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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report (Resubmission)

NUSINERSEN (SPINRAZA)

(Biogen Canada Inc.)

Indication: Treatment of patients with 5q spinal muscular atrophy.

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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.

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Abbreviations

CDR	CADTH Common Drug Review
CHOP INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
EQ-5D	EuroQol 5-Dimensions questionnaire
EQ-5D-Y	child-friendly EuroQol 5-Dimensions questionnaire
HFMSE	Hammersmith Functional Motor Scale – Expanded
LY	life-year
QALY	quality-adjusted life-year
RWC	real-world care
SMA	spinal muscular atrophy

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Nusinersen (Spinraza) 2.4 mg/mL solution for intrathecal injection
Study Question	What is the estimate incremental cost per quality-adjusted life-year (QALY) gained for nusinersen compared to Canadian standard of care for patients with 5q spinal muscular atrophy (SMA)?
Type of Economic Evaluation	Cost-utility analysis (CUA)
Target Population	Patients with 5q SMA — stratified by SMA type — type I, II, and III
Treatment	Nusinersen — 5 mL solution for intrathecal injection administered in four loading doses (days 0, 4, 28, and 63) followed by maintenance treatment of 5 mL solution every four months — in addition to real-world care (RWC), which includes supportive symptomatic treatment of respiratory, nutritional, and orthopaedic function decline
Outcomes	• Life-years (LYs) • QALYs
Comparator	• Standard of care (or RWC)
Perspective	Canadian public health care payer
Time Horizon	Type I — 25 years Type II — 50 years Type III — 80 years
Results for Base Case	For type I: • nusinersen led to greater QALYs (gain of 4.80), LYs (gain of 4.79), and cost (increase of $3.1 million), for an incremental cost per QALY gained of $665,570. For type II: • nusinersen led to greater QALYs (gain of 3.67), LYs (gain of 2.18), and cost (increase of $7.6 million), for an incremental cost per QALY gained of $2.1 million. For type III: • nusinersen led to greater QALYs (gain of 1.56), no difference in LYs (gain of 2.18), and an increase in cost ($4.5 million), for an incremental cost per QALY gained of $2.9 million. For all three SMA types: • the probability that nusinersen was cost-effective assuming that the threshold value for a QALY was $300,000 was 0%. No new analysis was provided within the manufacturer's resubmission.
Key Limitations	• Utility values were derived from unpublished studies provided for Biogen Idec, which the CADTH Common Drug Review (CDR) did not consider had appropriate methodology for the estimation of utility. • The manufacturer made inappropriate assumptions relating to disease progression for patients with SMA types I, II, and III receiving nusinersen. • The manufacturer made inappropriate assumptions relating to mortality within SMA types I and II. • Certain health states within the model were inappropriate as they were reflective relative rather than absolute health states. • The manufacturer's submission did not allow further stratification by disease status within SMA type, which would have been highly informative. • The CDR clinical expert has raised a number of concerns with the clinical trial data for nusinersen, which undermines the ability to facilitate the economic evaluation. This particularly relates to the lack of appropriate clinical data for assessing the effectiveness of nusinersen in SMA type III. • The manufacturer did not provide new economic information as part of their resubmission and did not further address the previously cited limitations.

CDR Estimate(s)	• CDR reanalysis addressed the first three previously mentioned limitations, but could not address the further limitations identified.
	• The CDR reanalysis found a similar finding to the manufacturer's, in that nusinersen was not cost-effective for the three SMA types. CDR reanalysis noted much higher incremental cost-utility ratios:
	  ○ SMA type I: $9.2 million per QALY
	  ○ SMA type II: $24.4 million per QALY
	  ○ SMA type III: $7.4 million per QALY — results should be considered speculative given the concerns raised regarding the lack of appropriate clinical data.
	• For each SMA type, the probability that nusinersen was cost-effective at a willingness-to-pay threshold of $500,000 was 0%.

Drug	Nusinersen (Spinraza)
Indication	Treatment of 5q spinal muscular atrophy (SMA)
Reimbursement Request	Treatment of patients with 5q SMA across all types (including presymptomatic patients and all ages)
Dosage Form(s)	5 mL solution for intrathecal injection administered in four loading doses (days 0, 4, 28, and 63) followed by maintenance treatment of 5 mL solution every four months
NOC Date	August 14, 2018
Manufacturer	Biogen Canada Inc.

Executive Summary

Background

Spinal muscular atrophy (SMA) is a severe neuromuscular disease and is the leading genetic cause of infant death. It is characterized by the degeneration of alpha motor neurons in the anterior horn of the spinal cord, leading to progressive muscle weakness. The most common form of SMA, 5q SMA, makes up more than 95% of all cases and is an autosomal recessive disorder caused by homozygous deletion or deletion and mutation of the alleles of the survival motor neuron 1 gene. SMA is a rare disease and estimates of its incidence and prevalence vary between studies. The incidence of SMA is often cited as being approximately 10 in 100,000 live births. Four clinical subtypes of SMA are described: SMA type I makes up about 60% of SMA diagnoses where patients show symptoms before six months of age, never achieve the motor milestone of sitting unsupported, and generally do not survive past two years of age due to respiratory failure. Those with SMA type II achieve the milestone of sitting unsupported, but never walk independently; symptoms generally appear between six and 18 months after birth and most patients will survive past the age of 25,[1,2] with life expectancy improved by aggressive supportive care. SMA type III makes up approximately 10% to 20% of SMA cases[3] and presents between 18 months of age and adulthood. These patients are able to walk independently at some point in their lives and typically have a normal life expectancy. SMA type IV constitutes a very small proportion of SMA cases, has an adult onset, and is the mildest form of the disease. Although muscle weakness is present, these patients retain the ability to walk, have a normal life expectancy, and do not suffer from respiratory or nutritional issues.

Nusinersen (Spinraza) is a solution for intrathecal injection, indicated for the treatment of 5q SMA.[4] It is available as a single-use solution in a 5 mL vial size (12 mg) administered intrathecal by lumbar puncture. The recommended dose is initial treatment with four loading doses, with the first three loading doses administered at 14-day intervals (day 0, day 14, and day 28), and a final loading dose approximately 30 days after the third loading dose (day 63); maintenance treatment is 12 mg every four months.[4] At the marketed price of $118,000 per 5 mL vial, the annual cost of treatment with nusinersen ranges from $354,000 for maintenance treatment (three doses) to $708,000 in the first year (six doses).[5] The manufacturer's listing request is per the Health Canada indication.[5]

As part of a resubmission the manufacturer provided new clinical information relating to different subpopulations with SMA (see CADTH Common Drug Review [CDR] Clinical Report). The manufacturer, however, did not provide a revised economic submission nor did it provide any discussion relating to the new clinical information and how this may impact the findings of the economic review based on the original submission. Thus, the CDR economic review remains unchanged with no further data provided to refute the original issues or limitations identified.

The manufacturer submitted three cost-utility analyses for SMA type I, type II, and type III. Each analysis was based on a Markov state-transition model comparing nusinersen with current standard of care (or real-world care, which includes supportive symptomatic treatment of respiratory, nutritional, and orthopaedic function decline) for patients with 5q SMA.

In the SMA type I model, health states included baseline clinical status; whether clinical status improved, worsened, or had no improvement; milestones consistent with SMA type II (e.g., sits without support, stands with assistance, walks with assistance, and stand/walks unaided); and death.[6] The analysis was conducted over a time horizon of 25 years. Transition probabilities relating to disease progression and mortality within the first thirteen months were derived from the ENDEAR study.[7] Subsequent probabilities were based on assumptions.

