CADTH

CADTH Drug Reimbursement Review

Pharmacoeconomic Report

ONASEMNOGENE ABEPARVOVEC (ZOLGENSMA)

(Novartis Pharmaceuticals Canada Inc.)

Indication: For the treatment of pediatric patients with 5q spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene and:

- 3 or fewer copies of SMN2 gene; or
- infantile-onset SMA.

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

BIA	budget impact analysis
BSC	best supportive care
ICER	incremental cost-effectiveness ratio
MAIC	matching-adjusted indirect comparison
OCCI	Ontario Case Costing Initiative
QALY	quality-adjusted life-year
SMA	spinal muscular atrophy
SMN1	survival motor neuron 1
SMN2	survival motor neuron 2

Executive Summary

The executive summary is comprised of 2 tables (Table 1: Background and Table 2: Economic Evaluation) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Onasemnogene abeparvovec (Zolgensma), given as a single-dose intravenous infusion of 1.1×10^{14} vector genomes/kg
Submitted price	Onasemnogene abeparvovec, 2×10^{13} vector genomes/mL, intravenous infusion: $2,910,500 per kit (kit contains between 2 to 14 vials; number of vials is determined based on patient body weight)
Indication	For the treatment of pediatric patients with 5q SMA with bi-allelic mutations in the SMN1 gene and: • 3 or fewer copies of the SMN2 gene; or • infantile-onset SMA.
Health Canada approval status	Approved
Health Canada review pathway	Priority review
NOC date	December 15, 2020
Reimbursement request	As per indication
Sponsor	Novartis Pharmaceuticals Canada Inc.
Submission history	Previously reviewed: No

NOC = Notice of Compliance; SMA = spinal muscular atrophy; SMN1 = survival motor neuron 1; SMN2 = survival motor neuron 2.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Patients with SMA type 1 with an onset of symptoms at ≤ 6 months of age, who are symptomatic at baseline, and with 2 copies of the SMN2 gene. Note: Indication does not specify SMA type 1, nor are there restrictions outlined based on symptom onset or being symptomatic at baseline. It does specify patients must be < 2 years of age.
Treatment	Onasemnogene abeparvovec
Comparators	BSC Nusinersen
Perspective	Canadian publicly funded health care payer
Outcome	QALYs
Time horizon	Lifetime (80 years)
Key data source	Compared to BSC, a naïve unanchored comparison was conducted, with natural history data from the NeuroNext dataset used to inform BSC. Compared to nusinersen, a matching-adjusted indirect comparison was conducted, using pooled data from the START and STR1VE-US trials for onasemnogene abeparvovec and data from the SHINE and ENDEAR trials for nusinersen.
Submitted results for base case (and key scenario analyses)	ICER vs. BSC = $293,521 per QALY (incremental costs: $3,133,944; QALYs: 10.68). ICER vs. nusinersen = dominant (onasemnogene abeparvovec is associated with lower total costs and greater QALYs). A scenario analysis was submitted to reflect patients with 3 copies of the SMN2 gene, based on interim data from the SPR1NT trial. This analysis produced results that were broadly similar to the sponsor's base case: ICER vs. BSC = $193,239 per QALY; ICER vs. nusinersen = onasemnogene abeparvovec dominant (lower total costs and greater QALYs).
Key limitations	• Limitations with the sponsor's submitted comparative clinical efficacy data render the magnitude of clinical benefit, with regards to motor milestone achievement and survival (i.e., mortality and requirement of permanent ventilation), with onasemnogene abeparvovec in comparison to BSC and nusinersen highly uncertain. There is also no evidence on the long-term comparative efficacy of onasemnogene abeparvovec or nusinersen adding to the extent of uncertainty. • The target population in the base case (symptomatic patients with 2 copies of the SMN2 gene) does not reflect all patients likely to receive onasemnogene abeparvovec, which includes pre-symptomatic patients and patients with 1 or 3 SMN2 gene copies. The generalizability of results to such patients is uncertain. • The submitted model structure may not appropriately capture all key changes in patient quality of life, including SMA-related developments such as the requirement of nutritional support or loss in functional status, for patients other than those who discontinue nusinersen. • Several issues were identified with assumptions relating to the utility values used in the sponsor's submission which biased incremental QALYs in favour of onasemnogene abeparvovec. This included an assumed increment for patients in the "unable to sit unassisted" and "sitting unassisted" health states for the achievement of interim milestones; assigning a utility of 0 to the permanent ventilation health state; and assuming patients able to walk unassisted had a quality of life similar to that of the general population. None of these assumptions were evidence-based and their validity is questionable.

Component	Description
	• Issues were identified with ventilation costs, as well as an inappropriate assumption that patients could be "within a broad range of normal development," which biased costs and QALYs in favour of onasemnogene abeparvovec.
CADTH reanalysis results	• In reanalysis, CADTH assumed the following: equal motor milestone achievement and survival for both patients receiving onasemnogene abeparvovec and nusinersen; removed utility increments for patients in the "unable to sit unassisted" or "sitting unassisted" health states; assigned utility values to the "walking unassisted" and "requiring permanent assisted ventilation" health states to align with the expectations of clinical experts; and updated permanent ventilation costs. • ICER = $334,090 per QALY compared to BSC. The probability of onasemnogene abeparvovec being cost-effective at a willingness-to-pay threshold of $50,000 per QALY is 0%. • Onasemnogene abeparvovec is dominant compared to nusinersen; onasemnogene abeparvovec is associated with lower costs and more QALYs. • The majority of the incremental benefits for onasemnogene abeparvovec (96% vs. BSC 98%, vs. nusinersen) were accrued beyond the time points for which clinical data were available. The results from the cost-utility analysis are therefore highly uncertain given the limited evidence around long-term effectiveness. • Results from the sponsor's scenario analysis suggest that the conclusions drawn from the CADTH reanalysis may be broadly applicable to SMA type 1 patients with 3 SMN2 gene copies who are pre-symptomatic at baseline, but limitations within the clinical data make the results from this analysis highly uncertain. The cost-effectiveness of onasemnogene abeparvovec in patients with a single SMN2 gene copy is unknown.

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY= quality-adjusted life-year; SMA = spinal muscular atrophy; SMN2 = survival motor neuron 2; vs. = versus.

Conclusions

Several major limitations were identified but could not be addressed within the sponsor's submitted model. In particular, there is a lack of information on the long-term comparative clinical effectiveness of onasemnogene abeparvovec. The indirect comparison technique used by the sponsor was insufficient to establish the comparative effectiveness of nusinersen. Within the model, 96% and 98% of the quality-adjusted life-year (QALY) benefit compared to best supportive care (BSC) and nusinersen, respectively, was estimated through extrapolation beyond the observed trial data. The cost of nusinersen is the key cost driver but the actual price for participating plans is unknown. Additionally, the sponsor's submission only considered patients with spinal muscular atrophy (SMA) type 1 who were younger than 2 years, who were symptomatic at baseline prior to 6 months of age, and who had 2 copies of the survival motor neuron 2 (SMN2) gene, rather than the full indicated population. The sponsor submitted a scenario analysis suggesting similar results in patients with 3 copies of the SMN2 gene who were pre-symptomatic at baseline, but limitations within the clinical data informing this analysis result in a high degree of uncertainty.

CADTH was able to address some of these limitations through reanalysis. The CADTH findings were in line with those of the sponsor. CADTH estimated that onasemnogene abeparvovec was associated with an incremental cost-effectiveness ratio (ICER) of $334,090 per QALY compared to BSC; onasemnogene abeparvovec appeared to dominate nusinersen. Compared with BSC, onasemnogene abeparvovec would not be considered cost-effective at a conventional willingness-to-pay threshold. A price reduction of greater than 90% is required for onasemnogene abeparvovec to be considered the cost-effective strategy compared to BSC at a willingness-to-pay threshold of $50,000 per QALY. Because

of the limitations of the evidence supporting the comparative efficacy of onasemnogene abeparvovec to nusinersen, these cost-effectiveness findings must be interpreted with a great deal of caution.

When considering the key limitations noted above that could not be addressed, the cost-effectiveness of onasemnogene abeparvovec in the indicated population is highly uncertain. Additionally, the cost-effectiveness of onasemnogene abeparvovec is unknown in patients who are older than 6 months or with a single copy of the SMN2 gene.

Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received that pertains to the economic submission from the patient groups that participated in the CADTH review process.

Two patient groups provided input for this submission. Cure SMA Canada, which supports individuals and families affected by SMA, conducted semi-structured interviews and an online survey to collect patient input. Muscular Dystrophy Canada, which offers a range of programs in support of those affected by neuromuscular disorders, gathered information via semi-structured telephone interviews. Three patients providing input via Muscular Dystrophy Canada had prior experience with onasemnogene abeparvovec. Both submissions cited key issues for patients with SMA which included: physical functioning, the ability to breathe unassisted, difficulties swallowing, and the ability to conduct activities of daily living. The submissions noted using mobility aids, breathing support, spinal treatment, feeding tube, physiotherapy, and medications to manage symptoms. Patients providing input with experience on nusinersen noted several side effects, including spinal headaches, vomiting, and sleeping troubles, while patients who had experience with onasemnogene abeparvovec noted minimal side effects which included elevated liver enzymes, lethargy, and mood changes. The importance of newborn screening for SMA was also raised. The patients interviewed expressed a desire for onasemnogene to be accessible beyond 2 years of age, as well as for patients who were pre-symptomatic.

Several of these concerns were addressed in the sponsor's model:

- The model captured the impact of treatment on improvement of quality of life via the use of health states and utility values, based on motor function milestones.
- Additional health care resource utilization related to symptom management was included within the analysis.
- Costs related to newborn screening were captured in the sponsor's base case.

However, some of these concerns were not or could not be addressed by CADTH:

- The model only considered patients with SMA type 1 who were symptomatic at baseline. The generalizability of results to other types of SMA beyond SMA type 1 and in patients who are pre-symptomatic is unknown.
- The model only considered symptomatic patients with an onset of symptoms at 6 months of age or younger, and did not consider patients older than 2 years.
- Adverse events related to treatment were not included in the sponsor's submission and could not be added in by CADTH.
- The model did not consider the impacts of treatment on swallowing or nutritional support.

Economic Review

The current review is for onasemnogene abeparvovec (Zolgensma) for the treatment of pediatric patients younger than 2 years with SMA with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene.

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

The sponsor submitted a cost-utility analysis assessing onasemnogene abeparvovec compared to nusinersen or BSC, for the treatment of patients with SMA type 1 with an onset of symptoms at 6 months of age or younger, who are symptomatic at baseline, and with 2 copies of the SMN2 gene. The modelled population differs from the anticipated Health Canada indication and funding request, which do not specify SMA type 1, restrict to patients with symptoms, or restrict to patients aged 6 months or younger.[1]

The recommended dose of onasemnogene abeparvovec, which is available as a solution for intravenous infusion, is based on patient weight. Kits containing anywhere between 2 to 14 vials with 2×10^{13} vector genomes per mL are to be customized based on the patient's weight, with all kits priced at $2,910,500, regardless of the number of vials needed.[2] The comparator regimens included in the model consisted of BSC and nusinersen. BSC was primarily palliative in nature, consisting of a combination of physician visits, surgical interventions, hospitalizations, respiratory assistance, and gastrointestinal and nutritional care. Nusinersen was assumed to be administered as per the recommended dosage in its product monograph, with 4 loading doses in the first 63 days, followed by a maintenance dose every 4 months.[2] For onasemnogene abeparvovec and nusinersen, other costs that were considered as part of treatment costs included administration costs and newborn screening costs.

The clinical outcomes predicted by the model were QALYs and life-years. The economic analysis was undertaken over a lifetime time horizon (80 years) from the perspective of the public health care payer. Discounting (1.5% per annum) was applied to both costs and outcomes.

