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CADTH COMMON DRUG REVIEW

Clinical Review Report (Resubmission)

NUSINERSEN (SPINRAZA)

(Biogen Canada Inc.)

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

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Abbreviations

ACEND	Assessment of Caregiver Experience in Neuromuscular Disease
AE	adverse event
BiPAP	bi-level positive air pressure
CDEC	CADTH Canadian Drug Expert Committee
CDR	CADTH Common Drug Review
CI	confidence interval
CHOP INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CMAP	compound muscle action potential
CORD	Canadian Organization for Rare Disorders
GMFM	Gross Motor Function Measure
GMFCS	Gross Motor Function Classification System
HFMSE	Hammersmith Functional Motor Scale – Expanded
HINE	Hammersmith Infant Neurological Examination
HRQoL	health-related quality of life
ICC	intraclass correlation coefficient
ITT	intention-to-treat population
MCID	minimal clinically important difference
MDC	Muscular Dystrophy Canada
PedsQL	Pediatric Quality of Life Inventory
QoL	quality of life
RCT	randomized controlled trial
RULM	Revised Upper Limb Module
SAE	serious adverse event
SD	standard deviation
SMA	spinal muscular atrophy
SMN	survival motor neuron
WHO	World Health Organization

Drug	Nusinersen (Spinraza)
Indication	Treatment of 5q spinal muscular atrophy (SMA)
Reimbursement Request	Treatment of patients with 5q SMA across all types (including pre-symptomatic 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

Introduction

Spinal muscular atrophy (SMA) is a severe neuromuscular disease and is the leading genetic cause of infant death.[1,2] It is characterized by the degeneration of alpha motor neurons in the anterior horn of the spinal cord, leading to progressive muscle weakness.[1] 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 (SMN1) gene.[3,4] A second set of survival motor neuron gene (SMN2) acts in a similar capacity to SMN1 but is usually not sufficient on its own to maintain motor neurons. The number of SMN2 genes usually determines the severity of SMA. 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.[4] Prevalence is estimated to be approximately one to two in 100,000 persons[4] and is affected by the drastically shortened life expectancy in the most common type of SMA. However, one study that examined the Cure SMA database (a voluntary registry that is one of the largest patient-reported repositories in the world) reported the birth prevalence in the US at about 1 in 20,000 live births.[5] 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, with life expectancy improved by aggressive supportive care. SMA type III makes up about 10% to 20% of SMA cases and presents between 18 months of age and early 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. The correlation between the genotype, specifically the number of SMN2 genes, and the clinical phenotype (SMA types) is probabilistic in nature, with patients possessing two SMN2 copies likely to develop SMA type 1. In one natural history study, of 39 patients diagnosed as SMA type Ib or Ic, 16 patients (41%) had two copies of the SMN 2 gene, 21 patients (54%) had three copies of the SMN2 gene, and one patient (3%) had four copies of the SMN2 gene.[6] The same study showed that out of 87 patients diagnosed as SMA types IIa or IIb, two patients (2%) had two copies,

75 patients (86%) had three copies, and seven patients (8%) had four copies of the SMN2 gene.[6] Of 66 patients that were diagnosed as SMA type IIIa or IIIb assessed in the same study, one patient (2%) had two copies, 19 patients (29%) had three copies, 40 patients (61%) had four copies, and two patients (3%) had five copies of the SMN2 gene.[6] The study also assessed five patients diagnosed as SMA type IV; of these patients, four (80%) had four copies of the SMN2 gene, and one patient was not reported.[6]

Aside from the reviewed drug, there are currently no treatments available for SMA. Standards of practice revolve around supportive care, addressing the symptoms of the disease, and attempting to improve quality of life. Nusinersen (Spinraza) is indicated for the treatment of 5q SMA. It is an antisense oligonucleotide that increases the proportion of exon 7 inclusion in SMN2 messenger ribonucleic acid transcripts made, through binding to a specific site in the SMN2 pre-messenger ribonucleic acid. This leads to the translation of a specific site in the SMN2 pre-messenger ribonucleic acid into functional full-length SMN protein. Nusinersen is administered intrathecally by lumbar puncture in a 5 mL solution containing 12 mg of nusinersen. It is given in a regimen of four loading doses at day 0, day 14, day 28, and day 63, with subsequent maintenance doses at a four-month frequency.

On December 20, 2017, the CADTH Canadian Drug Expert Committee (CDEC) issued a final recommendation regarding Spinraza treatment for patients diagnosed with SMA. The recommendation was based on evidence presented in a CADTH Common Drug Review (CDR) report of Spinraza. CDEC identified the following areas as constituting an evidence gap: patients with symptom onset at birth or within one week of birth; patients with advanced SMA who require ventilation; patients older than seven months of age; patients with more than two copies of the SMN2 gene; patients diagnosed at later stages of disease; and patients who are pre-symptomatic. A copy of the CDEC original recommendation can be viewed in Appendix 4. The manufacturer provided this resubmission with additional data and information from ongoing and recently conducted studies that were not available during the original submission. In light of new the information, this resubmission has been conducted with the primary goal of attempting to provide and assess any clinical studies that can fill the evidence gaps identified by CDEC.

Results and Interpretation

Included Studies

A total of 15 studies were included in this report. As part of the resubmission of nusinersen to CADTH, the manufacturer provided 19 reports representing data from 10 nusinersen development studies, two observational studies, and one letter from a clinical centre. Of the 10 Spinraza development studies, three were randomized controlled trials (ENDEAR [N = 121], CHERISH [N = 126], and EMBRACE [N = 27]), four were phase I uncontrolled trials along with their extension studies (CS1 [N = 28], CS2 [N = 34], CS10 [N = 18], and CS12 [N = 47]), two were phase II uncontrolled trials (CS3A [N = 21], and NURTURE [N = 25]), and one was an extension study that included participants from all trials except EMBRACE and NURTURE (SHINE [N = 207]). Of the included studies, ENDEAR was reviewed in detail in the original nusinersen submission to CADTH and will not be discussed in detail in this report. A copy of the original Clinical Report discussing the ENDEAR trial is attached in Appendix 6. In addition to nusinersen's development studies, the manufacturer provided two observational studies that were case series of adult patients receiving nusinersen treatment for SMA. The case series were not published but were available as abstracts from poster presentations.[7,8] The manufacturer also provided CADTH

with a letter from a clinical centre outlining its experience in treating adult patients with nusinersen. This letter did not contain any clear data and was thus presented in the discussion of this report.[9] Further to the previously mentioned studies, our systematic search identified three case series observational studies outlining the experience with expanded access programs in several countries for patients diagnosed with SMA. These three observational studies regarding the expanded access program focused on nusinersen treatment for patients with type I SMA but did not restrict the patients' age below seven months.

The included single arm studies share a common limitation pertaining to the study design: the lack of a control group to draw a statistical causal inference. Without a control group, it is difficult to attribute any benefit observed to nusinersen alone, where other confounding factors are potentially present. In addition, while objective clinical outcomes such as death or need for ventilation may have less potential to be biased by the open-label design of the study, other more subjective outcomes may be biased. More specific limitations are present in these studies beyond the single arm design; NURTURE is an ongoing trial and the interim results presented here may not reflect the final planned analysis of the predefined end point, also considering that for some outcomes, not all patients were assessed and this missing data might affect the outcome. SHINE is also an ongoing extension study and the interim results may be confounded by the drop-outs and missing data from the original trials. Also, the inclusion of patients who participated in dose-finding studies resulted in a heterogeneous population in terms of drug exposure, further reducing our ability to extrapolate observed results into the Canadian population undergoing Health Canada–indicated dosages.

Of the three included double-blind, randomized, sham controlled trials, ENDEAR was discussed in detail in the original Spinraza submission. EMBRACE was a small exploratory phase II trial that showed significant imbalances in the baseline characteristics of randomized patients and was terminated prematurely. CHERISH had a main limitation of using a nusinersen dosage schedule that is different from the Health Canada's recommended dosage schedule.

The five included observational, non-comparative, case-series studies share a common limitation pertaining to the study design: the study design is descriptive in nature and cannot draw any association between an observed potential benefit and nusinersen treatment. The value of any observed benefits as compared with baseline is limited as no measure was taken to control for any potential confounders or natural disease fluctuations, and such results can only be used for hypothesis generation. Two of these studies were addressing SMA in adult patients; these studies further suffer from important limitations in reporting pertinent information and data regarding the patient population and outcome, and thus are unable to provide evidence of nusinersen efficacy in adult patients with SMA.