In the SMA type II model, health states included baseline clinical status; whether clinical status worsened, had no improvement, had mild improvement, or had moderate improvement; whether the patient could stand or walk with assistance and milestones consistent with SMA type III (e.g., stand unaided and walks unaided); and death. The analysis was run over a time horizon of 50 years. Transition probabilities relating to disease progression and mortality within the first fifteen months were derived from the CHERISH study.[8] Subsequent probabilities were based on assumptions.

In the SMA type III model, health states included non-ambulatory, ambulatory, and death. The analysis was run over a time horizon of 80 years. For treatment with nusinersen, transition probabilities relating to disease progression within the first 24 months were derived from the CS2 and CS12 studies.[5] Subsequent probabilities were based on assumptions. For real-world care, patients were assumed to maintain ambulatory status.

For all three SMA types, analysis conformed with the recent Canadian guidelines in that they were conducted from the health care system perspective, outputs were derived from probabilistic analysis, and outcomes and costs were discounted at 1.5% per annum.[9]

The manufacturer reported that for all three SMA types, nusinersen was associated with greater quality-adjusted life-years (QALYs) and greater costs. For SMA types I and II, nusinersen was associated with longer life expectancy, while for SMA type III, no difference in life expectancy was estimated. For SMA type I, nusinersen led to 4.80 more QALYs, 4.79 more life-years, and an increased cost of $3.1 million, resulting in an incremental cost per QALY gained of $665,570. For SMA type II, nusinersen led to 3.67 more QALYs, 2.18 more life-years, and an increased cost of $7.6 million, resulting in an incremental cost per QALY gained of $2.1 million. For SMA type III, nusinersen led to 1.56 more QALYs and an increase in costs of $4.5 million, resulting in an incremental cost per QALY gained of $2.9 million.

The manufacturer reported that the probability that nusinersen was cost-effective assuming a willingness-to-pay threshold of $300,000 per QALY was 0% for all SMA types. The manufacturer reported a number of scenario analyses; however, for all SMA types, the incremental cost per QALY gained for nusinersen exceeded $500,000 in all analyses.

Summary of Identified Limitations and Key Results

CDR identified the following primary limitations relating to the manufacturer's economic model. In the design of the economic model for SMA types I and II, all patients enter the model in the baseline state. Within subsequent cycles, patients can stay in the baseline state (stabilization), improve their functioning without reaching a milestone, reach a milestone, or worsen their functioning. The limitation with this approach is that the stabilization, improvement, and worsening states are relative states that are characterized by the patient's baseline status. In economic modelling, it is desirable that states are absolute states that relate to the level of functioning at that time, not relative to previous functioning.

A number of limitations were identified with respect to the inputs used into the model. Utility values for the SMA type I and SMA type III models were derived from an unpublished analysis provided for Biogen Idec; utility values for the SMA type II model were based on an unpublished mapping exercise.[10,11] CDR did not consider the approach adopted in these studies as appropriate for the estimation of utility values for numerous reasons, including that the valuation process was not appropriate and the health states that were valued were not specific. Assumptions within the manufacturer's submission relating to disease progression for patients with SMA types I, II, and III receiving nusinersen post the time frame of the clinical studies and mortality for patients with SMA types I and II being based on milestones reached were unfounded and biased in favour of nusinersen.

The clinical expert consulted for this review raised a number of concerns regarding the clinical trial data for nusinersen that undermine the ability to facilitate the economic evaluation. Primarily, the expert felt that the population who may receive nusinersen is not reflected in the clinical trials as they represent only a subset of those with SMA; the expert felt that this may favour response compared with real-world clinical practice. In particular, the expert highlighted the lack of comparative clinical trial data for SMA type III. The CDR Clinical Review reached a similar conclusion by determining that the two studies used for SMA type III do not directly capture clinical outcomes of interest.

While analysis can be conducted by SMA type (i.e., for types I and II), further stratified analysis by disease status would be desirable. As subgroup analysis of Hammersmith Functional Motor Scale – Expanded responders by age category suggest that nusinersen is effective in those aged under six, but not effective in those aged 6 and over, stratified cost-effectiveness analysis by age would be highly informative.

CDR was able to conduct reanalysis to address the limitations identified regarding choice of utility values and assumptions for disease progression and mortality. The CDR reanalysis was aligned with the manufacturer's findings that nusinersen was not cost-effective for any of the three SMA types. However, CDR reanalysis reported much higher incremental cost per QALY estimates: $9.2 million for SMA type I and $24.4 million for SMA type II. Results for SMA type III should be considered speculative given the concerns raised related to the lack of appropriate clinical data. However, analysis based on the limited data available concluded nusinersen was unlikely to be cost-effective with an incremental cost per QALY of

$7.4 million for SMA type III. For each SMA type, the probability that nusinersen was cost-effective at a willingness-to-pay threshold of $500,000 was 0%.

Conclusions

In alignment with the manufacturer's results of its pharmacoeconomic submission, CDR found that nusinersen was not a cost-effective treatment for patients with 5q SMA types I, II, or III.

This finding has not been affected by the clinical information provided within the manufacturer's resubmission.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted separate economic models for each spinal muscular atrophy (SMA) type: type I, type II, and type III.[6] The models allowed estimation of health care costs, life-years (LYs), and quality-adjusted life-years (QALYs). The models had initial cycles that reflected the timing of outcome assessment in the relevant clinical studies. For time points beyond the time horizon of the clinical studies, cycles corresponded with the timing of the administration of nusinersen (every four months). Time horizon varied by SMA type: 25 years for type I, 50 years for type II, and eight years for type III. The analyses were conducted from the Canadian public health care system perspective. Costs and outcomes were discounted at an annual rate of 1.5%, and expected values of costs, QALYs, and LYs were obtained through probabilistic analysis.

Model Structure

Three distinct Markov models were developed for three SMA types: type I, type II, and type III (Figure 1).

In the SMA type I model, the cohort entered the model at their baseline clinical status. Each cycle patients could transition to other health states that included maintenance of baseline clinical status; whether this improved, worsened, or had no improvement; milestones consistent with SMA type II (e.g., sits without support, stands with assistance, walks with assistance and stand/walks unaided); and death. The analysis was run over a time horizon of 25 years. Cycle length varied at the onset of the model. Patients could transition between health states at 2, 6, 10, 13, and 14 months. The first four transition points related to the timing of clinical assessment in the ENDEAR study[7] and the latter cycle corresponded to a dosage of nusinersen. Subsequent cycles were every four months, which conformed to the timing of dosages of nusinersen.

In the SMA type II model, the cohort entered the model at their baseline clinical status. Each cycle patients could transition to health states reflecting worsening, no improvement, mild improvement, and moderate improvement from baseline clinical status; states relating to whether the patient could stand or walk with assistance; milestones consistent with SMA type III (e.g., stand unaided and walks unaided); and death. The analysis was run over a time horizon of 50 years. For the first 15 months of the model, the cycle length was three months conforming to the timing of clinical assessment in the CHERISH study.[8] Subsequent cycles were every four months, which conformed to dosages of nusinersen.

In the SMA type III model, health states included non-ambulatory, ambulatory, and death. Patients could enter the model at either the ambulatory or non-ambulatory health states. The analysis was run over a time horizon of 80 years. For the first 27 months of the model, the cycle length was three months, which conformed to the timing of clinical assessment in the CS2 and CS12 clinical studies.[5] Subsequent cycles were very four months, which conformed to dosages of nusinersen.

