TAR 398 – Nusinersen for Spinal Muscular Atrophy

This assessment provides an estimate of likely cost effectiveness range of nusinersen for spinal muscular atrophy (SMA)

A summary of the proposal is provided in the table below.

PROPOSAL OVERVIEW
Pharmaceutical Nusinersen heptadecasodium (Spinraza®) *Presentation:* 12mg / 5ml injection, 5ml vial *Therapeutic class:* Antisense oligonucleotide
Supplier Biogen NZ Biopharma Limited
Proposed Indications Supplier has applied for each of the following patient subgroups: 1 Infantile onset SMA (type I) 2. Childhood onset SMA (types II and IIIa) 3 Pre-symptomatic individuals with SMA Following clinical advice, PHARMAC staff have reconsidered the indications as: 1. Symptomatic SMA (types I, II and IIIa) 2 Pre-symptomatic individuals with SMA 3. Combined pre-symptomatic and symptomatic SMA (types I, II, and IIIa)
Dosing Loading: 12mg/5ml intrathecal on days 0, 14, 28, and 63 Maintenance: 12mg/5ml intrathecal every 4 months thereafter
Pharmaceutical Price [redacted] per 12mg/5ml dose Source of price: Biogen revised proposal (A1374498), 28th February 2020
PTAC PRIORITY High for all requested indications (February 2020)

Executive Summary

An application for the funding of nusinersen for treatment of spinal muscular atrophy (SMA) type I, II and IIIa was received from Biogen in August 2018. A further application was received from Biogen in August 2019 for the additional indication of pre symptomatic treatment of individuals carrying genetic mutations responsible for SMA. This report considers the use of nusinersen for both symptomatic and pre-symptomatic treatment of SMA.

SMA describes a group of autosomal recessive neuromuscular disorders caused by homozygous mutations or deletions in the survival motor neuron 1 (SMN 1) gene on chromosome 5q. This gene is essential to the normal production of survival motor neuron (SMN) protein, which is vital for maintaining the health and normal function of motor neurons. Absence of this protein is incompatible with life. Fortunately, humans have a second gene (SMN 2) that can also produce some SMN protein, albeit not as effectively as SMN 1.

Affected patients develop bulbar and proximal motor weakness, with onset and severity related to the residual SMN protein produced via the SMN 2 gene. Invariably, disease progression results in loss of control of essential skeletal muscle activity, such as speaking, walking, breathing and swallowing. Health related quality of life is consequently severely reduced for both patients and caregivers. Respiratory failure especially results in significant morbidity and premature mortality.

Utilisation of health care services is high for SMA patients. Current management comprises supportive care only, including physiotherapy and nutritional support to assist with mobility and feeding difficulties. Breathing support is also frequently required following the onset of respiratory decline, administered in the form of non invasive nasal cannula or via face mask. Invasive permanent assisted ventilation is discouraged in New Zealand.

Nusinersen (Spinzara®) is an antisense oligonucleotide protein that helps the 'back up' SMN 2 gene to become nearly as efficient as the defective SMN 1 gene at producing adequate quantities of SMN protein. This medicine requires injection into the fluid surrounding the spinal cord every four months for the rest of the patient's life. Interim data indicates significant gains in both overall survival and motor milestone development for patients already living with SMA, effectively shifting the severity profile experienced by each SMA patient towards a milder disease phenotype. Interim data also suggests for patients treated prior to the onset of symptoms an almost complete absence of the development of SMA-related neurological deficit. However, the outcome data available at present is immature, leading to significant uncertainty around the magnitude of long-term benefit.

Review of Cost Utility Analyses

The applications to PHARMAC for the listing of nusinersen included three separate CUAs, one for each of infantile onset (SMA type I), childhood onset (SMA II and IIIa) and pre symptomatic individuals with SMA. With the most recent pricing received to date ($[redacted] per 12mg/5ml vial), these models report a QALYs per $1 million invested of between [redacted] (base case)

PHARMAC staff have reviewed the Supplier provided CUAs and note several areas of uncertainty. These include the claimed effectiveness of treatment (known as the 'conversion rate'), incremental quality of life gained from treatment, choice of appropriate horizon and estimated management costs associated with each SMA subtype. PHARMAC staff also noted that the supplier omitted consideration of the impact that uncertainty in the diagnostic test for pre-symptomatic SMA would have on the model. PHARMAC have consequently reverse engineered and rebuilt each of the three models in line with the principles outlined in the Prescription for Pharmacoeconomic Analysis v2.2.

NICE considered an alternative cost effectiveness model for SMA I, II and IIIa as part of the UK's evaluation of nusinersen in August 2018. Cost effectiveness was reported on the basis of list price only, at less than <2 QALYs per $1m NZD. Assuming a crude 100% correlation between

pharmaceutical cost and cost effectiveness, it can be extrapolated that the NICE base case using the net pricing offered to PHARMAC would be approximately [redacted], similar to the higher end of the cost effectiveness range estimated by PHARMAC. While specific information on the methods used by NICE have not been made publicly available, the deliberations of the NICE appraisal committee have been published in a recent technology appraisal guidance [TA588], providing insight into NICEs concerns around cost effectiveness modelling of nusinersen.

A supplier sponsored CUA specific to the treatment of infantile onset and childhood onset SMA in Sweden has also been recently published [1], although the analysis was conducted from a societal perspective, limiting the generalisability of this model to New Zealand. At current exchange rate, the estimated cost effectiveness was 1 (infantile onset) to 2 (childhood onset) QALYs per $1m

Summary of PHARMAC Cost Utility Analysis

Three separate cost utility analyses (CUA) were undertaken by PHARMAC staff to estimate the cost effectiveness of nusinersen for spinal muscular atrophy All models use natural history data derived from an Australian cohort of SMA type I, II and III patients born after 1995, following the introduction of genetic testing for SMA in Australia [2]. The pre-symptomatic economic model used interim data derived from the NURTURE trial which suggested that patients with three or less copies of the SMN 2 gene achieve near normal motor milestone development (i.e. near cure) [3]. The infantile onset economic model was informed by data reported in the ENDEAR trial, which indicated significant overall survival and motor milestone development gains for SMA type I patients treated with nusinersen compared to sham control [4]. The childhood onset economic model was informed by data reported in the CHERISH trial, which indicated significant motor milestone development gains for SMA type II and IIIa patients treated with nusinersen compared to sham control [5]

All three models indicated nusinersen would provide substantive incremental benefits over current treatment, even when the most conservative scenarios were considered However, the very high cost of treatment resulted in the cost effectiveness for all models to be considerably lower than what PHARMAC would historically consider to be good value. The incremental QALYs gained per $1 million invested of nusinersen compared to supportive care for treating infantile and childhood onset SMA is estimated to be in the range of [redacted]. This range increases to [redacted] QALYs per $1 million invested if access is widened to (or restricted to) include pre-symptomatic treatment of individuals with less than or equal to 3 copies of the SMN-2 gene.

Summary of Budget Impact Analysis

Symptomatic treatment of infantile (SMA type I) and childhood onset (SMA type II and IIIa) SMA

Patient numbers are estimated to be 50 in year 1, increasing marginally to 52 in year 5

The net cost to the community pharmaceutical schedule is estimated to be [redacted] in year 1 with a 5 year net present value (NPV) of [redacted] The net cost to DHBs is expected to be [redacted] in year 1 with a 5-year NPV of [redacted] The difference in cost to DHBs compared with the pharmaceutical schedule is driven by the incremental cost associated with the increased demand on DHB intrathecal injections services

Pre-symptomatic treatment of individuals with SMA

Incidence is estimated to be 4 new patients each year. All patients started on pre-symptomatic therapy are anticipated to remain throughout the model duration. Consequently, patients on treatment are estimated to equal 4 in year 1, increasing to 20 by year five.

The net cost to the community pharmaceutical schedule is estimated to be [redacted] in year 1 with a 5-year NPV of [redacted]. The net cost to DHBs is expected to be [redacted] in year 1 with a 5 year NPV of [redacted]. The difference in cost to DHBs compared to the pharmaceutical schedule is driven by the incremental cost associated with providing newborn screening tests for SMN 1 gene mutations, as well as SMN 2 copy number testing for those newborns identified from screening, and cost associated with the increased demand on DHB intrathecal injection services.

PHARMAC staff acknowledge that at time of writing this report considerable uncertainty remained regarding the estimated cost of newborn screening for SMA in New Zealand and that estimation of this cost would require additional consultation with other health sector agencies prior to service rollout

Combined treatment of symptomatic and pre-symptomatic treatment of SMA.

Patient numbers were estimated to be 50 in year 1, rising to 58 in year 5. This is greater than symptomatic treatment of SMA alone, as patients treated pre-symptomatically are anticipated to live longer on treatment.

The net cost to the community pharmaceutical schedule is estimated to be [redacted] in year 1 with a 5-year NPV of [redacted]. The net cost to DHBs is expected to be [redacted] in year 1 with a 5-year NPV of [redacted].

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1. Proposal Overview

1.1 Summary

The original application for the funding of nusinersen for the treatment of paediatric patients (18 years or under) with SMA Types I, II and IIIa with symptom onset before 3 years of age was received in August 2018 This application was considered by the Rare Disorders Subcommittee (RDSC) in November 2018 At this meeting, the Rare Disorders Subcommittee recommended that:

- Nusinersen for the treatment of spinal muscular atrophy type 1 be deferred until longer term follow up analyses are published from the SHINE and/or NURTURE trials
- Nusinersen for the treatment of spinal muscular atrophy type II and IIIa be deferred until longer-term follow-up analyses are published from the SHINE and/or NURTURE trials

A resubmission for funding of nusinersen was received by PHARMAC in August 2019, which included clarification of proposed eligibility criteria, longer-term data from the CHERISH-SHINE and ENDEAR-SHINE trials, and a revised price offer. In addition, the supplier additionally requested PHARMAC to consider funding of nusinersen for the treatment of pre-symptomatic individuals with SMA. The resubmission was considered by the RDSC in September 2019. At this meeting, the RDSC recommended that:

- Nusinersen be funded with a high priority, within the context of the rare disorders therapeutic area, for the treatment of pre-symptomatic individuals with spinal muscular atrophy and two or three SMN2 copies, subject to Special Authority criteria.
- Nusinersen be funded with a medium priority, within the context of the rare disorders therapeutic area, for the treatment of symptomatic patients with type I, II, and IIIa spinal muscular atrophy, subject to the Special Authority criteria

In February 2020, PTAC considered the minutes of the previous RDSC meetings as well as additional analysis undertaken by PHARMAC staff subsequent to the September 2019 RDSC meeting. At this meeting, PTAC recommended that:

- Nusinersen be funded with a high priority for the treatment of pre symptomatic individuals with spinal muscular atrophy and two or three SMN2 copies, subject to Special Authority criteria.
- Nusinersen be funded with a high priority for the treatment of symptomatic patients with type I, II and IIIa spinal muscular atrophy, subject to Special Authority criteria

Table 1 below provides a summary of the patient population; intervention; comparator treatment; and main outcomes of treatment

Table 1. PICO.

Population	Either; 1. Patients aged under 18 years with confirmed diagnosis of spinal muscular atrophy (SMA) type I, II or IIIa, as determined by both mutation analysis of the SMN1 gene, and by clinical manifestation of defined signs and symptoms of SMA type I, II or IIIa; and/ or; 2. Patients genetically diagnosed with pre-symptomatic SMA (as assessed by heel-prick blood test at day 3 of life), whereby patients are found to have ≤3 copies of the SMN2 gene
Intervention	Nusinersen, 12mg per dose, administered intrathecal *Loading dosing* 12mg intrathecal on day 0, 14, 28 and 63 *Maintenance dosing* 12mg intrathecal every four months thereafter for life *Stopping criteria* Treatment to be ceased when invasive permanent assisted ventilation is required in the absence of a potentially reversible cause while being treated with this drug
Comparator(s) (NZ context)	Best supportive care
Outcome(s)	Improved overall survival Improved WHO motor milestone achievement

1.2 Patient Population

Classification.

Spinal muscular atrophy (SMA) is a progressive neuromuscular disease, where the most severe cases are associated with an earlier age of onset, lower achievement of maximal motor milestone development during the patient's lifetime, and a lower life expectancy The classification system outlined below for SMA 0 IV is referred to throughout this report to describe the various subtypes of SMA eligible for treatment.

Table 2. Classification of SMA based on age of onset and maximal motor function achieved (Supplier application; August 2018)

Terminology	SMA Type	Age at Symptom Onset	Highest Motor Function Achieved	Average Life Expectancy
Pre natal	0	Prenatal	None unable to sit or roll	Death within weeks
Infantile-onset	I	< 6 months	None unable to sit or roll	Death within 2 years
Childhood-onset	II	6 18 months	Sitting Unable to walk independently.	Survival into adulthood
	III	< 3 years (IIIa) >3 years (IIIb) > 12 to ≤18 years (IIIc)	Independently stand and walk May lose ability to walk over time	Normal lifespan
Adult-onset	IV	> 18 years	Normal Mild motor impairment	Normal lifespan

Natural history.

SMA is a spectrum disorder where it can be difficult to differentiate between each subtype due to the considerable overlap in clinical presentation between patients. However, all patients classically experience disease progression in three phases: preclinical, subacute, and chronic as outlined in Figure 1 below.

