consultation with clinicians.

9.20 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because ONA is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over NUSI or RIS, the criteria

prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.

9.21 The PBAC noted that this submission is not eligible for an Independent Review.

Outcome:

Recommended

Web outcome

10 Recommended listing

To be finalised.

11 Context for Decision

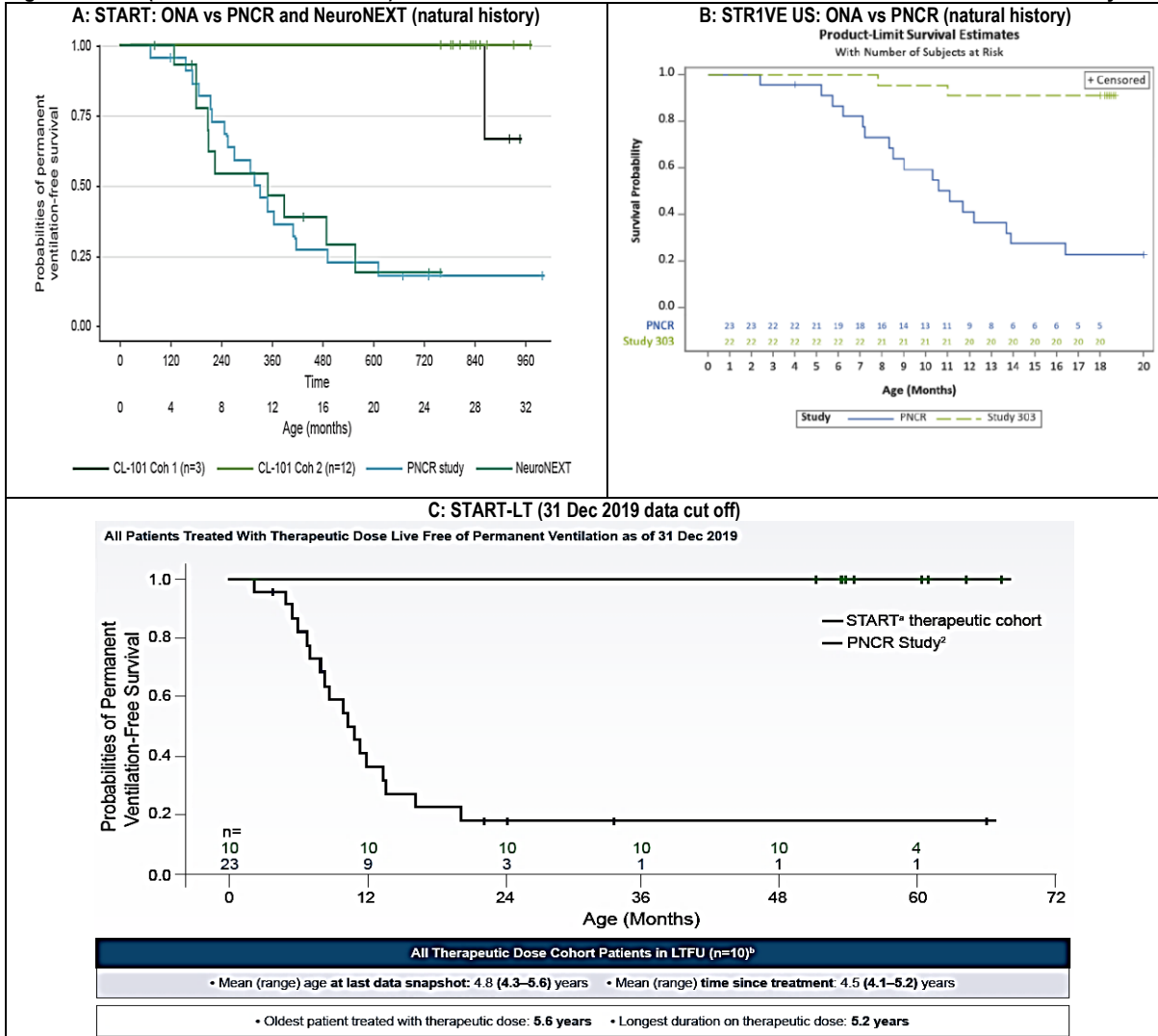
The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. 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.