Model Inputs

For SMA type I, the transition probabilities for nusinersen and real-world care (RWC) were obtained from the ENDEAR trial for the period of the model covering the trial follow-up period. For treatment discontinuation, it was assumed that individuals would stop treatment after scoliosis surgery or after entering the worsening state. For long-term survival, data were used that were derived from a survival analysis of observational data from Zerres and Rudnik-Schoneborn.[12] It was assumed that patients receiving nusinersen would have a reduced risk of mortality up to 50 months beyond the trial follow-up period. In addition, it was assumed that all patients who reached milestones consistent with SMA type II would experience mortality rates associated with SMA type II. Progression data beyond the trial time horizon were modelled based on an assumed relationship between Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) scores and the health states within the model.

For SMA type II, the transition probabilities for nusinersen and RWC were obtained from the CHERISH trial for the period of the model covering the trial follow-up period. For treatment discontinuation, it was assumed that individuals could stop treatment after scoliosis surgery or after entering the worsening state. For long-term survival, data were used that were derived from a survival analysis of observational data from Zerres et al.[13] It was assumed that all patients who reached milestones consistent with SMA type III would experience mortality rates associated with SMA type III. Progression data beyond the trial time horizon were modelled based on an assumed relationship between Hammersmith Functional Motor Scale – Expanded (HFMSE) scores and the health states within the model.

For SMA type III, the proportion of patients entering the model in the ambulatory versus the non-ambulatory states was derived from the CS2 and CS12 studies. Transition probabilities during the study period (first 24 months) between non-ambulatory and ambulatory for patients receiving nusinersen were obtained from the CS2 and CS12 studies. No transitions were assumed for patients receiving RWC either during or beyond the study period. No mortality was assumed in the study period. Long-term mortality was assumed to be the same as for the general population.[14] Beyond the study period, it was assumed that 50% of those continuing to receive nusinersen would regain the ability to walk each cycle. This was based on data from the first [redacted] of the CS2 and CS12 studies.

For both SMA types I and III, utility values were derived from a vignette study where five experts in SMA rated derived health state descriptions relating to the health states within the models. For SMA type II, utility values were obtained from a mapping study of quality of life values observed in the CHERISH trial and EuroQol 5-Dimensions questionnaire values. Both studies used to estimate utility values were unpublished.[10,11]

The reporting of the cost estimates used within the model lacked transparency and health care costs appear to be derived from a German study.[15] The methods for interpolating the costs of care into the Canadian context are limited; however, given the high cost of nusinersen, the impact of additional health care cost would be limited.

Manufacturer's Base Case

The manufacturer reported that for SMA type I, nusinersen was associated with greater costs (an increase of $3.2 million), greater QALYs (4.801), and greater LYs (4.791) compared with RWC (Table 2). This leads to an incremental cost per QALY gained of $665,570.

For SMA type II, nusinersen was associated with greater costs ($7.6 million), greater QALYs (3.675), and greater LYs (2,179). This leads to an incremental cost per QALY gained of $2.1 million.

For SMA type III, nusinersen was associated with greater costs ($4.4 million) and greater QALYs (1.563), but with no increase in life expectancy (4.791). This leads to an incremental cost per QALY gained of $2.8 million.

Table 2: Summary of Results of the Manufacturer's Base Case

	Total Costs ($)	Incremental Cost Vs. RWC ($)	Total QALYs	Incremental QALYs Vs. RWC	Total LYs	Incremental LYs Vs. RWC	ICER ($/QALY) Vs. RWC
SMA Type I							
Real-world care	339,683		–0.881		3.583		
Nusinersen	3,534,854	3,195,171	3.919	4.801	8.373	4.791	665,570
SMA Type II							
Real-world care	708,620		19.602		26.348		
Nusinersen	8.336.271	7,627,652	23.278	3.675	28.527	2.179	2,075,435
SMA Type III							
Real-world care	1,091,307		10.490		44.155		
Nusinersen	5,554,707	4,463,400	12.053	1.563	44.155	0	2,855,818

ICER = incremental cost-effectiveness ratio; LY = life-year; SMA = spinal muscular atrophy; QALY = quality-adjusted life-year; RWC = real-world care; vs. = versus.

Note: All costs are presented in 2017 Canadian dollars.

Source: Total costs, LYs, and QALYs are probabilistic values, as reported in the manufacturer's submission report and based on the original economic model submitted to CADTH.

Summary of Manufacturer's Sensitivity Analyses

The manufacturer conducted a variety of scenario analyses.

For SMA type I, analysis involved changing time horizon (15 and 40 years), discount rate (0% and 3%), the measure of response, survival functions, external data for extrapolation, treatment stopping rule, effect of treatment after trial follow-up, mortality rates, disease progression rates, costs of drug administration, health state costs, and utility values. The estimates of the incremental cost per QALY gained ranged from $603,229 based on alternative assumptions relating to external data used for long-term projections to $1.2 million based on alternate utility values.

For SMA type II, analysis involved changing time horizon (40 and 60 years), discount rate (0% and 3%), survival functions, external data for extrapolation, treatment stopping rule,

effect of treatment after trial follow-up, mortality rates, disease progression rates, costs of drug administration, health state costs, and utility values. The estimates of the incremental cost per QALY gained ranged from $541,412 based on alternative utility values to $4.2 million based on alternate mortality rates.

For SMA type III, analysis involved changing time horizon (50 years), discount rate (0% and 3%), estimates of loss of ambulation, survival function relating to loss of ambulation, treatment stopping rule, effect of treatment after trial follow-up, disease progression rates, costs of drug administration, health state costs, and utility values. The estimates of the incremental cost per QALY gained ranged from $1.9 million based on alternative treatment stopping rules to $23 million based on alternate utility values.

Base-case estimates were obtained through probabilistic analysis as recommended in the recently revised CADTH guidelines.

For all three SMA types, the probability that nusinersen was cost-effective assuming that the threshold value for a QALY was $300,000 was 0%.

Limitations of Manufacturer's Submission

CDR identified the following key limitations with the manufacturer's model:

Health States Within the Model

Within the models for SMA types I and II, all patients enter the model in the baseline state. Within subsequent cycles they can stay in the baseline state (stabilization), improve their functioning without reaching a milestone, reach a milestone, or worsen their functioning. The limitation with this approach is that the stabilization, improvement, and worsening states are relative states that are characterized by the patient's baseline status. In economic modelling, it is desirable that states are absolute states that relate to the level of functioning at that time, not relative to previous functioning. It is important to note that a patient who started at a relatively high level of functioning could enter the worsening state yet still have better functioning than a patient who started at a low level of functioning who subsequently improved. This issue with the model is illustrated by Table 13 in the manufacturer's submission where the mean HFMSE score for worsened and stabilization states are the same. States based on absolute HFMSE score would have been preferable.

Utility Values

In the manufacturer's submission, utility values for SMA types I and III were derived from an unpublished analysis provided for Biogen Idec. In consultation with experts, the authors derived vignettes of SMA types I, II, and III. From here the authors created health state descriptions for a variety of health states and then asked clinical experts to rate these states using the child-friendly EuroQol 5-Dimensions questionnaire (EQ-5D-Y).[16]

The approach adopted in this study is not appropriate for the estimation of utility values for a number of reasons. Scenarios were created by the authors and not the clinical experts. Utility values for the EQ-5D-Y are unavailable and the approach adopted by the authors of using the tariff for the EuroQol 5-Dimensions questionnaire (EQ-5D) 3-Levels is argued by the creators of the EQ-5D-Y to be inappropriate. Scenarios do not describe specific health states. There is frequent use of terms such as "might have." Thus, based on the interpretation of the scenarios, experts may not be rating identical health states. Scenarios

refer to specific ages (e.g., for type I disease less than two years of age) that do not reflect the time horizon of the model.

