CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

NUSINERSEN (SPINRAZA)

(Biogen Canada Inc.)

Indication: Treatment of patients with 5q 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.

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Abbreviations

CUA	cost-utility analysis
ICER	Incremental cost effectiveness ratio
IV	intravenous
LY	life-year
mg	milligram
ml	millilitre
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 – 5ml solution for intrathecal injection administered in four loading disease (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 orthopedic function decline
Outcome(s)	• 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%
Key Limitations	• Utility values were derived from unpublished studies provided for Biogen Idec which 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 type 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 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.

CDR Estimate(s)	• CDR re-analysis addressed the first three limitations listed above 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 ICURs:
	  ○ 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 due to 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 patients with 5q SMA
Listing Request	Treatment of patients with 5q SMA
Dosage form(s)	5 ml solution for intrathecal injection administered in four loading disease (days 0, 4, 28 and 63) followed by maintenance treatment of 5 ml solution every four months
NOC date	June 29, 2017
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 over 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 (SMN1) 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 about 60% of SMA diagnoses where patients show symptoms before 6 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; SMA type II achieve the milestone of sitting unsupported, but never walk independently. Symptoms generally appear between 6 to 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 about 10% to 20% of SMA cases3 and presents between 18 months of age and adulthood. These patients are able to walk independently at some point in their life and typically have a normal life expectancy; SMA type IV constitutes very small proportion of SMA cases, has an adult onset SMA, 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 spinal muscular atrophy (SMA).[4] It is available as a single use solution in a 5mL vial size (12 mg) administered intrathecal by lumbar puncture. The recommended dose is: initial treatment with 4 loading doses, with the first 3 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 4 months.[4] The marketed price of $118,000 per 5mL vial, the annual cost of treatment with nusinersen ranges from $354,000 for maintenance treatment (3 doses) to $708,000 in the 1st year (6 doses).[5] The manufacturer's listing request is as per the Health Canada indication.[5]

The manufacturer submitted three cost-utility analyses for SMA type I, II and II. Each analysis was based on a Markov state-transition model comparing nusinersen with current standard of care (or real world care [RWC] which includes supportive symptomatic treatment of respiratory, nutritional, and orthopedic function decline) - for patients with q5 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 can stand/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+CS12 study.[5] Subsequent probabilities were based on assumptions. For RWC, patients were assumed to maintain ambulatory status.

For all three SMA types, analysis conformed with the recent Canadian guidelines in that they were conducted form 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 QALYs and greater costs. For SMA types I and II, nusinersen was associated with longer life expectancy, while for SMA type III no differences in life expectancy was estimated. For SMA type I, nusinersen led to 4.80 more QALYs, 4.79 more LYs 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 LYs 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 the probability that nusinersen was cost effective assuming a willingness to pay 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 type 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 which are characterized by the patient's baseline status. In economic modelling, it is desirable that states are absolute states which 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, and for the SMA type II model based on an unpublished mapping exercise;[10,11] CDR did not consider the approach adopted in these study 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 type I, II and III receiving nusinersen post the time frame of the clinical studies; and, mortality for patients with SMA type I and II being based on milestones reached – were unfounded and biased in favour of nusinersen.

The clinical expert has raised a number of concerns regarding the clinical trial data for nusinersen which undermines the ability to facilitate the economic evaluation. Primarily, the expert felt that the population which may receive nusinersen is not reflected in the clinical trials as they represent only a subset of SMA and this may favour response compared to real world clinical practice. In particular the expert highlighted the lack of comparative clinical trial data for SMA type III. The CADTH clinical review reached a similar conclusion by determining that the 2 studies used for SMA type III do not directly capture clinical outcomes of interest.

Whilst, 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 HFMSE responders by age category suggest that nusinersen whilst effective in those aged under 6 was 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 costs 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 due 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

Aligned with the manufacturer's results of their pharmacoeconomic submission, CDR found that nusinersen was not a cost-effective treatment for patients with q5 SMA type I, II or III.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's PE submission

The manufacturer submitted separate economic models for each SMA type: type I, II and III.[6] The models allowed estimation of health care costs, life years (LYs) and QALYs. The models had initial cycles which 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 8 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, quality adjusted life years (QALYs) and life years (Lys) were obtained through probabilistic analysis.

Model Structure

Three distinct Markov models were developed for three SMA types: type I, II and 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 which 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 conforming 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 and states relating to whether the patient can stand/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. For the first 15 months of the model, the cycle length was 3 months conforming to the timing of clinical assessment in the CHERISH study.[8] Subsequent cycles were every four months conforming 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 3 months conforming to the timing of clinical assessment in the CS2+CS12 clinical studies.[5] Subsequent cycles were very four months conforming to dosages of nusinersen.