Efficacy

Patients Who Are Pre-symptomatic

Addressing this population was the phase II single arm trial NURTURE. [redacted]

[redacted]

Patients With Infantile Onset SMA, Including Patients With SMN2 Gene Copy Greater Than Two

Addressing this population was the extension study SHINE, which contrasted the assessed outcome with the baseline of patients that originally enrolled in the CS3A phase II, single arm study. [redacted]

Patients With Mixed Infantile and Early Childhood Onset, Including Patients With SMN2 Gene Copy Greater Than Two

Addressing this patient population was the phase II, randomized, sham controlled, exploratory trial EMBRACE. [redacted]

Patients With Early Childhood SMA Onset, Including Patients With SMN2 Gene Copy Greater Than Two

Addressing this population was the phase III, randomized, double-blind, sham controlled trial CHERISH. The primary outcome, the change in Hammersmith Functional Motor Scale – Expanded (HFMSE) score from baseline to month 15, showed a statistically significant and potentially clinical meaningful difference between groups (least squares mean difference = 5.9 [95% confidence interval [CI], 3.7 to 8.1]). This was further supported by a statistically significant difference in the first secondary outcome of HFMSE responders (≥ 3 points increase) at 15 months, showing a difference in proportion of 30.5% (95%CI, 12.74 to 48.31). The second outcome to be tested in the statistical hierarchy (proportion of patients achieving new motor milestones at 15 months) failed to show statistical significance. All reported *P* values in subsequent outcomes are thus not adjusted for multiple testing. Overall, patients in the nusinersen group had a mean of 0.2 new motor milestones achieved (95% CI, 0.1 to 0.3) compared with a mean of –0.2 in the sham control group (95% CI,–0.4 to 0). Supporting the positive primary finding, patients in the nusinersen group exhibited a mean improvement of 4.2 (95%CI, 3.4 to 5.0) from baseline in the outcome of the Revised Upper Limb Module test at 15 months compared with a mean improvement of 0.5 (95%CI, –0.6 to 1.6) from baseline in the sham control group. [redacted]

[redacted] One patient in each group was able to stand alone at 15 months, while only one patient in the study from the nusinersen group was able to demonstrate the milestone of walking with assistance at 15 months.

Patients With Later Childhood Onset, Including Patients With SMN2 Gene Copy Greater Than Two

Addressing this population was the extension study SHINE, which contrasted the assessed outcome with the baseline of patients that originally enrolled in the phase I trials (CS1 and CS2). [redacted]

Adult Patients

Two case series observational studies poster abstracts address this patient population. Unfortunately, no explicit description of the characteristics of the included patients was reported. Elsheikh 2018 observed that three patients reported subjective improvement in stamina and endurance, one patient's HFMSE score did not improve, one patient's HSFMSE score improved from 31 to 34, and one patient had an increase of 25 metres in the six-minute walk test. [redacted]

Patients Diagnosed Before Seven Months of Age But Who Received Treatment After Seven Months of Age

Addressing this population was the SHINE extension study of patients previously enrolled in ENDEAR with the assessment contrasted against the SHINE baseline. Additionally, two case series, Pane 2018 and Aragon 2018, also addressed this patient population. Time to death or permanent ventilation was only reported in the SHINE — ENDEAR index study. At the start of SHINE, [redacted]

[redacted] Aragon 2018 reports a median Hammersmith Infant Neurological Examination (HINE) score of 3.5 (range: 0 to 11) at six months contrasted with the baseline median value of 1 (range: 0 to 6). Pane 2018 reported that the mean change in HINE score was 1.3 (standard deviation: 2.2). Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) scores in SHINE (ENDEAR index), at last observed visit, show a change of [redacted] Aragon 2018 reports a median score of 35 (range: 19 to 51) at six months contrasted with the baseline median value of 31.5 (range: 6 to 45). Pane 2018 did not provide a summary measure for this outcome; instead, they reported that the CHOP INTEND changes ranged between –7 and 27 points.

Patients With Spinal Muscular Atrophy Who Require Ventilation

Addressing this population was a single, observational, non-comparative, case series of Pechmann 2018. At six months after nusinersen treatment, Pechmann 2018 reports a mean change from baseline of 9.0 (SD: 8.0) points — starting from a mean baseline value of 22.3 to a mean value at assessment date of 31.2 (SD: 16.2). In a subgroup of patients that started the study requiring permanent ventilation (18 patients [30%]), the mean change in the CHOP INTEND score from baseline was 5.6 points (SD: 7.5). At six months after nusinersen treatment, Pechmann 2018 reports a mean change in HINE score from baseline of 1.4 (SD: 2.1) points — starting from a mean baseline value of 0.8 to a mean value at assessment date of 2.5 (SD 3.3). These results were not reported in the subgroup of patients that started the study requiring permanent ventilation. At the beginning of the study, 26 patients (43%) did not require ventilation; at six months, 19 patients (31%) did not require ventilation. Non-invasive ventilation less than 16 hours per day was required by 17 patients at the start and at the end of the study (28%). The number of patient requiring ventilation more than 16 hours per day or requiring a tracheostomy increased from 18 (30%) at the beginning of the study to 25 (41%) at the end of the study.

Harms

Throughout all the manufacturer-provided trials, the most common adverse events (AEs) were related to infections and/or respiratory problems, two common complications of SMA. A number of patients (5%) in the nusinersen treatment group experienced vomiting, which was related to the lumbar puncture procedure. A lower percentage of serious AEs were reported in the nusinersen group (76%) than in the sham-procedure group (95%). Extension and long-term safety studies reported a similar safety profile. The Health Canada product monograph suggests that the majority of the reported AEs are related to the disease process or the lumbar puncture procedure.[6]

Limitations of the safety results in the ENDEAR study included the inability of patients to report AEs that do not show clinical signs. These include AEs that may be related to the lumbar puncture procedure (e.g., headache and backache). In addition, there is lack of long-term safety data, which is important to note considering the lifelong nature of the disease.

Potential Place in Therapy

The following is based on information and opinions provided by the clinical experts consulted by CDR for the purpose of this review.

SMA results in the irreversible loss of motor neurons and motor nerves. The loss of these nerves causes skeletal muscles to become progressively weaker, giving rise to swallowing

problems and breathing difficulties and/or weakness of the limbs and trunk. A natural history study using a specialized neurophysiological technique called motor unit number estimation has found that there is a relatively rapid loss of motor neurons early in the course of the disease followed by a more gradual decline.[10] Given that children's muscle fibres undergo an increase in size over the first few years of life (a process known as physiological hypertrophy) any intervention to prevent the irreversible loss of motor neurons and consequently allow muscle fibres the potential for more normal development is advantageous; consequently, the optimal time for intervention is early in the course of the disease before rapid and irreversible loss of motor neurons has occurred. While early diagnosis of SMA and treatment is important in all patients, it is particularly important in patients with types I and II SMA, as these patients will develop more severe SMA symptoms more rapidly than patients with other types of SMA.

SMA is diagnosed in Canada via genetic testing. Initial testing evaluates for the homozygous 5q deletion within the SMN1 gene, which identifies 95% of cases. If negative, SMN1 gene sequencing will be performed as a second step. Nerve conduction studies and electromyography is performed in some patients; however, even when evidence of a motor neuropathy is identified this way, it is followed up with confirmatory genetic testing.

Motor function is the most important aspect of the disease that affects patients' quality of life; deterioration of motor function leads to loss of ambulation, difficulties in verbal communication, and inability to handle secretions. Deterioration of respiratory function is a critical aspect that may lead to severe and life-threatening complications. In patients who lose ambulation, maintaining function in the upper limbs becomes important.

Current standard of care practice for patients with genetically confirmed SMA includes surveillance and anticipatory management of symptoms. Patients with SMA receive monitoring for 1) growth, gastrointestinal function, and nutrition; 2) respiratory complications; and 3) orthopaedic complications (i.e., scoliosis and/or contractures).

Anticipatory management of respiratory complications is particularly important for children with SMA type I and type II because these patients are at high risk of having a weak cough with impaired clearance of airway secretions, nocturnal hypoventilation, and recurrent pulmonary infections. Patients who are diagnosed with SMA type II usually fail to achieve new motor milestones; thus, the most impactful outcome for these patients is achieving and maintaining new motor milestones. Consequently, assessment of respiratory function and motor function, through the achievement of major milestones, are key outcomes to assess disease progression in patients with SMA type I and type II. This standard of care is not expected to change with emerging therapies; however, it is hoped that the progression and complications of this disease would be ameliorated by a treatment that delayed the progression of disease.

Patients with SMA type III make up approximately 10% to 20% of all patients with SMA. These patients typically have developed the ability to walk, but this milestone can be lost as the disease progresses. Patients who manifest the disease shortly after achieving the milestone of walking and who may have a fewer number of SMN2 genes are more likely to lose their ability to walk. Early treatment of patients with SMA type III, particularly young patients with apparent rapid disease progression, would have the theoretical potential of preventing loss of ambulation with the significant gain of independence and avoidance of numerous medical complications that can result in non-ambulatory patients. Because patients with SMA type III usually lose motor milestones, maintaining motor milestones such as walking is an important outcome for these patients.

Adult patients with SMA are typically either patients with SMA type III who have reached adulthood, or are patients diagnosed as SMA type IV where symptoms manifested after reaching adulthood. Patients with SMA type III who have reached adulthood make up a larger group of the adult patients with SMA seen in clinical practice than patients with SMA type IV. Of patients with SMA type III who reach adulthood and are able to walk, risk of falls, ability to use stairs, and the distance they are able to walk before feeling fatigued are the most common issues reported in the clinic. Thus, an assessment of the distance patients are able to walk is commonly used in clinical practice to assess disease progression. If a patient loses the ability to walk, maintaining upper limb function to allow for the use of a wheelchair becomes an important outcome.