Model Structure

A cohort-state transition model (Markov) was developed in Microsoft Excel. The model consisted of 5 health states based on motor function milestones achieved by the patient, including "within a broad range of normal development," "walking unassisted," "sitting unassisted," "unable to sit unassisted," and "requiring permanent assisted ventilation" (Figure 1). The model consisted of 2 phases, with the first phase ("early") capturing patient movement between health states within the first 30 months of treatment with onasemnogene abeparvovec and 40 months for patients on nusinersen, based on the observed clinical trial data for patients on pharmacotherapy and offset by 6 additional months to account for delays in motor milestone achievement as a conservative assumption. The second phase ("extrapolated") was a long-term extrapolation (remaining 77 years of the model time horizon), used to model patient survival according to natural history data based on the patient's health state at the end of the short-term model. The model cycle length was 6 months in the early phase and yearly in the extrapolation phase.

All patients entered the model in the "unable to sit unassisted" state, and at the end of each cycle over the course of the first 3 to 4 years of the model, they could transition into a different health state or stay in the same state. Transition to higher functioning health states could only happen 1 cycle at a time and only to the next higher motor function state (i.e., patients could not skip a motor functioning milestone). For patients in the higher motor function health states (i.e., "sitting unassisted," "walking unassisted," or "within a broad range of normal development"), it was assumed motor function milestones achieved at the end of the early phase of the model were sustained until death as long as they did not discontinue therapy. As a result, patients in these states were not at risk of permanent ventilation and were only at risk of death based on natural history data or general population mortality, which is further described in the model inputs section. Transition to the "requiring permanent assisted ventilation" state was only possible for patients in the "not sitting" state. Onasemnogene abeparvovec is a 1-time gene therapy. The model considered the possibility that patients receiving nusinersen may discontinue treatment at each cycle. Patients who discontinued were at risk of regression from their current health state to a lower motor function health state during each cycle, in addition to the risk of death.

Additionally, patients who received onasemnogene abeparvovec and were in the "walking unassisted" health state at 2 years of age were assumed to transition to the "within a broad range of normal development" health state at 5 years of age.[3] This assumption did not apply to patients treated with nusinersen or BSC, as no patients were assumed to walk unassisted on BSC.

Model Inputs

The clinical efficacy of onasemnogene abeparvovec, nusinersen, and BSC used to inform the early phase of the model was evaluated based on 2 separate analyses conducted by the sponsor. In both analyses, data for onasemnogene abeparvovec was pooled from the START and STR1VE-US trials.[4,5] For the comparative efficacy versus nusinersen, a matching-adjusted indirect comparison (MAIC) was conducted using this pooled data, with the data for nusinersen obtained from the SHINE trial, with matching based on [redacted].[6,7] . For comparative efficacy versus BSC, the sponsor drew survival information from the NeuroNext natural history cohort, which was selected based on having similar patient population characteristics to the pooled trial data, using a naïve and unanchored comparison approach.[8] These analyses primarily informed patient transitions from the "unable to sit unassisted" health state at baseline to the other motor function milestone health states through to the end of the 30-month early phase of the model for onasemnogene abeparvovec, and 40 months for nusinersen, based on the duration of follow-up of their respective trials. The SHINE trial also informed the probability of discontinuing nusinersen, while the annual probability of regression to a lower motor function health state (e.g., from "walking unassisted" to "sitting unassisted") after discontinuation was estimated based on clinical expert opinion.[6,7] This was the only way in which regression to a lower motor function health state could occur within the model. The respective data sources for each comparator also informed the survival curves used to derive the transition probability from "unable to sit unassisted" to "requiring permanent assisted ventilation" in the short-term phase of the model. In the extrapolated phase of the model, this transition was informed by the NeuroNext data for all comparators.[8]

Mortality was dependent on health state. In the early phase of the model, transition probabilities for mortality and related assumptions were based on the trial data for onasemnogene abeparvovec and nusinersen, and the natural history cohort for BSC. Of

note, patients receiving onasemnogene abeparvovec were assumed to have 100% survival in the first 30 months if they were in the "sitting unassisted" and "walking unassisted" health states, after which their mortality rate was the same as that applied to the comparators. Long-term mortality was based on natural history data identified in the literature, with data identified for different SMA types, as well as the general population, used as proxies for each health state. Long-term mortality for patients in the "unable to sit unassisted" health state was based on the NeuroNext natural history cohort, which described patients with SMA type 1 who are treated with BSC and not receiving permanent ventilation.[8] Mortality for the "sitting unassisted" state was assumed to be similar to a patient with SMA type 2, and was derived from the literature,[9] while mortality for the patients in the "walking unassisted" and "within a broad range of normal development" states was assumed to be the same as that for the general population.[10] Patients in the "requiring permanent ventilation" health state were assumed to have survival similar to that of patients with SMA type 1 receiving non-invasive ventilation.

An estimate of health state utility for the "unable to sit unassisted" health state was identified from the literature,[11] while the "requiring permanent ventilation state" was assumed to have a utility of 0. The value for the "sitting unassisted" state was obtained from a National Institute for Health and Care Excellence appraisal of nusinersen.[12] Values reflecting the health state utility of the general population were derived from the literature and adjusted for age and sex and used for the "walking unassisted" and "within broad range of normal development" health states.[13] The sponsor's base case also included a utility increase of 0.1 for patients receiving onasemnogene abeparvovec or nusinersen treatment in the "unable to sit unassisted" state and 0.05 in the "sitting unassisted" state to reflect interim milestones, such as head control or improvements in non-verbal communication, which were assumed to not be captured by the motor function-defined health states and their assigned utility values.

Costs considered in the model included treatment costs and health state costs. Treatment costs included costs for the drug, screening, and baseline tests. The cost of onasemnogene abeparvovec was provided by the sponsor, while the cost of nusinersen was obtained from the Ontario Exceptional Access Program formulary.[14] Costs related to treatment administration were obtained from the Ontario Schedule of Benefits for physician services.[15] Screening costs were based on expert opinion, suggesting that 10,000 live births would need to be screened to identify 1 case of SMA type 1, at a cost of $10 per neonate. Health state costs in the model were based on an unpublished health care resource utilization study conducted by the sponsor. For this study, the sponsor asked clinical experts to provide input on the BSC clinical management needs of SMA patients by type for the following categories: drugs, medical tests, medical visits, hospitalization and surgeries, general practitioner and emergency visits, and ventilator use. Unit costs for each health care resource use category were derived from the literature, including costs related to non-invasive ventilation and invasive permanent ventilation. In the final step, the clinical experts were asked to assign each SMA type as a proxy for the relevant motor function milestone health states. As a result, SMA type 1 (most severe) costs were applied to patients in the "unable to sit unassisted" and "requiring permanent ventilation" health states, SMA type 2 costs were applied to patients in the "sitting unassisted" health state, and SMA type 3 (least severe) costs were applied to patients in the "walking unassisted" and "within a broad range of normal development" health states. Costs, mortality, and disutility due to adverse events were not considered.

Summary of Sponsor's Economic Evaluation Results

All analyses were run probabilistically (5,000 iterations for the base case and all scenarios).

Base-Case Results

Results of the sponsor's base-case analysis were presented sequentially in their submission. Given that the clinical efficacy data for onasemnogene abeparvovec in comparison with nusinersen or BSC were assessed in 2 separate analyses and not in a common framework, CADTH deemed pairwise comparisons to be most appropriate. Onasemnogene abeparvovec was associated with expected costs of $3,266,544 and 10.89 QALYs. The ICER for onasemnogene abeparvovec compared with BSC was $293,521. BSC had the highest probability of being cost-effective below thresholds of $275,000 per QALY. Above that threshold, onasemnogene abeparvovec had the highest probability of being cost-effective, with the probability rising to 100% above a threshold of $300,000 per QALY. In comparison to nusinersen, onasemnogene results in greater QALYs and fewer costs, and was thus dominant.

Table 3: Summary of the Sponsor's Economic Evaluation Results

Drug	Total costs ($)	Total QALYs	ICER ($/QALY)
Best supportive care	132,600	0.21	Ref.
Onasemnogene abeparvovec	3,266,544	10.89	293,521
Onasemnogene abeparvovec	3,266,544	10.89	Dominant
Nusinersen	3,938,147	4.54	Dominated

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; Ref. = reference

Source: Sponsor's pharmacoeconomic submission.[2]

Sensitivity and Scenario Analysis Results

The sponsor conducted several sensitivity and scenario analyses. These analyses found that the cost-effectiveness results were most sensitive to changes in assumptions around treatment efficacy and transition probabilities that were more favourable to onasemnogene abeparvovec, as well as alternative health state utility values.

A supplementary scenario analysis was conducted to evaluate the use of onasemnogene abeparvovec in patients with 3 SMN2 gene copies, using interim data from cohort 2 of the ongoing SPR1NT phase III single-arm study. [redacted]. This scenario, included by the sponsor as an exploratory analysis, produced similar results to the sponsor's base case. The ICER compared to BSC was $193,239 (incremental cost = $3,731,473; incremental QALYs = 16.17); onasemnogene abeparvovec dominated nusinersen (lower cost, with greater QALYs). No information was provided for patients with 1 SMN2 gene copy.[16]

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the economic analysis and its interpretation:

- **Uncertain comparative clinical efficacy of onasemnogene abeparvovec with nusinersen or BSC for motor milestone achievement.** Several major limitations were identified with the comparative clinical efficacy data, as well as its implementation within the model, which lead to uncertainty with the magnitude of benefit observed with onasemnogene abeparvovec in comparison with nusinersen or BSC with regards to motor milestone achievement. These issues were limitations with the short-term comparative clinical efficacy data related to motor milestone achievement, a lack of evidence regarding the durability of such a treatment effect with onasemnogene abeparvovec and nusinersen, and no parameter uncertainty around clinical efficacy parameters related to motor milestone achievement within the model.
- **Short-term comparative clinical efficacy of onasemnogene abeparvovec with BSC and nusinersen is uncertain.** The CADTH clinical review assessed the pivotal studies and MAIC submitted by the sponsor. The review notes that there is some consistent evidence of a benefit across the trials for onasemnogene abeparvovec in comparison to BSC for symptomatic patients with SMA type 1 and 2 copies of the SMN2 gene, and that the substantial improvements in motor function skills are highly unlikely to be observed in patients treated with BSC alone. With that said, the clinical review also noted that the statistical generalizability or the comparative efficacy of onasemnogene abeparvovec with BSC cannot be assessed. Feedback from the clinical experts consulted by CADTH also noted that SMA is diagnosed more quickly in current practice than it was for the natural history cohorts, which makes comparability of such populations difficult to determine.
- Short-term comparative clinical efficacy of onasemnogene abeparvovec with nusinersen is uncertain with regards to motor milestone achievement following assessment of the sponsor's MAIC. To choose potential effect modifiers to include in the MAIC analysis, the sponsor's clinical team [redacted] with a number of other effect modifiers left unaccounted for. The clinical experts consulted by CADTH for this review did not agree with the order of importance of the variables selected. The CADTH clinical review also noted that the sponsor did not clearly state what effect modifiers they had attempted to collect data on and include within their analysis, and instead only provided information on the effect modifiers they had data for, which makes appraisal of the residual bias from their analysis difficult. The clinical experts consulted by CADTH noted that the patients treated in the onasemnogene abeparvovec trials were younger and treated more quickly after diagnosis in comparison to the patients in the nusinersen trials. These were considered to be key differences within the trials that made a comparison difficult and inappropriate. As a result, there is an unknown amount of residual bias with the MAIC leading to significant uncertainty with the comparative efficacy of onasemnogene abeparvovec with nusinersen.
- **Limited evidence on the durability of the treatment effect for onasemnogene abeparvovec and nusinersen.** The model relied heavily on the assumption of sustained benefit for both onasemnogene abeparvovec and nusinersen beyond the data (from separate trials) that informed the model's early phase. Patients in the model responding to treatment were assumed to maintain the highest functional status observed in the early phase of the model for the remainder of the 77-year model time horizon until their death, except for patients on nusinersen who discontinued their treatment and could

subsequently experience regression to lower motor function milestone health states. No data were available for critical appraisal or inclusion within the model beyond 24 months for onasemnogene abeparvovec and 34 months for nusinersen. Feedback from the clinical experts consulted by CADTH for this review indicates that there is limited evidence of the long-term durability of the treatment effect with either treatment, that it is highly uncertain that survival motor neuron protein expression would remain constant throughout a patient's lifetime, and that it is theoretically possible for patients receiving onasemnogene abeparvovec or nusinersen to experience a regression in motor function as a result of a lack of survivor motor neuron protein expression. The longer treatment effect duration meant that patients maintain their 30-month or 40-month outcomes, for onasemnogene abeparvovec and nusinersen, indefinitely. This is of note, as only up to 8% of the QALY benefit with onasemnogene abeparvovec compared to nusinersen or BSC, in the sponsor's base case, was from the observed period for which there was trial data. This results in bias favouring the cost-effectiveness of onasemnogene abeparvovec.