Model Inputs

For SMA Type I, the transition probabilities for nusinersen and 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 derived from survival analysis of observational data from Zerres and Rudnik-Schoneborn.[12] It was assumed that patients receiving nusinersen would have reduced risk of mortality up to 50 months beyond the trial follow up period. In addition it was assumed that all patents who reached milestones consistent with SMA type II would experience mortality rates associated with type II. Progression data beyond the trial time horizon were modelled based on an assumed relationship between 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 derived from survival analysis of observational data from Zerres et al.[13] It was assumed that all patents who reached milestones consistent with SMA type III would experience mortality rates associated with type III. Progression data beyond the trial time horizon were modelled based on an assumed relationship between HFSME 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+CS12 study. Transition probabilities during the study period (first 24 months) between non-ambulatory and ambulatory for patients receiving nusinersen were obtained from the CS2+CS12 study. 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+CS12 study.

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 which QL values observed in the CHERISH trial and EQ-5D values. Both studies used to estimate utility values were unpublished. [10,11]

The reporting of the cost estimates used within the model lacked transparency but 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 costs of nusinersen, the impact of additional health care cost will 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 life years (4.791) compared to 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 life years (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

All costs are presented in 2017 Canadian dollars
ICER = incremental cost-effectiveness ratio; Incr. = incremental; LY = life year; SMA = spinal muscular atrophy; QALY = quality-adjusted life year
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 type 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 which are characterized by the patient's baseline status. In economic modelling, it is desirable that states are absolute states which 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 are the same. States based on absolute HFMSE score would have been preferable.

Utility Values

In the manufacturer's submission utility values for SMA type I and III were derived from an unpublished analysis provided for Biogen Idec. In consultation with experts, the authors derived vignettes of SMA type 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 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 EQ-5D-3L is argued by the creators of the EQ-5D-Y to be inappropriate.[61] 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 2 years of age) which 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 PedsQL quality of life instrument at each assessment point which 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, re-analysis 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-3L to elicit utility values. Analysis took the approach suggested by the manufacturer where the average of scores for type I and II ([redacted]) is applied to all health states except stands/walks unaided which has a health state of [redacted].

Disease Progression within SMA 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 5 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 will either maintain their level of function or lose their level of function each cycle.

The above assumptions are highly uncertainty. In the ENDEAR study, while the CHOP INTEND scores appear to improve at 302 days, the number of patients remaining in the study were small (16 and 36 in the control and treatment arms, 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.

Re-analysis adopted two alternative assumptions – that patients on v will maintain their level of function post trial, and for patients not on v 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 v and those not post the clinical trial period.

Disease Progression within SMA Type 2

In the manufacturer's submission, it is assumed that for 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.

Re-analysis adopted a revised assumption – that patients on nusinersen will maintain their level of function post trial whilst patients not on nusinersen will either maintain or lose their level of function as 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 SMA 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 2 out of 4 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 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, 2 out of 4 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 will regain their ability to walk at any time.

Re-analysis adopted a revised assumption – that patients on nusinersen will maintain their level of function post trial whilst 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, re analysis 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 life years and with the revised assumption adopted in the re-analysis 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 SMA 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, 6 out of 7 patient had continued improvement in CHOPINTEND 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 1 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 re-analysis, 95.7%% of the estimated increase in life expectancy comes from the post trial period. Thus, although the re-analysis 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, II and 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 whilst effective in those aged under 6 was not effective in those aged 6 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 which may receive nusinersen is not reflected in the clinical trials as they represent only a subset of SMA. The expert felt that the age of patients within the clinical trials would likely favour response compared to real world clinical practice. In particular the expert highlighted the lack of comparative clinical trial data for SMA type III. This has been discussed above 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 SAM type II for outcomes of interest. Thus, the limitations with the clinical trial portfolio should be considered when evaluating the evidence form the economic submission.

CADTH Common Drug Review Reanalyses

As noted in the limitations, CDR identified several important shortcomings relating 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 SAM Type III should be considered highly speculative given the limitations of the available clinical data. The modifications made to the manufacturer-submitted model include:

- 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 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 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 whilst 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: CDR 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; Incr. = incremental; LY = life year; SMA = spinal muscular atrophy; QALY = quality-adjusted life year
Source: Total costs, LYs, and QALYs are probabilistic values, obtained by rerunning the probabilistic analysis within the manufacturer's model employing the revised assumptions.
All costs are presented in 2017 Canadian dollars

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 re-analysis, 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 ICER for SMA type II – though an increased ICER for SMA Type 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 real world care 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 but for Type III the assumptions relating to utility values had the greater effect.