According to the clinical experts consulted for this review, nusinersen would be beneficial to all infants with SMA type I, regardless of SMN2 gene copy number. Based on the available clinical data, the mechanism of action of nusinersen, and clinical experience, the two most important factors in determining an optimal response to treatment with nusinersen are time since symptom onset and the age of the patient; this is due to the fact that motor neuron deterioration is irreversible and early intervention is essential to prevent deterioration of motor function. The shorter the duration since symptom onset, the younger the patient, and the more severe the prognosis (based on genetic testing), the higher the likelihood of observing a clinically meaningful response to treatment with a drug such as nusinersen. Clinical experts believe that an assessment of whether patients have responded to treatment should be carried out approximately 18 months after the initiation of the first dose of nusinersen, when patients are expected to have gained and maintained new motor milestones.

In adults with SMA (including those with type IV and type III who reach adulthood), it is unclear what the potential benefits of treatment with a drug such as nusinersen would be, as clinical experience and natural history data indicate a plateau of the disease progression in the adult population. It is also unknown which adult patients with SMA are likely to respond to treatment. Progression of SMA in adult patients is slow, and signs of progression may become clinically detectable only every five years. As such, if an adult patient were to be treated with nusinersen, it is unlikely to that the effects of the treatment would be observed as quickly as in a younger population where the disease progression is much faster. Potentially, assessment of the response of treatment may be conducted after five years of treatment, when the signs of disease progression usually manifest.

Implementation of nusinersen treatment may present some challenges. Patients with potential spinal deformity would likely require a radiographic guided lumbar puncture. While access to radiographic services may not be very challenging in the pediatric population, adults may be deferred frequently due to the use of these services for urgent stroke management. In addition, the most appropriate site at which treatment should be administered requires further discussion to take into account the needs of patients who may live in areas that are not in close proximity to a tertiary medical facility. Ideally, assessment of motor function should be conducted by a physiotherapist before every injection (which takes place approximately every four months); this might not be feasible due to the length of time such assessment would take and the busy schedule of physiotherapists.

Because pre-symptomatic treatment with nusinersen offers the greatest potential for preventing irreversible loss of motor neurons, physicians and public health agencies must consider what can be done to ensure early diagnosis, including the potential for incorporating SMA into provincial newborn screening programs. The potential benefit of pre-

symptomatic treatment is especially important for infants with two copies of the SMN2 gene, who are most likely to develop SMA type I.

Conclusions

Higher-quality evidence assessing the clinical efficacy of nusinersen in the SMA population is presented in the ENDEAR and CHERISH studies. The ENDEAR study was reviewed in the original submission and was used as the basis of the CDEC recommendation. CHERISH demonstrated a statistically significant, and potentially clinically meaningful, change in the HFMSE score from baseline in the nusinersen group when compared with the sham control group. The result of this primary outcome was further supported by a statistically significant secondary outcome of HFMSE responders and by the exploratory outcomes of change in Revised Upper Limb Module test, [redacted], and hospitalization. Exploratory outcomes were not adjusted for multiple testing. The main limitation in CHERISH is the dosage schedule of nusinersen not matching Health Canada's approved schedule, which reduces the generalizability of the results. One ongoing single arm study, NURTURE, addressed SMA pre-symptomatic patients with two or three SMN2 gene copies, and was available for inclusion; [redacted] However, due to the lack of a control group, CDR was unable to determine the extent of the benefit attributed to nusinersen treatment. Also, due to the potential variability in disease progression of pre-symptomatic patients, the drug protective mechanism of action, and the deteriorating nature of the condition, the informal contrast of findings from pre-symptomatic patients with SMA type 1 natural history is likely to overestimate the effect due to the assumption that all NURTURE patients would have developed SMA type I. The studies addressing the older patient population with later SMA onset (likely to be considered as SMA type III) were single arm descriptive studies. While these studies show an improvement in motor development and function, considering the heterogeneity of the disease presentation and progression in this population, the results from the single arm studies do not provide high-quality evidence of the magnitude of the benefit of nusinersen beyond potential confounders, expectation bias, and other systematic biases. Studies addressing the adult population with SMA do not provide informative evidence due to the limitations associated in the design, conduct, and reporting of these studies. The lack of a control in the single arm studies limits the generalizability of the results, and an informal contrast with the natural history of patients with SMA is highly susceptible to overestimation of the treatment effect. No sufficient evidence exists to address the potential beneficial effect of nusinersen in patients with SMA who require permanent ventilation at treatment initiation.

The collective evidence suggests that harms associated with nusinersen are largely related to the disease progression and the complications that may arise due to the lumbar puncture administration of nusinersen.

Table 1: Summary of Results

Addressed SMA Population	Patients Who Are Pre-symptomatic			
Outcome	**NURTURE**			
	2 SMN2 [redacted]	3 SMN2 [redacted]	Total N = 25	
Time to Death or Respiratory Intervention (Primary Outcome)				
Number of patients who died or required respiratory Intervention, n (%)	[redacted]	[redacted]	[redacted]	
HINE Score				
HINE motor milestone responders, N (%)	[redacted]	[redacted]	[redacted]	
Baseline score, mean (SD)	[redacted]	[redacted]	[redacted]	
Change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]	
CHOP INTEND				
Baseline score, mean (SD)	[redacted]	[redacted]	[redacted]	
Assessment visit (day 183) mean score, mean (SD)	[redacted]	[redacted]	[redacted]	
WHO Motor Milestones				
Baseline score, mean (SD)	[redacted]	[redacted]	[redacted]	
Assessment visit (day 183) mean score, mean (SD)	[redacted]	[redacted]	[redacted]	
Growth Failure				
Number of patients with a post-baseline weight below the 5th percentile, n (%)	[redacted]	[redacted]	[redacted]	
Number of subjects with a weight dropping > = 2 major percentiles in 6 months, n (%)	[redacted]	[redacted]	[redacted]	
Patients Manifesting Spinal Muscular Atrophy Symptoms				
Number of patients assessed, N	[redacted]	[redacted]	[redacted]	
Number of patients with SMA symptoms in observed up to 6 months of age, n (%)	[redacted]	[redacted]	[redacted]	
Withdrawals				
Total, n (%)	[redacted]	[redacted]	[redacted]	
SAEs				
n (%)	[redacted]	[redacted]	[redacted]	
WDAEs				
n (%)	[redacted]	[redacted]	[redacted]	
Notable Harms(s)				
n (%)	[redacted]	[redacted]	[redacted]	

Addressed SMA Population	Patients With Infantile Onset SMA, Including Patients With SMN2 Gene Copy > 2		
Outcome	**SHINE** (Population of CS3A Index Study)		
	Nusinersen N = 20		
Time to Death or Permanent Ventilation			
Number of patients who died or required permanent ventilation, n (%)	[redacted]		
Time (weeks) to death or permanent ventilation			
5th percentile	[redacted]		
10th percentile	[redacted]		
25th percentile	[redacted]		
50th percentile — median (95% CI)	[redacted]		
75th percentile	[redacted]		
90th percentile	[redacted]		
HINE Score			
Baseline score, mean (SD)	[redacted]		
Change from baseline, mean (95%CI)	[redacted]		
CHOP INTEND Score			
Baseline score, mean (SD)	[redacted]		
Change from baseline, mean (SD)	[redacted]		
Withdrawals			
Total, n (%)	[redacted]		
SAEs			
n (%)	[redacted]		
WDAEs			
n (%)	[redacted]		
Deaths			
n (%)	[redacted]		
Notable Harms(s)			
n (%)	[redacted]		

Addressed SMA population	Patients With Mixed Infantile and Early Childhood Onset, Including Patients With SMN2 Gene Copy > 2			
Outcome	**EMBRACE**			
	Sham Control [redacted]	**Nusinersen** [redacted]		
Ventilation Use – Number of Hours Per Day				
Change from baseline, mean (SD)	[redacted]	[redacted]		
HINE Score				
Baseline score, mean (SD)	[redacted]	[redacted]		
Change from baseline, mean (SD)	[redacted]	[redacted]		
Time to Death or Permanent Ventilation				
n (%)	[redacted]	[redacted]		
Withdrawals				
Total, n (%)	[redacted]	[redacted]		
SAEs				
n (%)	[redacted]	[redacted]		
WDAEs				
n (%)	[redacted]	[redacted]		
Notable Harms(s)				
n (%)	[redacted]	[redacted]		
Addressed SMA Population	**Patients With Early Childhood SMA Onset, Including Patients With SMN2 Gene Copy > 2**			
Outcome	**CHERISH**			
	Sham Control N = 42	**Nusinersen N = 84**		
HFMSE : Change From Baseline to Month 15 (Primary Outcome Main Analysis)				
Baseline HFMSE score, mean (SD)	19.9 (7.2)	22.4 (8.3)		
Change in HFMSE, least squares mean (95% CI)	–1.9 (–3.8 to 0.0)	4.0 (2.9 to 5.1)		
Between-groups difference, least squares mean difference (95% CI)	**5.9 (3.7 to 8.1)**			
P value	**< 0.0001**			
HFMSE Responders (≥ 3 Points Increase) at 15 Months				
Proportion of responders, %	26.3	56.8		
Between-groups difference in proportion, % (95% CI)	**30.5 (12.74 to 48.31)**			
OR (95% CI)	**5.59 (2.09 to 14.91)**			
P value	**0.0006**			
Proportion of Patients Achieving New Motor Milestones at 15 Months				
Responders, n (%)	2 (5.9)	13 (19.7)		
Between-groups difference in proportion, % (95% CI)	13.8 (–6.64 to 34.17)			
P value	0.0811[a]			