- **Uncertainty with the transition probabilities between motor function milestones not appropriately captured within the model.** Despite the above limitations which note the uncertainty with the clinical data, the transition probabilities for improvement of motor function milestones within the sponsor's submission did not vary between probabilistic model runs. Even with the most robust clinical efficacy data, the variability around the clinical efficacy parameters should be captured with an appropriate probability distribution, from which a range of values can be drawn. The sponsor's model therefore does not adequately reflect the role that the uncertainty around treatment effectiveness plays in estimates of cost-effectiveness.
    - The issues with the comparative efficacy of onasemnogene abeparvovec with nusinersen or BSC, as well as its implementation within the model, lead to meaningful but unquantifiable uncertainty in the magnitude of clinical benefit observed with onasemnogene abeparvovec in the early phase of the model. These effects were then extrapolated over the rest of the time horizon, potentially overestimating the incremental benefit observed with onasemnogene abeparvovec and biasing results in its favour.
    - CADTH assumed equal efficacy for onasemnogene abeparvovec and nusinersen in the CADTH reanalysis, with the transition probabilities for onasemnogene abeparvovec applied to nusinersen for the early phase of the model. CADTH could not address the duration of treatment effect or the propagation of uncertainty with the clinical efficacy data due a lack of flexibility with the sponsor's submitted model. The results of the economic evaluation therefore cannot accurately reflect the uncertainty surrounding the decision problem, which limits the inferences that can be drawn from its findings.

Generalizability of the results of the sponsor's submission to patients other than those represented within the model and likely to be prescribed onasemnogene abeparvovec in Canadian clinical practice is unknown. The modelled population was patients who were symptomatic at baseline with an onset of symptoms before 6 months of age and with 2 copies of the SMN2 gene. This is aligned with the studied population from whom trial data were available and used to populate treatment efficacy for onasemnogene abeparvovec within the model. The proposed Health Canada indicated population is broader, with the only restriction being patients must have 3 or fewer copies of the SMN2 gene or have infantile-onset of SMA symptoms. Feedback from clinical experts consulted by CADTH noted that the inclusion and exclusion criteria of the pivotal trials do not align with the proposed Health Canada indication. As a result, the cost-effectiveness of onasemnogene abeparvovec in patients who are pre-symptomatic, as well as those with 1 copy of the SMN2 gene, is not reflected in the economic analysis results.

The sponsor included a supplementary analysis for patients with 3 SMN2 gene copies, based on interim data from the single-arm SPR1NT study. Due to the study sample size and the lack of direct comparative evidence, this evidence is subject to the same uncertainty around clinical efficacy as described above. This supplementary analysis did not include patients with a single copy of the SMN2 gene.

CADTH could not address the limitations within reanalyses. The cost-effectiveness of onasemnogene abeparvovec is uncertain in patients who are pre-symptomatic; unknown in patients with 1 copy of the SMN2 gene.

- **Short-term mortality and event-free survival with onasemnogene abeparvovec compared with nusinersen is unknown.** In the early phase of the model, the risk of mortality, as well as the risk of requiring permanent ventilation while in the "unable to sit unassisted" health state (i.e., event-free survival) while on onasemnogene abeparvovec and nusinersen was based on their respective observed trial data. This resulted in different survival rates for patients in the "unable to sit unassisted," "sitting unassisted," and "walking unassisted" health states based on whether they had received nusinersen or onasemnogene abeparvovec. This was despite there being no comparative efficacy data related to these outcomes. Notably, patients receiving onasemnogene abeparvovec who were in the "sitting unassisted" and "walking unassisted" states were assumed to have 100% survival in the first 30 months based on the observed START and STR1VE-US trial data.[4,17] Given the small sample size of these trials, 100% survival is highly unlikely in the Canadian clinical practice setting. Additionally, the comparative mortality and event-free survival of nusinersen and onasemnogene was not assessed, and only naïve rates were used. As a result, the true difference in event-free survival and mortality between nusinersen and onasemnogene abeparvovec as they correlate to these motor function milestones is unknown. This assumption introduced a survival bias in favour of onasemnogene abeparvovec.

CADTH addressed this limitation by applying the survival rates for patients on onasemnogene abeparvovec to those receiving nusinersen in the "unable to sit unassisted," "sitting unassisted," and "walking unassisted" health states. Also, of note, the sponsor's submitted model did not appropriately calculate life-years gained, which made it difficult to appraise this limitation. CADTH corrected the miscalculations in subsequent analyses, though this did not impact the sponsor's base-case results with regards to the ICER (i.e., cost per QALY).

- **Submitted model does not capture all key changes in patient quality of life due to SMA.** Issues were identified with the model structure, which lead to potential limitations with the way in which key changes in patient quality of life are captured. First, the submitted model structure, which is based on patient achievement of motor function milestones, may not adequately represent all key disease events affecting patient quality of life. Feedback from the clinical experts consulted by CADTH indicated that quality of life for patients with SMA is not solely determined by their physical ability. Other components, such as the requirement of nutritional support, may have a significant impact on quality of life and are not captured by the model. Additionally, the clinical experts consulted by CADTH suggested that many of the largest changes in patient quality of life occur when some type of functional status has been lost, for example losing the ability to walk after having gained this ability. The clinical experts consulted by CADTH also noted that acute events like falls could lead to changes in motor function status. The model does not reflect the possibility of such losses within the possible patient transitions unless patients discontinued nusinersen. Patients discontinuing nusinersen had a high likelihood of experiencing regression to a lower motor function state, leading to lower QALYs. Patients on onasemnogene abeparvovec, and those continuing nusinersen, were assumed to maintain motor function for the entire time horizon as noted above. The impact of this limitation on model results is unknown,

leading to meaningful uncertainty with the estimate of the cost-effectiveness of onasemnogene abeparvovec.

CADTH could not address this limitation within reanalyses.

Several other limitations were identified with the sponsor's submission which affected the cost-effectiveness results, but have a lesser impact on the model in comparison with the considerable uncertainty with the comparative clinical efficacy data, generalizability of the results to the population likely to receive onasemnogene abeparvovec, and limitations with the submitted model structure. These additional limitations are as follows:

- Uncertainty with the health state utility values. There was considerable parameter uncertainty around health state utility values used in the sponsor's submission. Utility estimates used in the sponsor's base case were identified from multiple sources that used different elicitation methods which led to a potential lack of consistency with the value set used in the sponsor's base case. There has been limited research in the area of SMA, and as a result, some of the values used are highly uncertain. Specific issues with the health state utility values and their associated assumptions were identified as follows.
- Utility increment for interim milestone achievement while in the "unable to sit" and "sitting unassisted" health states lacks face validity. It was assumed patients on treatment with nusinersen or onasemnogene abeparvovec in the "sitting unassisted" and "unable to sit unassisted" health states would receive a health state utility improvement of 0.05 and 0.1, respectively, to reflect the achievement of interim milestones (e.g., head control) not captured by the health state utility values used in the model. These increments were applied for the entirety of the time horizon. While it is possible that there would be some transient increase in patient quality of life due to achieving such milestones in the first few cycles of the model, there is no evidence to support the value of the increment selected, nor is there evidence to support that the health state utility values selected by the sponsor did not already incorporate such gains from the population from whom the health state utility values were elicited or meant to represent. Given more patients on onasemnogene abeparvovec were in these 2 health states over the course of the model time horizon than nusinersen or BSC, the incremental QALYs were likely biased in its favour.

CADTH removed the utility increments in its reanalysis.

- The utility value for the "requiring permanent ventilation" health state is likely underestimated. In their base case, the sponsor applied a utility value of 0 to the "requiring permanent ventilation" health state based on an assumption that the value had to be lower than the value of 0.190 applied to the "unable to sit unassisted" health state. A utility value of 0.0 represents a state of health that is equally preferable to death. The sponsor's justification for this value was that it was in line with their submission to the National Institute for Health and Care Excellence. No evidence was offered to support this assumption. For the remainder of their base-case health state utility value assumptions, the sponsor adopted the approach taken by the Institute for Clinical and Economic Review in an independent review of their own of onasemnogene abeparvovec for the treatment of SMA. [18] In their base-case analysis, ICER set this health state utility value to be equal to that of patients in the "unable to sit" health state. Given more patients on BSC and nusinersen required permanent ventilation in the model, the sponsor's assumption biased the incremental QALYs in favour of onasemnogene abeparvovec.

In the absence of evidence to quantify the utility of the "requiring permanent ventilation" state, CADTH made no assumption about a decrease in utility. Accordingly, CADTH set the health state utility value for permanent ventilation to be equal to the health state utility value for being unable to sit (0.190).

- The assumption of patients with SMA type 1 who are symptomatic at baseline who are able to walk unassisted with treatment having a quality of life similar to that of the general

population is not appropriate. The sponsor assumed patients who are able to walk unassisted would have a quality of life similar to that of the general population. This does not align with the rest of their assumptions regarding this state, which assumed a life expectancy and costs similar to that of a patient with SMA type 3, which is not equivalent to the life expectancy and costs of the general population. Feedback from the clinical experts consulted by CADTH indicated that patients with SMA type 1 who were symptomatic at baseline and responding to treatment would still not attain a quality of life similar to that of the general population due to already having experienced some sort of decline or deficit that they could not regain. More patients on onasemnogene abeparvovec achieved the "walking unassisted" motor milestone than either of the other comparators, and as a result, this assumption biased results in its favour.

CADTH applied a value corresponding to 0.760 from Love et al., for patients with SMA type 3 [19] to the "walking unassisted" health state in its reanalysis.

- **Serious adverse events were excluded from the model:** The sponsor noted that the adverse events associated with onasemnogene abeparvovec observed in the pivotal trials were difficult to disentangle from the complications of SMA. As a result, adverse events were excluded from the model for all comparators. The clinical experts consulted by CADTH noted that thrombocytopenia has been reported in patients, and that there had been a case of hydrocephalus in the STR1VE-US trial, a case of [redacted] in the STR1VE-EU trial,[17] as well as cardiotoxicity and dorsal root ganglion degeneration documented in animal models.[1,20] Further, the long-term adverse events associated with a gene therapy of this nature are unknown. It is difficult to quantify the direction and magnitude of bias that these adverse events would have on the cost-effectiveness of onasemnogene abeparvovec in comparison with nusinersen, considering the adverse events associated with nusinersen were also excluded. The exclusion of adverse events was likely to bias incremental costs and QALYs in favour of onasemnogene abeparvovec in comparison to BSC.