Although utility values for SMA type II were available form this study, the manufacturer used a different set of utility values for the SMA type II model. This unpublished study used data from the CHERISH study relating to responses to the Pediatric Quality of Life Inventory instrument at each assessment point that were then mapped to the EQ-5D utility scores based on a published mapping algorithm to derive utility values for each state. The manufacturer chose to not use the actual values for specific states when it was felt the ordering of states by utility value was incorrect. The recent CADTH guidelines for economic evaluation suggest that direct measurement should be used to elicit utility values and mapping should be discouraged.[9]

Due to the inappropriateness of the utility values adopted in the manufacturer's model, the CDR reanalysis adopted the utility value from the [redacted] study of a sample of patients with SMA. In this study, caregivers acted as a proxy for patients and completed the EQ-5D 3-Levels to elicit utility values. Analysis took the approach suggested by the manufacturer where the average of scores for types I and II [redacted] is applied to all health states except stands/walks unaided, which has a health state of [redacted].

Disease Progression Within Spinal Muscular Atrophy Type I

In the manufacturer's submission, it is assumed that patients with SMA type I receiving nusinersen may continue to improve in functioning beyond the time horizon of the clinical trial. For each cycle post thirteen months, patients on nusinersen were assumed to either maintain their level of function or improve their level of function each cycle. This includes the assumption that 100% of patient classified as "sits without support" will improve to the "stands with assistance" classification during the next four-month cycle. Based on these assumptions, 44% of SMA type I patients who receive nusinersen will be alive at five years and of these 81% will be classified as "stands/walks unaided." None of the patients within the ENDEAR study reached this milestone. Conversely, it was assumed that patients not receiving nusinersen would either maintain their level of function or lose their level of function each cycle.

These assumptions are highly uncertain. In the ENDEAR study, while the CHOP INTEND scores appear to improve at 302 days, the number of patients remaining in the study was small (16 and 36 in the control and treatment groups, and 11 and 26, respectively, at 394 days), which questions the assumptions of continued improvement in functioning with nusinersen beyond the trial duration, as well as the reduced functioning in the control group. Furthermore, the assumption of an increase in CHOP INTEND scores of 1.09 per month for nusinersen is not detailed within the manufacturer's report of the ENDEAR study.

Reanalysis adopted two alternative assumptions — that patients on nusinersen will maintain their level of function post trial, and for patients not on nusinersen their level of function will decline based on natural history data from Finkel. This approach still assumes a widening of the differences in level of functioning between patients on nusinersen and those not post the clinical trial period.

Disease Progression Within Spinal Muscular Atrophy Type II

In the manufacturer's submission, it is assumed that patients with SMA type II receiving nusinersen may continue to improve in symptoms beyond the time horizon of the clinical trial. For each cycle post fifteen months, patients on nusinersen are assumed to either maintain their level of function or improve their level of function each cycle. Conversely, it is assumed that patients not receiving nusinersen will either maintain their level of function or lose their level of function each cycle.

Reanalysis adopted a revised assumption — that patients on nusinersen will maintain their level of function post trial while patients not on nusinersen will either maintain or lose their level of function, per the manufacturer's assumption. This approach still assumes a widening of the differences in level of functioning between patients on nusinersen and those not post the clinical trial period.

Regaining Ambulation in Spinal Muscular Atrophy Type III Patients

In the manufacturer's submission, it is assumed that 50% of patients receiving nusinersen 50% who are not ambulatory after the 24-month clinical trial period will become ambulatory each cycle. This is based on evidence combining the single arms of the CS2 and CS12 studies where two out of four non-ambulatory patients regained the ability to walk. This assumption is not justified for several reasons.

The CADTH Clinical Review and the clinical expert both concluded that there was no available clinical data for assessing the effectiveness of nusinersen in those with SMA type III. The manufacturer's analysis is based on the CS2 and CS12 clinical studies. The CS2 and CS12 studies are not comparative studies.

Within the CS2 and CS12 studies, two out of four non-ambulatory patients were able to walk within the first twelve months of treatment and this is fully incorporated already within the manufacturer's model. The manufacturer's assumption is not that 50% of patients will regain their ability to walk but 50% of those unable to walk will regain this ability each cycle. In the CS2 and CS12 studies, no patients on nusinersen regained their ability to walk after 12 months. For patients not on nusinersen, it was assumed that no patients would regain their ability to walk at any time.

Reanalysis adopted a revised assumption — that patients on nusinersen will maintain their level of function post trial while patients not on nusinersen will not regain their ability to walk. This approach assumes a consistency in differences in level of functioning between patients on nusinersen after twelve months, despite the lack of comparative trial evidence.

Reduced Mortality Based on Milestones Reached

In the manufacturer's submission it is assumed that patients in a given disease type who achieve milestones consistent with a different disease type will have a lower risk of death than patients in other states. For SMA type I patients who reach milestones consistent with SMA type II, mortality rates consistent with type II were applied. The same approach was applied for patients with SMA type II who reached milestones consistent with SMA type III. Currently, there is no data supporting this supposition. If such survival data existed for patients who achieve milestones associated with other disease types then such an assumption could be considered.

Given the absence of such data, reanalysis will assume no such changes in risk of death. For type 1 patients, the estimated life expectancy gain from nusinersen based on the original assumption was 5.65 LYs; with the revised assumption adopted in the reanalysis it was 2.73 year. For type II patients, the manufacturer's assumption led to an estimated increase in survival of 3.64 years. However, given there were no differences in survival during the CHERISH trial, the revised assumption that there were no changes in risks of death based on milestones reached leads to no increase in survival for patients on nusinersen.

Hazard Ratio for Death Post Trial for Spinal Muscular Atrophy Type I

In the manufacturer's submission it is assumed that after the trial period there would be a continued treatment effect with nusinersen in terms of long-term survival for SMA type 1. The argument in favour of the assumption is that in the CS3A study, six out of seven patients had continued improvement in CHOP INTEND score at 63 months. This was argued to be evidence of a continued treatment effect with respect to mortality. The approach adopted is to apply the same hazard ratio for mortality identified in the clinical trial post trial but that the hazard ratio is tapered to one after 63 months. The impact of this approach is to lead to a life expectancy over a lifetime of 5.65 years. The life expectancy gain estimated during the first 13-month equivalent to the time horizon of the ENDEAR trial was 0.19 years. Thus, 96.7% of the estimated life expectancy gain from nusinersen is obtained through the proposed extrapolation method.

However, the data provided is non-comparative and there is no data relating specifically to mortality. Thus, a more reasonable assumption would be to assume equal hazard rate for mortality for both treatment and non-treatment post trial, which would still lead to an extrapolation of the survival benefit from nusinersen. Adopting this assumption leads to an estimated increase in life expectancy of year with nusinersen of 4.3 years. In this reanalysis, 95.7% of the estimated increase in life expectancy comes from the post-trial period. Thus, although the reanalysis leads to a reduced life expectancy gain from nusinersen, it still requires acceptance that most of the life expectancy gain occurs beyond the clinical trial horizon and is assumed through extrapolation.

Ability to Conduct Stratified Analysis

Analysis can be conducted by SMA type — i.e., for type I, type II, and type III. However, further stratified analysis by disease status would be desirable — i.e., analysis within type II based on ability to sit or stand with or without assistance at baseline and analysis by type III based on ability to walk at baseline. However, the data to facilitate such analyses are not provided and it is likely that the small sample sizes within the clinical trial preclude such analyses. Subgroup analysis of HFMSE responders by age category do suggest that nusinersen, while effective in those aged under six, was not effective in those aged six and over. Stratified cost-effectiveness analysis by age is not possible and would be highly informative.