Addressed SMA Population	Patients With Early Childhood SMA Onset, Including Patients With SMN2 Gene Copy > 2			
Outcome	**CHERISH**			
Number of New Motor Milestones Achieved at 15 Months				
Number of new motor milestones achieved, least square mean (95% CI)	–0.2 (–0.4 to 0)	0.2 (0.1 to 0.3)		
Between-groups difference, least squares mean difference (95% CI)	0.4 (0.2 to 0.7)			
P value[b]	0.0001			
Change From Baseline in Revised Upper Limb Module Test at 15 Months				
Baseline score, mean (SD)	17.3 (5.3)	18.9 (6.3)		
Change from baseline, least squares mean difference (95% CI)	0.5 (–0.6 to 1.6)	4.2 (3.4 to 5.0)		
Between-groups difference, least squares mean difference (95% CI)	3.7 (2.3 to 5.0)			
P value[b]	0.0000001			
Proportion of Patients Achieving Standing Alone at 15 Months				
Responders, n (%)	1 (2.9)	1 (1.5)		
Between-groups difference in proportion, % (95% CI)	–1.4 (–21.8 to 19.3)			
P value[b]	> 0.9999			
Proportion of Patients Achieving Walking With Assistance at 15 Months				
Responders, n (%)	[redacted]	[redacted]		
Between-groups difference in proportion, % (95% CI)	[redacted]			
P value[b]	[redacted]			
Change From Baseline in PedsQL (Total Score – Patient Assessment) at 15 Months				
Change from baseline, least squares mean difference (95% CI)	[redacted]	[redacted]		
Between-groups difference, least squares mean difference (95% CI)	6.8 (–9.5 to 23.1)			
P value[b]	0.3836			
Change From Baseline in PedsQL (Total Score — Parent Assessment) at 15 Months				
[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]			
[redacted]	[redacted]			
[redacted]				
[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]			
[redacted]	[redacted]			

Addressed SMA Population	Patients With Early Childhood SMA Onset, Including Patients With SMN2 Gene Copy > 2			
Outcome	**CHERISH**			
Hospitalization				
[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]			
[redacted]		[redacted]		
Withdrawals				
Total, n (%)	0	0		
SAEs				
n (%)	12 (29)	14 (17)		
WDAEs				
n (%)	0	0		
Notable Harms(s)				
n (%)	NR	NR		
Addressed SMA Population	**Patients With Later Childhood Onset, Including Patients With SMN2 Gene Copy > 2**			
Outcome	**SHINE** (Patients Previously Participating in CS12)			
	Designated as Type II SMA	**Designated as Type III SMA**		
HFMSE : Change From Baseline				
Number of patients assessed	[redacted]	[redacted]		
Change from baseline, mean (SD)	[redacted]	[redacted]		
HFMSE responders, n (%)	[redacted]	[redacted]		
Change From Baseline in Upper Limb Module Test				
Number of patients assessed	[redacted]	[redacted]		
Baseline score, mean (SD)	[redacted]	[redacted]		
Change from baseline, mean (SD)	[redacted]	[redacted]		
Change From Baseline in 6-Minute Walk Test				
Number of patients assessed	[redacted]	[redacted]		
Baseline score, mean (SD)	[redacted]	[redacted]		
Change from baseline, mean (95% CI)	[redacted]	[redacted]		
Withdrawals				
Total, n (%)	[redacted]			
SAEs				
n (%)	[redacted]			
WDAEs				
n (%)	[redacted]			
Notable Harms(s)				
n (%)	[redacted]			

Addressed SMA Population	Adult Patients			
Outcome	Elsheikh 2018		Day 2018	
No clear outcome results were reported				
No explicit harms data were reported				
Addressed SMA Population	**Patients Diagnosed Before Seven Months of Age But Receive Treatment After Seven Months of Age**			
Outcome	**Pane, 2018**	**Aragon, 2018**	**SHINE (ENDEAR Index Study [Represent Characteristics at the Start of SHINE Study])**	
	Nusinersen N = 104	Nusinersen N = 33	Previous Control [redacted]	Previous Nusinersen [redacted]
Time to Death or Permanent Ventilation				
Number of patients who died or required permanent ventilation, n (%)	NR	NR	[redacted]	[redacted]
Time (weeks) to death or permanent ventilation	NR	NR		
50th percentile — median (95% CI)	NR	NR	[redacted]	[redacted]
HINE Score				
Change from baseline, mean (SD)	1.3 (2.2)	NR	[redacted]	[redacted]
HINE-2 Motor Milestone Responders				
Motor milestone responders, n (%)	NR	NR	[redacted]	[redacted]
CHOP INTEND Score				
Change from baseline, mean (SD)	44.5 (5.80)	NR	[redacted]	[redacted]
Withdrawals				
Total, n (%)	NR	NR	[redacted]	[redacted]
SAEs				
n (%)	NR	NR	[redacted]	[redacted]
WDAEs				
n (%)	NR	NR	[redacted]	[redacted]
Notable Harms(s)				
n (%)	NR	NR	[redacted]	[redacted]

Addressed SMA Population	Patients With SMA Who Require Ventilation		
Outcome	Pechmann, 2018		
	Total **N = 61**		
CHOP INTEND Score — Overall Population			
Change from baseline, mean (SD)	9.0 (8.0)		
CHOP INTEND Score — Patients Requiring Permanent Ventilation			
Change from baseline, mean (SD)	5.6 (7.5)		
HINE Score			
Change from baseline, mean (SD)	1.4 (2.1)		
Motor milestone responders, n (%)	21 (34.4)		
Ventilator Support			
No support			
At baseline, n (%)	26 (43)		
After 6 months, n (%)	19 (31)		
Non-invasive ventilation (< 16 hours per day)			
At baseline, n (%)	17 (28)		
After 6 months, n (%)	17 (28)		
Non-invasive ventilation (> 16 hours per day) or tracheostomy			
At baseline, n (%)	18 (30)		
After 6 months, n (%)	25 (41)		
Withdrawals			
Total, n (%)	NR		
SAEs			
n (%)	NR		
WDAEs			
n (%)	NR		
Notable Harms(s)			
n (%)	NR		

CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CI = confidence interval; HFMSE = Hammersmith Functional Motor Scale – Expanded; HINE = Hammersmith Infant Neurological Examination; NR = not reported; OR = odds ratio; PedsQL = Pediatric Quality of Life Inventory; SAE = serious adverse event; SD = standard deviation; SMA = spinal muscular atrophy; SMN = survival motor neuron; WDEAs = withdrawal due to adverse events; WHO = World Health Organization.

[a] Failure to achieve statistical testing led to the discontinuation of the testing hierarchy.

[b] *P* value falls outside of the hierarchy of testing, thus is unadjusted for multiple testing.

Introduction

Disease Prevalence and Incidence

Spinal muscular atrophy (SMA) is a severe neuromuscular disease and is the leading genetic cause of infant death.[1,2] It is characterized by the degeneration of alpha motor neurons in the anterior horn of the spinal cord, leading to progressive muscle weakness.[1] 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 (SMN1) gene.[3,4] While deletion or mutation of the SMN1 gene results in SMN protein deficiency, a second nearby gene, the SMN2 gene, produces a relatively small amount of functional SMN protein and SMN2 copy number modulates the severity of the disease.[1-3,16]

SMA is a rare disease and estimates of its incidence and prevalence vary between studies. Most of these studies relied on clinical rather than genetic diagnosis and were often performed in small cohorts based in Europe.[4] The incidence of SMA is often cited as being approximately 10 in 100,000 live births.[4] One recent review found estimates ranging from 5.0 to 24 in 100,000 births.[4] Prevalence is estimated to be approximately one to two in 100,000 persons[4] and is affected by the drastically shortened life expectancy in the most common type of SMA. However, one study that examined the Cure SMA database (a voluntary registry that is one of the largest patient-reported repositories in the world) reported the birth prevalence in the US at about 1 in 20,000 live births.[5]