12 Sponsor's Comment

Novartis is pleased to receive the positive recommendation for Zolgensma. We are appreciative of the willingness of the PBAC and Department to work with us to finalise the recommendation. We look forward to this work providing timely access to the first gene therapy for SMA on the PBS

Appendix 1 – Additional figures and tables referred to in text

Figure 4: EFS (ventilation free survival) from ONA studies START, STR1VE US and START-LT vs natural history



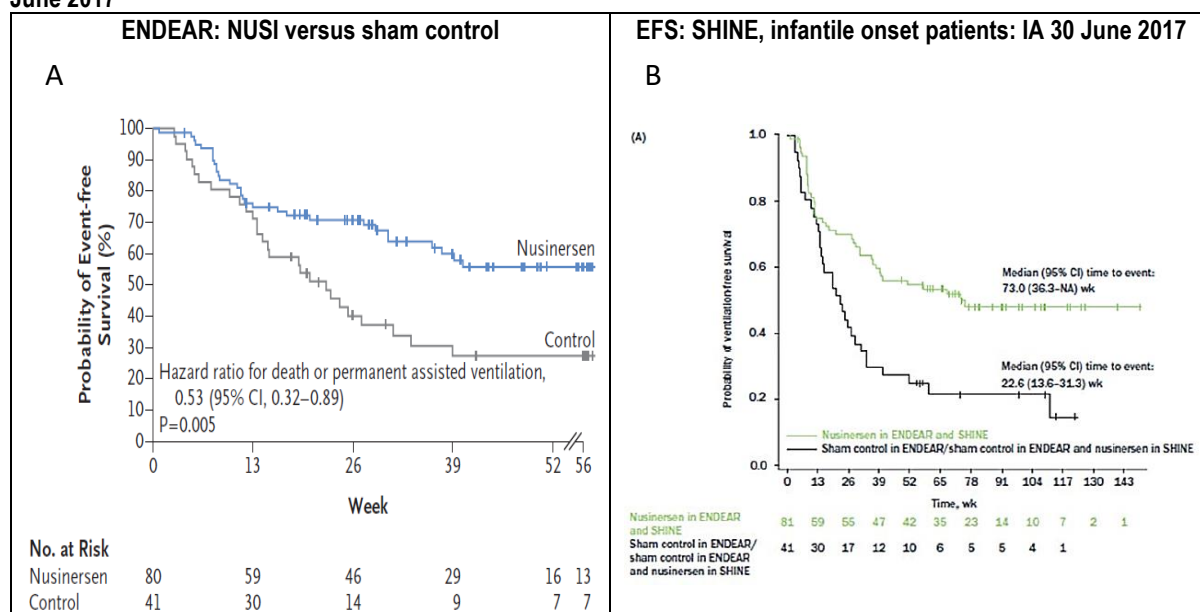
Source: Figure 2.12 p112, Figure 2.17, p121, Figure 2.28, p143 of the submission. Finkel et al 2014, Kolb et al 2017, Attachment 9 of submission.

Note: The percentages of infants who were event-free in a study of SMA conducted by the PNCR network included ventilation-free survival measured as time until death or the need for ventilation for at least 16 hours/day for at least 14 consecutive days. In the NeuroNEXT study, a prospective natural history study in SMA infants with two copies of SMN2, survival is defined as alive without tracheostomy.

^a: Study number: NCT02122952

²: 2 patients discontinued from START-LT are being followed by PNCR

Figure 5: EFS NUSI studies: A: ENDEAR (NUSI versus sham control) B: SHINE, infantile-onset patients: IA: 30th June 2017



Source: Figure 2, Finkel et al 2017 for ENDEAR trial, Figure 2.40, p171 of the submission, NICE Assessment Report, page 238-9 Attachment 5.

IA=interim analysis

Table 8: Motor milestones and other achievements in Cohort 2 at 24 months post ONA administration in START vs historical cohorts

Endpoint	Cohort 2 (n=12)	Historical cohorts (N=33)
Motor milestone achievements, n (%)		
Brings hand to mouth	12 (100)	NR
Controls head	11 (91.7)	0‡
Rolls over†	9 (75.0)	0‡
Sits with assistance	11 (91.7)	0‡
Sits unassisted§		
≥5 seconds	11 (91.7)	0‡
≥10 seconds	10 (83.3)	0‡
≥30 seconds	9 (75.0)	0‡
Stands with assistance	2 (16.7)	0‡
Stands unassisted	2 (16.7)	0‡
Walks unassisted	2 (16.7)	0‡

Sources: Table 2.23, p115 of the submission.

n/N, number of infants meeting the criterion/number of infants in the group; NR, not reported; SMA, spinal muscular atrophy; WHO, World Health Organization.