Table 4: CDR 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	N/A

CDR = Common Drug Review; ICER = incremental cost effectiveness ratio; RWC = real world care, N/A = not applicable as no revised assumptions were made for SMA type III

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 to 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: CDR Re-Analysis Price Reduction Scenarios

ICER ($/QALY) for Nusinersen versus RWC						
Price	**Based on Manufacturer's Base Case**			**Based on CDR Base Case***		
	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 = Common Drug Review; ICER = incremental cost effectiveness ratio; RWC = real world care
Source: Reanalysis of the manufacturer's model based on deterministic results. Thus, minor difference 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 which may receive nusinersen is not reflected in the clinical trials as they represent only a subset of SMA. Thus, the limitations with the clinical study portfolio should be considered when evaluating the evidence form 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 type III and IV), there is not sufficient clinical data to fully explore the implications. For SMA type I and II, the manufacturer's economic model does not provide the flexibility to consider the impact of stopping nusinersen once patients experiencing a worsening of their condition or require ventilation support.

Patient Input

One patient submission was received, which was prepared jointly by the Canadian Organization for Rare Disorders (CORD) 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, 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 the 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 SAM 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 ICURs exceeding $400,000.

Appendix 1: Cost Comparison

The comparators presented in the table below 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: CDR 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†**	**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**

mg = milligrams; ml – milliliters
† 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

Appendix 3: Summary of Other HTA Reviews of Drug

Note there are no reviews for nusinersen conducted by HTA organizations available at the time of this review.