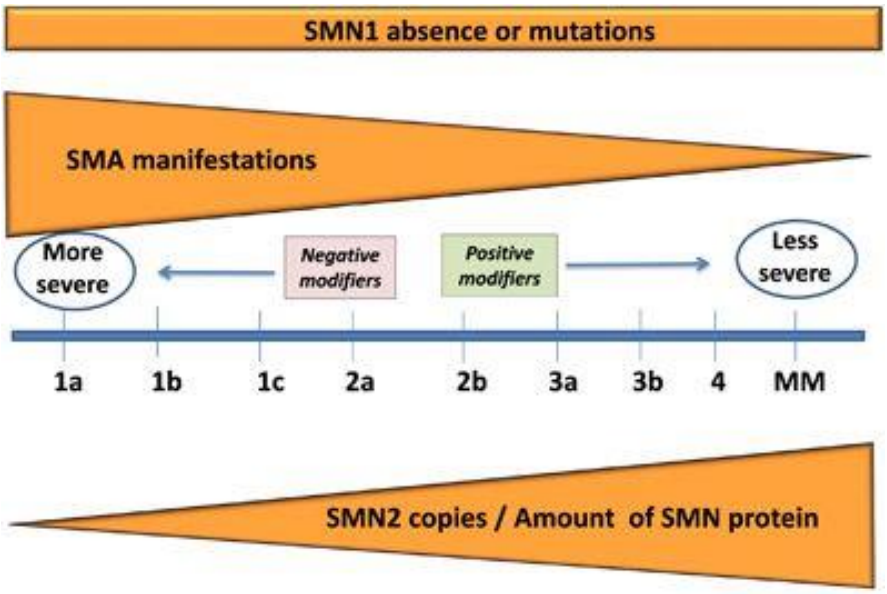
The disease first manifests in various ways, depending on age of onset. Infants present with severe hypotonia and feeding difficulties while later onset in young children may appear as difficulty with stairs and frequent falls.[17] Adult onset SMA presents as mild proximal muscle weakness.[2] Genetic testing gives a definitive diagnosis for 5q SMA and the first step is to test for SMN1 gene deletion.[1] If homozygous SMN1 deletion is not found, sequencing of the SMN1 coding region may identify a causative mutation.[1] The patients input received echoes these findings, where it describes SMA affecting patients with widely ranging degrees of severity depending on age of onset. SMA type I presents by the age of six months and is the most common genetic cause of infant mortality. In SMA type II, age of onset is six to 18 months and patients have delayed motor milestones, respiratory issues, and the possibly of a shortened life expectancy. Patients with SMA type III are those with onset from 18 months to 18 years of age; they experience muscle weakness. SMA type IV is adult onset with varying degrees of muscle weakness. Common to all types of SMA is a progressive decline in muscle function.

SMN deficiency results in defects in multiple components of the motor system, including the motor neurons.[2] Electrophysiological studies and clinical findings in patients with SMA show that patients typically experience a sharp decline in motor function with motor unit loss soon after symptom onset, followed by a long plateau period of relative stability in motor function.[2,18] Clinical expert input to CADTH indicated that motor function decline is irreversible aside from possible gains in strength and gross motor abilities in infants still undergoing normal muscle hypertrophy in the first two years of life. Muscle weakness tends to be symmetrical, more proximal rather than distal, and more severe in the lower limbs than in the upper limbs.[1]

SMA is divided into four clinical subtypes that vary in age of onset, highest motor milestone achieved, and prognosis. While the subtypes provide a convenient means of classifying

patients, it should be noted that patients exist along a continuum of disease severity with overlap in symptoms between subtypes. This spectrum is represented in Figure 1, as published in Talbot 2017.[19]

Figure 1: Continuous Spectrum of Spinal Muscular Atrophy Phenotype



MM = minimal manifestations; SMA = spinal muscular atrophy; SMN = survival motor neuron.

Source: Talbot K, Tizzano EF. The clinical landscape for SMA in a new therapeutic era. Gene Ther. 2017; 24:529-533. Licensed under: https://creativecommons.org/licenses/by-nc-nd/4.0/.

Type I: These 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.[1-3,5,16] SMA type I is the most common type of SMA, accounting for about 60% of SMA diagnoses.[4] Almost all patients with SMA type I have two or three copies of SMN2, giving rise to a broad range of phenotypes.[6] Additional subtypes of Ia, Ib, and Ic have been proposed based on age of onset, with Ia being the earliest and most severe subtype. SMA type 0 is sometimes included in classification systems and presents in neonates as joint contractures, severe weakness and hypotonia, respiratory insufficiency, and a life expectancy of less than six months.[3,16] Muscle weakness in patients with SMA type I is severe to the point where patients typically cannot perform antigravity limb movements and have no head control, though facial muscles are spared.[1] Fine motor skills are affected, with infants unable to grasp using their whole hand.[20] Weakness in the intercostal muscles in combination with sparing of the diaphragm leads to paradoxical breathing and a bell-shaped chest.[1,3] Bulbar weakness results in difficulty swallowing and feeding, with risk of failure to thrive and aspiration.[1,3] Reflux and impaired cough and swallowing contribute to risk of aspiration and recurrent pulmonary infections.[1-3,16] A gastrostomy tube for feeding combined with nighttime and possibly daytime non-invasive ventilation with bi-level positive airway pressure (BiPAP) can improve quality of life (QoL)[3,16] and life expectancy.[21] Aggressive intervention with a tracheostomy and permanent ventilation is also possible and can prolong life expectancy; however, this is a decision to be made by the family with the support of health care providers.[3,16] In one study that examined

1,966 patients in the Cure SMA database (with data available between 2010 and 2016), the median survival for those with type I SMA was 13.6 months.[5]

Type II: Patients with type II SMA 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,[16,17] with life expectancy improved by aggressive supportive care.[17] Patients with type II SMA represent about 20% to 30% of SMA cases[2] and most patients with SMA type II have three copies of SMN2.[6] In addition to the inability to walk independently, common symptoms are fine tremors of the upper extremities, tongue fasciculation, joint contractures, and scoliosis.[1,3,17] Scoliosis and weak intercostal muscles can cause restrictive lung disease.[3] There is a range in severity, with weaker patients requiring non-invasive ventilation.[1] Difficulty swallowing is less common than in patients with type I and difficulty with feeding comes from masticatory muscle weakness.[1] In one study that examined 1,966 patients in the Cure SMA database (with data available between 2010 and 2016), the median survival for those with type II SMA was 59.9 years.[5]

Type III: Type III SMA makes up about 10% to 20% of SMA cases[4] 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.[17] Most patients with type III SMA have three or four copies of SMN2.[6] An age of onset prior to three years is associated with estimated probabilities of 73%, 44%, and 34% of walking 10, 20, and 40 years after onset.[22] In those with age of onset after three years, the estimated probabilities are 97%, 89%, and 67% for walking 10, 20, and 40 years after onset.[22] Patients with SMA type III have little or no respiratory weakness.[3] Ambulatory patients may exhibit abnormal gait characteristics due to proximal weakness,[17] while patients who lose the ability to walk often develop scoliosis.[1]

Type IV: A very small proportion of SMA cases are type IV or adult onset SMA, 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.[1]

The correlation between the genotype, specifically the number of SMN2 genes, and the clinical phenotype (SMA types) is probabilistic in nature. In one natural history study, of 39 patients diagnosed as SMA types 1b or 1c, 16 patients (41%) had two copies of the SMN 2 gene, 21 patients (54%) had three copies of the SMN2 gene, and one patient (3%) had four copies of the SMN2 gene.[6] The same study showed that out of 87 patients diagnosed as SMA types 2a or 2b, two patients (2%) had two copies, 75 patients (86%) had three copies, and seven patients (8%) had four copies of the SMN2 gene.[6] Of 66 patients that were diagnosed as SMA types 3a or 3b assessed in the same study, one patient (2%) had two copies, 19 patients (29%) had three copies, 40 patients (61%) had four copies, and two patients (3%) had five copies of the SMN2 gene.[6] The study also assessed five patients diagnosed as SMA type IV; of these patients, four (80%) had four copies of the SMN2 gene, and one patient was not reported.[6] A summary of these subtypes is presented in Table 2, as published in Talbot 2017.[19]

Table 2: Spinal Muscular Atrophy Clinical Classification

SMA type	*Onset*	*Milestones achieved*	*Evolution / natural history*	*Typical SMN2 copy number*
1 A (also referred as type 0)	Prenatal	None	Death in weeks, contractures, cardiopathy	1
1B	< 3M	Poor or absent head control	Feeding and respiratory problems, linear decline. Death by second or third year of life	2
1C	> 3M	Cephalic control	Feeding and respiratory problems. Plateau in first two years	3
2	> 6M	Able to sit unaided	Scoliosis. Survival to adolescence/adulthood Weaker cases may lose sitting capability (2a) and stronger cases may stand with support (2b)	3
3a	Between 18 and 36 months	Walking unaided	Scoliosis Early loss of ambulation Normal lifespan	3
3b	> 3 years	Walking unaided	Later loss of ambulation Normal lifespan	3–4
4	Second or third decade of life	Walking unaided	Ambulant until late in life Normal lifespan	4

M = months; SMA = spinal muscular atrophy; SMN = survival motor neuron.