At baseline, none of the infants in Cohort 2 had achieved any of the listed motor milestones, except for bringing a hand to the mouth. During the 24-month study period, the majority of these infants had reached ≥1 major motor milestone. No infants in Cohort 1 are listed, since none attained any motor milestones and did not receive the correct dose of ONA.

† According to item 20 on the Bayley-III assessment tool, rolling over is defined as movement of ≥180 degrees both left and right from a position of lying on the back.

‡ Data are from De Sanctis et al, 2016 for PNCR.

§ Sitting unassisted for ≥5 seconds is in accordance with the criteria of item 22 on the Bayley-III assessment tool gross motor subtest. Sitting unassisted for ≥10 seconds is in accordance with the criteria used in the WHO Multicentre Growth Reference Study. Sitting unassisted for ≥30 seconds defines functional independent sitting and is in accordance with the criteria of item 26 on the Bayley-III assessment tool gross motor subtest.

Table 9: ONA: Highest Development Milestone Achievement in START and START-LT and concomitant NUSI usage (As of 31 Dec 2019)

Patient ID	Highest Milestone Achieved in START(Video-Confirmed)	Highest Milestone Achievement in START-LT	NUSI Usage at Baseline in START-LT	NUSI Usage at Year 1 START-LT
E-01-643	None	None	Yes	Yes
E-02-491	None	None	No	Yes
E-03-285	None	Sitting with support	Yes	Yes
E-04-186*	Sits alone ≥5 seconds	Sitting without support	No	No
E-05-829*	Sits alone ≥30 seconds	Sitting without support	Yes	Yes
E-06-965*	Walks alone	Walk alone	No	No
E-07-254*	Sits alone ≥15 seconds	Stand with assistance	Yes	Yes
E-08-208*	None	Not in study	-	-
E-09-860*	Sits alone ≥30 seconds	Not in study	-	-
E-10-243*	Walks alone	Walk alone	No	No
E-11-174*	Sits alone ≥30 seconds	Stand with assistance	No	No
E-12-343*	Sits alone ≥30 seconds	Sitting without support	No	Yes
E-13-842*	Sits alone ≥30 seconds	Sitting without support	No	Yes
E-14-078*	Sits alone ≥30 seconds	Stand with assistance	No	No
E-15-098*	Sits alone ≥30 seconds	Sitting without support	No	No

Source: Table 2.31 of the submission, Study LT-001 Listing 16.2.4, Total patients in table is 15, so include 3 patients who were in Cohort 1 of START.

* Cohort 2, determined by cross checking against PrecisionHEOR indirect comparison report, p49, Attachment 11 of the submission.

Table 10: Highest milestone attained in long term follow up studies for ONA (START-LT) and NUSI (SHINE/ENDEAR)

n/N(%)	None	Sit with support	Sit without support	Hand & knees crawling	Stand with assistance	Walk with assistance	Stand alone	Walk alone	Co admin NUSI
START-LT/START									
- end of START (≥20mth of age, mean age 27.9mth)	4/15 (27%)	2 [^] /15 (13%)	9/15 (60%)	NR	-	-	-	2/15 (13%)	NR
- Mean age 4.8 yrs*	2/15 (13%)	1/15 (7%)	5/15 (33%)	NR	3/15 (20%)	-	-	2/15 (13%)	7/15 (47%)
SHINE/ENDEAR (NUSI in ENDEAR)									
- 2.08 yrs since 1 st dose	NR	NR	22/59 (37%)	1/59 (2%)	5/59 (8%)	3/59 (5%)	0/59 (0%)	0/59 (0%)	-
- 3.4 yrs since 1 st dose of NUSI	NR	NR	37/58 (64%)	3/58 (5%)	11/58 (19%)	4/58 (7%)	1/58 (2%)	1/58 (2%)	-
SHINE/ENDEAR (Sham control in ENDEAR)									
- 1.34 yrs since 1 st dose	NR	NR	0/22 (0%)	0/22 (0%)	0/22 (0%)	0/22 (0%)	0/22 (0%)	0/22 (0%)	-
- 2.65 yrs since 1 st dose of NUSI	NR	NR	1/20 (5%)	0/20 (0%)	0/20 (0%)	0/20 (0%)	0/20 (0%)	0/20 (0%)	-

Source: Compiled during the evaluation from Table 2.31 of the submission and Castro 2020 (p8).

[^] assumed to be those who could sit for ≥5 and ≤15 sec.

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