CADTH could not address this limitation within its reanalyses.

- **The costs associated with permanent ventilation were overestimated.** The sponsor conducted their own health care resource utilization study to identify health state costs. The costs of ventilation in the pediatric intensive care unit setting were based on a Canadian Institute for Health Information estimate of the per diem cost of an average pediatric intensive care unit stay, while ventilation in a rehabilitation setting was based off of a cost assessing both public and private payer costs of non-invasive ventilation in a rehabilitation setting.[21] CADTH conducted a search of inpatient and ambulatory costs related to ventilation in Ontario using the Ontario Case Costing Initiative (OCCI) costing tool. The OCCI costs indicate that the sponsor's estimates of daily costs were higher than what was expected in Ontario when compared to using the codes for invasive tracheostomy in an inpatient setting and non-invasive positive pressure in an ambulatory setting, respectively, in patients 0 to 17 years of age. This overestimated the costs associated with ventilation, biasing the incremental costs in favour of onasemnogene abeparvovec given fewer patients on this drug required permanent ventilation in comparison to patients receiving BSC or nusinersen.

For the CADTH reanalysis, the costs identified from the OCCI were inflated to 2019 Canadian dollars using the Consumer Price Index, and an average cost per day was determined based on dividing this cost by the average length of stay obtained from the OCCI for the relevant procedure.

Additionally, the following key assumptions were made by the sponsor and have been appraised by CADTH (Table 4).

Table 4: Key Assumptions of the Submitted Economic Evaluation (Not Noted as Limitations to the Submission)

Sponsor's key assumption	CADTH comment
Survival is improved in correlation with motor function milestone achievement.	Appropriate.
Sponsor's assessment of NeuroNext cohort is most appropriate source of natural history data for BSC and long-term extrapolation of survival with the "unable to sit" state.	The sponsor submission included their analysis of the PNCR dataset as the natural history cohort for comparison of results. In order to align the CADTH estimate with the CADTH clinical review, the sponsor's analysis of the PNCR dataset was selected for use in the CADTH estimate.
The model included a health state for "within a broad range of normal development," which was only applicable to patients on onasemnogene abeparvovec.	Not appropriate. Patients with symptomatic SMA type 1 would have already experienced some form of decline that could not be regained. CADTH removed the possibility of achieving this health state as part of the reanalysis of equal efficacy of motor milestone achievement for onasemnogene abeparvovec and nusinersen.
Life expectancy, costs, and utilities for certain health states based on motor function milestones can be estimated using proxies (i.e., for patients who sit unassisted, patients with SMA type 2 treated with BSC may be used as proxy for life expectancy, costs, and utilities; for patients who walk unassisted, patients with SMA type 3 treated with BSC may be used as a proxy for life expectancy and costs).	Considered appropriate with regards to the "unable to sit" (SMA type 1) and "sitting unassisted" (SMA type 2) health state. Clinical expert feedback noted that the use of SMA type 3 as a proxy for "walking unassisted" is uncertain given the broad spectrum of disease severity with SMA type 3. Life expectancy may be reasonable, though there is variation in the motor function abilities which could affect quality of life, which was assumed to be equivalent to that of the general population. This was considered unlikely.
Patients on nusinersen in the "unable to sit unassisted" and "sitting unassisted" health states have a 3% annual risk of treatment discontinuation.	Real-world discontinuation is uncertain. CADTH assessed this assumption within scenario analyses.
Upon discontinuation of nusinersen, patients were assumed to have a 90% annual probability of regression to the next lower health state.	This remains uncertain. While regression is possible upon discontinuation, the likelihood is unknown. This assumption only has an impact when discontinuation with nusinersen is high, unless the rate of regression is assumed to be drastically reduced.
100% of patients on onasemnogene are assumed to survive up to 30 months of age while in the "sitting unassisted" and "walking unassisted" health states, based on the START and STR1VE-US trials.	Not appropriate. There would be some form of background mortality among these patients corresponding to a similar mortality rate as that in the general population. Correcting this does not impact the cost-effectiveness of onasemnogene abeparvovec.
Patients in the not sitting state are assumed to follow natural history and permanent ventilation-free survival curves for patients with SMA type 1, with a maximum survival of 48 months.	Natural history and permanent ventilation-free survival curves are likely appropriate; maximum survival is uncertain.
AAV9 antibody testing for patients on onasemnogene abeparvovec will be covered by Novartis.	No further details were provided. The cost is too small to materially affect cost-effectiveness of onasemnogene abeparvovec.

Sponsor's key assumption	CADTH comment
The distribution of the setting of ventilation by ventilation type was assumed as follows: **Ventilation group** / **Intensive care (%)** / **High dependency (%)** / **Home-based (%)** Patients on non-invasive ventilation < 16 hours per day / 0.0 / 2.5 / 97.5 Patients on non-invasive ventilation > 16 hours per day / 5.0 / 10 / 85 Tracheostomy patients / 2.5 / 10 / 87.5	Clinical expert feedback indicated the high-dependency ventilation setting (i.e., rehab setting) may not be used in the Canadian context. Altering this assumption had limited impact on the cost-effectiveness of onasemnogene abeparvovec or the rest of the model results.

AAV9 = adeno-associated virus serotype 9; BSC = best supportive care; PNCR = Pediatric Neuromuscular Clinical Research Network; SMA = spinal muscular atrophy.

CADTH Reanalyses of the Economic Evaluation

Base-Case Results

Given the significant uncertainty associated with the comparative clinical effectiveness of onasemnogene abeparvovec compared to BSC or nusinersen, CADTH conducted reanalyses to obtain insight on the possible cost-effectiveness of onasemnogene abeparvovec. CADTH undertook reanalyses that addressed some of the limitations with the model, as summarized in Table 5. CADTH could not address several limitations, including issues related to the model structure, the exclusion of adverse events, and the generalizability of the results to the population most likely to receive onasemnogene abeparvovec (i.e., pre-symptomatic patients).

Table 5: CADTH Revisions to the Submitted Economic Evaluation

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Changes to derive the CADTH estimate		
1. Comparative efficacy of onasemnogene abeparvovec with nusinersen (motor function milestone achievement)	Based on the sponsor-submitted indirect treatment comparison; onasemnogene is generally more effective than nusinersen with respect to motor milestone achievement. All patients standing at age 5 on onasemnogene abeparvovec are considered to be "within a broad range of normal development." Note: In the early phase of the model, the highest state obtained was maintained for patients on either onasemnogene abeparvovec and nusinersen. The only difference between the 2 comparators was the discontinuation rate applied to nusinersen, which could subsequently lead to regression.	Assumed equal efficacy for nusinersen and onasemnogene abeparvovec, with transition probabilities for the first 8 cycles for onasemnogene abeparvovec applied to nusinersen. No patients on onasemnogene could reach "within a broad range of normal development" at age 5. Note: Extrapolation phase of the model and its assumptions were not altered.
2. Survival on nusinersen compared with onasemnogene abeparvovec	On-trial survival (mortality and requirement of permanent ventilation from the unable to sit state) was used for the early phase of the model (approximately 30 months), leading to different survival rates for patients on nusinersen in comparison to onasemnogene abeparvovec.	Assumed equal survival for patients on nusinersen and onasemnogene abeparvovec, with the survival with onasemnogene abeparvovec for the entire time horizon applied to patients on nusinersen.
3. Utility increment while in the "unable to sit assisted" and "sitting unassisted" health states for interim milestone achievement.	"Unable to sit unassisted": All patients receive 0.1 increase in health state utility value. "Sitting unassisted": All patients receive 0.05 increase in health state utility value while on treatment.	No increment applied to either health state.
4. Utility value for patients on permanent ventilation	0.0 (equivalent to death).	0.190, the same value as that for patients in the "unable to sit unassisted" health state.
5. Utility value for patients "walking unassisted"	Age-adjusted general population utility was 0.954 at age 25 to 0.685 at age ≥ 75	0.760 from Love et al. (2019), for patients with SMA type 3.[19]
6. Ventilation costs	Intensive care: $3,595 per day, $1,439,535 per year. Rehabilitation: $1,127 per day, $489,346 per year.	Intensive care: $2,783.39 per day (total cost of $24,772.21 divided by the average length of stay of 8.9 days); cost of invasive tracheostomy from OCCI in inpatient setting, inflated to 2019 costs is

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Changes to derive the CADTH estimate		
		$1,013,154 per year. Rehabilitation: $684 per case of non-invasive positive pressure ventilation according to OCCI in an ambulatory setting in 2018, inflated to 2019 costs is $249,660 per year.
7. Natural history cohort data informing best supportive care and survival from the "unable to sit unassisted" health state within the model	Sponsor's analysis of the NeuroNext cohort.	Sponsor's analysis of the PNCR cohort.
CADTH estimate		1+2+3+4+5+6+7

OCCI = Ontario Case Costing Initiative; PNCR = Pediatric Neuromuscular Clinical Research Network; SMA = spinal muscular atrophy.

In the CADTH estimate, onasemnogene abeparvovec was associated with estimated total costs of $3,249,578 and total QALYs of 9.883. The ICER compared to BSC was $334,090 per QALY. Based on this analysis, if a decision-maker were willing to pay below $334,090 per QALY, then BSC would be the optimal therapy, while at a willingness-to-pay threshold at or above $334,090 per QALY, onasemnogene abeparvovec would be the optimal therapy. Onasemnogene abeparvovec had a 0% chance of being the most cost-effective option at willingness-to-pay thresholds less than $320,000 per QALY. In comparison with nusinersen, onasemnogene abeparvovec was dominant, resulting in lower costs and greater QALYs. Of note, 96% of the QALY benefit accrued with onasemnogene abeparvovec in comparison to both nusinersen and BSC was from the extrapolation period beyond the period for which there was observed trial data. As noted above, CADTH could not address several key limitations, notably related to the long-term comparative clinical efficacy, and the results should be interpreted with caution.

The CADTH step-wise analysis, presented in Appendix 4, Table 10, indicated the change to the CADTH estimate with the greatest impact on the ICER of onasemnogene abeparvovec versus BSC was the exclusion of a utility increment for interim milestones achieved while in the "unable to sit unassisted" and "sitting unassisted" health states, but this did not alter overall results. The rest of the changes had limited impact on model results for either pairwise comparison. None of the stepped analyses altered the results in comparison with nusinersen. The assumption of equal comparative treatment efficacy between nusinersen and onasemnogene abeparvovec had the greatest impact on incremental QALYs, while incremental costs increased substantially due to more patients on nusinersen being alive and incurring drug costs. It is also important to note that the reanalyses are based on the publicly available price for nusinersen and do not account for any additional reductions in the price paid by the drug plans, potentially exaggerating the size of incremental cost savings with onasemnogene abeparvovec.

A detailed breakdown of the disaggregate results is also available in Appendix 4, Table 11.

Table 6: Summary of the CADTH Reanalysis Results – CADTH Estimate[a]

Drug	Total costs ($)	Total QALYs	ICER ($/QALY)
Best supportive care	137,171	0.567	Ref.
Onasemnogene abeparvovec	3,249,578	9.883	334,090
Onasemnogene abeparvovec	3,249,578	9.883	Dominant
Nusinersen	4,881,630	6.295	Dominated

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; Ref. = reference

[a] This analysis reflects symptomatic patients at less than 6 months of age with 2 copies of survival motor neuron 2.

Scenario Analysis Results

CADTH undertook price reduction analyses based on the sponsor's base case and CADTH's estimate analyses, assuming proportional price reductions for onasemnogene abeparvovec (Table 7). Based on the CADTH reanalysis, a price reduction of greater than 90% would be required for onasemnogene abeparvovec to be considered the optimal therapy at a willingness-to-pay threshold of $50,000 per QALY in comparison with BSC. Given nusinersen was dominated by onasemnogene abeparvovec in both the sponsor's base case and CADTH's estimate, no price reductions were reported for this pairwise comparison.