Source: Talbot K, Tizzano EF. The clinical landscape for SMA in a new therapeutic era. Gene Ther. 2017; 24:529-533. Licensed under: https://creativecommons.org/licenses/by-nc-nd/4.0/

Standards of Therapy

Aside from nusinersen, there are currently no approved treatments for SMA and supportive care seeks to improve QoL. Respiratory management is essential for all children with type I SMA and some with type II. Non-invasive ventilation with BiPAP can help with disordered breathing at nighttime and can be used during the day as needed for hypercapnia.[3] Secretion mobilization is also important in patients with weak cough and this can be achieved with postural drainage, assisted coughing, and oral suction.[1,16] When non-invasive ventilation is no longer sufficient, tracheostomy and permanent, invasive ventilation is an option. However, there is no consensus in guidelines over the suitability of this invention and its implementation remains a choice for the family.[16,17]In patients with difficulty chewing and swallowing, changing food consistency can help with feeding and reduce risk of aspiration. A gastrostomy tube can also be placed, though there is no consensus on when this should occur.[17]

For gross motor function, management strategies include mobility aides, bracing, and physical therapy. Patients able to bear weight may make use of a standing frame or ankle-foot orthoses and physical activity such as swimming can increase stamina.[17] Manual and motorized wheelchairs provide mobility to those who can use them. Scoliosis is very common in patients with non-ambulatory types II and III SMA and can be corrected with surgery.[17] Bracing, seating modification, and physical therapy may slow scoliosis progression in a child until they can undergo surgery.[16] Recommendations for the diagnosis and management of patients with SMA were published earlier in 2018. The recommendations added emphasis on a proactive approach in respiratory management, whereby clinicians are encouraged to use non-invasive ventilation before any respiratory symptoms manifest.[23,24]

Drug

Nusinersen (Spinraza) is indicated for the treatment of 5q SMA. It is an antisense oligonucleotide that increases the proportion of exon 7 inclusion in SMN2 messenger ribonucleic acid transcripts made, through binding to a specific site in the SMN2 pre-messenger ribonucleic acid. This leads to the translation of the messenger ribonucleic acid into functional full-length SMN protein. Nusinersen is administered via intrathecal injection by lumbar puncture in a 5 mL solution containing 12 mg of nusinersen. It is given in a regimen of four loading doses at day 0, day 14, day 28, and day 63, with subsequent maintenance doses at a four-month frequency.[25]The manufacturer has requested nusinersen be reimbursed for the treatment of 5q SMA across all types, including pre-symptomatic patients, and all ages.

Submission History

Basis of Resubmission

On December 20, 2017, the CADTH Canadian Drug Expert Committee (CDEC) issued a final recommendation regarding nusinersen treatment for patients diagnosed with SMA (Appendix 4). The recommendation was based on evidence presented in a CADTH Common Drug Review (CDR) report of Spinraza (Appendix 6). The CDR report followed a systematic review approach, which included published and unpublished phase III randomized clinical trials of Spinraza as indicated by Health Canada, along with clinical trials considered pivotal by Health Canada. CDEC assessed the evidence reported in the CDR report and issued a recommendation to reimburse Spinraza with the following clinical criteria: [26]

- “Genetic documentation of 5q SMA homozygous gene deletion, homozygous mutation, or compound heterozygote.
- Genetic documentation of two copies of the survival motor neuron 2 (SMN2) gene.
- Disease duration less than 26 weeks with onset of clinical signs and symptoms consistent with SMA after the first week after birth and on or before 7 months of age.
- Patient is not currently requiring permanent invasive ventilation.
- Treatment should be discontinued if, prior to the fifth dose or every subsequent dose of nusinersen:
  - there is no demonstrated maintenance of motor milestone function (as assessed using the Hammersmith Infant Neurological Examination [HINE] Section 2); or
  - there is no demonstrated improvement in motor milestone function (as assessed using the HINE Section 2); or
  - if permanent invasive ventilation is required.”

In addition, CDEC identified the following areas as constituting and evidence gap:[26]

- patients with symptom onset at birth or within one week of birth
- patients with advanced SMA who require ventilation
- patients older than seven months of age
- patients with more than two copies of the SMN2 gene
- patients diagnosed at later stages of disease

- patients who are pre-symptomatic.

The manufacturer provided this resubmission with additional data and information from ongoing and recently conducted studies that were not available during the original submission. In light of the new information, this resubmission has been conducted with the primary goal of attempting to provide and assess any clinical studies that can fill the evidence gaps identified by CDEC.

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of nusinersen for the treatment of patients with 5q SMA.

Methods

All manufacturer-provided studies will be included in the systematic review. Published studies will be selected for inclusion based on the selection criteria presented in Table 3.

Table 3: Inclusion Criteria for the Systematic Review

Patient Population	Patients with 5q spinal muscular atrophy (SMA) Subgroups: SMA type (type I, type II, type III, and type IV) Time since symptom onset until initiation of nusinersen treatment
Intervention	Nusinersen (Spinraza)
Comparators	• Best supportive care • Placebo or sham • None
Outcomes	**Efficacy outcomes:** Motor function related outcomes: • Assessment of muscle strength and/or mobility using a validated scale[a] • Assessment of gross and fine motor skills development in pediatric population using a validated scale • The need for enteral or parenteral feeding[a] Respiratory related outcomes: • Assessment of pulmonary function[a] • Use of respiratory or ventilatory assist devices Survival-related outcomes: • Overall survival • Event-free survival (e.g., invasive ventilation, hospitalization) Patient-reported outcomes: • Health-related quality of life using a validated scale[a] • Assessment of symptoms severity using a validated scale[a] • Caregiver burden Weight percentile in pediatric population Hospitalization

	Harms outcomes: • Adverse events, serious adverse events, withdrawals due to adverse events, mortality • Adverse events of special interest: serious infection, serious respiratory infection, respiratory complication related to drug anesthesia, lumbar puncture–related adverse events (e.g., bleeding, brainstem herniation, meningitis, pain post lumber puncture), coagulation abnormalities, renal toxicity
Study Design	Published and unpublished phase III or higher randomized controlled trials. In addition, any study that addresses gaps in evidence as defined by the CDEC Recommendation[b]

CDEC = CADTH Canadian Drug Expert Committee.

[a] These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

[b] CDEC recommendation for nusinersen, published December2017, identified the following areas as having insufficient evidence regarding the efficacy and safety of nusinersen, specifically:

- patients with symptom onset at birth or within one week of birth
- patients with advanced SMA who require ventilation
- patients older than seven months of age
- patients with more than two copies of the SMN2 gene
- patients diagnosed at later stages of disease
- patients who are pre-symptomatic.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Spinraza and nusinersen.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on August 22, 2018. Regular alerts were established to update the search until the meeting of CDEC on November, 2018. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters):

- health technology assessment agencies
- health economics
- clinical practice guidelines
- drug and device regulatory approvals
- advisories and warnings
- drug class reviews
- databases (free)
- Internet search.

Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

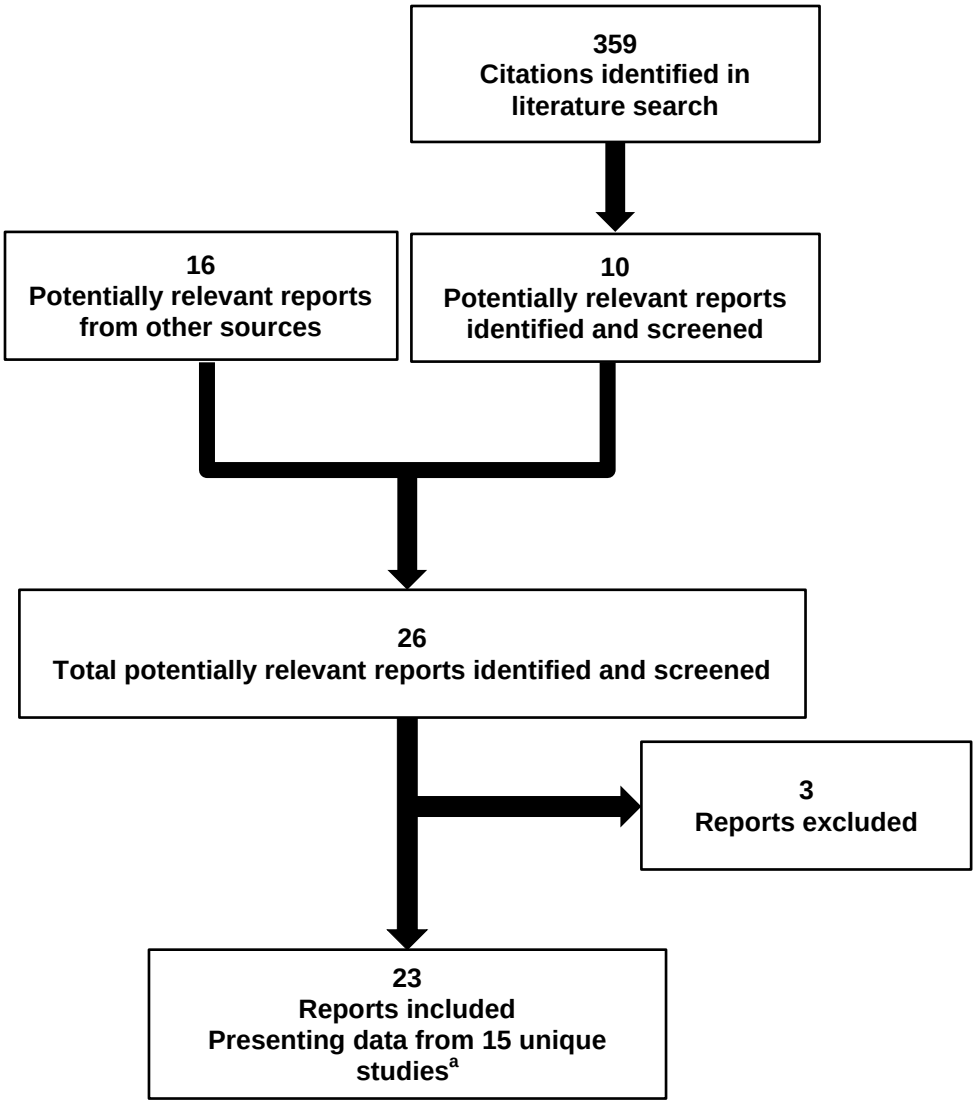
Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4; excluded studies (with reasons) are presented in Appendix 3.