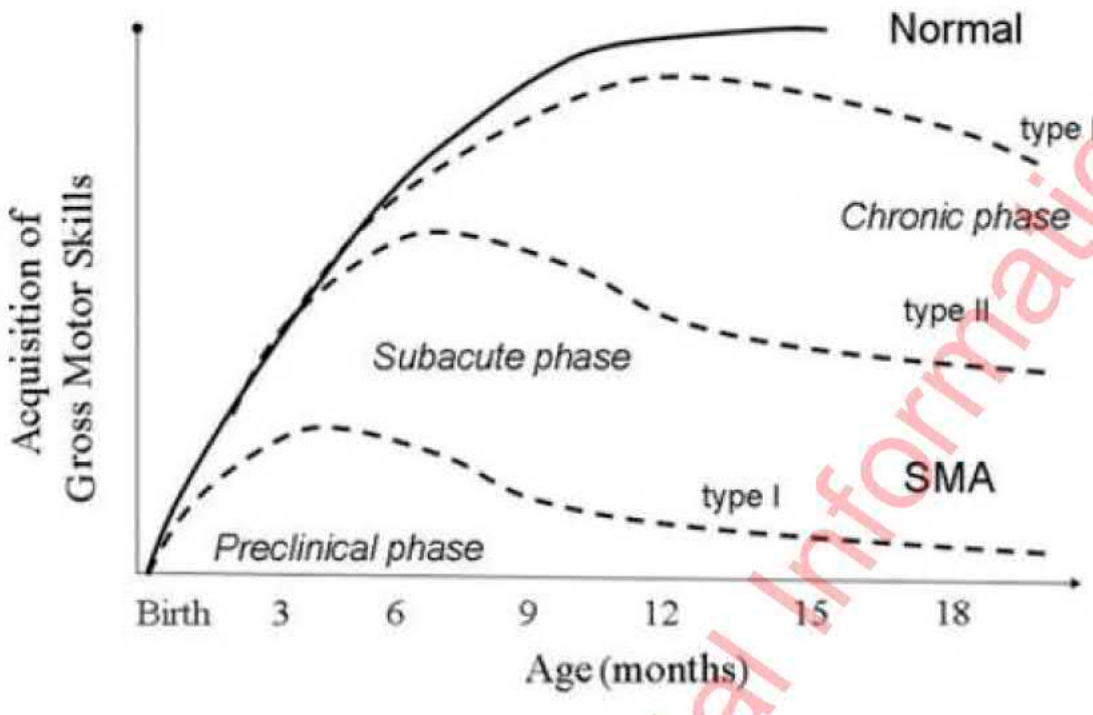

Figure 1 Acquisition of gross motor milestones in normal infants versus infants with SMA (adapted from [6]).

In the preclinical phase, SMA patients appear normal despite progressive loss of motor function. In the subacute phase, weakness becomes apparent, reflecting the loss of functional motor units as the disease progresses relatively quickly. Weakness can range from progressive paralysis in type I patients to missed milestone development in less severe type II and IIIa patients The chronic phase represents a relative stabilisation of disease progression [6] Life expectancy is less than one year of age in SMA type I patients, and on average 40 years of age in SMA type II patients Life expectancy in SMA type III patients is thought to be unaffected by the disease [2] In terms of quality adjusted life years (QALYs) lost per patient, PHARMAC staff estimate that each SMA type I-IIIa patient loses on average 81, 67, and 23 years respectively to morbidity and premature mortality.

Genetics.

SMA is an autosomal recessive condition usually involving the survival motor neuron 1 (SMN1) gene, whereby the symptomatic patient inherits either a defective copy (mutation) or no copy (deletion) of the SMN1 gene from both parents

SMN1 encodes the genetic information required to produce survival motor neuron (SMN) protein SMN protein has a vital role in numerous intracellular processes throughout the body, including messenger RNA synthesis and dendrite formation in nerve cells [7]. So vital is SMN protein to normal cellular function that complete absence has been found to be incompatible with life, as evidenced by genetic knock-out studies in mice [8]. Alpha motor neurons located within the spinal cord and brain stem are particularly affected by lower than normal SMN protein levels. These motor neurons are responsible for controlling the action of skeletal muscle located in the limbs and trunk of the body In SMA, the relative lack of SMN protein results in motor neuron degeneration [9] The muscles these neurons innervate subsequently atrophy, resulting in loss of function Loss of function can manifest as an inability to achieve or maintain key motor milestones, such as sitting or walking, to more serious complications involving swallowing and breathing. Respiratory failure

is a common cause of morbidity and premature mortality for patients diagnosed with the severest SMA subtypes [10], as highlighted in Table 2 above

Fortunately, humans have a second SMN protein encoding gene called SMN2, located on the same chromosome as SMN-1 (5q) though closer to the centromere [11]. However, SMN2 is unable to produce the same quantity or quality of SMN protein as SMN1 can provide, with most SMN protein formed via SMN2 being truncated during translation and consequently rapidly degraded [12]. Severity of SMA phenotype is dependent on the residual quantity of normal derived SMN protein produced via this 'back up' pathway, where clinical onset of symptoms occurs earlier in more severe cases.

Humans can have more than one copy of the SMN2 gene Generally, the more gene copies of SMN2 an individual possesses, the less severe the SMA phenotype, suggesting a greater quantity of residual SMN2 derived protein is produced in patients with multiple copies of SMN2 gene In one large study correlating known clinical cases of SMA with multiplex PCR determined SMN2 copy number, SMA type I patients were predominantly found to possess only two copies of SMN2, whereas SMA type II and IIIa patients predominantly had three copies [13]. While not perfect, the correlation between SMN2 copy number and SMA phenotype provides the only current means of predicting which SMA subtype a patient will develop during their lifetime. This is relevant in the context of pre-symptomatic treatment and genetic counselling of SMA. The decision to treat requires consideration of the threshold number of SMN2 gene copies to base this clinical decision upon, should newborn screening for this condition in New Zealand be considered as part of funding access to nusinersen in this country [14]

Diagnosis.

Currently, SMA affected patients in New Zealand present to health practitioners with characteristic signs and symptoms of lower motor neuron disease. As highlighted earlier in this report, severity of SMA is inversely correlated to age of onset, informing classification of SMA subtype. Confirmation of diagnosis requires genetic testing for homozygous deletion or mutation of the SMN1 gene. From communication with a paediatric neurologist at Auckland DHB (Auckland, New Zealand), PHARMAC staff understand that approximately 80% of SMA cases are currently able to be diagnosed by local testing of exon 7 deletion of chromosome 5q In cases of negative test results but high clinical suspicion, the more accurate SMN1 gene sequencing test can be requested from the Victorian Clinical Genetic Service in Australia (A171815)

Screening for SMA in New Zealand.

Both Auckland DHB and the Rare Disorders Subcommittee advise that the introduction of a nationwide newborn screening test for SMA would be readily achievable for New Zealand laboratories to implement should PHARMAC fund nusinersen for pre symptomatic treatment of SMA PHARMAC understand screening in New Zealand would likely involve a two step process, involving diagnosis of SMA using dried whole blood obtained from a heel prick at the time of newborn metabolic screening If positive, a follow up test would be conducted to determine SMN2 copy number status However, the exact nature and implementation of a SMA screening programme in New Zealand would be dependent on collaboration with the National Screening Unit (Ministry of Health, New Zealand Government). Further consideration of the implications of screening would be required to support any funding decision.

1.3 Current Treatment in New Zealand

There are no current disease modifying treatments for SMA in New Zealand Supportive care is routinely provided and can include regular physiotherapy and nutritional support Respiratory support is provided where required, although usually is limited to non invasive ventilation via nasal prongs or Hudson mask. Invasive methods of ventilation including the use of tracheostomy are discouraged in New Zealand.

1.4 Intervention

Nusinersen is an antisense oligonucleotide therapy that modifies SMN2 gene splicing, greatly enhancing the translation of full length SMN protein. Treated patients experience a shift in severity profile of their SMA disease towards a milder phenotype, rather than a cure per se

Each dose is administered via an injection in the fluid surrounding the spinal cord (intrathecal administration) All patients irrespective of age are recommended to receive 12mg in 5ml per dose Four loading doses are required in the first year, on day 0, 14, 28 and 63. Maintenance doses are then administered every four months thereafter.

Currently it is assumed that patients are required to continue with maintenance therapy indefinitely for the remainder of their lives, however this is not certain from the available short term evidence. As highlighted in the earlier natural history section, it is conceivable that patients could trial discontinuation of therapy following transition into the expected chronic phase of the disease, where loss of neuromuscular motor units has abated following the subacute phase of the disease For purposes of this economic evaluation, it has been assumed that patients will remain on treatment lifelong.

2. Health Benefits

2.1 Clinical Evidence

Overview.

Table 3 below provides an overview of the key clinical trials provided by the Supplier in support of this proposal

Table 3. Overview of pivotal nusinersen trials.

Patient subgroup	**Trial name (phase; n)**	**Open label extension (n)**
Infantile onset (SMA type I)	ENDEAR (III; 121)	ENDEAR SHINE (274)
Childhood onset (SMA type II and IIIa)	CHERISH (III; 126)	CHERISH SHINE (126)
Pre-symptomatic	NURTURE (II; 25)	

Infantile onset SMA (ENDEAR-SHINE) evidence.

The Supplier provided PHARMAC with initial results from the ENDEAR trial prior to the August 2018 RDSC meeting, as reported in Finkel et al 2017 [4]. Updated results from the ENDEAR SHINE study were additionally provided prior to the September 2019 RDSC meeting, showing the cross over effect for patients previously treated with sham subsequently receiving nusinersen in the open label extension of the trial The latest interim results as included in Table 4 below were taken from a conference presentation provided at the American Academy of Neurology (AAN) meeting in May 2019 (A1300197), though have yet to be formally published The latest results represent 32 months of follow up data.

Table 4 Summary of Infantile onset (SMA type I) pivotal trial

Trial name (NCT)	**ENDEAR** (NCT02193074)
Study design	Phase 3 randomised (2:1) double blind sham controlled trial with open label extension (SHINE)
Strength and quality of evidence	Noted by PTAC to be interim level only pending publication of final results.
Population (n=121)	Patients aged ≤7mths with: • homozygous deletion or mutation in the SMN 1 gene, and • 2 copies of the SMN2 gene, and • onset of SMA symptoms at ≤6mths (but not within first week of birth), and • did not have low peripheral oxygen saturation
Intervention(s) (N=80)	Intrathecal admin of nusinersen on days 1, 15, 29, 64 and maintenance doses on days 183 and 302

Comparator(s) (N=41)	Sham procedure on same days as nusinersen.
Results clinical effectiveness	**Finkel et al, 2017** Motor milestone responders according to the Hammersmith Infant Neurological Examination (HINE) tool: • Interim analysis: 21/51 (41%) of nusinersen treated infants vs 0/27(0%) of controls (p<001) had a motor-milestone response. • Final analysis: 37/73(51%) of nusinersen treated infants vs 0/37(0%) of controls (no P value reported) had a motor milestone response Time to death or permanent ventilation: • Overall, the risk of death or the use of permanent ventilation was 47% lower in the nusinersen group than in the control group (hazard ratio, 0.53; 95% confidence interval, 0.32 to 0.89; P=0.005). **Updated results reported at AAN, May 2019.** • Died or required permanent ventilation: 40 patients (49%) who had previously received nusinersen in ENDEAR vs 33 patients (80%) who had received sham • Median time to event: 75 weeks nusinersen vs 22 6 weeks sham • Of the 12 infants who received sham control in ENDEAR who were alive and without ventilation at baseline in SHINE, 7 (58%) of these infants were alive without permanent ventilation at the October 2019 interim analysis • CHOP INTEND (Children's Hospital Philadelphia Infant Test of Neuromuscular Disorders) improvement was 16.8 points; 93% of patients alive and in the study at the time of the assessment were CHOP INTEND responders (≥4 points) The greatest improvements were seen in patients who received nusinersen at a younger age. • 51% of patients in ENDEAR SHINE achieved sitting without support (inconsistent with natural history of SMA Type I)
Results - safety	The overall incidence of adverse events was similar in the nusinersen group and the control group (96% and 98% respectively).
Interpretation of evidence	PTAC considered that although the results have yet to be published, the updated data provided some assurance that the treatment response and large magnitude of effect size was sufficiently persistent and durable to make a recommendation for funding. The Committee considered that, based on the evidence reviewed, nusinersen does not cure SMA but likely shifts the severity profile towards a milder disease phenotype The Committee considered that the evidence supported the assumption that Type I severity is likely to shift to that of a type IIIa severity. However, the Committee considered that due to the short duration of the data reported to date, it was uncertain that there would be 100% disease re categorisation of phenotypes to milder phenotypes and considered that assuming so would be an optimistic assumption.

Childhood onset SMA (CHERISH-SHINE) evidence.

The Supplier provided PHARMAC with initial results from the CHERISH trial prior to the August 2018 RDSC meeting, as reported in Mercuri et al 2018 [5]. Updated results from the CHERISH SHINE study were additionally provided prior to the September 2019 RDSC meeting, showing the cross over effect for patients previously treated with sham subsequently receiving nusinersen in the open label extension of the trial The latest interim results as included in Table 5 below were taken from a conference presentation provided at the American Academy of Neurology (AAN) meeting in May 2019 (A1300203), though have yet to be formally published. The latest results represent 38 months follow up.

Table 5 Summary of Childhood onset (SMA type II and IIIa) pivotal trial

Trial name (NCT)	**CHERISH** (NCT02594124)
Study design	Phase 3 randomised (2:1) double blind sham-controlled trial with open label extension (SHINE)
Strength and quality of evidence	Noted by PTAC to be interim level only pending publication of final results.
Population (n=126)	Patients aged 2-12yrs with: • Genetic documentation of 5q SMA • Symptom onset after 6 months age • Able to sit independently • No history of the ability to walk independently • No respiratory insufficiency • No gastric feeding tube
Intervention(s) (N=84)	Intrathecal administration of nusinersen 12mg or sham injection on days 1, 29, and 85, followed by a maintenance dose at day 274 (9 months)
Comparator(s) (N=42)	Sham procedure on same days as nusinersen.
Results – clinical effectiveness	**Mercuri et al, 2018.** Motor milestone development as determined by Hammersmith Functional Motor Scale-Expanded (HFMSE): • Improvement in HFMSE score evident in nursinersen group (4.0 points) vs deterioration in control group (1 9 points) at 15 months follow up (P<0 001) **Updated results reported at AAN, May 2019.** • Overall mean change in HFMSE score was 3.7 points in those treated with nusinersen in CHERISH and SHINE (38 months follow up). • Patients receiving sham control in CHERISH showed a decline in HFMSE of 0.4 points during the trial; this was reverse following initiation of nusinersen in SHINE which demonstrated an increase of 0.4 from SHINE baseline

	• Treatment effect was reported to be strongest in those who initiated treatment before 3 69 years
Results - safety	Adverse events were reported to be similar in the nusinersen and the control group (93% and 100%) respectively
Interpretation of evidence	PTAC considered that although the final results are yet to be published, the updated data provided some assurance that the treatment response and large magnitude of effect size was sufficiently persistent and durable to make a recommendation for funding. The Committee considered that there was uncertainty around whether Type II severity shifts to a IIIa or a IIIb phenotype Furthermore, the Committee considered that due to the short duration of the data reported to date, it was uncertain that there would be 100% disease re categorisation of phenotypes to milder phenotypes and considered that assuming so would be an optimistic assumption.