Clinical Trial Design

The clinical expert has raised a number of concerns with the clinical trial data for nusinersen which undermines the ability to facilitate the economic evaluation. The expert felt that the population who may receive nusinersen is not reflected in the clinical trials as they represent only a subset of those with SMA. The expert felt that the age of patients within the clinical trials would likely favour response compared with real-world clinical practice. In particular, the expert highlighted the lack of comparative clinical trial data for SMA type III. This has been previously discussed with respect to the assumptions relating to disease progression

within SMA type III. The CADTH Clinical Review similarly concluded that there were no available clinical data for SMA type II for outcomes of interest. Thus, the limitations with the clinical trial portfolio should be considered when evaluating the evidence from the economic submission.

Although the resubmission provides new clinical information, the manufacturer has not directly addressed the previously identified limitations.

CADTH Common Drug Review Reanalyses

As noted in the limitations, CDR identified several important shortcomings related to the manufacturer's model. CDR presents a revised probabilistic analysis (CDR base case) in Table 3 with alternations based on several of these limitations. The analysis for SMA type III should be considered highly speculative given the limitations of the available clinical data. The modifications made to the manufacturer-submitted model include:

- The adoption of utility values from the [redacted] study for the UK for all models.[11] A utility value of [redacted] is applied to ambulatory patients and a utility value of [redacted] is applied to all other health states.
- For SMA type I, patients on nusinersen will maintain their level of function post trial, and for patients not on nusinersen their level of function will decline based on natural history data from Finkel.[17]
- For SMA type II, patients on nusinersen will maintain their level of function post trial — no change will be made to the manufacturer's assumption around patients not on nusinersen.
- For SMA type III, beyond the CS2 and CS12 study time horizons, patients on nusinersen will continue to maintain their level of function while patients not on nusinersen will not gain the ability to walk.
- Patient survival will be based on their initial SMA type.
- For SMA type I, the hazard rate for mortality for both treatment and non-treatment post trial is equal, which leads to an extrapolation of the survival benefit from nusinersen.

The CDR reanalysis found a similar finding to the manufacturer's submission in that nusinersen was not cost-effective for any of the three SMA types. However, CDR reanalysis reported much higher incremental costs per QALY gained; $9.2 million for SMA type I, $24.4 million for SMA type II, and $7.4 million for SMA type III.

For each SMA type, the probability that nusinersen was cost-effective at a willingness-to-pay threshold of $300,000 remained 0%.

Table 3: CADTH Common Drug Review Base Case

	Total Costs ($)	Incremental Cost Vs. RWC ($)	Total QALYs	Incremental QALYs Vs. RWC	Total LYs	Incremental LYs Vs. RWC	ICER ($/QALY) Vs. RWC
SMA Type I							
Real-world care	341,060		0.65		3.90		
Nusinersen	2,410,906	2,069,846	0.90	0.25	5.39	1.48	9,161,397
SMA Type II							
Real-world care	704,769		4.64		26.26		
Nusinersen	7,653,525	6,948,755	4.93	0.28	26.26	0	24,387,422
SMA Type III							
Real-world care	1,096,196		10.82		44.17		
Nusinersen	5,271,475	4,175,261	11.38	0.56	44.17	0	7,429,834

ICER = incremental cost-effectiveness ratio; LY = life-year; SMA = spinal muscular atrophy; QALY = quality-adjusted life-year; RWC = real-world care; vs. = versus.

Note: All costs are presented in 2017 Canadian dollars.

Source: Total costs, LYs, and QALYs are probabilistic values, obtained by rerunning the probabilistic analysis within the manufacturer's model employing the revised assumptions.

To explore the impact each of the revised assumptions adopted by CDR, reanalysis was conducted based on the manufacturer's analysis changing one of the three areas of assumptions: utility values, progression, and mortality (Table 4).

For each reanalysis, the CDR base case estimated nusinersen to be less cost-effective than the manufacturer's submission, but for one exception, using revised utility values found a reduced incremental cost-effectiveness ratio for SMA type II — though an increased incremental cost-effectiveness ratio for SMA types I and III. The different assumptions have a synergistic effect on estimated incremental costs and QALYs; i.e., no one assumption seemed to dominate in terms of their impact on the revised estimates. For SMA type I, the revised assumption relating to disease progression (that patients on nusinersen maintained their health status post trial) did lead to nusinersen being less effective than RWC in terms of utility values based on the manufacturer's base utility values. For both type I and type II, the assumptions relating to progression appeared to have the most effect; however, for type III, the assumptions relating to utility values had the greater effect.

Table 4: CADTH Common Drug Review Reanalysis Based on Individual Issues

ICER ($/QALY) for Nusinersen Versus RWC			
Price	**SMA Type I**	**SMA Type II**	**SMA Type III**
Manufacturer's base-case analysis	665,570	2,075,435	2,885,818
CDR base-case analysis	9,161,397	24,387,422	7,429,834
Analysis based on revised assumptions relating to utility values	1,122,829	1,274,011	5,082,045
Analysis based on revised assumptions relating to disease progression	Dominated by RWC	13,204,415	4,276,636
Analysis based on revised assumptions relating to mortality	751,116	3,933,135	NA

CDR = CADTH Common Drug Review; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-years; RWC = real-world care, NA = not applicable as no revised assumptions were made for SMA type III; SMA = spinal muscular atrophy.

CDR undertook a price reduction analysis based on the manufacturer-submitted and the CDR base-case analyses assuming proportional price reductions for nusinersen (Table 5). Given the inability to run the probabilistic analysis with the same random seed, the required price reductions were obtained using deterministic analysis.

Using the manufacturer's base-case analysis, the price reduction required for nusinersen to have an incremental cost per QALY gained of $100,000 compared with RWC was 83% for SMA type I, 94% for type II, and 97% for type III. For an incremental cost per QALY gained of $50,000, the required price reduction was 91% for SMA type I, 97% for type II, and 98% for type III.

Based on the CDR reanalysis, if a price reduction of 90% was obtained, the incremental cost per QALY gained from nusinersen versus RWC was $963,724 for SMA type I, $2,992,193 for type II, and $780,804 for type III. If a price reduction of 95% was obtained, the incremental cost per QALY gained from nusinersen versus RWC was $508,297 for SMA type I, $1,489,668 for type II, and $402,885 for type III.

Table 5: CADTH Common Drug Review Reanalysis Price Reduction Scenarios

ICER ($/QALY) for Nusinersen Versus RWC						
Price	**Based on Manufacturer's Base Case**			**Based on CDR Base Case[a]**		
	SMA I	SMA II	SMA III	SMA I	SMA II	SMA III
Submitted price	663,686	2,082,119	2,800,887	9,161,397	30,037,656	7,583,344
10% reduction	595,932	1,872,027	2,521,174	8,250,544	27,032,605	6,827,506
20% reduction	528,179	1,661,935	2,241,462	7,339,692	24,027,553	6,071,668
30% reduction	460,425	1,451,842	1,961,749	6,428,839	21,022,502	5,315,831
40% reduction	392,672	1,241,750	1,682,037	5,517,987	18,017,450	4,559,993
50% reduction	324,918	1,031,658	1,402,324	4,607,134	15,012,399	3,804,155
60% reduction	257,164	821,566	1,122,611	3,696,281	12,007,348	3,048,317
70% reduction	189,411	611,474	842,899	2,785,429	9,002,296	2,292,479
80% reduction	121,657	401,381	563,186	1,874,576	5,997,245	1,536,642
90% reduction	53,904	191,289	283,474	963,724	2,992,193	780,804
95% reduction	20,027	86,243	143,617	508,297	1,489,668	402,885

CDR = CADTH Common Drug Review; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-years; RWC = real-world care; SMA = spinal muscular atrophy.