Results

Findings From the Literature

A total of 15 studies were included in the systematic review (Figure 2). The included studies are summarized in Table 4. A list of excluded studies is presented in **Error! Reference source not found.**. Subsequent to Table 4, the included studies will be presented in separate tables/ sections that would address each of the identified evidence gaps as identified by previous CDEC recommendations.

Figure 2: Flow Diagram for Inclusion and Exclusion of Studies



[a] Additional one letter representing the experience of one medical centre with treating adult patients with spinal muscular atrophy — as submitted by the manufacturer.

Table 4: Details of Included Studies

		NURTURE (CS5)	CS3A	ENDEAR (CS3B)	CHERISH (CS4)
Designs and Populations	**Study design**	Phase II, multi-centre, open-label, uncontrolled single arm trial	Phase II, open-label, multiple dose, uncontrolled, multi-centre trial	Phase III, randomized, double-blind, sham-procedure controlled, multi-centre trial	Phase III, randomized, double-blind, sham-procedure controlled, multi-centre trial
	Locations	Australia, Argentina, Germany, Israel, Italy, Qatar, Taiwan, Turkey, the UK, and the US	Canada, US	North America (Canada and US), Europe, Asia-Pacific region	North America (Canada and US), Europe, Asia-Pacific region
	Randomized/ enrolled (N)	25	21	121	126
	Inclusion criteria	• Genetic documentation of 5q SMA homozygous gene deletion or mutation or compound heterozygous mutation • Genetic documentation of 2 or 3 copies of SMN2 • Age ≤ 6 weeks at first dose • Ulnar CMAP ≥ 1 mV at baseline	• Genetic documentation of 5q SMA homozygous gene deletion or mutation • Onset of clinical signs and symptoms consistent with SMA at ≥ 21 days and ≤ 6 months (180 days) of age • Males and females between ≥ 21 days and ≤ 7 months (210 days) of age at screening	• Genetic documentation of 5q SMA homozygous gene deletion, homozygous mutation, or compound heterozygote • Genetic documentation of 2 copies of SMN2 • Onset of clinical signs and symptoms consistent with SMA at ≤ 6 months (180 days) of age • Males and females ≤ 7 months (210 days) of age at screening • Patients were the product of a pregnancy of 37 to 41 weeks gestation	• Genetic documentation of 5q SMA homozygous gene deletion, homozygous mutation, or compound heterozygote • Onset of clinical signs and symptoms consistent with SMA at > 6 months of age • Males and females 2 to 12 years of age • Could sit independently, but has never had the ability to walk independently • Motor Function Score (HFMSE) ≥ 10 and ≤ 54 at screening
	Exclusion criteria	• Hypoxemia • Signs or symptoms at screening or immediately prior to the first dosage (day 1) that are strongly suggestive of SMA • History of or active condition that would interfere with lumbar puncture or assessment of study • Treatment with an investigational drug given for the treatment of SMA (e.g., oral albuterol/salbutamol, riluzole, carnitine, sodium phenylbutyrate, valproate, hydroxyurea, etc.), biological agent, or device. Any history of gene therapy, prior ASO treatment, or cell transplantation	• Hypoxemia • History of or active condition that would interfere with lumbar puncture or assessment of study • Treatment with another investigational drug (e.g., albuterol, riluzole, carnitine, creatine, sodium phenylbutyrate, salbutamol, valproate, hydroxyurea), biological drug, or device within 90 days prior to enrolment or anytime during the study. Any history of gene therapy or cell transplantation	• Hypoxemia • Signs or symptoms of SMA present at birth or within the first week after birth • History of or active condition that would interfere with lumbar puncture or assessment of study • Treatment with an investigational drug given for the treatment of SMA (e.g., oral albuterol/salbutamol, riluzole, carnitine, sodium phenylbutyrate, valproate, hydroxyurea, etc.), biological drug, or device within 30 days prior to screening or anytime during the study. Any history of gene therapy, prior ASO treatment, or cell transplantation	• Respiratory insufficiency • Gastric feeding tube • History of or active condition that would interfere with lumbar puncture or assessment of study • Treatment with another investigational drug (e.g., oral albuterol/salbutamol, riluzole, carnitine, creatine, sodium phenylbutyrate, etc.), biological drug, or device within 1 month of screening or 5 half-lives of study agent, whichever was longer • Treatment with valproate or hydroxyurea within 3 months of screening. Any history of gene therapy, antisense oligonucleotide therapy, or cell transplantation

		NURTURE (CS5)	CS3A	ENDEAR (CS3B)	CHERISH (CS4)
DRUGS	**Intervention**	12 mg (in a 5 mL solution) scaled equivalent dose based on CSF volume scaling of nusinersen administered intrathecal by lumbar puncture on days 1, 15, 29, 64, 183, 302, 421, 540, 659, and 778 of the study	Cohort 1: 6 mg (in a 5 mL solution) scaled equivalent dose based on CSF volume scaling of nusinersen on days 1, 15, 85 Cohort 2: 12 mg (in a 5 mL solution) scaled equivalent dose based on CSF volume scaling of nusinersen on days 1, 15, 85 Subsequently, both cohorts receive 12 mg equivalent on days 253, 379, 505, 631, 757, 883, 1,009, 1,135, and 1,261	12 mg (in a 5 mL solution) scaled equivalent dose based on CSF volume scaling of nusinersen administered via intrathecal injection by lumbar puncture on says 1, 15, 29, 64, 183, and 302	12 mg (in a 5 mL solution) nusinersen administered intrathecal by lumbar puncture days 1, 29, 85, and 274.
	Comparator(s)	NA	NA	Sham procedure on days 1, 15, 29, 64, 183, and 302	Sham procedure on days 1, 29, 85, and 274
DURATION	**Phase**				
	Run-in/ Screening	21 days	21 days	21 days	28 days
	Double-blind	NA (treatment period until day 778, or 111 weeks)	NA (treatment period until day 1,261)	10 months	9 months
	Follow-up	3 months	3 months	3 months	6 months
OUTCOMES	**Primary end point**	• Time to death or respiratory intervention (invasive or non-invasive ventilation for ≥ 6 hours/day continuously for ≥ 7 days OR tracheostomy)	HINE Section 2 score	• Proportion of HINE Section 2 motor milestone responders • Time to death or permanent ventilation	• Change from baseline in HFMSE score at 15 months
	Other end points	• Respiratory events • Growth parameters • CHOP INTEND • WHO motor milestones • HINE Section 2	• Event-free survival and survival • CHOP INTEND • Ventilator use • Growth parameters	• Proportion of CHOP INTEND responders • Survival rate • Proportion ventilation free • Growth parameters • Hospitalization	• Proportion of HFMSE responders • RULM • WHO motor milestones • Pediatric Quality of Life Inventory • Assessment of caregiver experience with neuromuscular disease • Hospitalization
NOTES	**Publications**	"None"	Finkel 2016[12]	Finkel 2017[13]	Mercuri 2018[15]

		SHINE (CS11)	EMBRACE (CS7)	Pane 2018	Pechmann 2018
Designs and Populations	**Study design**	Phase III, multi-centre, open-label extension study for patients who previously participated in index studies CS3B (ENDEAR), CS4 (CHERISH), CS12, and CS3A	Phase II, multi-centre study for patients with SMA not eligible to participate in ENDEAR or CHERISH with two parts: • Part 1 is a randomized, double-blind, sham-procedure controlled study • Part 2 is an open-label extension study	Case series of patients with type I SMA receiving Spinraza as part of an expanded access program	Case series of patients with type I SMA receiving Spinraza as part of an expanded access program
	Locations	North America (Canada and US), Europe, Asia-Pacific region	Germany, US	Italy	Germany
	Randomized/ enrolled (N)	207	21	122	61
	Inclusion criteria	Completion of the index study in accordance with the study protocol within the preceding 12 weeks	• Genetic documentation of 5q SMA homozygous gene deletion, mutation, or compound heterozygote • One of the following: ○ onset of clinical signs and symptoms consistent with SMA at ≤ 6 months of age and documentation of 3 copies of the SMN2 gene ○ onset of clinical signs and symptoms consistent with SMA at ≤ 6 months of age, > 7 months of age at screening, and documentation of 2 copies of the SMN2 gene ○ onset of clinical signs and symptoms consistent with SMA at > 6 months of age, ≤ 18 months of age at screening, and documentation of 2 or 3 copies of the SMN2 gene	• Patients diagnosed with type I SMA	• SMA diagnosis as proven with genetic documentation of 5q SMA • Onset of symptoms before 6 months of age • Patient care in accordance with the consensus statement regarding the guidelines of standard of care published in 2007[27]