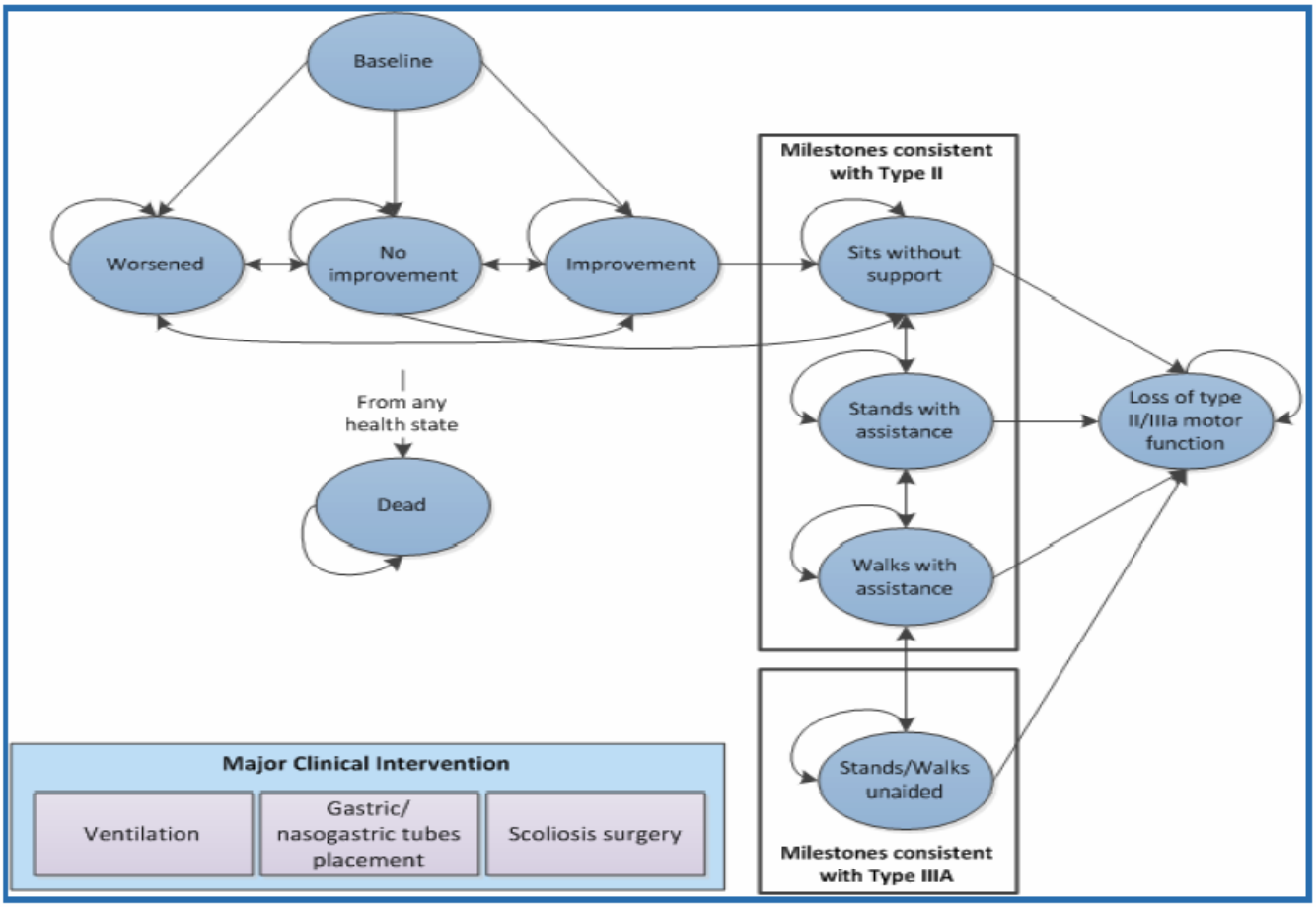
Appendix 4: Reviewer Worksheets

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

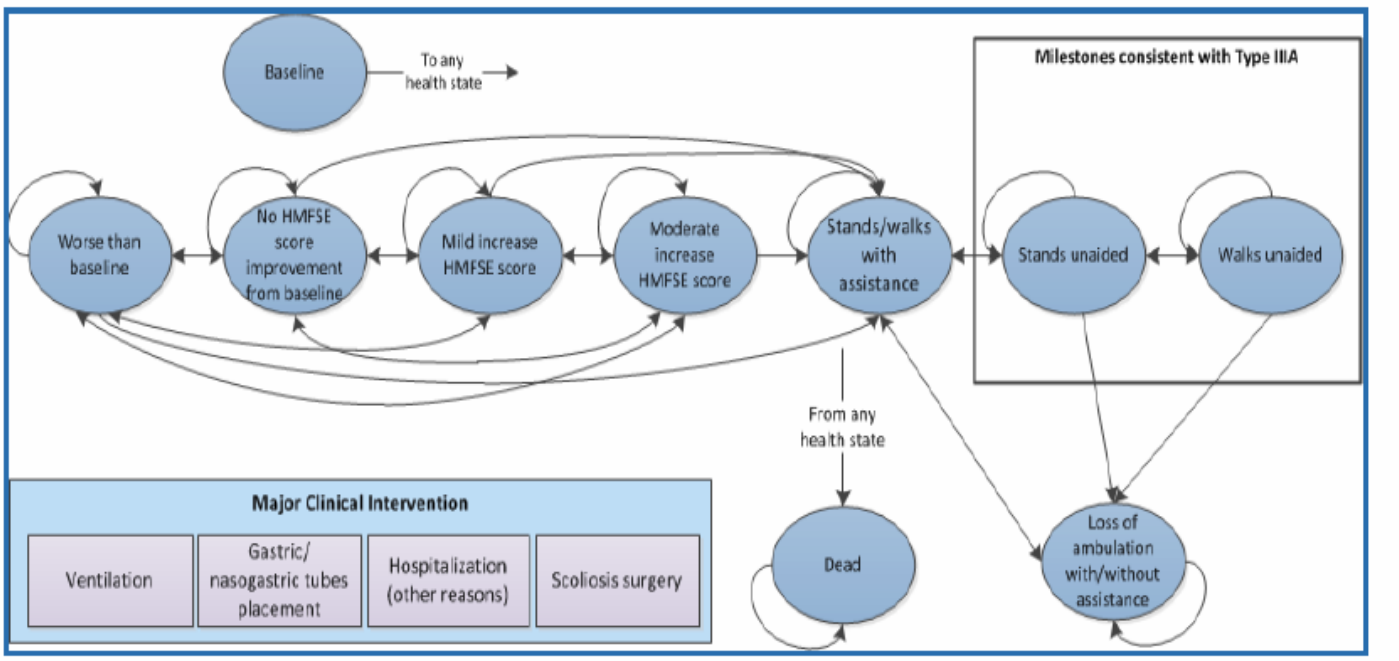
Model Structures

Figure 1: SMA type 1 model structure



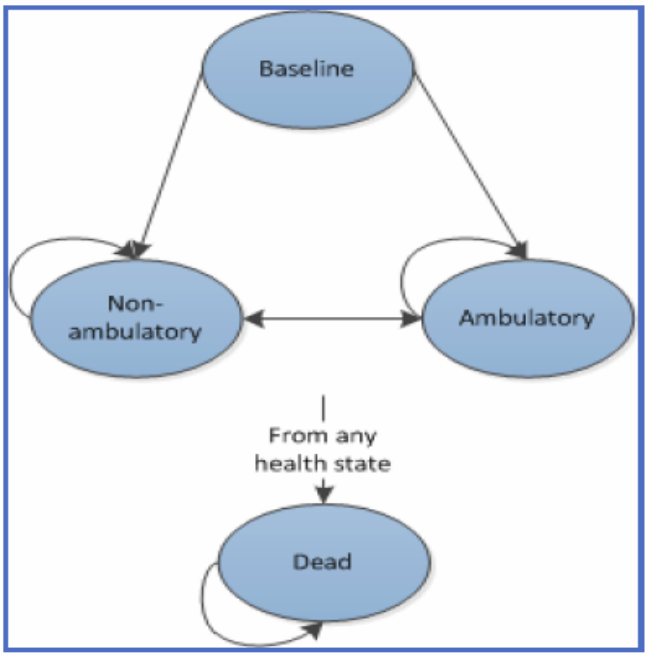
Source: Manufacturer's Pharmacoeconomic Submission[6]

Figure 2: SMA type 2 model structure



Source: Manufacturer's Pharmacoeconomic Submission[6]

Figure 3: SMA type 3 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 year
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)
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 year
Source: manufacturer's Pharmacoeconomic submission[6]

Table12: 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 year
Source: manufacturer's Pharmacoeconomic submission[6]

CDR Reanalysis

Base case analysis

Table 13: CDR Base Case Analysis Type I

	Costs ($)	LYs	QALYs	Incr Costs ($)	Incr LYs	Incr 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

Incr=incremental; RWC=real world care

Table 14: CDR Base Case Analysis Type II

	Costs ($)	LYs	QALYs	Incr Costs ($)	Incr LYs	Incr 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

Incr=incremental; RWC=real world care

Table 15: CDR Base Case Analysis Type III

	Costs ($)	LYs	QALYs	Incr Costs ($)	Incr LYs	Incr 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

Incr=incremental; RWC=real world care

CDR Re-analysis by Issue

a) Alternative Utility Values

Table 16: CDR Analysis using Alternative Utility Values Type I

	Costs ($)	LYs	QALYs	Incr Costs ($)	Incr LYs	Incr 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

Incr=incremental; RWC=real world care

Table 17: CDR Analysis using Alternative Utility Values Type II

	Costs ($)	LYs	QALYs	Incr Costs ($)	Incr LYs	Incr 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

Incr=incremental; RWC=real world care