Source: Reanalysis of the manufacturer's model based on deterministic results. Thus, minor differences exist between estimates in Table 4.

Issues for Consideration

- **Inability to conduct stratified analysis:** The results of the analysis may vary within SMA type. It was not possible to conduct such analysis, though this may inform identification of appropriate niche populations.
- **Clinical trial design:** Concerns have been raised that the population who may receive nusinersen is not reflected in the clinical trials as they represent only a subset of those with SMA. Thus, the limitations with the clinical study portfolio should be considered when evaluating the evidence from the economic submission.
- **Stopping rules:** Based on consultation with the CDR clinical expert, a number of potential initiation and stopping criteria were suggested (CDR Clinical Report). In some cases (SMA types III and IV), there is not sufficient clinical data to fully explore the implications. For SMA types I and II, the manufacturer's economic model does not provide the flexibility to consider the impact of stopping nusinersen once patients experience a worsening of their condition or require ventilation support.
- **Resubmission:** The manufacturer has submitted a resubmission that contains new clinical information. The manufacturer has not updated the economic submission and has not provided any further comments with respect to the original CADTH economic review. Thus, the resubmission does not lead to any changes to the findings with respect to the economic review.

Patient Input

One patient submission was received, which was prepared jointly by the Canadian Organization for Rare Disorders and Cure SMA Canada. The submission was based on the results of one focus group, four interviews, and a survey. Most of the respondents were caregivers and family members. The submission cited 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 manufacturer accounted these aspects within their economic model by considering aspects of SMA in the model health states. Impacts on families and caregivers were raised as an aspect of the condition, as well. This was not considered by the manufacturer in its pharmacoeconomic submission.

Conclusions

Nusinersen would be considered cost-effective based on the results of the manufacturer-submitted analysis only if a decision-maker was willing to pay in excess of $600,000 per QALY. The CDR reanalysis found that the estimated incremental cost per QALY gained is likely much greater than the manufacturer's estimates, ranging from $9.2 million for SMA type I to $24.4 million for SMA type II. Reanalysis for SMA type III should be considered speculative, but concluded nusinersen was unlikely to be cost-effective given an incremental cost per QALY gained of $7.4 million.

Reanalysis suggested that even with a 95% price reduction for nusinersen, it was unlikely to be considered cost-effective, with incremental cost-utility ratios exceeding $400,000.

This finding has not been affected by the clinical information provided within the manufacturer's resubmission.

Appendix 1: Cost Comparison

The comparators presented in the following table have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice, versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

Table 6: CADTH Common Drug Review Cost Comparison Table for the Treatment of Spinal Muscular Atrophy

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dosage	Average Weekly Drug Cost ($)	Average Annual Drug Cost ($)
Nusinersen (Spinraza)	**12 mg — 5 mL vial**	**Intrathecal injection**	**118,000[a]**	**Day 1, 15, 30, and 60 then every 4 months**	**Year 1: 13,578** **Subsequent years: 6,789**	**Year 1: 708,000** **Subsequent years: 354,000**

[a] Unit prices of nusinersen as provided by manufacturer.

Appendix 2: Additional Information

Table 7: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments Reviewer to provide comments if checking “no”			
Was the material included (content) sufficient?	X		
Comments Reviewer to provide comments if checking “poor”			
Was the submission well organized and was information easy to locate?		X	
Comments Reviewer to provide comments if checking “poor”	None		

Table 8: Authors Information

Authors of the Pharmacoeconomic Evaluation Submitted to CDR

☐ Adaptation of global model/Canadian model done by the manufacturer

☒ Adaptation of global model/Canadian model done by a private consultant contracted by the manufacturer

☐ Adaptation of global model/Canadian model done by an academic consultant contracted by the manufacturer

☐ Other (please specify)

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis			X

CDR = CADTH Common Drug Review.

Appendix 3: Summary of Other HTA Reviews of Drug

At the time of this review, there are no available reviews for nusinersen conducted by health technology assessment organizations.

Appendix 4: Reviewer Worksheets

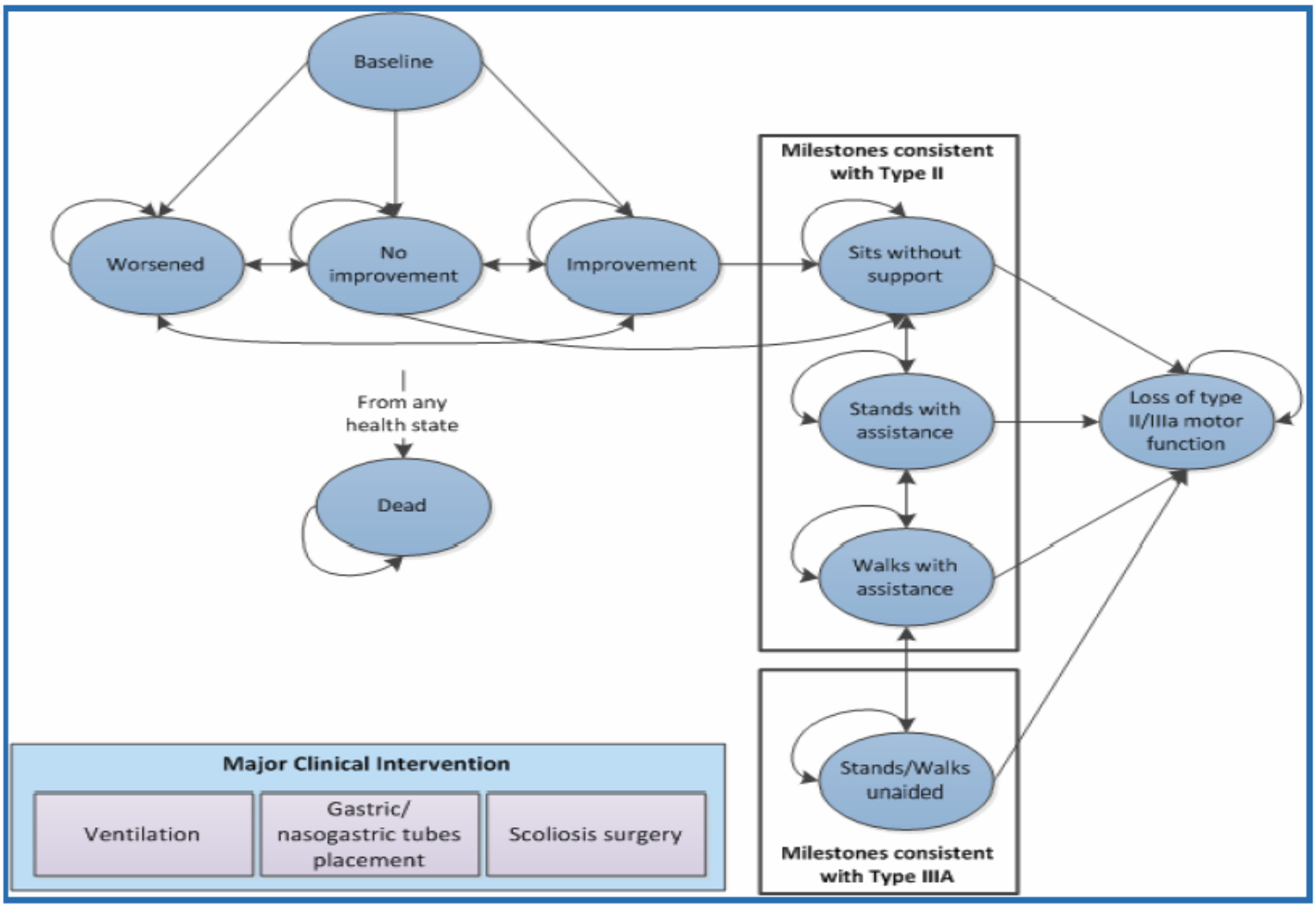
Table 9: Data Sources and Assumptions

	SMA Type I	SMA Type II	SMA Type III
Disease progression during study period	ENDEAR[7]	CHERISH[8]	Nusinersen: CS2+CS12[5] RWC: Assumption
Disease progression after study period	Assumption	Assumption	Assumption
Mortality during study period	ENDEAR	CHERISH	Assumed none
Mortality post study period	Zerres and Rudnik-Schineborn[12] Zerres et al.[13]	Zerres et al.[13] Statistics Canada	Statistics Canada
Utility values	Unpublished study[10,11]	Unpublished study[10,11]	Unpublished study[10,11]
Cost data	German study Ontario costs	German study Ontario costs	German study Ontario costs

RWC = real-world care; SMA = spinal muscular atrophy.