Treatment of individuals with genetically diagnosed and pre-symptomatic SMA (NURTURE) evidence.

The Supplier requested the additional indication of pre symptomatic treatment for individuals identified with SMA (homozygous SMN1 deletion / mutation) with less than or equal to three SMN2 copies at time of the August 2019 resubmission, providing interim data from the NURTURE phase II clinical trial in support of this proposal This interim data represents approximately 35 months of follow up and has been subsequently published in a paper by De Vivo et al, 2019 [3]

Table 6 Summary of pre symptomatic SMA pivotal trial

Trial name (NCT)	**NURTURE** (NCT02386553)
Study design	Phase 2 single arm open label study
Strength and quality of evidence	Noted by PTAC to be interim level only pending publication of final results.
Population (n=25)	• Age ≤ 6 weeks at first dose • Genetic documentation of 5q SMA homozygous gene deletion or mutation or compound heterozygous mutation. • Genetic documentation of 2 or 3 copies of SMN2 • No evidence of clinical signs or symptoms suggestive of SMA
Intervention (N=25)	Intrathecal administration of nusinersen 12mg on days 1, 15, 29, and 65, followed by a maintenance dose every 119 days thereafter
Results – clinical effectiveness	**De Vivo et al, 2019** • Over a median follow up duration of 2 9 years, 100% (25/25) of patients in NURTURE were alive without the need for permanent ventilation • All 25 participants achieved the ability to sit without support, 23/25 (92%) achieved walking with assistance, and 22/25 (88%) achieved walking independently.

	• It is unclear what proportion of patients would have SMA Type I vs SMA Type II Motor function data demonstrate: • Functional capability has been maintained over the study period • In patients with an SMN2 copy number of 3, HINE scores had stabilised around a maximum score of 26. In patients with an SMN2 copy number of 2, HINE scores had continued to improve over time reaching a mean score of 23.97 out of 26. • Benefits were shown regardless of age, with the greatest benefits observed in those treated early
Results - safety	• Eight infants had adverse events considered possibly related to nusinersen by the study investigators. All of these resolved despite continued nusinersen therapy. • There were no serious adverse events considered related to nusinersen reported in this interim analysis
Interpretation of evidence	Based on the evidence (published and unpublished), PTAC considered that, in summary, patients with pre-symptomatic disease (with either 2 or 3 copies) have the largest magnitude of clinical benefit in terms of life years and quality-adjusted life years gained from treatment with nusinersen.

2.2 Review of Clinical Evidence

Nusinersen for SMA has been reviewed at three clinical advice meetings to date Nusinersen was first reviewed by the RDSC in August 2018, at which time only interim data for infantile and childhood onset SMA was presented. The RDSC considered at this time that the maturity of the data submitted was such that no firm conclusions could be drawn about the durability of the suggested response.

Nusinersen was reviewed a second time by the RDSC at the September 2019 meeting, at which both longer term data for infantile and childhood onset SMA was submitted, as well as an additional submission for treatment of genetically diagnosed and pre symptomatic individuals identified with SMA The longer-term data presented at this meeting was considered sufficiently mature for the Subcommittee to provide a recommendation for funding, as outlined above.

Nusinersen was reviewed a third time by PTAC at the February 2020 meeting, at which the data submitted in time for the RDSC meeting in September 2019 was re reviewed, as well as additional analysis provided by PHARMAC staff. As a result of the deliberations and additional information considered by PTAC at this meeting, PTAC agreed with the RDSC in terms of the maturity of the data presented. PTAC similarly provided a recommendation for funding, as outlined above

3. Supplier and International Cost-Utility Analyses

3.1 Cost Utility Analysis in Application

The supplier submitted three separate CUAs in support of the nusinersen application: one for each of infantile onset (SMA type I), childhood onset (SMA type II and IIIa) and pre symptomatic individuals Following clinical advice, PHARMAC staff have reconsidered the economic evaluation

of nusinersen in terms of how this medicine would be logically funded, in terms of discrete patient groups These groups include symptomatic SMA (SMA I IIIa), pre-symptomatic SMA (genetically diagnosed and pre symptomatic SMA where individuals possess equal to or less than 3 SMN2 copies) and combined symptomatic and pre-symptomatic groups combined

Symptomatic SMA (SMA I IIIa)

The original application submitted in August 2018 included cost utility analyses for both infantile onset and childhood onset SMA (SMA types I-IIIa). Both models have been constructed as partition survival analyses, where patients move between two mutually exclusive health states depending on whether they convert on or off treatment to having a very mild form of the disease. Following inclusion of the latest price update received by PHARMAC in February 2020, both models estimate that funding of nusinersen for this indication would return [redacted] per $1 million invested as the base case. No cost effectiveness range was provided for either model

PHARMAC staff have reviewed the CUA and noted several parameters that appeared to be inconsistent with the standards outlined in the *Prescription for Pharmacoeconomic Analysis* (PFPA; version 2 2), including estimation of management costs, background mortality rates, and quantification of health related quality of life associated with different health states. PHARMAC staff also noted that the base case in effect represented a situation whereby nusinersen provided a near cure of SMA related morbidity and premature mortality for treatment patients, with all treated patients converting after 12 months of treatment to a health state similar to living with SMA type IIIb (mild phenotype with normal life-expectancy)

PHARMAC staff have rebuilt the supplier models for symptomatic SMA in line with the standards outlined in the PFPA. Both models were reverse engineered to allow a detailed examination of their construction Redundancy, where identified in the models, was removed Recalculation of parameters was undertaken where required. Results have been aggregated across the two rebuilt models using proportional population distribution weights to inform a singular economic evaluation for symptomatic SMA.

Pre symptomatic SMA

The resubmission from the supplier in August 2019 included a cost utility analysis for pre symptomatic SMA This model has been constructed as a decision tree analysis, whereby the patient either lives in full health on treatment or lives a life according to the natural history of the disease as described by Farrar et al, 2013 [2] Following inclusion of the latest price update received by PHARMAC in February 2020, this model estimates that funding of nusinersen for this indication would return [redacted] per $1m invested as the base case Again, no cost effectiveness range was provided for this model.

PHARMAC staff reviewed the CUA, again noting the same inconsistencies in this model with the PFPA as included in the symptomatic CUA models. PHARMAC staff also noted that the model did not appear to allow for consideration of the uncertainty in the sensitivity of the SMN2 copy number test and the impact that this would have on the model outcomes.

PHARMAC staff rebuilt the supplier model for pre symptomatic SMA in line with the standards outlined in the PFPA As for the symptomatic models, the supplier model was reverse

engineered, redundancy removed, and parameters recalculated as required. The model was also extended by building in additional components to allow for variable SMN2 copy number test validity, variable copy number thresholds eligible for funding, and a scenario where funding of pre-symptomatic access could be simultaneously be complemented by symptomatic access This final component allowed for quantification of the cost effectiveness of the combined proposal, whereby the few pre symptomatic patients identified by SMN2 copy number testing as being false negatives would still have access to nusinersen, albeit delayed

3.2 International Cost-Utility Analyses

Several HTA agencies have undertaken economic appraisal of nusinersen for SMA, as presented in Table 7 below A detailed critical appraisal from each of the authoring agencies can be accessed via the provided hyperlinks. The broad consensus reached from each of these authors was that while there was evidence to support nusinersen having a meaningful clinical effect for SMA type I, II and IIIa patients, the pricing of nusinersen resulted in ICERs considerably higher than conventional willingness to pay thresholds.

Table 7 International cost utility analyses

Author (Year; country)	Methods	Results
SMC (2018; Scotland)	Two de novo Markov models; one for each of: Infantile onset (horizon set at 40 years) Childhood onset (horizon set at 80 years) Perspective: Scotland public health care payer. Discounting: 3% per annum for both costs and outcomes.	Infantile onset: ICER £0.4 million / QALY Childhood onset: ICER £1.6 million / QALY
Zuluga Sanchez et al (2019; Sweden)	Two de novo Markov models; one for each of: Infantile onset (horizon set at 40 years) Childhood onset (horizon set at 80 years). Perspective: Societal in Sweden Discounting: 3% per annum for both costs and outcomes.	Infantile onset: ICER €5.6 million / QALY Childhood onset: ICER €3 2 million / QALY
CADTH (2018, Canada)	Re-analysis of supplier provided modelling for each of: SMA type I (horizon set at 25 years) SMA type II (horizon set at 50 years) SMA type III (horizon set at 80 years)	In Canadian $: SMA type I (infantile onset) ICER $9 2 million / QALY SMA type II

	Perspective: Canadian public health care payer Discounting: 1.5% per annum for both costs and outcomes	ICER $24 4 million / QALY SMA type III ICER $7.4 million / QALY
NCPE (2017; Ireland)	Re-analysis of supplier provided modelling for each of: Infantile onset (horizon set at lifetime). Childhood onset (horizon set at lifetime) Perspective: Ireland public health care payer. Discounting: 5% per annum for both costs and outcomes	Infantile onset: ICER €0 5 million / QALY Childhood onset: ICER €2 2 million / QALY
ICER (2019; USA)	Three de novo Markov models, one for each of: Infantile onset (horizon set at lifetime). Childhood onset (horizon set at lifetime). Pre-symptomatic SMA (horizon set at lifetime) Perspective: US health care sector Discounting: 3% per annum for both costs and outcomes	Infantile onset: ICER $1.1 million / QALY Childhood onset: ICER $8 2 million / QALY Pre symptomatic SMA ICER $0 7 million / QALY
NICE (2019; UK)	Minimal publicly released information is available beyond the deliberations of the evaluating committee.	ICERs redacted.

4. PHARMAC Cost-Utility Analysis for Symptomatic SMA (SMA I-IIIa)

Cost utility analyses (CUA) were undertaken to estimate the cost effectiveness of nusinersen for patients with infantile and childhood onset SMA (type I, II and IIIa).

4.1 Scope of Analysis

The analysis was undertaken from the perspective of the funder, with regards to PHARMAC's Factors for Consideration.

4 1 1 Target Population

The target population for this analysis was defined in line with the special authority criteria as outlined in the PTAC minutes from the February 2019 meeting These criteria included all of the following:

1. Genetic documentation of 5q SMA homozygous gene deletion, homozygous mutation, or compound heterozygous mutation; and
2. Patient must have experienced the defined signs and symptoms of SMA type I, II or IIIa prior to 3 years of age; and
3. Patient must be 18 years of age or under.

4 1 2 Comparator

The comparator used in the analysis was supportive care only Clinical advice received from the RDSC and PTAC advised that supportive care in New Zealand for SMA patients did not include invasive ventilation, as is occasionally undertaken in select jurisdictions outside of Australasia.

4.2 Model Structure

Separate partition survival analyses were constructed for infantile onset and childhood onset SMA to model the different treatment strategies.

4.2.1 Time Horizon

The time-horizon of the CUA was 10 years This contrasted with the Supplier models which set the time horizon at 80 years. However, PHARMAC staff noted that considerable uncertainty remained regarding the long term durability of the clinical effect demonstrated in the interim data from the pivotal trials in this target population, likely overestimating the incremental benefit derived from treatment with nusinersen. It was however considered plausible that the clinical effect could reasonably be extrapolated to 10 years, approximately 2-3 times the median follow-up duration reported in the open label extensions of the ENDEAR and CHERISH trials.

Cycle length in both models was four months, reflecting the length of time between each maintenance dose. Two exceptions to this cycle length were modelled, the first exception being the accommodation of an initial two month cycle at the start of each model to allow the costs associated with loading doses to be assigned within a more representative time period as would be expected to occur in real life The second exception included the accommodation of an

additional follow up visit for infantile onset SMA patients at 12 months in the model, in effect mid cycle

All costs and benefits were discounted at 3 5%

4.2.2 Model Structure

The infantile onset SMA model included the following three mutually exclusive health states:

SMA type I phenotype (initial health state)
SMA type III phenotype
Dead

The childhood onset SMA model included the following three mutually exclusive health states:

- SMA type II/IIIa phenotype (initial health state)
- SMA type IIIb phenotype
- Dead

A health state transition diagram (STD) representing the infantile onset model is shown below. The childhood onset model has a near identical model structure, albeit with labels matching the described health states as outlined in the paragraph above.