Table 7: CADTH Price Reduction Analyses

	ICERs for onasemnogene abeparvovec vs. BSC	
Price reduction (%)	**Sponsor base case ($)**	**CADTH reanalysis ($)**
0 (no price reduction)	293,521	334,090
10	266,181	302,867
20	238,978	271,694
30	211,772	240,420
40	184,368	209,147
50	157,150	177,850
60	129,950	146,581
70	102,620	115,442
80	75,326	84,128
90	47,996	52,997

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; vs. = versus.

Note: Analysis based on publicly available price for nusinersen.

CADTH also undertook several scenario analyses of the CADTH estimate to determine the impact of several alternative assumptions on the cost-effectiveness of onasemnogene abeparvovec. These included:

1. Reduce the time horizon to 5 years, given there is limited data on the long-term efficacy of onasemnogene abeparvovec or nusinersen. CADTH notes that it would be more appropriate to limit the time horizon to the length of time for which there is observed data (approximately 30 months), but the sponsor's model was insufficiently flexible to accommodate this length of time horizon. Only increments of 5 years were allowed with the model.
2. Apply the alternative set of utility values identified from Love et al.,[19] In the CADTH estimate, the health state utility values for "requiring permanent ventilation," "unable to

sit unassisted," "sitting unassisted," and "walking unassisted" were 0.19, 0.19, 0.60, and the general population utility (approximately 0.954, adjusted by age), respectively. The corresponding values from Love et al., are 0.42, 0.42, 0.49, and 0.76, respectively. This was done to test the impact of alternative utility values identified from a single source given the uncertainty with the utility values used in the sponsor's base case.

3. Alter the discontinuation rate for patients on nusinersen in the "unable to sit" and "sitting unassisted" health states from 3% to 0%. This value was arbitrarily chosen to determine the impact of no discontinuation rate and was not based on the literature or clinical expert opinion.
4. Alter the discontinuation rate for patients on nusinersen in the "unable to sit" and "sitting unassisted" health states from 3% to 20%. This value was arbitrarily chosen to determine the impact of higher discontinuation rates and was not based on the literature or clinical expert opinion.
5. Utilize the sponsor's base case transition probabilities for motor function milestone achievement for nusinersen and onasemnogene abeparvovec, based on the sponsor's MAIC (i.e., preserve the sponsor's assumed treatment benefit with onasemnogene abeparvovec).
6. Utilize the survival data and assumptions from the sponsor's base case for nusinersen and onasemnogene abeparvovec (i.e., preserve the sponsor's assumed survival benefit with onasemnogene abeparvovec in the early phase).
7. Base the BSC natural history and survival for all comparators in the "unable to sit" health state on the sponsor's assessment of the NeuroNext dataset.
8. Apply the sponsor's assumption of a utility increment for patients on treatment.
9. Apply a health state utility value of 0 for patients on permanent ventilation, as per the sponsor's assumption.
10. Apply price reductions to nusinersen, given the CADTH Canadian Drug Expert Committee recommendation for nusinersen noted a substantial reduction in price, up to 95%.[22] The price reductions considered, while holding the price of onasemnogene abeparvovec constant, were 25%, 50%, and 95%.

The results of these analyses are presented in Appendix 4, Table 12. The results were generally robust to changes to the inputs and assumptions assessed in the scenario analyses. The scenario analysis that led to the greatest change when compared with the CADTH estimate results for the comparison of onasemnogene abeparvovec with BSC was shortening the time horizon (Scenario Analysis 1). The ICER for onasemnogene abeparvovec compared with BSC was $2,866,859 per QALY. This analysis highlights the high up-front costs associated with onasemnogene abeparvovec, as well as the limited gains in QALYs over the short-term phase of the model in comparison to the long-term extrapolation phase. For the comparison of onasemnogene abeparvovec with BSC, the use of an alternative set of utility values (Scenario Analysis 2) was the only other analysis that resulted in substantial changes to the ICER. For Scenario Analysis 2, the ICER for onasemnogene abeparvovec compared with BSC rose to $410,448 per QALY. This finding highlights the crucial role that the uncertain evidence of patient utility plays in estimating the true cost-effectiveness of onasemnogene abeparvovec.

When considering onasemnogene abeparvovec in comparison with nusinersen, the scenario analysis that led to the greatest change when compared with the CADTH estimate was shortening the time horizon (Scenario Analysis 1). The ICER for onasemnogene abeparvovec compared with nusinersen was $8,109,261 per QALY, where again, the high up-front costs of onasemnogene abeparvovec play a key role given the limited QALY gains

in the early phase in comparison with nusinersen. The scenarios assessing price reductions of 50% and 95% for nusinersen (Scenario Analysis 10) had the next greatest impact on results in the pairwise comparison with nusinersen, highlighting the costs of nusinersen as a key driver in the analysis. When a price reduction of 50% was considered, onasemnogene abeparvovec was no longer dominant at its submitted price, resulting in an ICER of $178,899 per QALY. When a price reduction of 95% for nusinersen was considered, the ICER rose to $749,930 per QALY.

Issues for Consideration

Feedback from the clinical experts consulted by CADTH for this review noted that pre-symptomatic patients are most likely to be benefit from onasemnogene abeparvovec. Pre-symptomatic detection will depend highly on the availability of newborn screening, which will vary between health care jurisdictions (provinces and territories), as well as within them. The cost-effectiveness and budget impact of this treatment will likely vary between jurisdictions as a consequence. Jurisdictions with higher rates of pre-symptomatic detection will experience larger health benefits, but with higher rates of treatment utilization. CADTH was not able to estimate the impact of screening from the submitted evidence.

There is the potential for use of nusinersen at some point either prior to or after the administration of onasemnogene abeparvovec. The CADTH clinical review noted that 4 patients in the pivotal trials for onasemnogene abeparvovec had received nusinersen at some point. Feedback from clinical experts consulted by CADTH noted that functional regression as per a patient's own highest level of functioning achieved might constitute a point where other pharmacological options would be explored. Clinical experts indicated that they did not believe nusinersen would confer any additional clinical benefit to patients who did not respond to onasemnogene abeparvovec, but that it may nonetheless be used in clinical practice in Canada as a second-line therapy. The impact of the use of nusinersen prior to or after onasemnogene abeparvovec on potential costs and QALYs is unknown.

Overall Conclusions

CADTH identified several limitations with the sponsor's submission, which were primarily related to the available evidence of treatment efficacy and to structural assumptions made within their cost-utility model. The lack of robust evidence of the comparative efficacy of onasemnogene abeparvovec, nusinersen, and BSC, particularly related to the long-term effect of the 2 active treatments, contributed a high level of uncertainty to the economic analysis. Importantly, the sponsor's analysis did not consider all patients who would be eligible to receive the new treatment according to the Health Canada indication.

The results should be interpreted with caution given substantial uncertainty remains due to limitations that could not be addressed within the CADTH estimate. CADTH was not able to address many of the limitations regarding either the short- or long-term comparative effectiveness of onasemnogene abeparvovec compared to nusinersen or BSC. The results of the CADTH reanalysis were also restricted to the subset of SMA patients who were symptomatic at younger than 6 months with 2 copies of the SMN2 gene, which does not necessarily reflect the full indicated population.

CADTH undertook reanalyses which altered inputs and assumptions related to limitations that could be addressed, including assuming equal effectiveness of onasemnogene abeparvovec and nusinersen, adjusting a series of assumptions about health state utility,

and updating permanent ventilation costs. CADTH's reanalysis of the sponsor's economic model estimated that the ICER of onasemnogene abeparvovec compared with BSC was $334,090 per QALY gained, while onasemnogene abeparvovec dominated nusinersen (fewer costs and more QALYs). A price reduction of greater than 90% would be needed to achieve an ICER of $50,000 per QALY compared to BSC. Of note, 96% to 98% of the QALY benefit accrued with onasemnogene abeparvovec was accrued through extrapolation beyond the period for which there was observed trial data, based on assumptions for which there was similarly little evidence. CADTH's estimate of the ICER for onasemnogene abeparvovec in comparison with nusinersen during the model's early phase was in excess of $8,000,000 per QALY.

The cost-effectiveness of onasemnogene abeparvovec compared to nusinersen is driven by the drug acquisition costs of nusinersen. The sponsor's submission considered the list price of the drug and does not account for any additional reductions in the price paid by the drug plans. The recommendation for nusinersen was conditional on a substantial price reduction. In scenario analyses where price reductions for nusinersen were considered, substantially different results were obtained, and onasemnogene abeparvovec was no longer cost-effective in comparison to nusinersen in the scenario which considered a 50% price reduction.

It is also important to note that the sponsor's submission and resulting CADTH reanalyses only considered patients with SMA type 1 who were younger than 2 years and who were symptomatic at baseline. The sponsor's scenario analysis of patients with 3 SMN2 gene copies was based on a small number of patients with a short follow-up period; the cost-effectiveness of onasemnogene abeparvovec in this patient population is therefore highly uncertain. The cost-effectiveness of onasemnogene abeparvovec for pre-symptomatic patients is uncertain and is unknown for patients with a single SMN2 gene copy.

Appendix 1: Cost Comparison Table

The comparators presented in the Table 8 have been deemed to be appropriate based on feedback from clinical experts. Comparators may be recommended (appropriate) practice or actual practice. Existing product listing agreements are not reflected in the table and as such, the table may not represent the actual costs to public drug plans.

Table 8: CADTH Cost Comparison for Spinal Muscular Atrophy

Treatment	Strength	Form	Price ($)	Recommended dosage	Daily cost ($)	Annual cost ($)
Onasemnogene abeparvovec (Zolgensma)	**1.1×10^{14} vg/kg**	**IV**	**2,910,500.0000[a]**	**1-time dose**	**NA[b]**	**NA[b]**
Antisense oligonucleotide						
Nusinersen (Spinraza), first year	12 mg/5 mL	Injection	118,000.0000[c]	6 injections per year	1,939.73	708,000
Subsequent years				3 injections per year	969.86	354,000

IV: intravenous; NA = not applicable; vg = vector genome.

[a] Source: Sponsor's pharmacoeconomic submission[2] and does not include administration costs.

[b] Onasemnogene abeparvovec is delivered as a 1-time dose. Daily and annual costs were not calculated.