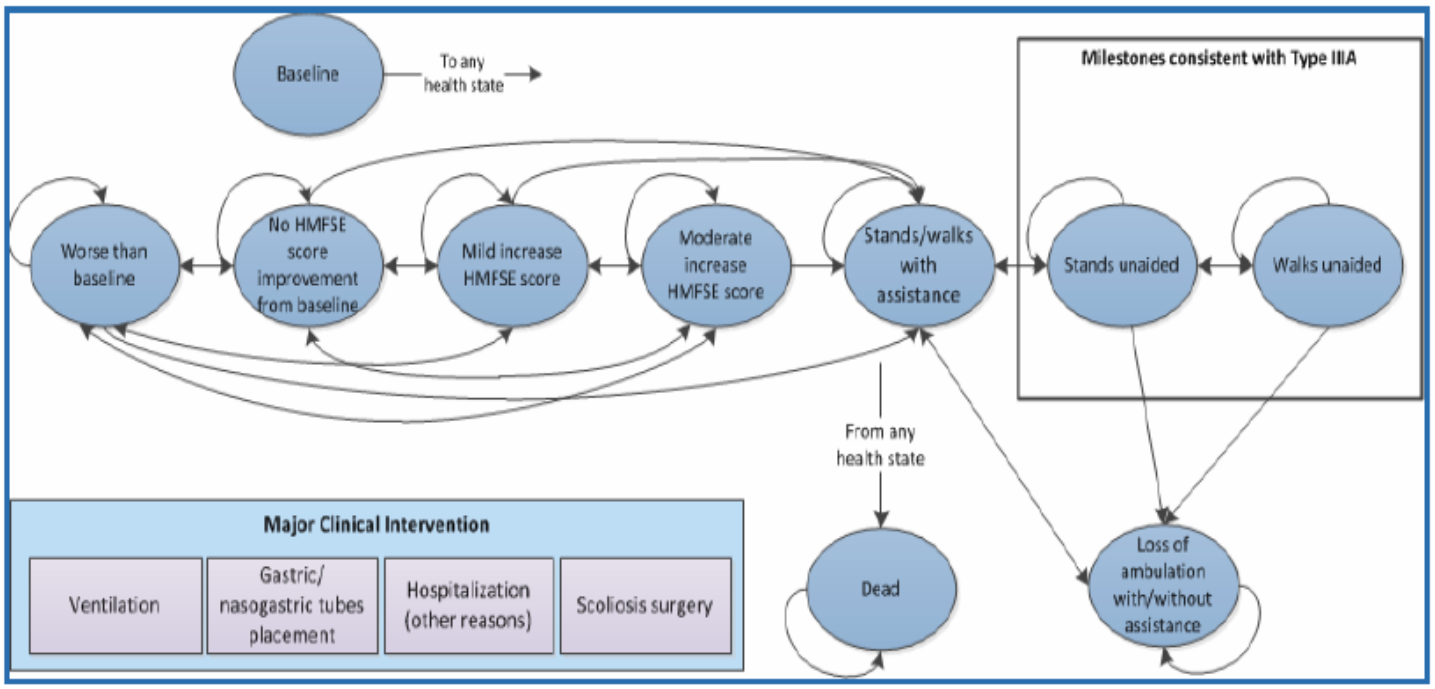
Model Structures

Figure 1: Spinal Muscular Atrophy Type I Model Structure



Source: Manufacturer's pharmacoeconomic submission.[6]

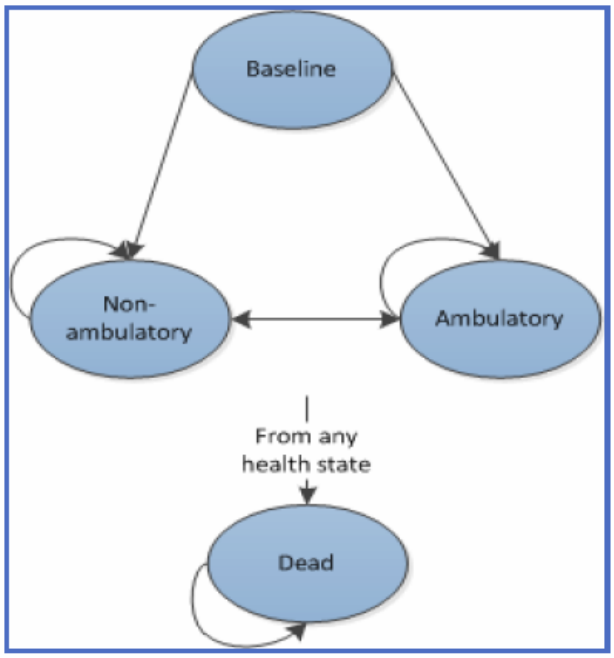
Figure 2: Spinal Muscular Atrophy Type II Model Structure



HMFSE = Hammersmith Functional Motor Scale – Expanded.

Source: Manufacturer's pharmacoeconomic submission.[6]

Figure 3: Spinal Muscular Atrophy Type III Model Structure



Source: Manufacturer's pharmacoeconomic submission.[6]

Manufacturer's Results

Table 10: Summary Base-Case Results: Type I

	Costs ($)	LYs	QALYs	Incremental Costs ($)	Incremental LYs	Incremental QALYs	ICER (SPINRAZA Vs. Comparator) ($/QALY)
Real-world care	339,683	3.583	–0.881	–			
SPINRAZA	3,534,854	8.373	3.919	3,195,171	4.791	4.801	665,570

ICER = incremental cost-effectiveness ratio; LYs = life-years; QALYs = quality-adjusted life-years; vs. = versus.

Source: Manufacturer's pharmacoeconomic submission.[6]

Table 11: Summary Base-Case Results: Type II

	Costs ($)	LYs	QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER (SPINRAZA Vs. Comparator) ($/QALY)
Real-world care	708,620	26.348	19.602	–			
SPINRAZA	8,336,271	28.527	23.278	7,627,652	2.179	3.675	2,075,435

ICER = incremental cost-effectiveness ratio; LYs = life-years; QALYs = quality-adjusted life-years; vs. = versus.

Source: Manufacturer's pharmacoeconomic submission.[6]

Table 12: Summary Base-Case Results: Type III

	Costs ($)	LYs	QALYs	Incremental Costs ($)	Incremental LYs	Incremental QALYs	ICER (SPINRAZA Vs. Comparator) ($/QALY)
Real-world care	1,091,307	44.155	10.490	–			
SPINRAZA	5,554,707	44,155	12.053	4,463,400	–	1.563	2,855,818

ICER = incremental cost-effectiveness ratio; LYs = life-years; QALYs = quality-adjusted life-years; vs. = versus.