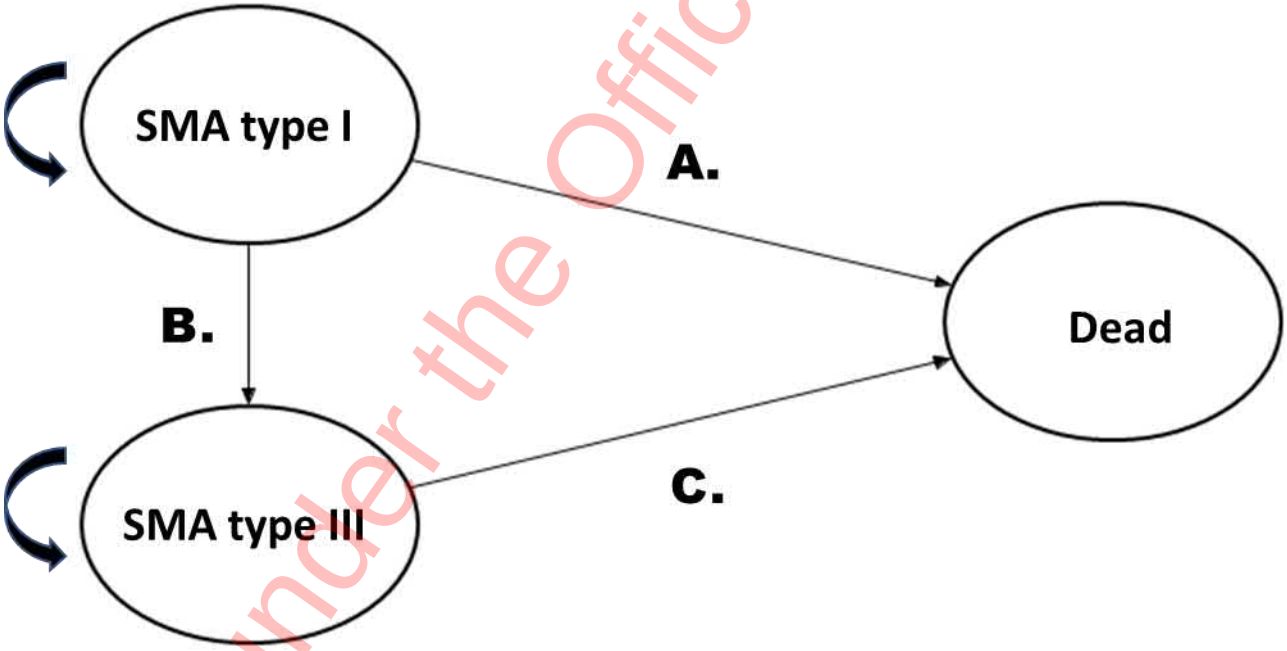

Figure 2 Health state transition diagram for infantile onset SMA

All patients in the infantile onset model start the model in an initial high health need state, representing SMA type I disease Patients in this health state have a high rate of progression to death, represented as a survival function at point 'A' in Figure 2 above. Following 12 months post the start of the model, patients in either arm have a one time chance of 'converting' to a lower health need state, equivalent to SMA type III disease[1]. This one time conversion event is represented at point 'B'. Patients with SMA type III disease have a lower rate of progression to

[1] In the childhood onset SMA (type II/IIIa) model, this conversion event occurs at 15 months

death than patients with SMA type I, represented as survival function at point 'C' No patients are able to 'de-convert' from SMA type III to SMA type I in this model.

4.3 Transformation and Extrapolation of Clinical Evidence

Infantile onset model (SMA type I).

Table 8 below outlines the key clinical parameters used to inform the infantile onset model Explanation of how each of these parameters were transformed and extrapolated from the clinical evidence is provided under section 4.3.1.

Table 8. Clinical parameters and values as used in the infantile onset (type I) SMA model.

Parameter	Supplier	PHARMAC	Rationale
Conversion rate	100%	60%	PHARMAC value based on percentage of cohort still alive after 12 months in ENDEAR. Applied in the model as a one-time transitional probability. It could be considered that this value should alternatively be based on the number of patients still in PFS at 12 months, which was only 30% (see graphs in section 4.3.1).
Overall survival to 12 months	Untreated Weibull distribution derived from PFS data for untreated patients in ENDEAR: α = 7.786 β = 1 003 Treated Weibull distribution derived from PFS data for untreated patients in ENDEAR: α = 28.851 β = 0 602		PFS rather than OS as described in ENDEAR is considered as being more representative of OS in New Zealand as unlike patients in ENDEAR, patients in New Zealand do not have access to invasive permanent ventilation.
Overall survival beyond 12 months for untreated and treated patients who don't convert	Weibull derived survival function using natural history OS data from Farrar et al, 2013: α = 1 444 β = 1.054		Data used to inform OS beyond the reported PFS from the ENDEAR trial has been obtained from real world natural history data provided by an Australian cohort of SMA patients, from 1995 2010
Overall survival for treated patients who convert to SMA type III at 12 months	Background mortality rates as informed from New Zealand Period Life Tables (2005 07).	Background mortality rates as informed from New Zealand Period Life Tables (2012 14).	SMA type III patients are not known to be affected by premature mortality as a result of the underlying disease. PHARMAC staff have consequently derived age dependant probabilities of death from New Zealand Period Life Tables for 2012-14

The infantile onset model uses data derived from the ENDEAR trial which indicated that treatment with nursinersen significantly improved OS compared to sham control [3] However, OS data as reported in the ENDEAR trial is unlikely to be representative of OS experienced by SMA type I patients in New Zealand This is because patients in ENDEAR had access to invasive permanent ventilation at advanced stages of the disease progression, whereas in New Zealand this intervention is not routinely offered Instead, the reported data for PFS in the ENDEAR trial has been used to model OS in New Zealand, being reflective of SMA type I disease patients who do not require invasive ventilation.

The survival benefit evident from the ENDEAR trial for patients receiving nusinersen has been modelled up until the point of disease re-categorisation (12 months post initiating treatment) This has been achieved by applying a proportional hazard ratio (0 372) to baseline PFS data for the sham control arm, which is represented in the model by a fitted Weibull distribution

The percentage of treated patients converting, or being re-categorised, to the milder SMA type III phenotype is a major source of uncertainty in the model. The supplier claimed that it was appropriate to assume that 100% of patients still alive after 12 months could be recategorized as responders, on the basis of an estimated trial response rate of 91% at 12 months, with rounding to 100% for simplicity PHARMAC considers it would be more appropriate to conservatively base this conversion rate on the proportion of patients still alive in the treated population at 12 months (60%), noting that this might underestimate the true clinical effectiveness, as the non responders might reasonably be considered to have already died prior to 12 months.

After disease re-categorisation at 12 months, patients responding to treatment experience a milder phenotype of disease represented as SMA type IIIa. Background mortality data derived from New Zealand Period Life Tables inform OS for patients responding to treatment[2]. Conversely, natural history data for SMA type I patients inform OS for both untreated and non responding patients [2], which are represented in the model by a fitted Weibull distribution.

Childhood model (SMA type II)

Table 9 below outlines the key clinical evidence used to inform the childhood onset model.

Table 9 Transformation and extrapolation of clinical evidence as used in the childhood onset (type II/IIIa) SMA model.

Parameter	Supplier	PHARMAC	Rationale
Conversion rate	100%	90%	PHARMAC value based on advice received during in house peer review process (see A1360491). Applied in the model as a one-time transitional probability
Overall survival untreated and treated patients who don't convert at 15 months	Weibull distribution derived from natural history OS data in Farrar et al, 2013 [2] α = 38.8140 β = 3.7448		
Overall survival for patients converting to SMA type III at 15 months	Background mortality rates as informed from New Zealand Period Life Tables (2005 07)	Background mortality rates as informed from New Zealand Period Life Tables (2012 14)	SMA type III patients are not known to be affected by premature mortality as a result of the underlying disease PHARMAC staff have derived age dependant probabilities of death from New Zealand Period Life Tables for 2012 14.

[2] New Zealand Period Lifetables have been obtained from Statistics New Zealand (New Zealand Government) for use in these models

The childhood onset model uses data derived from the CHERISH trial which indicated that treatment with nusinersen shifted the severity profile of affected childhood onset SMA patients to a milder form of the disease Consequently, all patients who respond to treatment are converted to a milder form of SMA at 15 months, categorised in this model as SMA type IIIb

This conversion event provides a proxy to represent the effect of nusinersen therapy as demonstrated in the CHERISH trial for patients to achieve and maintain motor function during their lifetime, incongruent with the natural history of the underlying SMA subtype they were born with.

No difference in OS survival has been reported in the CHERISH trial, as no patients have died in either arm to date Therefore, unlike the infantile model, no survival gain has been modelled for patients on treatment prior to the conversion event at 15 months Instead, the entire cohort experiences a probability of survival during the first 15 months of the model informed by natural history data for SMA II patients, represented in the model as a Weibull distribution.

Following the conversion event at 15 months, the same natural history data for SMA type II patients has been used to inform OS for untreated and non responding patients. Background mortality data derived from New Zealand Period Life Tables (Statistics New Zealand) inform OS for patients responding to treatment after 15 months

It is important to note that the modelled cohort is inclusive of patients with SMA type IIIa at baseline, representative of the patients enrolled in the CHERISH trial. Rationale for this combined modelling approach is provided by both clinical advice received at the February 2020 PTAC meeting and the previously discussed difficulty differentiating SMA II from IIIa at onset due to the spectrum nature of the disease. Further rationale is also provided by information contained in the New Zealand Neuromuscular Disease Patient Registry, which indicates that 66% of SMA IIIa patients require use of a wheelchair despite a median age of only 11 (refer 'NZ Registry' tab, A1359808) This suggests that the majority of SMA type IIIa patients in New Zealand regress to a phenotype more consistent with SMA type II patients during their childhood or early adolescence

4 3 1 Clinical Parameter Estimates

Both the infantile and childhood models required data from the clinical trials to be transformed to clinical parameter estimates as shown in Table 8 and Table 9 above. Specifically, transformation was required for each of the following:

- Overall survival to 12 months (Infantile onset; both treated and untreated)
- Overall survival beyond 12 months (Infantile onset; both treated and untreated)
- Overall survival (Childhood onset; untreated)
- Overall survival (Childhood onset; treated)

PHARMAC staff have reviewed the mathematical methods employed by the Supplier to transform the clinical data to these parameters as used in the models, and found the methods and derived values to be acceptable for modelling purposes. A detailed explanation, with consideration of alternative modelling strategies not ultimately utilised, can be obtained directly from the 2018 Supplier submission (A1175176) A brief description of how each of these estimates were derived is also provided below

Overall survival to 12 months (Infantile onset; both treated and untreated)

As outlined above, reported data for PFS in the ENDEAR trial was used to model OS in New Zealand, reflecting SMA type I disease patients who do not require invasive ventilation PFS data from the ENDEAR trial is shown for both treated and untreated (sham) patients in Table 10 below.

Table 10. Survival data from ENDEAR used for the within trial survival analyses (adapted from A1175176; see page 18)

Months	Overall survival		Progression-free survival (PFS)	
	Nusinersen	Sham (SoC)	Nusinersen	Sham (SoC)
0	1	1	1	1
3	0 899	0 805	0 76	0.732
6	0 859	0 652	0 706	0 395
9	0 827	0 618	0 596	0 298
12	0 827	0 581	0.553	0 265

To extrapolate the trial PFS data, alternative parametric regression models were fitted to the PFS trial observations as shown in Table 10 above, using statistical analytical software (Datafit; Oakdale Engineering, USA). Weibull curves, as shown in Figure 3 and Figure 4 below, demonstrated the highest R^2 values of the fitted curves and were hence selected for modelling. The derived Weibull parameters describing these curves is provided in Table 11 below.

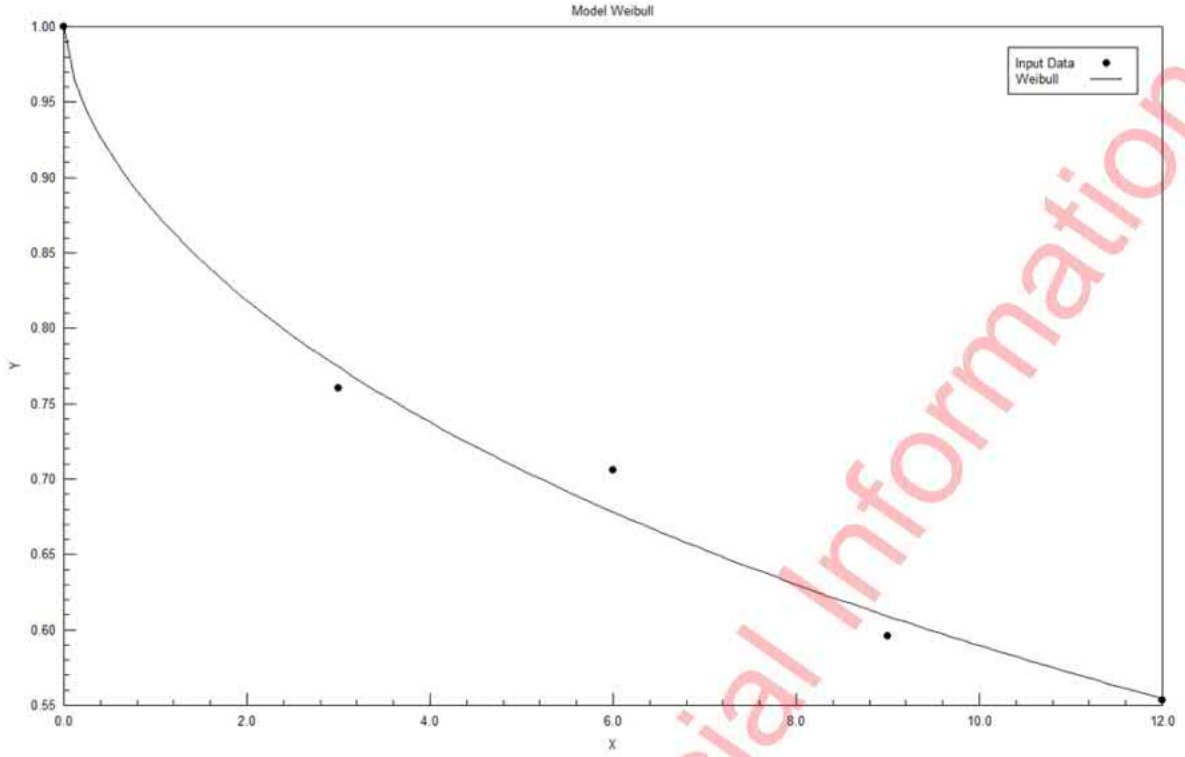

Figure 3. Weibull curve fit to the ENDEAR PFS data for treated patients (R^2 = 99.1%; A117510).