Table 18: CDR Analysis using Alternative Utility Values Type III

	Costs ($)	LYs	QALYs	Incr Costs ($)	Incr LYs	Incr 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

Incr=incremental; RWC=real world care

b) Alternative Progression Assumptions

Table 19: CDR Analysis using Alternative Progression Assumptions Type I

	Costs ($)	LYs	QALYs	Incr Costs ($)	Incr LYs	Incr 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

Incr=incremental; RWC=real world care

Table 20: CDR Analysis using Alternative Progression Assumptions Type II

	Costs ($)	LYs	QALYs	Incr Costs ($)	Incr LYs	Incr 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

Incr=incremental; RWC=real world care

Table 21: CDR Analysis using Alternative Progression Assumptions Type III

	Costs ($)	LYs	QALYs	Incr Costs ($)	Incr LYs	Incr 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

Incr=incremental; RWC=real world care

c) Alternative Survival Assumptions

Table 22: CDR Analysis using Alternative Survival Assumptions Type I

	Costs ($)	LYs	QALYs	Incr Costs ($)	Incr LYs	Incr 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

Incr=incremental; RWC=real world care

Table 23: CDR Analysis using Alternative Survival Assumptions Type II

	Costs ($)	LYs	QALYs	Incr Costs ($)	Incr LYs	Incr 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

Incr=incremental; RWC=real world care

Additional CDR analyses were conducted considering the price of nusinersen on the ICUR (Table 24). Even if the average cost of nusinersen was $100,000 per patient annually, the ICURs would be over $2miliion for SMA type I and over $8million for SMA type II.

Table 24: CDR Analysis – Additional price analyses (using CDR 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

Note: Results based on deterministic analysis

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