Source: Manufacturer's pharmacoeconomic submission.[6]

CADTH Common Drug Review Reanalysis

Base-Case Analysis

Table 13: CADTH Common Drug Review Base-Case Analysis: Type I

	Costs ($)	LYs	QALYs	Incremental Costs ($)	Incremental LYs	Incremental QALYs	ICER (Nusinersen Vs. RWC) ($/QALY)
Real-world care	341,060	3.90	0.65	–	–	–	–
Nusinersen	2,410,906	5.39	0.90	2,069,846	1.48	0.25	9,161,397

ICER = incremental cost-effectiveness ratio; LYs = life-years; QALYs = quality-adjusted life-years; RWC = real-world care; vs. = versus.

Table 14: CADTH Common Drug Review Base-Case Analysis: Type II

	Costs ($)	LYs	QALYs	Incremental Costs ($)	Incremental LYs	Incremental QALYs	ICER (Nusinersen Vs. RWC) ($/QALY)
Real-world care	704,769	26.26	4.64	–	–	–	–
Nusinersen	7,653,525	26.26	4.93	6,948,755	0	0.28	24,387,422

ICER = incremental cost-effectiveness ratio; LYs = life-years; QALYs = quality-adjusted life-years; RWC = real-world care; vs. = versus.

Table 15: CADTH Common Drug Review Base-Case Analysis: Type III

	Costs ($)	LYs	QALYs	Incremental Costs ($)	Incremental LYs	Incremental QALYs	ICER (Nusinersen Vs. RWC) ($/QALY)
Real-world care	1,096,196	44.17	10.82	–	–	–	–
Nusinersen	5,271,475	44.17	11.38	4,175,261	0	0.56	7,429,834

ICER = incremental cost-effectiveness ratio; LYs = life-years; QALYs = quality-adjusted life-years; RWC = real-world care; vs. = versus.

CADTH Common Drug Review Reanalysis by Issue

A) Alternative Utility Values

Table 16: CADTH Common Drug Review Analysis Using Alternative Utility Values: Type I

	Costs ($)	LYs	QALYs	Incremental Costs ($)	Incremental LYs	Incremental QALYs	ICER (Nusinersen Vs. RWC) ($/QALY)
Real-world care	342,392	3.59	0.60	–	–	–	–
Nusinersen	3,516,962	8.32	3.42	3,174,569	4.73	2.83	1,122,189

ICER = incremental cost-effectiveness ratio; LYs = life-years; QALYs = quality-adjusted life-years; RWC = real-world care; vs. = versus.

Table 17: CADTH Common Drug Review Analysis Using Alternative Utility Values: Type II

	Costs ($)	LYs	QALYs	Incremental Costs ($)	Incremental LYs	Incremental QALYs	ICER (Nusinersen Vs. RWC) ($/QALY)
Real-world care	704,936	23.36	4.73	–	–	–	–
Nusinersen	8,333,108	28.52	10.70	7,628,172	2.16	5.99	1,274,011

ICER = incremental cost-effectiveness ratio; LYs = life-years; QALYs = quality-adjusted life-years; RWC = real-world care; vs. = versus.

Table 18: CADTH Common Drug Review Analysis Using Alternative Utility Values: Type III

	Costs ($)	LYs	QALYs	Incremental Costs ($)	Incremental LYs	Incremental QALYs	ICER (Nusinersen Vs. RWC) ($/QALY)
Real-world care	1,094.668	44.15	11.72	–	–	–	–
Nusinersen	5,565,605	44.15	10.84	4,470,937	1.33	0.88	5,082,045

ICER = incremental cost-effectiveness ratio; LYs = life-years; QALYs = quality-adjusted life-years; RWC = real-world care; vs. = versus.

B) Alternative Progression Assumptions

Table 19: CADTH Common Drug Review Analysis Using Alternative Progression Assumptions: Type I

	Costs ($)	LYs	QALYs	Incremental Costs ($)	Incremental LYs	Incremental QALYs	ICER (Nusinersen Vs. RWC) ($/QALY)
Real-world care	346,959	3.62	0.90	–	–	–	–
Nusinersen	3,112,905	6.66	0.88	2,069,846	1.48	–0.02	Dominated by RWC

ICER = incremental cost-effectiveness ratio; LYs = life-years; QALYs = quality-adjusted life-years; RWC = real-world care; vs. = versus.

Table 20: CADTH Common Drug Review Analysis Using Alternative Progression Assumptions: Type II

	Costs ($)	LYs	QALYs	Incremental Costs ($)	Incremental LYs	Incremental QALYs	ICER (Nusinersen Vs. RWC) ($/QALY)
Real-world care	346,959	26.35	19.58	–	–	–	–
Nusinersen	7,742,298	26.50	20.11	7,036,596	0.15	0.53	13,204,415

ICER = incremental cost-effectiveness ratio; LYs = life-years; QALYs = quality-adjusted life-years; RWC = real-world care; vs. = versus.

Table 21: CADTH Common Drug Review Analysis Using Alternative Progression Assumptions: Type III

	Costs ($)	LYs	QALYs	Incremental Costs ($)	Incremental LYs	Incremental QALYs	ICER (Nusinersen Vs. RWC) ($/QALY)
Real-world care	1,095,874	3.90	10.61	–	–	–	–
Nusinersen	5,266,975	5.39	11.58	4,171,101	1.48	0.98	4,276,636

ICER = incremental cost-effectiveness ratio; LYs = life-years; QALYs = quality-adjusted life-years; RWC = real-world care; vs. = versus.

C) Alternative Survival Assumptions

Table 22: CADTH Common Drug Review Analysis Using Alternative Survival Assumptions: Type I

	Costs ($)	LYs	QALYs	Incremental Costs ($)	Incremental LYs	Incremental QALYs	ICER (Nusinersen Vs. RWC) ($/QALY)
Real-world care	345,210	3.58	–0.90	–	–	–	–
Nusinersen	2,256,660	4.96	1.64	1,911,450	1.38	2.54	751,116

ICER = incremental cost-effectiveness ratio; LYs = life-years; QALYs = quality-adjusted life-years; RWC = real-world care; vs. = versus.

Table 23: CADTH Common Drug Review Analysis Using Alternative Survival Assumptions: Type II

	Costs ($)	LYs	QALYs	Incremental Costs ($)	Incremental LYs	Incremental QALYs	ICER (Nusinersen Vs. RWC) ($/QALY)
Real-world care	706,820	26.29	19.53	–	–	–	–
Nusinersen	7,637,946	26.29	21.30	6,931,126	0	1.76	3,933,135

ICER = incremental cost-effectiveness ratio; LYs = life-years; QALYs = quality-adjusted life-years; RWC = real-world care; vs. = versus.

Additional CDR analyses were conducted considering the price of nusinersen on the incremental cost-utility ratio (Table 24). Even if the average cost of nusinersen was $100,000 per patient annually, the incremental cost-utility ratios would be more than $2 million for SMA type I and more than $8 million for SMA type II.

Table 24: CADTH Common Drug Review Analysis — Additional Price Analyses (Using CADTH Common Drug Review Base Case)

Annual Price of Nusinersen (Per Patient Annually)	Costs ($)	LYs ($)
	SMA I	SMA II
Price as submitted	9,161,397	30,037,656
$100,000	2,180,604	8,023,597
$150,000	3,254,808	12,052,327
$200,000	4,329,012	16,081,057
$250,000	5,403,215	20,109,787
$300,000	6,477,419	24,138,516
$350,000	7,551,623	28,167,246

LYs = life-years; SMA = spinal muscular atrophy.

Note: Results based on deterministic analysis.

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