[c] Saskatchewan Drug Benefit (accessed August 2020).[23]

Appendix 2: Submission Quality

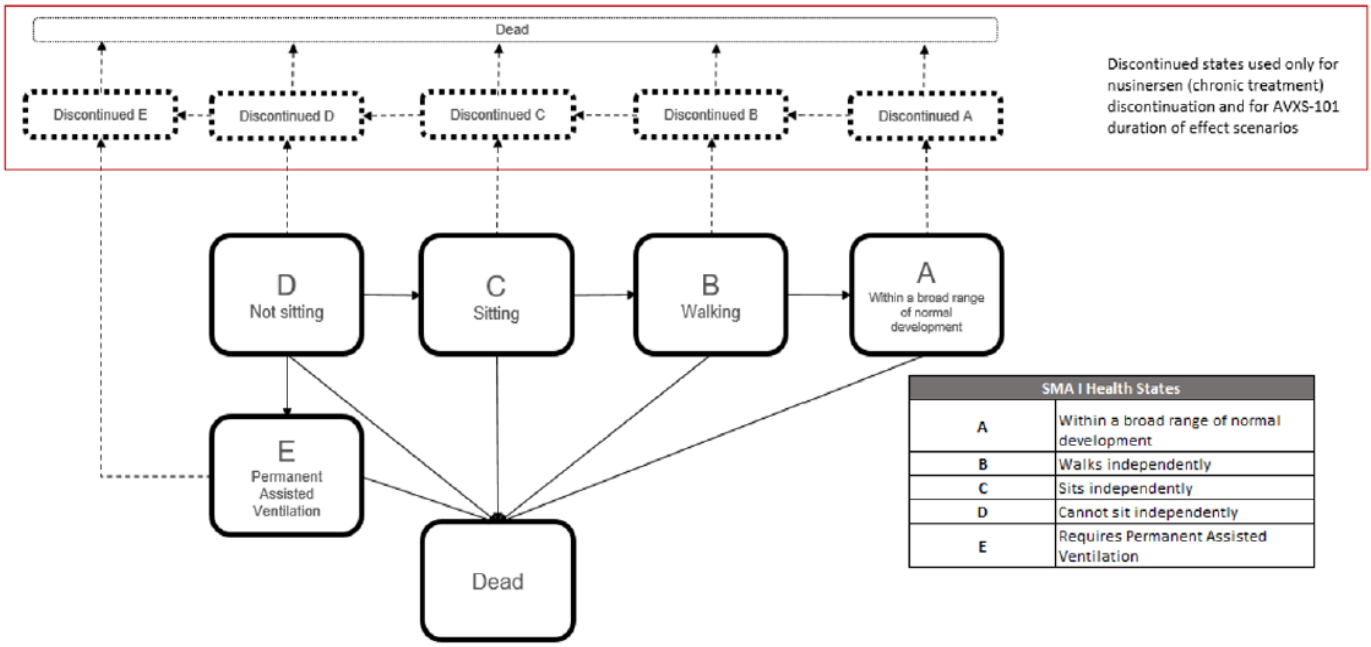
Table 9: Submission Quality

Description	Yes	No	Comments
Population is relevant, with no critical intervention missing, and no relevant outcome missing	☐	☒	Target population included in the economic evaluation is restrictive when compared with the proposed indication. The submission excludes pre-symptomatic patients, as well as those with greater or less than 2 copies of the SMN2 gene.
Model has been adequately programmed and has sufficient face validity	☐	☒	There are issues with the programming of the model that have led to issues with calculation of results. For example, the discounting of life-years was incorrect, though this did not impact the sponsor's base-case results with regards to the ICER (i.e., cost per QALY).
Model structure is adequate for decision problem	☐	☒	The applicability of the model structure to the decision problem is uncertain, as noted in the key limitations section.
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis)	☒	☐	
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem	☐	☒	Uncertainty around the clinical efficacy data was not assessed with an appropriate distribution and transitions were non-varying.
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough details)	☐	☒	There was a lack of clarity with how the MAIC was used to derive transition probabilities.

MAIC = matching-adjusted indirect comparison; SMN2 = survival motor neuron 2.

Appendix 3: Additional Information on the Submitted Economic Evaluation

Figure 1: Model Structure



Source: Sponsor's pharmacoeconomic submission.[2]

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

Table 10: Summary of the Stepped Analysis of the CADTH Reanalysis Results[a]

	Drug	Total costs ($)	Total QALYs	ICER ($/QALY)
1. Equal efficacy (efficacy for onasemnogene abeparvovec applied to nusinersen)	Best supportive care	132,501	0.211	Ref.
	Onasemnogene abeparvovec	3,266,035	10.886	293,549
	Onasemnogene abeparvovec	3,266,035	10.886	Dominant
	Nusinersen	3,662,052	4.108	Dominated
2. Equal short-term survival (short-term survival for onasemnogene abeparvovec applied to nusinersen)	Best supportive care	132,648	0.212	Ref.
	Onasemnogene abeparvovec	3,266,754	10.887	293,603
	Onasemnogene abeparvovec	3,266,754	10.887	Dominant
	Nusinersen	4,290,065	5.477	Dominated
3. Exclusion of utility increment for interim milestone achievement for patients unable to sit unassisted and sitting unassisted	Best supportive care	133,035	0.212	Ref.
	Onasemnogene abeparvovec	3,266,329	9.967	321,201
	Onasemnogene abeparvovec	3,266,329	9.967	Dominant
	Nusinersen	3,944,485	4.080	Dominated
4. Utility for patients requiring permanent ventilation equal to that of patients unable to sit	Best supportive care	132,411	0.338	Ref.
	Onasemnogene abeparvovec	3,265,065	10.930	295,779
	Onasemnogene abeparvovec	3,265,065	10.930	Dominant
	Nusinersen	3,940,877	4.749	Dominated
5. Utility value for patients walking unassisted changed to lower value compared to general population, based on value for SMA type 3 from Love et al. (2019)[19]	Best supportive care	132,955	0.211	Ref.
	Onasemnogene abeparvovec	3,266,442	10.871	293,954
	Onasemnogene abeparvovec	3,266,442	10.871	Dominant
	Nusinersen	3,947,262	4.486	Dominated
6. Updated ventilation costs	Best supportive care	126,766	0.212	Ref.
	Onasemnogene abeparvovec	3,242,069	10.891	291,737
	Onasemnogene abeparvovec	3,242,069	10.891	Dominant
	Nusinersen	3,873,012	4.537	Dominated
7. Natural history data based on the PNCR dataset	Best supportive care	145,437	0.276	Ref.
	Onasemnogene abeparvovec	3,275,381	10.904	294,495
	Onasemnogene abeparvovec	3,275,381	10.904	Dominant
	Nusinersen	3,946,108	4.541	Dominated

ICER = incremental cost-effectiveness ratio; PNCR = Pediatric Neuromuscular Clinical Research Network; QALY = quality-adjusted life-year; Ref. = reference

[a] This population reflects symptomatic patients at less than 6 months of age with 2 copies of the survival motor neuron 2 gene.

Note: Reference product is least costly alternative.

Detailed Results of CADTH Estimate

Table 11: Disaggregated Summary of CADTH's Economic Evaluation Results[a]

Treatment	Component	Value	Incremental (vs. reference)	% of total incremental[b]
Discounted LYs[c]				
Best supportive care	Total	2.988	NA	NA
Onasemnogene abeparvovec	Total	17.83	14.84	NA
Nusinersen	Total	12.22	NA	NA
Onasemnogene abeparvovec	Total	17.83	5.61	NA
Discounted QALYs				
Best supportive care	Permanent ventilation	0.291	NA	NA
	Unable to sit	0.276	NA	NA
	Sitting unassisted	0.000	NA	NA
	Walking unassisted	0.000	NA	NA
	Total	0.567	NA	NA
Onasemnogene abeparvovec	Permanent ventilation	0.058	–0.232	–2
	Unable to sit	0.394	0.118	1
	Sitting unassisted	8.642	8.642	93
	Walking unassisted	0.788	0.788	8
	Total	9.883	9.316	NA
Nusinersen	Permanent ventilation	0.118	NA	NA
	Unable to sit	0.426	NA	NA
	Sitting unassisted	5.067	NA	NA
	Walking unassisted	0.683	NA	NA
	Total	6.295	NA	NA
Onasemnogene abeparvovec	Permanent ventilation	0.058	–0.060	–2
	Unable to sit	0.394	–0.032	–1
	Sitting unassisted	8.642	3.575	100
	Walking unassisted	0.788	0.105	3
	Total	9.883	3.588	NA
Discounted costs ($)				
Best supportive care	Acquisition	0	NA	NA
	Administration (includes screening costs)	99,970	NA	NA
	Health state costs	37,200	NA	NA
	Total	137,171	NA	NA
Onasemnogene abeparvovec	Acquisition	2,910,500	2,910,500	94
	Administration (includes screening costs)	100,153	183	0
	Health state costs	238,925	201,724	6
	Total	3,249,578	3,112,407	NA
Nusinersen	Acquisition	4,547,901	NA	NA

Treatment	Component	Value	Incremental (vs. reference)	% of total incremental[b]
	Administration (includes screening costs)	110,619	NA	NA
	Health state costs	223,109	NA	NA
	Total	4,881,630	NA	NA
Onasemnogene abeparvovec	Acquisition	2,910,500	–1,637,401	100
	Administration (includes screening costs)	100,153	–10,466	1
	Health state costs	238,925	15,815	–1
	Total	3,249,578	–1,632,052	NA

LY = life-year; NA = not applicable; QALY = quality-adjusted life-year; vs. = versus.

[a] This population reflects symptomatic patients at less than 6 months of age with 2 copies of the survival motor neuron 2 gene.

[b] Percentage of total incremental (e.g., if total incremental LY is 5 and incremental LY in state XXX is 2, the percent of the total is 2 of 5, which is 40%).

[c] CADTH corrected a computational error within the sponsor's model that led to life-years being overestimated. This error did not affect the calculation of QALYs.

Source: Sponsor's pharmacoeconomic submission.[2]

Scenario Analyses

Table 12: Summary of the CADTH Scenario Analyses Results[a]

		Drug	Total costs ($)	Total QALYs	ICER ($/QALY)
CADTH reanalysis		Best supportive care	137,171	0.567	Ref.
		Onasemnogene abeparvovec	3,249,578	9.883	334,090
		Onasemnogene abeparvovec	3,249,578	9.883	Dominant
		Nusinersen	4,881,630	6.295	Dominated
1	5-year time horizon	Best supportive care	137,413	0.481	Ref.
		Onasemnogene abeparvovec	3,098,729	1.514	2,866,859
		Nusinersen	2,034,209	1.383	Ref.
		Onasemnogene abeparvovec	3,098,729	1.514	8,109,261
2	Utility values from Love et al. (2019) [19]	Best supportive care	136,783	1.259	Ref.
		Onasemnogene abeparvovec	3,249,856	8.844	410,448
		Onasemnogene abeparvovec	3,249,856	8.844	Dominant
		Nusinersen	4,872,748	6.014	Dominated
3	Discontinuation with nusinersen is 0% for patients unable to sit or sitting unassisted	Best supportive care	137,518	0.571	Ref.
		Onasemnogene abeparvovec	3,249,900	9.889	334,017
		Onasemnogene abeparvovec	3,249,900	9.889	Dominant
		Nusinersen	7,259,494	9.889	Dominated
4	Discontinuation with nusinersen is 20% for patients unable to sit or sitting unassisted	Best supportive care	136,866	0.573	Ref.
		Onasemnogene abeparvovec	3,250,415	9.885	334,325
		Nusinersen	1,831,674	1.671	Ref.
		Onasemnogene abeparvovec	3,250,415	9.885	172,722
5	Sponsor base-case efficacy and survival assumptions for nusinersen vs.	Best supportive care	137,396	0.569	Ref.
		Onasemnogene abeparvovec	3,249,484	10.014	329,485
		Onasemnogene abeparvovec	3,249,484	10.014	Dominant

		Drug	Total costs ($)	Total QALYs	ICER ($/QALY)
	onasemnogene abeparvovec	Nusinersen	4,404,523	5.205	Dominated
6	Sponsor base-case survival assumptions for nusinersen vs. onasemnogene abeparvovec	Best supportive care	137,249	0.569	Ref.
		Onasemnogene abeparvovec	3,249,291	9.886	334,005
		Nusinersen	2,208,077	1.493	Ref.
		Onasemnogene abeparvovec	3,249,291	9.886	124,057
7	Best supportive care natural history and survival in the unable to sit state is based on the NeuroNext cohort	Best supportive care	126,972	0.341	Ref.
		Onasemnogene abeparvovec	3,242,115	9.866	327,075
		Onasemnogene abeparvovec	3,242,115	9.866	Dominant
		Nusinersen	4,844,223	6.273	Dominated
8	Sponsor's assumption of a utility increment for patients on treatment	Best supportive care	136,861	0.569	Ref.
		Onasemnogene abeparvovec	3,249,841	10.810	303,953
		Onasemnogene abeparvovec	3,249,841	10.810	Dominant
		Nusinersen	4,875,126	6.882	Dominated
9	Health state utility 0 for patients requiring permanent ventilation	Best supportive care	137,261	0.276	Ref.
		Onasemnogene abeparvovec	3,249,199	9.825	325,895
		Onasemnogene abeparvovec	3,249,199	9.825	Dominant
		Nusinersen	4,870,746	6.158	Dominated
10 a	25% price reduction for nusinersen	Onasemnogene abeparvovec	3,250,368	9.883	Dominant
		Nusinersen	3,744,055	6.284	Dominated
10 b	50% price reduction for nusinersen	Nusinersen	2,606,419	6.294	NA
		Onasemnogene abeparvovec	3,249,691	9.890	178,899
10 c	95% price reduction for nusinersen	Nusinersen	561,753	6.300	NA
		Onasemnogene abeparvovec	3,250,059	9.885	749,930

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs. = versus; NA = not applicable; Ref. = reference

[a] This population reflects symptomatic patients at less than 6 months of age with 2 copies of the survival motor neuron 2 gene.