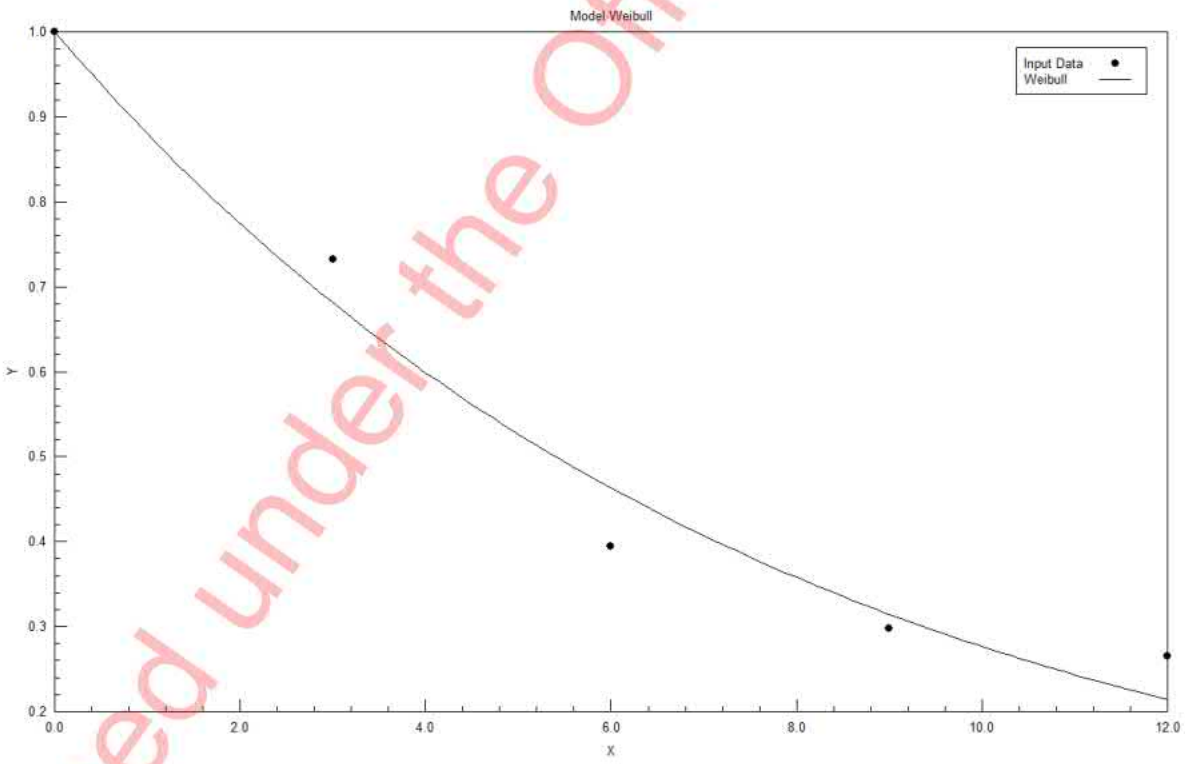

Figure 4. Weibull curve fit to the ENDEAR PFS data for untreated patients (R^2 = 97 5%; A117510)

Table 11. Derived parameters for the Weibull curves for OS (Finkel et al 2017).

Patient subgroup	Weibull parameters	Estimate
Treated SMA type I	α	28.851
	β	0.602
Untreated SMA type I	α	7.786
	β	1.003

Overall survival beyond 12 months (Infantile onset; both treated and untreated)

As outlined above, data used to inform OS for untreated patients beyond reported PFS from the ENDEAR trial (i e after 12 months in the model) has been obtained from real world natural history data provided by an Australian cohort of SMA patients, from 1995-2010 [2] OS data from this cohort is shown in Table 12 below

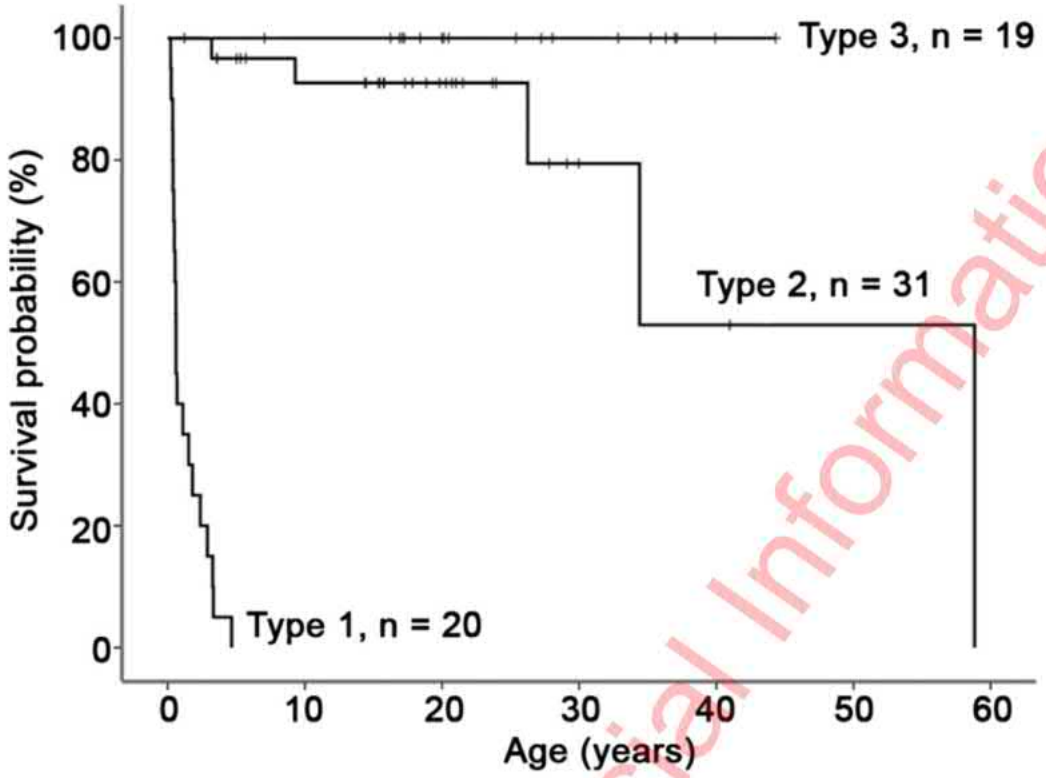

Figure 5 Kaplan Meier survival curve for SMA types I, II and III (Farrar et al, 2013 [2])

Table 12. Kaplan-Meier survival probabilities for Australian SMA patients, 1995-2010 (Farrar et al, 2013 [2])

SMA type	Age in years					
	1	2	4	10	20	40
	Survival probability at a certain age (%)					
I	40	25	6	0	0	0
II	100	100	97	93	93	52
IIIa	100	100	100	100	100	100
IIIb	100	100	100	100	100	censored

In order to transform data from this study to estimate survival parameters, datapoints from the Kaplan Meier survival curves have been digitised to enable fitting of a survival curve. These datapoints are shown in Table 13 below. A Weibull distribution as shown in Figure 6 below was selected as best representing the digitised OS datapoints. The derived Weibull parameters describing this curve are provided in Table 14 below.

Table 13. Plot digitised natural history data for SMA type I patients.

Months	Years	Survival probability
0	0	1
4.68	0.39	0.902367
6.36	0.53	0.754438
9.36	0.78	0.656805
9.42	0.785	0.60355
9.48	0.79	0.446746
11.04	0.92	0.399408
22.2	1.85	0.298817
25.2	2.1	0.251479
30	2.5	0.201183
36	3	0.153846
43.2	3.6	0.050296
58.8	4.9	0

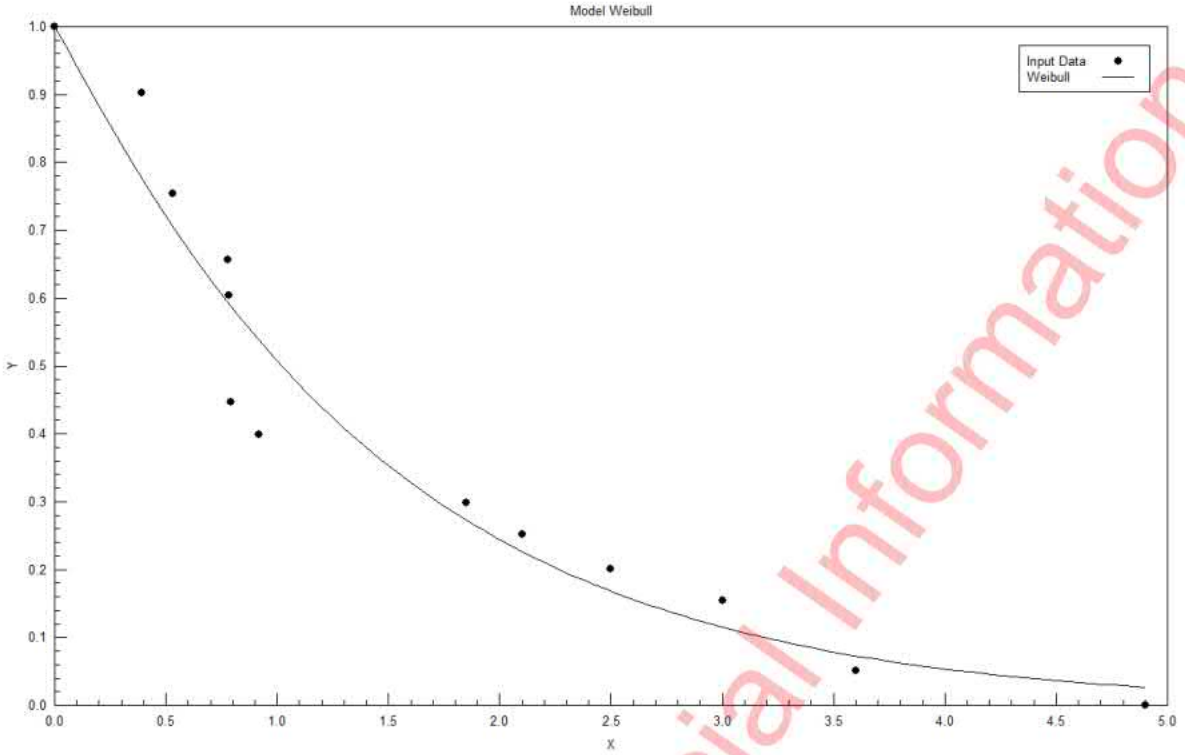

Figure 6. Weibull curve fit to the Farrar et al 2013 data for untreated SMA type I patients (R^2 = 94.7%; A117510)

In order to quantify the treatment effect of nusinersen on OS for treated patients, a hazard ratio of death for treated as compared to untreated patients as reported in the ENDEAR trial (0 372) has been applied to the Weibull curve as shown in Figure 6 above. It has been assumed that this hazard ratio remains constant over time, beyond the 13 months of follow up data reported in the ENDEAR trial at time of publication [4].

Table 14 Derived parameters for the Weibull curve informing OS for untreated SMA type I patients and applied OS hazard ratio for patients on treatment.

Patient subgroup	Weibull parameters	Estimate
Untreated SMA type I	α	1
	β	0.902367
Treated SMA type I	**Likelihood of death as compared to untreated**	
	HR = 0.372	

Overall survival (Childhood onset; untreated)

The childhood onset model has a simpler approach to modelling OS compared to the infantile model. Only untreated and treated patients who fail to respond to nusinersen therapy (quantified in the model as the rate of conversion at 15 months) remain at an increased probability of premature mortality This increased probability has been extrapolated from the natural history data for SMA type II patients as shown in Figure 5 and Table 12 above. As for the infantile model,

datapoints from the accompanying Kaplan Meier survival curve for SMA type II patients have been digitised to enable fitting of a survival curve These datapoints are shown in Table 15 below A Weibull distribution as shown in Figure 7 below was selected as best representing the digitised OS datapoints The derived Weibull parameters describing this curve are provided in Table 16 below.

Table 15 Plot digitised natural history data for SMA type II patients

Years	Survival probability
0	1
3 3	0 973372781
9 3	0 931952663
26 1	0 801775148
34 3	0 532544379
58 9	0

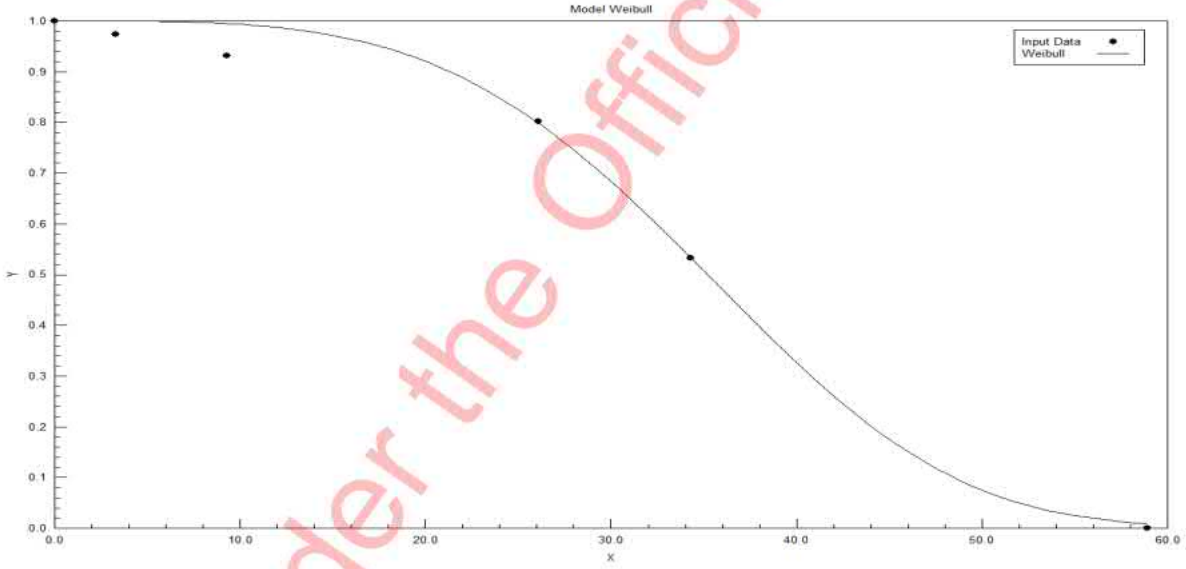

Figure 7 Weibull curve fit to the Farrar et al 2013 data for untreated SMA type II patients (R^2 = 99 4%; A117510).