Note: Reference product is least costly alternative.

Exploratory Analyses

Alternative Payment Models

CADTH also undertook exploratory analyses to assess the impact of hypothetical alternative payment models, where onasemnogene abeparvovec would be reimbursed based on achieving a response after a certain period of time had elapsed. The following 2 exploratory analyses were conducted.

- Cost of onasemnogene abeparvovec is only applied to people who are able to sit unassisted or walk unassisted as of year 3 in the model.
- Cost of onasemnogene abeparvovec is only applied to people who are able to walk unassisted as of year 4 in the model.

The years selected represented the approximate duration of the early phase of the model for onasemnogene abeparvovec and nusinersen rounded up to a whole year. The first exploratory analysis, which considered the reimbursement of patients who are sitting or walking unassisted at 3 years of age, represents a less restrictive definition of responders,

whereas the second exploratory analysis considered a successful response as walking as of 4 years of age. The cost of onasemnogene abeparvovec among responders was not incurred until years 3 and 4 of the model, respectively, with appropriate discounting applied based on the year in which the costs were incurred. When considering reimbursement for only those patients who are sitting or walking unassisted, the ICER for onasemnogene abeparvovec compared with BSC decreased relative to the CADTH reanalysis to $213,650 per QALY, while onasemnogene continued to dominate nusinersen. In this scenario, onasemnogene abeparvovec would be reimbursed for approximately 65% of the patients who started on this therapy. In the more restrictive scenario where only the cost of onasemnogene abeparvovec is reimbursed for patients able to walk unassisted at 4 years of age, the ICER was $28,896 per QALY in comparison with BSC, and nusinersen was dominated by onasemnogene abeparvovec. In this scenario, onasemnogene abeparvovec was reimbursed for only 2.5% of the population starting on the therapy.

Table 13: Summary of the CADTH Exploratory Analyses Results

	Drug	Total costs ($)	Total QALYs	ICER ($/QALY)
Onasemnogene abeparvovec reimbursed in patients who are sitting or walking unassisted at 3 years of age	Best supportive care	136,986	0.569	Ref.
	Onasemnogene abeparvovec	2,127,993	9.888	213,650
	Onasemnogene abeparvovec	2,127,993	9.888	Dominant
	Nusinersen	4,877,146	6.287	Dominated
Onasemnogene abeparvovec reimbursed in patients who are walking unassisted at 4 years of age	Best supportive care	136,568	0.569	—
	Onasemnogene abeparvovec	405,678	9.882	28,896
	Onasemnogene abeparvovec	405,678	9.882	Dominant
	Nusinersen	4,878,091	6.286	Dominated

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Note: Reference product is least costly alternative.

Estimation of Time to Equivalent Cost – Onasemnogene Abeparvovec Versus Nusinersen

An additional exploratory analysis was performed to estimate the length of time at which the cumulative cost of onasemnogene abeparvovec was comparable to that of nusinersen. This analysis considers the difference in the dosing schedule between these 2 treatments where onasemnogene is a 1-time injection given at the beginning of the disease course and nusinersen is administered at regular intervals over the course of a patient's lifetime. The comparatively high up-front cost of onasemnogene abeparvovec, considered in conjunction with lower estimated lifetime cost, implies a point in time at which the 2 treatments are equally costly.

CADTH examined the cumulative costs in each 1-year cycle of the economic model used for the CADTH base case. Results for the first 15 years are presented in Table 14.

Table 14: Summary of the Cumulative Cost Analysis

	Cumulative cost ($, average per patient)	
Years elapsed	**Onasemnogene abeparvovec**	**Nusinersen**
1	3,022,724	697,319
2	3,048,239	1,063,842
3	3,068,616	1,372,580
4	3,091,431	1,856,158
5	3,113,787	2,118,931
6	3,137,881	2,366,503
7	3,160,996	2,596,637
8	3,182,153	2,809,754
9	3,201,723	3,009,319
10	3,219,851	3,196,196
11	3,236,664	3,371,179
12	3,252,273	3,535,002
13	3,266,779	3,688,344
14	3,280,271	3,831,838
15	3,292,831	3,966,074

Note: Deterministic results are presented. Probabilistic results were generally similar; costs reached equivalence between 12 and 13 years.

The results of the analysis suggest that the 2 treatments are equally costly 10 to 12 years after the initiation of treatment. It is important to note, however, that this analysis is subject to the same key limitations that are previously noted in this report. The long-term effectiveness of both of these treatments is highly uncertain. If nusinersen is less effective in achieving long-term stability in functional status than the model results predict, patients will discontinue treatment. This will result in lower costs. Patients cannot discontinue onasemnogene abeparvovec if they do not achieve long-term functional stability. Prices included in this analysis are also based on the list price of onasemnogene abeparvovec and nusinersen, and do not reflect any negotiated price reductions that may be in effect. Consequently, the estimated time to equivalence in costs is highly uncertain, but is likely an underestimate.

Appendix 5: Submitted Budget Impact Analysis and CADTH Appraisal

Key Take-Aways of the Budget Impact Analysis

CADTH identified the following key limitations with the sponsor's analysis:

- Mathematical errors led to incorrect handling of incident cases becoming prevalent cases in subsequent years of the analysis.
- Nusinersen is not available for coverage in Prince Edward Island and through the Non-Insured Health Benefits program. Accordingly, the budget impact estimate for these jurisdictions will not include nusinersen in the new and reference scenarios.
- The sponsor's model categorized patients based on SMA type, whereas the Health Canada indication assumed individuals will be eligible regardless of SMA type.

CADTH reanalyses corrected for the incident cases of SMA, nusinersen not being listed in 2 jurisdictions, and the use of SMA types in the model.

Based on CADTH reanalyses, the budget impact from the introduction of onasemnogene abeparvovec is expected to be $102,752,466 in year 1, $40,047,005 in year 2, and $31,681,768 in year 3, with a 3-year budget impact of $174,481,238.

Uncertainty remains in this analysis with regard to the Health Canada indication for this treatment. If patient eligibility for onasemnogene abeparvovec is dependent on SMA type or the number of SMN2 gene copies, that could impact the population size and the overall budget impact. Clinical experts consulted by CADTH assumed a very high market uptake for onasemnogene abeparvovec. In the scenario analysis of 100% market share, the 3-year budget impact rose to $209,554,518.

Summary of Sponsor's Budget Impact Analysis

The submitted budget impact analysis[2] (BIA) assessed the introduction of onasemnogene abeparvovec for the treatment of pediatric patients younger than 2 years with SMA with bi-allelic mutations in the SMN1 gene. Using an epidemiological approach, the BIA was conducted over a 3-year time horizon (January 2021 to December 2023) with 2020 as a baseline year 0. As this was conducted from the perspective of public drug plans, the BIA base case included only drug acquisition costs. Administration costs, anesthesia costs, and newborn screening costs were considered in scenario analysis. In the reference scenario, onasemnogene abeparvovec is not funded, and most of the patients were assumed to be treated with nusinersen. A small percentage of patients were assumed to be treated with BSC in case provinces do not reimburse nusinersen. In the new scenario, most of the patients were assumed to be treated with onasemnogene abeparvovec, with the remainder being treated by nusinersen or BSC. In the BIA base case, the sponsor assumed that any patients with SMA treated with nusinersen still alive and not on permanent ventilation from year 0 would be treated in year 1. The eligible population was estimated by multiplying the incidence of SMA by the number of live births in each year. An overview of the sponsor estimation of the eligible population size can be found in Figure 2, with key inputs to the BIA documented in Table 15.

Figure 2: Sponsor's Estimation of the Size of the Eligible Population

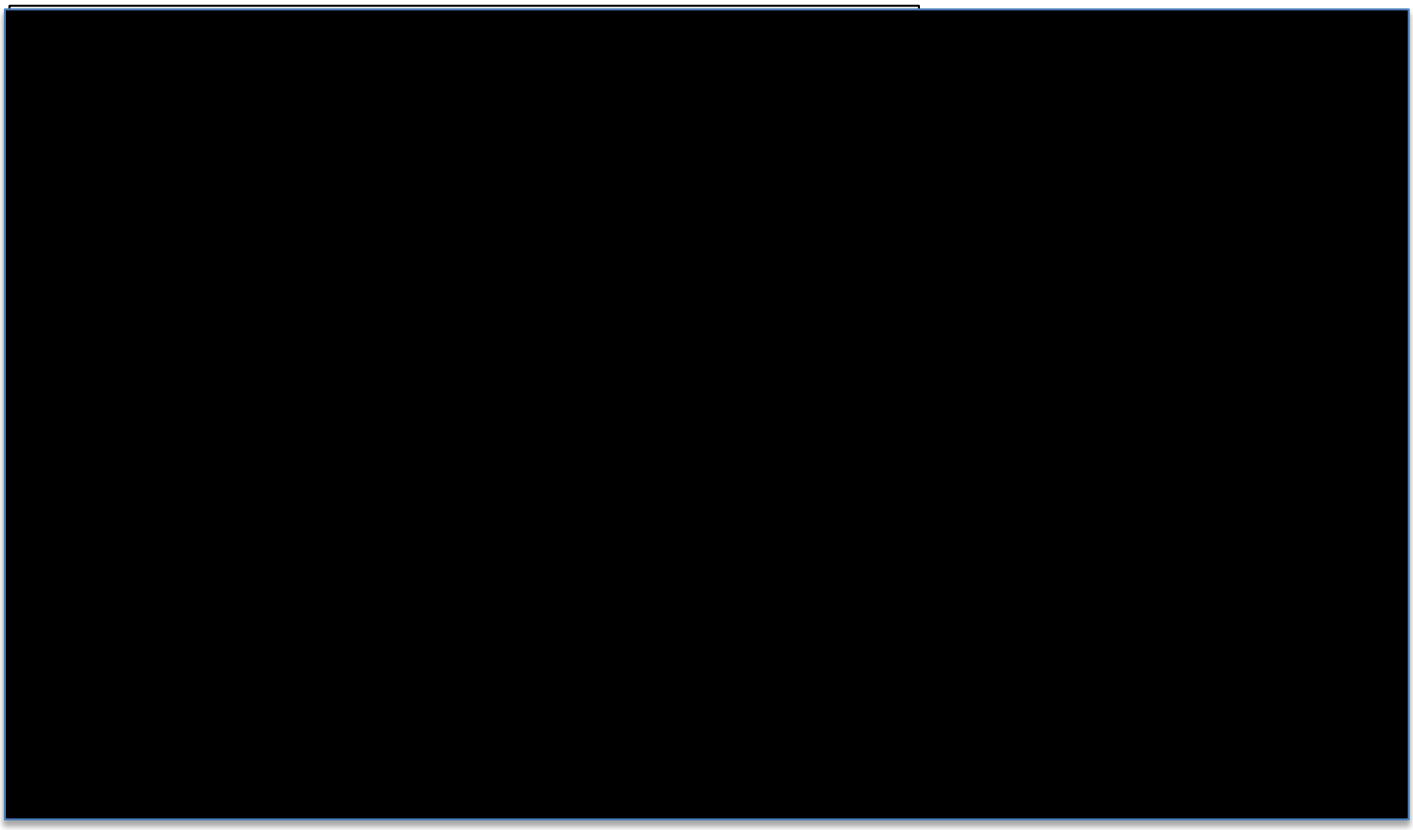


Table 15: Summary of Key Model Parameters

Parameter	Sponsor's estimate (reported as year 1 / year 2 / year 3 if appropriate)
Target population	
Total live births per year in Canada (excluding QC)	287,857[24]
Incidence of spinal muscular atrophy	1/10,000[25]
% type 1	60[25]
% type 2	25[25]
Estimated number of patients eligible for onasemnogene abeparvovec	24 / 24 / 24
Market uptake (3 years)	
Uptake (reference scenario) Nusinersen BSC	 95% / 95% / 95% 5% / 5% / 5%
Uptake (new drug scenario) Onasemnogene abeparvovec Nusinersen BSC	 [redacted]
Cost of treatment (per patient)	
Onasemnogene abeparvovec (1-time cost) Nusinersen (first year)	$2,910,500 $708,000

Parameter	Sponsor's estimate (reported as year 1 / year 2 / year 3 if appropriate)
Nusinersen (subsequent years)	$354,000

BSC = best supportive care; QC = Quebec.

Summary of the Sponsor's BIA Results

The sponsor's base case found that the incremental expenditures associated with the reimbursement of onasemnogene abeparvovec for pediatric patients with SMA are expected to be $84,829,725 in year 1, $34,027,045 in year 2, and $26,664,675 in year 3. The total 3-year budget impact for reimbursing onasemnogene abeparvovec was estimated to be $145,521,446.

CADTH Appraisal of the Sponsor's BIA

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the results of the BIA:

- **Incorrect handling of incident and prevalent cases according to market shares:** The model submitted by the sponsor did not correctly account for incident and prevalent cases of SMA in each year of the BIA. Specifically, the estimate of the number of patients being treated with nusinersen in subsequent years did not properly account for prevalent cases from previous years, resulting in an overestimate of the number of patients treated with nusinersen.

CADTH corrected these calculations as part of the base case.

- **Nusinersen is not available in all jurisdictions:** The model submitted by the sponsor assumed the same market shares across the various jurisdictions for onasemnogene abeparvovec, nusinersen, and BSC. However, nusinersen is not available for coverage in Prince Edward Island and through the Non-Insured Health Benefits program and should therefore not capture any market share from these jurisdictions. This resulted in overestimates of the costs in the reference scenarios for these jurisdictions, as nusinersen was assumed to take up most of the market share in the reference scenarios.

CADTH reallocated the market share of nusinersen in Prince Edward Island and for the Non-Insured Health Benefits program in the reference scenarios. Instead, for these jurisdictions, BSC was assumed to capture the entire market while in the new scenarios, the share of nusinersen was assumed to be taken up by onasemnogene abeparvovec.

- **Modelled population does not align with Health Canada indication:** The anticipated Health Canada indication for onasemnogene abeparvovec is as follows: "for the treatment of pediatric patients less than 2 years of age with SMA with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene." However, in the submitted BIA certain patients were considered eligible based on their SMA type (Figure 2), which is not addressed in the indication. The sponsor further noted in their report that "all SMA types will be eligible for treatment."[2] Excluding patients based on SMA type was therefore inappropriate.
- CADTH recognized that removing this exclusion resulted in greater influence being exerted by the estimate of the incidence of SMA on the overall budget impact. This incidence estimate is already generally uncertain due to the fact that newborn screening is not performed routinely and incidence is only estimated once the phenotype is expressed.[25] Clinical experts consulted by CADTH suggested that reliable estimates of SMA incidence in Canada would be available soon as a result of the Ontario newborn screening program, but these estimates were not currently available. In the absence of

more robust evidence, the incidence estimate of 1 per 10,000 live births used by the sponsor was used as a proxy.

CADTH removed the SMA type categorization from the BIA and considered all incident cases of SMA to be eligible within the base case.

- **Nusinersen discontinuation was only** considered **in patients from base year:** The sponsor assumed that patients in the base year of the BIA (i.e., 2020) who had been treated with nusinersen would be eligible for treatment with onasemnogene abeparvovec in year 1 (i.e., 2021), provided they were not on permanent ventilation or dead. The sponsor used an estimate of 60% of SMA type 1 patients from the ENDEAR trial who were still alive without permanent ventilation.[26] However, this discontinuation of nusinersen was not applied to the incident cases in years 1 and 2, which are considered to be treated on nusinersen in years 2 and 3 of the BIA. This resulted in an overestimation of the number of patients treated with nusinersen, and associated costs.

CADTH addressed this issue through scenario analysis, assuming a discontinuation rate of 40% from those treated with nusinersen in the first and second year of the BIA.

- **No consideration given to the SMN2 gene copy number:** The sponsor did not address the number of copies of the SMN2 gene as a condition for identifying the eligible population in their analysis. Clinical evidence suggests that only patients with 1 to 3 copies of the SMN2 gene are likely to benefit from onasemnogene abeparvovec. Should the SMN2 gene copy number be reflected in the final Health Canada indication, the eligible population size will consequently change, and with it the overall budget impact.

CADTH could not address this issue due to structural limitations in the model.

Finally, CADTH conducted a pair of scenario analyses in which onasemnogene abeparvovec would be conditionally funded for patients who achieve a designated functional milestone. Two milestones were chosen: those who are able to sit unassisted or walk unassisted as of year 3 in the pharmacoeconomic model, and those who are able to walk unassisted as of year 4 in the pharmacoeconomic model. The estimates used in the BIA were 65% of incident patients in the first scenario and 2.5% in the second scenario.

CADTH Reanalyses of the BIA

Based on the limitations identified, CADTH's base-case analysis included changes to patient numbers, reimbursement status of nusinersen, and the removal of SMA types from the model (Table 16).

Table 16: CADTH Revisions to the Submitted BIA

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Changes to derive the CADTH base case		
1. Incorporation of incidence and prevalence	Patients being treated with nusinersen were not properly carried through the BIA.	Corrected these formulas to ensure alignment of the new and reference populations.
2. Availability of nusinersen in PEI and NIHB program	Assumed nusinersen was available in all jurisdictions	Reallocated market share of nusinersen in jurisdictions who do not reimburse
3. Population alignment with HC indication	The SMA cases eligible for treatment with onasemnogene abeparvovec would be type 1 (60%) and types 2 and 3 (25%).	CADTH assumed all incidence cases of SMA would be eligible (100%).
CADTH base case	NA	Reanalyses 1 & 2 & 3

BIA = budget impact analysis; HC = Health Canada; NIHB = Non-Insured Health Benefit; PEI = Prince Edward Island; SMA = spinal muscular atrophy.; NA = not applicable

The results of the CADTH step-wise reanalysis are presented in summary format in Table 17 and a more detailed breakdown is presented in Table 18.

Based on the CADTH base case, the expected budget impact of funding onasemnogene abeparvovec for SMA patients younger than 2 years is expected to be $102,752,466 in year 1, $40,047,005 in year 2, and $31,681,768 in year 3, with a 3-year budget impact of $174,481,238.

Scenario analyses were conducted using the CADTH base case, with the scenario that considered onasemnogene abeparvovec capturing 100% of the market share having the largest impact on results. When this was assumed, the expected BIA was $121,649,792 in year 1, $48,627,054 in year 2, and $39,277,671 in year 3, for a 3-year budget impact of $209,554,518. When applying a 90% price reduction (the price at which the ICER was approximately $50,000/QALY) the expected budget impact in year 1 was –$10,504,002, –$24,303,261 in year 2, and –$32,668,498 in year 3, for a 3-year budget impact of –$67,475,761.

Table 17: Summary of the CADTH Reanalyses of the BIA

Stepped analysis	3-year total ($)
Submitted base case	145,521,446
CADTH reanalysis 1 – number of cases	142,922,962
CADTH reanalysis 2 – PEI and nusinersen	146,638,488
CADTH reanalysis 3 – all incident cases	174,481,238
CADTH base case	**174,481,238**

BIA = budget impact analysis; PEI = Prince Edward Island.

Table 18: Detailed Breakdown of the CADTH Reanalyses of the BIA

Stepped analysis	Scenario	Year 1 ($)	Year 2 ($)	Year 3 ($)	3-year total ($)
Submitted base case	Reference	24,685,595	32,914,126	41,142,658	98,742,378
	New drug	109,515,320	66,941,172	67,807,333	244,263,824
	Budget impact	**84,829,725**	**34,027,045**	**26,664,675**	**145,521,446**
CADTH base case	Reference	25,804,295	35,153,678	44,503,060	105,461,033
	New drug	128,556,761	75,200,682	76,184,828	279,942,272
	Budget impact	**102,752,466**	**40,047,005**	**31,681,768**	**174,481,238**
CADTH scenario analysis 1: 90% price reduction	Reference	25,804,295	35,153,678	44,503,060	105,461,033
	New drug	15,300,294	10,850,417	11,834,562	37,985,272
	Budget impact	**–10,504,002**	**–24,303,261**	**–32,668,498**	**–67,475,761**
CADTH scenario analysis 2: nusinersen discontinuation 40% per year	Reference	25,804,295	32,909,826	40,015,357	98,729,478
	New drug	128,556,761	74,964,487	75,712,438	279,233,687
	Budget impact	**102,752,466**	**42,054,662**	**35,697,081**	**180,504,209**
CADTH scenario analysis 3a: conditional funding – sit or walk unassisted by year 3 (65%)	Reference	16,772,792	22,849,891	28,926,989	68,549,672
	New drug	83,561,895	48,880,444	49,520,138	181,962,477
	Budget impact	**66,789,103**	**26,030,553**	**20,593,149**	**113,412,805**
CADTH scenario analysis 3b: conditional funding – walk unassisted by year 4 (2.5%)	Reference	645,107	878,842	1,112,577	2,636,526
	New drug	3,213,919	1,880,017	1,904,621	6,998,557
	Budget impact	**2,568,812**	**1,001,175**	**792,044**	**4,362,031**
CADTH scenario analysis 4: onasemnogene abeparvovec 100% market share	Reference	25,804,295	35,153,678	44,503,060	105,461,033
	New drug	147,454,088	83,780,732	83,780,732	315,015,551
	Budget impact	**121,649,792**	**48,627,054**	**39,277,671**	**209,554,518**
CADTH scenario analysis 5a: nusinersen 95% price reduction	Reference	1,290,215	1,757,684	2,225,153	5,273,052
	New drug	125,976,332	71,685,315	71,734,522	269,396,168
	Budget impact	**124,686,117**	**69,927,631**	**69,509,369**	**264,123,117**
CADTH scenario analysis 5b: nusinersen 50% price reduction	Reference	12,902,148	17,576,839	22,251,530	52,730,517
	New drug	127,198,641	73,350,489	73,842,562	274,391,691
	Budget impact	**114,296,493**	**55,773,650**	**51,591,032**	**221,661,174**
CADTH scenario analysis 5c: nusinersen 25% price reduction	Reference	19,353,222	26,365,258	33,377,295	79,095,775
	New drug	127,877,701	74,275,586	75,013,695	277,166,981
	Budget impact	**108,524,479**	**47,910,327**	**41,636,400**	**198,071,206**

BIA = budget impact analysis.

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