Table 16 Derived parameters for the Weibull curve informing OS for untreated SMA type II patients

Patient subgroup	Weibull parameters	Estimate
Untreated SMA type II	α	38 814
	β	3 745

Overall survival (Childhood onset; treated)

Until the one-time conversion event occurs at month 15 of the model, patients in both arms of the model have the same probability of death informed by the derived Weibull curve outlined for untreated SMA type II patients above After the conversion event, the treated patients are effectively partitioned into responders and non responders Those who respond are considered to experience a shift in disease severity equivalent to patients living with SMA type IIIb, and consequently transition to a probability of survival informed by background mortality rates for age matched New Zealanders. New Zealand Period Life Tables for 2012 14 have been used to inform the background mortality rates used in the model (Statistics New Zealand, New Zealand Government). Treated patients who do not respond continue to experience the same OS as the untreated SMA type II patients described above

4.4 Health-Related Quality of Life

The model submitted by the supplier included utility values for infantile and childhood onset patients. The utility values used by the supplier to inform their infantile and childhood onset models were informed by unpublished HRQOL research, although a poster outlining this research had been presented at ISPOR 2017 prior to this submission (A1357313) This research involved case vignettes, depicting SMA type I and II patients in various health states, being assessed by clinical experts to estimate QOL using the EQ-5D-5L

The supplier utility values derived from the HRQOL research are presented in Table 17 below. At the time of modelling, PHARMAC staff encountered difficulty understanding what was being valued for each subtype without being able to review the source material and health state descriptions used by clinical experts to estimate the supplier provided utilities values. PHARMAC staff subsequently identified a recent publication relating to this HRQOL research that had not been provided by the Supplier, although this publication still provides incomplete information on the health state descriptions considered [15]

Table 17. Supplier provided utility values for both infantile and childhood onset models (adapted from A1357313)

SMA subtype	Baseline	Patients who respond to treatment
Infantile onset	0 12	0 71
Childhood onset	0.04	0 72

Consequently, the New Zealand EQ 5D 3L was employed by PHARMAC staff to independently estimate QOL. Health state descriptions were informed by a Supplier commissioned literature review that sought to evaluate the natural history of SMA (A1175208). NZ tariff-2 EQ-5D weights were then applied to the generic health states to derive quality of life scores.

This approach resulted in PHARMAC staff accepting the supplier provided utility values as shown in Table 17 above for all health states except for the averaged baseline for childhood onset (i e representing both SMA types II and IIIa), which was considered incongruent with the information provided by the supplier in the natural history literature review The PHARMAC estimate utility value obtained using the EQ-5D used in the analysis is outlined in Table 18 below

Table 18 PHARMAC estimated HRQOL for childhood onset SMA

SMA subtype	Baseline	EQ-5D
Childhood onset	0.1245	2.5,3,3,2,2

As a comparison, a search of past TARs was undertaken for comparable conditions and health states. One such condition, adult late-onset Pompe disease was identified in the HRQOL library. The description characterising this condition is provided below:

'Adult late-onset Pompe disease is a rare, progressive debilitating and often fatal lysosomal storage disorder (LSD) Also known as acid maltase deficiency it is a metabolic disorder that causes muscle weakness progressing to respiratory weakness Patients with the adult form may

survive for decades following diagnosis Quality of life will continue to deteriorate over the years, with patients having significant problems with mobilisation and eventually becoming wheelchair bound, ventilator dependant and probably eventually die from respiratory failure'

The accompanying utility values for this condition are presented in Table 19 below. As shown in the table, moderate to severe Pompe patients are wheelchair dependant, with severe patients being ventilator dependant. Both wheelchair dependant and ventilator dependant utility values associated with these two health states are higher than that estimated by PHARMAC staff for childhood onset SMA, providing some degree of certainty that PHARMAC staff have not unduly overestimated the HRQOL associated with this health state as included in the updated version of the model

Table 19. HRQOL associated with late onset Pompe disease (A153931).

Health states	Utility	EQ 5D
Moderate	0 5455	2,1 5,2,2,1 5
Moderate to severe (i.e. wheelchair dependant)	0.2065	2.5,2,3,2,1.5
Severe (ventilator dependant)	0 1655	3,2 5,3,2 5,1 5

4.5 Costs

4 5 1 Pharmaceutical Cost

Nusinersen has been offered to PHARMAC at a confidential net price of [redacted] per 12mg / 5ml vial (A1374498).

The recommended dosage is 12 mg (5 mL) per administration, irrespective of age or bodyweight. Nusinersen should be initiated as early as possible after diagnosis with 4 loading doses on Days 0, 14, 28, and 63 A maintenance dose should be administered once every 4 months thereafter Treatment is currently assumed to be required for life

At current pricing, the cost per patient in the first year of treatment is [redacted] (representing 6 vials). Every subsequent year of treatment costs [redacted] (representing 3 vials). These estimates do not include further rebates, future generic pricing or wastage, none of which are considered relevant to this proposal.

The supplier claims two patents for nusinersen relevant to New Zealand, as shown in Table 20 below Both patents are due to expire in June 2030

Table 20. Patents held for nusinersen in New Zealand.

Patent Number	Expiration Date	Patent Type	Patent Owner
NZ597071	June 2030	Use for treating SMA	Biogen MA Inc and Cold Spring Harbor Laboratory
NZ624712	June 2030	Use for treating SMA	Biogen MA Inc. and Cold Spring Harbor Laboratory

4.5.2 Pharmacy Fees

Nusinersen would be listed on the Hospital Pharmaceutical Schedule if funded in New Zealand, as a result of inpatient administration being required for each dose Therefore, no additional pharmacy fees are likely to be incurred

4.5.3 *Health Sector Costs*

The models contain health sector costs as presented in Table 21 below:

Table 21. Health sector costs included in the infantile and childhood onset models.

Cost	Supplier	PHARMAC	Rationale
SMA type I (annual COI)	$91,302	$99,749	Supplier estimate is in $AUS. PHARMAC have converted the original € estimate into $NZD with adjustment for inflation.
SMA type II (annual COI)	$26,019	$28,329	Supplier estimate is in $AUS. PHARMAC have converted the original € estimate into $NZD with adjustment for inflation.
SMA type III (annual COI)	$15,513	$16,812	Supplier estimate is in $AUS. PHARMAC have converted the original € estimate into $NZD with adjustment for inflation.
Administration cost per dose	$675	$675	Cost considered acceptable to RDSC November 2019

Annual cost of illness (COI)

The high health burden resulting from SMA is logically associated with high direct medical costs Reliably quantifying these costs across each of the various SMA subtypes is challenging due to the considerable overlap between subtypes and the progressive nature of the disease. This increases the risk of considerably underestimating the true annual cost of illness associated with each subtype.

A German cost of illness study from 2013 has been used to inform modelling [16], albeit acknowledging the limitations as stated above This was a Germany wide cross sectional study involving 189 patients over a four-month period from April to August 2013 Patients and their caregivers were asked to recall the consumption of health care resources over a defined period of time. The cost associated with each resource was estimated in € for 2013, as shown in Table 22 below for each SMA subtype. PHARMAC staff have converted the original € values reported in this study to NZD$ (€1=$1.69; XE.com 30th Jan 2020) and have adjusted for inflation ($1.09; RBNZ Q1 2013 to Q4 2019).

Table 22. Mean cost of illness per SMA patient (annual cost in NZD$; adjusted for inflation)

Direct medical costs	Type I	Type II	Type III
Outpatient medical costs	$852	$722	$504
Inpatient medical costs	$73,574	$8,198	$4,580
Rehabilitation costs (in/outpatient)	$1,093	$1,787	$1,371
Drug treatment costs	$716	$451	$232
Costs for use of rehabilitation services	$6,420	$3,956	$3,339
Costs for artificial nutrition	$3,571	$455	$166
Costs for medical aids	$3,033	$8,071	$5,527
Costs for respiratory management	$10,488	$4,690	$1,093
Total direct medical COI (PHARMAC)	$99,749	$28,329	$16,812

Administration cost per dose

Clinical advice provided at the PTAC meeting in February 2020 indicated that it was probable that patients would require dose administration to be performed by an anaesthetist in an operating theatre, given the very young age of some of the patients, complexity involved in performing an intrathecal injection on patients with scoliosis, and very high cost of the medicine. An estimate for the cost associated with each dose has been obtained from a freely available schedule of surgical maximums published online by Southern Cross Health Society[3]

4.6 Cost Effectiveness Results

As informed by clinical advice, the results for both infantile and childhood onset models have been aggregated in proportion to the estimated population distribution of each subtype in New Zealand to inform a singular ranking on the *Options for Investment* list. This approach reflects clinical advice to consider funding nusinersen for all SMA patients with symptomatic SMA type I, II and IIIa, rather than sequentially as funding permits.

The incremental costs and QALYs associated with the base case for each of the models is shown in Table 23 below. The combined estimated QALYs per $1m is [redacted] (cost per QALY of [redacted]) once the distribution weights[4] have been applied to each base case

[3] See cost item 4677 on page 38 of this online document: www southerncross co nz/Portals/0/Society/EFulfillment/Product/Schedule_of_Surgical_Maximums_archive.pdf

[4] Distribution weights have been derived from Calucho et al, 2018 [13] See A1359808 for workings

Table 23. Cost effectiveness results for childhood and infantile onset CUA models.

	Childhood onset		
	Nusinersen	Standard of Care	Incremental
QALYs	5.14	0.96	4.19
Cost	[redacted]	[redacted]	[redacted]
QALYs per $1m	[redacted]		
	Infantile onset		
QALYs	1.48	-0.13	1.36
Cost	[redacted]	[redacted]	[redacted]
QALYs per $1m	[redacted]		
	Weighted (Childhood onset 52% : Infantile onset 48%)		
QALYs per $1m	[redacted]		

The primary cost driver in both models is the very high lifetime cost associated with nusinersen therapy, as shown in Table 24 below. As there is currently no funded pharmaceutical intervention for SMA patients in New Zealand, there is no pharmaceutical cost offset that can be applied against the cost of nusinersen

A small cost offset is however apparent for childhood onset SMA, where treatment with nusinersen meaningfully shifts the disease severity to a state associated with lower lifetime health sector costs, despite treated patients living considerably longer on average than untreated patients

Conversely, treatment of infantile onset SMA is associated with higher lifetime health sector costs compared to untreated patients. This is primarily the result of the very poor life expectancy (< 1 year) of patients who do not have treatment.

Table 24. Cost implications to the Pharmaceutical Schedule and DHBs.

	Childhood onset		
	Nusinersen	Standard of Care	Incremental
Cost to Pharmaceutical Schedule	[redacted]	[redacted]	[redacted]
Other costs to health sector	$164,267	$217,731	-$53,465
	Infantile onset		
Cost to Pharmaceutical Schedule	[redacted]	[redacted]	[redacted]
Other costs to health sector	$208,893	$109,223	$99,670

4.7 Sensitivity Analysis

Table 25 Sensitivity analysis

Input	Base Case Value	Low Value	High Value	Range QALYs per $m
Conversion rates	90% / 60%	25%	100%	[redacted]
100%				[redacted]
75%				[redacted]
50%				[redacted]
25%				[redacted]
Utilities				[redacted]
SMA II 0 2045				[redacted]
SMA II 0 04				[redacted]
Health sector costs		-		[redacted]
Cost of illness x 200%				[redacted]
Cost of illness x 300%				[redacted]
Horizon	10	5	20	[redacted]
Horizon 5 years				[redacted]
Horizon 20 years				[redacted]
Pharmaceutical costs	[redacted]	[redacted]	[redacted]	[redacted]
Nusinersen cost 75% of base				[redacted]
Nusinersen cost 50% of base				[redacted]
Nusinersen cost 25% of base				[redacted]

As shown in Table 25 above, the models are modestly sensitive to the cost of nusinersen None of the other inputs have been found to be sensitive, despite the high level of uncertainty associated with in effect all of them due to the interim nature of the available data

4.8 Summary of Overall Cost-Effectiveness

As outlined above, the base-case QALY per $1m estimate is [redacted] Taking into account the results of the sensitivity analysis, the highly likely range is estimated to be [redacted] This range captures the uncertainty of the durability of the clinical effect of nusinersen and is informed by adjustment of the model horizon The possible QALY per $1m range is [redacted] and takes into account the uncertainty around the applied conversion rates, and how well these inputs translate as proxy variables for lifelong treatment benefit

5. Budget Impact Analysis for symptomatic SMA types I, II and IIIa.

5.1 Summary of Budget Impact

The 5 year net present value (NPV) to the Combined Pharmaceutical Schedule of funding nusinersen is estimated to be [redacted], with a cost of the first 12 months of [redacted]. The 5 year NPV to DHBs is estimated to be [redacted]. All costs are discounted at a rate of 8%.

Key considerations informing these estimates:

1 Funding of nusinersen will add a new treatment for a previously untreated condition
2 Funding of nusinersen will have a considerable impact on health sector resources as a new intrathecal injection service will need to be created to meet demand for treatment
3. Funding of nusinersen will have a highly uncertain impact on additional direct medical costs associated with patients living longer with SMA. As such, this impact has not been quantified in either of the supplier or PHARMAC BIA estimates.
4. PHARMAC staff anticipate the risk of slippage to be negligible given the strict access criteria.

5.2 Patient Numbers

The estimated patient numbers informing the BIA over 5 years is presented in Table 26 below.

Table 26 Patient numbers for each of SMA types I, II and III assuming access limited to patients diagnosed with symptomatic disease.

Year of listing	**Y1**	**Y2**	**Y3**	**Y4**	**Y5**
Total SMA I on treatment	**12**	**9**	**7**	**6**	**6**
Prevalent SMA I	10	7	5	4	4
Incident SMA I	2	2	2	2	2
Total SMA II on treatment	**27**	**26**	**28**	**30**	**32**
Prevalent SMA II	25	24	26	28	30
Incidence SMA II	2	2	2	2	2
Total SMA IIIa on treatment	**11**	**11**	**12**	**13**	**14**
Prevalent SMA IIIa	10	10	11	12	13
Incidence SMA IIIa	1	1	1	1	1
Total patients on treatment	**50**	**46**	**47**	**49**	**52**

Patient estimates are informed by several considerations, as explained below

Incidence

Incidence of SMA is informed by a population-based study undertaken in Sweden by Arkblad el al, 2009 [17] In this study, the incidence of SMA types I, II and III was found to be 8 5 cases per 100,000 live births. This equates to approximately 5 new cases of SMA in New Zealand each year, where there are approximately 60,000 live births every year.

Distribution of SMA subtypes (as applied to incidence).

Determining how the 5 incident cases are distributed between each of SMA type I, II and IIIa can have a considerable impact on the impact to the CPB, with impact ranging between [redacted] million depending on the approach considered most accurate Three alternative approaches are shown in Table 27 below for illustration

Table 27 Alternative approaches to determining distribution of incident SMA subtypes

	Distribution of incident SMA across each subtype				
Subtype	I	II	IIIa	IIIb	5YR CPB
Supplier	42%	25%	14%	19%	[redacted]
Calucho et al (2018)	36%	34%	16%	15%	[redacted]
Arkblad et al, 2009	39%	27%	24%	10%	[redacted]

The distribution provided by the supplier was suggested to have been based on a combination of subtype data from the Arkblad et al, 2009 paper as used to inform overall incidence. In order to estimate the proportion of SMA III patients who might reasonably be considered as SMA IIIa, a weighting of 43% was applied to exclude SMA type IIIb patients, as informed by expert opinion from Australia This approach in effect results in there only being 4 cases of SMA each year in New Zealand meeting the eligibility criteria for treatment

PHARMAC staff have used the Arkblad cohort, which helpfully provides a breakdown of age of onset of symptoms for each individual SMA type III patient, to calculate the SMA I-IIIa distribution specific to the original cohort. The resulting distribution is considerably different to that suggested by the supplier, with 5 SMA cases each year in New Zealand meeting the eligibility criteria for treatment.

PHARMAC staff have additional considered SMA subtype data from Calucho et al, 2018, compiled from 2,834 cases reported globally [13] The resulting distribution derived by PHARMAC staff from this global study is slightly different to the that derived from the Arkblad cohort However, the overall impact on the CPB is identical, as this approach similarly results in there being 5 incident SMA cases each year in New Zealand meeting the eligibility criteria for treatment.

PHARMAC staff have elected to use the distribution derived from the Calucho et al, 2018 paper to inform the results of the BIA, as this is considered to represent the highest level of evidence available

Prevalence

Prevalence modelling has been undertaken using the estimated incidence and annual survival probability for SMA types II and IIIa to inform the potential number of patients who might reasonably be expected to be both alive and meet the proposed eligibility criteria (aged < 18 years). A breakdown by age group is provided in Table 28 below.

Table 28 Prevalent cases of SMA by subtype in New Zealand

SMA subtype	I	II	IIIa
Age 1 12 years	10	17	6
Age 13 15 years		4	2
Age 16 18 years		4	2

PHARMAC is aware of 10 SMA type I patients currently accessing nusinersen via compassionate access in New Zealand. These patients are denoted in the table as 'prevalent SMA I'. These patients do not require loading doses in the first year of funding, in contrast to the other prevalent patients in the table (SMA types II and IIIa) who do require loading dosing in the first year of listing

Uptake.

All incident cases of SMA types I-IIIa are considered likely to start nusinersin if funded. However, it is considered unlikely that all prevalent SMA type II and IIIa patients would elect to start therapy, as some patients may have survived into late adolescence without experiencing severe symptoms. To account for this, PHARMAC have considered that 80% of SMA type II and III patients would reasonably start and remain on nusinersen from the first year onwards if funded in New Zealand

Treatment discontinuation

Patients are considered to remain on treatment only if they are deriving clinical benefit. To account for this, the proportion of incident patients each year progressing to treatment in subsequent years is informed by the conversion rates outlined in Table 8 and Table 9 above (i.e. 60% for SMA type I and 90% for SMA type II and IIIa). The corresponding rate is applied as a linear rate each year for SMA type I patients, whereas for SMA type II and IIIa the rate is applied only once at the end of one full year on treatment.

5.3 Net Budget Impact to Pharmaceutical Schedule

The net impact to the hospital medicines list (HML) over 5 years is outlined in Table 29 below.

Table 29 Net Budget Impact to the Pharmaceutical Schedule

Year	1	2	3	4	5
Total patients on nusinersen	50	46	47	49	52
Number of nusinersen vials consumed	270	153	156	162	171
Proposed pharmaceutical cost to HML ($ millions)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Current pharmaceutical cost to HML	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Budget Impact to HML ($ millions)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5.4 Net Budget Impact to DHBs

The net budget impact to DHBs is included in Table 30 below.

Table 30. Net Budget Impact to DHBs.

Year	1	2	3	4	5
Net budget impact to other DHB costs (i e excluding pharmaceutical costs)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of injections performed	*270*	*153*	*156*	*162*	*171*
Net budget impact to DHBs total (i.e. including pharmaceutical costs; $ millions)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Listing nusinersen will require a new intrathecal injection service to be created by DHBs to meet demand It is unclear whether this service could be provided to patients at their nearest respective regional hospital, or whether travel to select tertiary level hospitals would be required for this treatment However, the cost associated with this service is anticipated to be the same wherever it is provided. PHARMAC have estimated the net budget impact to other DHB cost resulting from administration by multiplying the annual number of injections performed by the same unit cost applied in the CUA models ($675 per injection). Demand, and therefore cost, is estimated to be highest in the first year of listing as a result of all patients who are not already on compassionate access requiring loading doses of therapy This impact is estimated to significantly reduce from

the second year of listing onwards, as only newly incident cases will be requiring loading dosing each year thereafter The five-year NPV for this injection service is estimated to be [redacted]

5.5 Patient Costs

PHARMAC has been unable to quantify any additional costs that would be incurred by a patient or their caregivers should they elect to commence nusinersen therapy. It is possible that travel and accommodation costs for hospital visits might be incurred by families of children requiring treatment, should provision of an intrathecal injection service be limited to only one of the major centres in each island (i e Starship Hospital in Auckland and Christchurch Hospital)

6. PHARMAC Cost-Utility Analysis for pre-symptomatic patients genetically diagnosed with SMA.

A supplier CUA was amended by PHARMAC staff to estimate the cost-effectiveness of nusinersen for patients who have been genetically diagnosed with SMA, prior to the onset of symptoms. This scenario would require the Newborn Screening Programme to include testing for SMN1 mutations alongside metabolic screening, as well as a follow up test for SMN2 copy numbers in newborns who test positive to SMN1 mutations.

PHARMAC staff have also expanded the pre-symptomatic model to inform a scenario where access to nusinersen was made available for both patients diagnosed via genetic screening prior to the onset of symptoms, as well as patients with SMA types I, II and IIIa with symptom onset before 3 years of age This scenario would provide access to the widest number of patients with SMA in New Zealand and mitigate missed SMA diagnoses resulting from inaccurate genetic testing, if access to nusinersen was limited to pre-symptomatic patients only.

Consequently, this section informs the economic analyses relating to two separate items on the *Options for Investment* list

6.1 Scope of Analysis

The analysis was undertaken from the perspective of the funder, with regards to PHARMAC's Factors for Consideration

6 1 1 Target Population

The target population for this analysis was defined to reflect the recommended special authority criteria proposed by the RDSC in September 2019. Namely, eligibility for pre-symptomatic treatment would be limited to patients meeting the following criteria:

1. Genetic documentation of 5q SMA homozygous gene deletion, homozygous mutation, or compound heterozygous mutation, identified via newborn screening
2 Patient must have only two or three copies of SMN2

6 1 2 Comparator

The comparator used in the analysis was current standard of care, as described in section 4 1 2 above.

6.2 Model Structure

A decision tree analysis model was constructed to model the different treatment strategies.

6.2.1 Time Horizon

The time horizon of the CUA was 80 years, reflecting the assumption that patients treated with nursinersen prior to the onset of symptoms were expected to experience a life-course in line with that for patients with SMA type IIIb/IV PHARMACs horizon is different to the horizon chosen by

the Supplier (92 years) PHARMAC staff have elected to use contingent life expectancy of a newborn child in New Zealand, based on New Zealand period life tables published from Statistics New Zealand[5] The Supplier refers to New Zealand cohort life tables similarly published by Statistics New Zealand in their selection of the longer horizon value[6]

All costs and benefits were discounted at 3.5%.

6 2 2 Model Structure

The decision tree model reflects three scenarios.

The first scenario represents all patients meeting the eligibility criteria, receiving lifelong nusinersen therapy The relative benefit from treatment however is weighted according to the validity of SMN2 test parameters, namely, how well the SMN2 copy number test can predict patients who would otherwise have ended up developing symptoms prior to the age of 3 years. Both the false positive and false negative rates are therefore important considerations. Patients with a false positive test result will be treated with unnecessary lifelong intrathecal therapy and derive no benefit. Patients with a false negative test result will develop symptomatic SMA. If access is limited to pre-symptomatic patients only, then false negative patients will experience a reduced life course in line with the status quo.

The second scenario represents access to nusinersen therapy being extended to false negative patients who develop SMA symptoms prior to the age of three years, in line with the eligibility criteria as outlined in section 4 1 1 above Patients accessing treatment via this pathway enable the model to estimate the cost effectiveness of a combined symptomatic and pre-symptomatic listing.

The final scenario represents the comparator arm of the model, where otherwise eligible patients do not have access to nusinersen therapy, and experience a life course in line with infantile and childhood onset SMA as described in section 4 above. The lifetime costs and QALYs have been weighted according to the distribution of SMA subtypes, as discussed further in section 6 3 1 below

A state transition diagram representing the pre-symptomatic model is presented below.

[5] New Zealand Period Life Tables informing the horizon of the PHARMAC amended CUA can be reviewed directly from the follow link: Statistics New Zealand, May 2015
[6] See section 3.2 of the Supplier economic evaluation, p10 (A1356854). The cohort life tables referred to by the Supplier have can be reviewed from the following link: Statistics New Zealand, March 2019

6.3 Transformation and Extrapolation of Clinical Evidence

This economic model is based on the assumption that the 100% survival rate for pre symptomatically treatment SMA patients as derived from the NURTURE study (see Table 6 above) translates into treated patients being able to experience a life unaffected by SMA. In effect, this implies that rather than being a disease modifying treatment, nusinersen as used in this context can be considered a cure so long as the patient remains on therapy lifelong.

Beyond this assumption, the pivotal trial results from the NURTURE study do not inform the model Instead, the model is driven by the estimated relative distribution of SMA types within the cohort eligible for treatment (included in the supplier model), and the estimated SMN2 test parameters (added to the supplier model by PHARMAC staff).

6.3.1 Clinical Parameter Estimates

Table 31 and Table 32 below outline the key clinical parameters used to inform the pre symptomatic model Explanation of how each of these parameters were transformed and extrapolated from the clinical evidence is provided below

Table 31. SMA subtype profile of cohort treated pre-symptomatically (i.e. the expected phenotype of the cohort that would be expected to develop if eligible patients remained untreated, or SMN2 genotype-phenotype associated with threshold being set at ≤ 3 SMN2 copies).

Parameter		**Supplier**	**PHARMAC**
Distribution of SMA subtypes (%) among patients treated pre symptomatically	I	40 8 %	41 2 %
	II	40 8 %	38 7 %
	IIIa	13 1 %	14 4 %
	IIIb	5.4 %	5.7 %

Table 32 Impact on SMN2 copy number test validity with adjustment of eligibility criteria and false positive rate.

SMN2 copy number		**≤ 2 SMN2 copies**	**≤ 3 SMN2 copies**	**≤ 3 SMN2 copies if False +ves = 10%**
Test parameter	True +ve	27 45%	76 72%	71 00%
	False +ve	0.56%	4.28%	10%
	False ve	57 03%	7 76%	7 76%
	True - ve	14.96%	11.25%	11.25%
Total		100 00%	100 00%	100 00%

Distribution of SMA subtypes

The values provided by the supplier have been obtained from a recent Australian Government report [18] and are considered reasonable[7] To estimate these values, the authors amended the findings of a 2018 systematic review of phenotype-genotype correlation [13] with subsequently published data, although noted that the new data did not materially affect the original finding. PHARMAC staff have been unable to review the new data informing the Australian Government report. As such, PHARMAC staff have assessed the impact that reverting to the original 2018 distribution data would have on the model outcomes during sensitivity testing.

SMN2 copy number test parameters

The Australian Government report was primarily concerned with the prognostic value of using genetic testing for SMN2 copy number to predict the severity of SMA prior to the onset of symptoms. A major consideration of the work undertaken by the report authors was to estimate the rate of false positives, which depended on the threshold at which SMN2 copy number eligibility

[7] The Australian Government report being referred to here can be directly access from the following link: MSAC, August 2019

for treatment was set Drawing upon the amended distribution analysis described in the section above, the authors estimated that by setting the threshold at 3 or less copies of the SMN2 gene, an estimated 4 28% of patients diagnosed with SMA would otherwise not meet the eligibility criteria set for symptomatic patients, and therefore be treated unnecessarily [18]

Applied to the New Zealand setting, with an estimated 5-6 incident cases per year[8], a false positive rate of 4.28% would result in one newborn every 3 years being treated with nusinersen when otherwise they would never have developed symptomatic SMA prior to the age of 3 years.

The authors also noted that the false positive rate is dependant on the distribution of SMA subtypes within the local population and could range as high as 10% PHARMAC staff have proportionally adjusted the true positive and false positive rates (shown in the final column of Table 32 above) to account for this uncertainty during sensitivity analysis

6.4 Health-Related Quality of Life

The supplier CUA assumed that patients treated before the onset of symptoms can reasonably be assumed to live a near normal life expectancy, equivalent to a SMA type IV patient. As such, a weight value of 0.91 has been obtained from a HRQOL study of population norms in South Australia [19] and applied to patients treated pre symptomatically in the model If the clinical findings of the NURTURE study are durable over a lifetime (i e sustained neuromuscular milestones), then this utility value could be considered plausible

The other utility values included in the pre-symptomatic analysis are as outlined already in section 4 above for the symptomatic SMA models. All utility values are used in the pre-symptomatic model are presented in Table 33 below.

Table 33 Utility values as used in the pre symptomatic CUA

SMA phenotype	Utility value
SMA type I	0 12
SMA type II	0 1245
SMA type IIIa	0 71
SMA type IIIb	0 91
SMA type IV	0 91
SMA treated pre-symptomatically	0 91

[8] This has been estimated from the annual number of births in New Zealand (~60,000) x annual incidence rate (8 5 cases per 100,000 live births) as identified in the study by Arkblad et al, 2009 [18]

6.5 Costs

6 5 1 Pharmaceutical Cost

Pharmaceutical costs associated with nusinersen therapy have been described earlier in this report under section 4.5.1 above.

6.5.2 Health Sector Costs

Table 34. Additional health sector costs included in the pre-symptomatic model.

Cost	Supplier	PHARMAC
SMA type IV cost of illness	$0	$0
SMN2 copy number test	$361	$361

SMA type IV cost of illness

Annual costs of illness associated with SMA types I, II and IIIa have been described earlier in this report, and have been included in the pre-symptomatic model as outlined in Table 21 above. The annual cost of illness associated with SMA type IV patients (used by the supplier as a proxy to represent SMA patients treated pre-symptomatically) has been assumed to be $0.

SMA gene testing

The cost of introducing SMN1 gene mutation / deletion testing as part of a Newborn Screening Programme has been estimated by the Supplier as $2.60 per live birth, derived from a 2015 cost estimate for congenital adrenal hyperplasia screening in New Zealand [20]. PHARMAC staff have considerable doubts as to the generalisability of an immunoassay cost to a test requiring genomic DNA extraction for SMA diagnosis. Further consultation with the National Screening Unit will be required prior to this new service being established to accurately quantify associated costs.

SMN1 screening would be conducted from the same blood sample obtained as part of the heel prick (Guthrie) metabolic screening already being conducted on day ~3 for every newborn in New Zealand Consequently, no additional workforce cost is anticipated

The SMN2 copy number test is estimated to be NZD$361 per test, derived by the Supplier from the Victorian Clinical Genetics Services (VCGS) in Australia. PHARMAC staff have been unable to source a local price for this test from a laboratory in New Zealand. However, the cost of testing for SMN2 copy number does not materially influence the results of the pre-symptomatic CUA given the very high pharmaceutical cost of nusinersen therapy As such, the VCGS estimate has been retained in PHARMACs amended analysis

6.6 Cost Effectiveness Results

The scenario that results in the greatest quantity of incremental QALYs that can be achieved from listing nusinersen in New Zealand is where access is provided to both symptomatic SMA and pre-symptomatic SMA patients [redacted] QALYs compared to [redacted] QALYs if pre-symptomatic access is funded alone). The incremental cost effectiveness ratios are essentially identical, albeit the pre

symptomatic model is slightly more favourable ([redacted]QALYs per $1m compared to[redacted]QALYs if combined access if funded) Further details are provided below

Pre-symptomatic model, assuming no access for symptomatic SMA I IIIa patients

The incremental cost is estimated to be [redacted], with a QALY gain of 17.9. The estimated QALYs per $1million is therefore [redacted](cost per QALY of [redacted]. This is shown in Table 35 below.

Table 35 Cost effectiveness results for pre-symptomatic SMA model

	Nusinersen	**Status Quo**	**Incremental**
QALYs	22 69	4 83	17.86
Cost	[redacted]	[redacted]	[redacted]
QALYs per $1m	[redacted]		

A cost offset in the model is achieved as a result of considerably less demand for health services being required for patients who receive treatment; however, this saving is dwarfed by the high cost of nusinersen. This is illustrated in Table 36 below.

Table 36 Cost Implications to the Pharmaceutical Schedule and DHBs for the pre symptomatic SMA model.

	Nusinersen	**Status Quo**	**Incremental**
Cost to Pharmaceutical Schedule	[redacted]	[redacted]	[redacted]
Cost of administration	$43,110	$0	$43,110
Other costs to health sector	$63,372	$368,978	-$305,606
Total costs	[redacted]	[redacted]	[redacted]

Combined pre-symptomatic SMA and symptomatic SMA type I-IIIa.

The incremental cost is estimated to be [redacted]with a QALY gain of 18.8. The estimated QALYs per $1million is therefore [redacted]cost per QALY of [redacted] This is shown in Table 37 below.

Table 37. Cost effectiveness results for combined pre-symptomatic SMA and symptomatic SMA type I IIIa model.

	Nusinersen	**Status Quo**	**Incremental**
QALYs	23.63	4.83	18.80
Cost	[redacted]	[redacted]	[redacted]
QALYs per $1m	[redacted]		

A cost offset in the model is again achieved as a result of considerably less demand for health services being required for patients who receive treatment; however, this saving is dwarfed by the high cost of nusinersen This is illustrated in Table 38 below

Table 38. Cost Implications to the Pharmaceutical Schedule and DHBs for the combined pre symptomatic SMA and symptomatic type I IIIa model

	Nusinersen	**Status Quo**	**Incremental**
Cost to Pharmaceutical Schedule	[redacted]	[redacted]	[redacted]
Cost of administration	$49,039	$0	$49,039
Other costs to health sector	$37,562	$368,978	-$331,416
Total costs	[redacted]	[redacted]	[redacted]

6.7 Sensitivity Analysis

Table 39. Sensitivity analyses for both pre-symptomatic and combined pre-symptomatic and symptomatic models

Input	Pre-sym	Combined pre-sym & symptomatic
Base	[redacted]	[redacted]
Clinical parameters		
SMN2 false positive rate 10%	[redacted]	[redacted]
Calucho et al (2018) SMA distribution.	[redacted]	[redacted]
Utilities		
Utility SMA II 0.2045	[redacted]	[redacted]
Utility SMA II 0.04	[redacted]	[redacted]
Pharmaceutical costs		
Price 75%	[redacted]	[redacted]
Price 50%	[redacted]	[redacted]
Price 25%	[redacted]	[redacted]
Other health system costs		
Cost of health care x2	[redacted]	[redacted]
Cost of health care x3	[redacted]	[redacted]
Horizon		
Horizon 40 years	[redacted]	[redacted]
Horizon 20 years	[redacted]	[redacted]
Horizon 10 years	[redacted]	[redacted]
Horizon 5 years	[redacted]	[redacted]

As shown in Table 39 and Table 25 above, both SMA models are sensitive to the cost of nusinersen, again illustrating price being the primary driver. A modest effect is seen with variation of the cost of illness associated with untreated SMA patients, as well as variation of the extrapolated clinical effect of nusinersen (shown here by adjustment to the model horizon)

6.8 Summary of Overall Cost-Effectiveness

Pre-symptomatic model, assuming no access for symptomatic SMA I IIIa patients.

As outlined above, the base case QALY per $1m estimate is [redacted] Taking into account the results of the sensitivity analysis, the highly likely range is estimated to be [redacted] This range takes into consideration the uncertainty surrounding the prognostic value of the SMN2 copy number test, where a higher false positive rate results in a lower QALY per $1m estimate The higher end of the likely range is informed by the uncertainty surrounding the appropriate utility value to inform the average life experience of untreated SMA type II patients. The possible QALY per $1m range is [redacted] and takes into account the uncertainty surrounding the durability of the treatment effect of nusinersen at the lower end of the range (horizon reduced to 10 years). The higher end of the possible range is informed by uncertainty surrounding the cost of illness associated with untreated SMA patients (annual cost of illness tripled from base case).

Combined pre symptomatic SMA and symptomatic SMA type I IIIa

As outlined above, the base case QALY per $1m estimate is [redacted] aking into account the results of the sensitivity analysis, the highly likely range is estimated to be [redacted] This range takes into consideration the uncertainty surrounding the prognostic value of the SMN2 copy number test, where a higher false positive rate results in a lower QALY per $1m estimate. The higher end of the likely range is informed by the uncertainty surrounding the appropriate utility value to inform the average life experience of untreated SMA type II patients The possible QALY per $1m range i [redacted] and takes into account the uncertainty surrounding the durability of the treatment effect of nusinersen at the lower end of the range (horizon reduced to 10 years) The higher end of the possible range is informed by uncertainty surrounding the cost of illness associated with untreated SMA patients (annual cost of illness tripled from base case).

7. Budget Impact Analysis

7.1 Summary of Budget Impact

Pre symptomatic SMA only funded

The 5 year net present value (NPV) to the Hospital Pharmaceutical Schedule of funding nusinersen is estimated to be [redacted], with a cost of the first 12 months of [redacted]. The 5-year NPV to DHBs is estimated to be [redacted]. All costs are discounted at a rate of 8%.

Combined pre symptomatic and symptomatic SMA funded

The 5 year net present value (NPV) to the Hospital Pharmaceutical Schedule of funding nusinersen is estimated to be [redacted], with a cost of the first 12 months of [redacted]. The 5 year NPV to DHBs is estimated to be [redacted] All costs are discounted at a rate of 8%.

7.2 Patient Numbers

Pre symptomatic SMA only funded.
The estimated patient numbers over 5 years is included in the table below

Table 40. Patient numbers accessing treatment if access limited to pre-symptomatic SMA patients only

	Year 1	Year 2	Year 3	Year 4	Year 5
Total patients on treatment	4	8	12	16	20
Incident	4	4	4	4	4
Prevalent	0	4	8	12	16
Nusinersen doses administered	24	36	48	60	72

Incidence

The annual incidence of SMA patients access treatment prior to the onset of symptoms has been estimated from the annual incidence of SMA types I IIIa in New Zealand (5 cases) and the proportion of positive SMN2 test results (81%; the sum of the true and false positive SMN2 test rate, as shown in Table 32 above).

Treatment discontinuation.

All patients who start pre-symptomatic treatment are anticipated to remain on therapy for the duration of the five year BIA. This is informed from the results of the NURTURE trial where all patients accessing treatment are still alive and remain on treatment

Access provided to both SMA patients diagnosed prior to the onset of symptoms as well as patients with symptomatic SMA (combined access)

Table 41 below outlines the estimated patients in each subtype by year of listing. Note that pre symptomatic diagnosed SMA patients will not receive a clinical subtype classification as implied in this table. However, PHARMAC staff have anticipated the phenotype these patients would most likely have developed if they did not receive treatment, using the SMN2 genotype phenotype distribution data as presented in Table 31 above.

Table 41 Patient numbers if access is provided to both pre symptomatic SMA and symptomatic SMA types I-IIIa patients.

	Year 1	Year 2	Year 3	Year 4	Year 5
SMA I	**12**	**10**	**10**	**10**	**11**
Grandfathered SMA I	10	6	4	2	1
Incident symptomatic SMA I	0	0	0	0	0
Incident pre symp SMA I	2	2	2	2	2
Prevalent pre symp SMA I	0	2	4	6	8
SMA II	**27**	**27**	**29**	**31**	**33**
Incident symptomatic SMA II	0	0	0	0	0
Prevalent symptomatic SMA II	25	23	23	23	23
Incident pre-symp SMA II	2	2	2	2	2
Prevalent pre-symptomatic SMA II	0	2	4	6	8
SMA IIIa	**11**	**11**	**12**	**13**	**14**
Incident symptomatic SMA IIIa	1	1	1	1	1
Prevalent symptomatic SMA III	10	10	11	12	13
Incident pre-symptomatic SMA IIIa	0	0	0	0	0
Prevalent pre-symp SMA IIIa	0	0	0	0	0

The patient numbers here are informed as outlined for the previous patient number estimates The one SMA patient missed each year with population screening is assumed to develop symptomatic SMA type IIIa, given that higher SMN2 copy number is correlated with less severe SMA phenotype.

7.3 Net Budget Impact to Pharmaceutical Schedule

Pre-symptomatic SMA.

The net impact to the hospital medicines list over 5 years is outlined in the table below. The five year NPV is estimated to be [redacted]

Table 42 Net Budget Impact to the Pharmaceutical Schedule (Pre symptomatic SMA listing).

Year	1	2	3	4	5
Total patients on treatment	4	8	14	16	20
Nusinersen vials administered	24	36	48	60	72
Proposed pharmaceutical cost to HML	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Budget Impact to HML	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Combined pre symptomatic and symptomatic SMA.

The net impact to the hospital medicines list over 5 years is outlined in the table below The five year NPV is estimated to be [redacted]

Table 43. Net Budget Impact to the Pharmaceutical Schedule (Combined pre-symptomatic and symptomatic SMA listing)

Year	1	2	3	4	5
Total patients on treatment	50	48	51	54	58
Nusinersen vials administered	270	159	168	177	189
Proposed pharmaceutical cost to HML	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Budget Impact to HML	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

7.4 Net Budget Impact to DHBs

Pre-symptomatic SMA.

The net budget impact to other DHB budgets is presented in Table 44 below. The five-year NPV is estimated to be $0 8 million

Table 44. Net Budget Impact to other DHB budgets (Pre-symptomatic SMA listing).

Year	1	2	3	4	5
SMN2 copy number confirmation	$2,527	$2,527	$2,527	$2,527	$2,527
SMN1 screening of all infants in NZ	$156,000	$156,000	$156,000	$156,000	$156,000
Intrathecal injection costs	$16,200	$24,300	$32,400	$40,500	$48,600
Total to other DHB costs	$170,000	$180,000	$190,000	$200,000	$210,000

Combined pre symptomatic and symptomatic SMA

The net budget impact to other DHB budgets is presented in Table 45 below The five-year NPV is estimated to be $1.3 million.

Table 45 Net Budget Impact to other DHB budgets (Combined pre-symptomatic and symptomatic SMA listing).

Year	1	2	3	4	5
SMN2 copy number confirmation	$2,527	$2,527	$2,527	$2,527	$2,527
SMN1 screening of all infants in NZ	$156,000	$156,000	$156,000	$156,000	$156,000
Intrathecal injection costs	$182,250	$107,325	$113,400	$119,475	$127,575
Total to other DHB costs	$340,000	$270,000	$270,000	$280,000	$290,000

7.5 Patient Costs

As discussed in section 5.5, PHARMAC staff have been unable to quantify any additional costs that would be incurred by a patient or their caregivers should they elect to commence nusinersen therapy It is possible that travel and accommodation costs for hospital visits might be incurred by families of children requiring treatment, should provision of an intrathecal injection service be limited to only one of the major centres in each island (i.e. Starship Hospital in Auckland and Christchurch Hospital).

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