	SHINE (CS11)	EMBRACE (CS7)	Pane 2018	Pechmann 2018
		• For Part 2 only: participation in Part 1 and completion of the end of Part 1 evaluation assessments		
Exclusion criteria	• Any new condition or worsening of existing condition that, in the opinion of the investigator, would make the patients unsuitable for enrolment, or could interfere with the patients participating in or completing the study • Treatment with another investigational agent, biological agent, or device within 1 month of screening, or 5 half-lives of study agent, whichever is longer	• Any previous exposure to nusinersen other than during Part 1; previous dosage in this study or previous exposure in other studies with nusinersen • Signs or symptoms of SMA present at birth or within the first week after birth • Ventilation for ≥ 16 hours per day continuously for > 21 days at Screening • Permanent tracheostomy, implanted shunt for CSF drainage, or implanted central nervous system catheter at screening • History of brain or spinal cord disease that would interfere with the lumbar puncture procedure, CSF circulation, or safety assessments • Hospitalization for surgery (e.g., scoliosis surgery), pulmonary event, or nutritional support within 2 months prior to screening, or hospitalization for surgery planned during the study	• None reported	• Participating in a nusinersen ongoing trial • History of previous administration of nusinersen • History of brain or spinal cord disease • Within 6 months history of or currently participating in investigational SMA trial

		SHINE (CS11)	EMBRACE (CS7)	Pane 2018	Pechmann 2018
			• Treatment with an investigational drug for SMA (e.g., albuterol/salbutamol, riluzole, carnitine, sodium phenylbutyrate, valproate, hydroxyurea), biological agent, or device within 30 days prior to screening. Any history of gene therapy, prior antisense oligonucleotide treatment, or cell transplantation • Ongoing medical condition that according to the investigator would interfere with the conduct and assessments of the study		
DRUGS	**Intervention**	12 mg of intrathecally administered nusinersen [redacted]	12 mg of intrathecally administered nusinersen Part 1: 6 doses on days 1, 15, 29, 64, 183, and 302 Part 2, nusinersen group from Part 1: 7 doses on days 1, 120, 239, 358, 477, 596, and 715 Part 2, control group from Part 1: 10 doses on days 1, 15, 29, 64, 183, 302, 421, 540, 659, and 778	Nusinersen — dosage and regimen not specified	Nusinersen on days 1, 15, 30, 60, and 180 with a dose: Prior to nusinersen drug approval — age dependant analogous or the preceding trials Post approval: 12 mg, independent of age

		SHINE (CS11)	EMBRACE (CS7)	Pane 2018	Pechmann 2018
Drugs		[redacted]			
	Comparator(s)	NA	Double-blind period: Sham procedure Open-label extension study: NA	NA	NA
Duration	**Phase**				
	Run-in/ screening	≤ 21 days	28 days	NR	NR
	Double-blind	Treatment loading period ENDEAR: 183 days CHERISH: 264 days CS3A and CS12: NA	10 months – subsequent open-label extension phase and additional 778 days of treatment	NA (reported outcomes at 6 months)	NA (outcomes reported at 180 days [6 months])
	Follow-up	ENDEAR and CS3A: 120 days CHERISH and CS12: 180 days	4 Months	NR	NR
Outcomes	**Primary end point**	• Safety and tolerability	• Number of patients with adverse events • Number of patients with significant clinical or physiological abnormalities • Change in growth parameters	• Change from baseline in CHOP INTEND score • Change from baseline in HINE score	• Change from baseline in CHOP INTEND score • Change from baseline in HINE score
	Other end points	• Change from baseline in HINE score • Time to death or permanent ventilation	• Use of ventilator support • Change from baseline in HINE score	NA	NA

		• Survival rate • Change from baseline in CHOP INTEND score • HFMSE • Upper Limb Module (ULM) and Revised Upper Limb Module (RULM) • WHO motor milestones • 6-Minute Walk Test • Change in growth parameters			
Notes	**Publications**	Castro 2018	None	Pane 2018[28]	Pechmann 2018[29]
		CS1	**CS2**	**CS10**	**CS12**
Designs and Populations	**Study design**	Phase I, open-label, dose-finding, non-randomized, uncontrolled trial	Phase I, open-label, dose-finding, non-randomized, uncontrolled trial	Open-label, single arm extension study of CS1	Open-label, single arm extension study of CS 2 and CS 10
	Locations	US	US	US	US
	Enrolled (N)	28	34	18	47
	Inclusion criteria	• Genetic documentation of 5q SMA homozygous gene deletion, homozygous mutation • Age from 2 to 14 years • Clinical signs and symptoms attributed to SMA • Able to complete all study procedures • Life expectancy > 2 years from screening	• Genetic documentation of 5q SMA homozygous gene deletion, homozygous mutation • Age from 2 to 15 years • Clinical signs and symptoms attributed to SMA • Able to complete all study procedures • Life expectancy > 2 years from screening	• Satisfactory completion of CS1 • Able to complete all study procedures • Life expectancy > 2 years from screening	• Satisfactory completion of CS2 and CS10 • Able to complete all study procedures • Life expectancy > 2 years from screening

		CS1	CS2	CS10	CS12
Designs and Populations	**Exclusion criteria**	• Respiratory insufficiency as determined by the need to use invasive or non-invasive ventilation in 24 hours period • Presence of gastric feeding tube • History of, or a planned, scoliosis surgery • History of hospitalization for a respiratory or a surgical event within the last 2 months, or a planned hospitalization for surgical or respiratory causes • History of brain or spinal cord disease that would interfere with LP procedure • History of bacterial meningitis • Presence of an active infection requiring systemic antimicrobial or anti-viral treatment • Presence of an implanted shunt	• Respiratory insufficiency as determined by the need to use invasive or non-invasive ventilation in 24 hours period • Presence of gastric feeding tube • History of, or a planned, scoliosis surgery • History of hospitalization for a respiratory or a surgical event within the last 2 months, or a planned hospitalization for surgical or respiratory causes • History of brain or spinal cord disease that would interfere with LP procedure • History of bacterial meningitis • Presence of an active infection requiring systemic antimicrobial or anti-viral treatment • Presence of an implanted shunt • Enrolment in CS1 cohort 2, 3, or 4, or enrolment in CS10	• Worsening of existing conditions that makes patient unsuitable for enrolment in investigator opinion • Dosage in CS2 • Presence of an active infection requiring systemic antimicrobial or anti-viral treatment • Significant hematological or clinical chemistry abnormalities • Treatment with other investigational products	• Worsening of existing conditions that makes patient unsuitable for enrolment in investigator opinion • Dosage in CS2 • Presence of an active infection requiring systemic antimicrobial or anti-viral treatment • Significant hematological or clinical chemistry abnormalities • Treatment with other investigational products
Drugs	**Intervention**	Single dose of nusinersen on study day 1 (1 mg, 3 mg, 6 mg, or 9 mg).	Cohort 1: nusinersen 3 mg on days 1, 29, and 85 Cohort 2: nusinersen 6 mg on days 1, 29, and 85 Cohort 3: nusinersen 9 mg on days 1 and 85. Cohort 4: nusinersen 12 mg on days 1, 29, and 85	Single dose of nusinersen on study day 1 (61 mg or 9 mg)	Four doses of nusinersen on study days 1, 169, 351, and 533
	Comparator(s)	NA	NA	NA	NA

		CS1	CS2	CS10	CS12
DURATION	**Phase**				
	Run-in	29 days or 85 days	28 days	28-day screening period	28-day screening period
	Double-blind	NA — single treatment injection on study day 1	NA (last treatment dose reported on study day 85)	NA — single treatment injection on study day 1	NA (treatment period reports up to day 533)
	Follow-up	84 days	84 to 168 days	169 days	181
OUTCOMES	**Primary end point**	• Number of patients with adverse events	• Number of patients with adverse events	• Number of patients with adverse events • Number of patients with significant clinical or physiological abnormalities	• Number of patients with adverse events • Number of patients with significant clinical or physiological abnormalities
	Other end points	• Pharmacodynamics and pharmacokinetics related outcomes Exploratory outcomes: • HFMSE • Pediatric Quality of Life Inventory • CMAP • Upper Limb Module Test • Myometry • 6-minutes walk test • Assessment of caregiver experience with neuromuscular disease	• Pharmacodynamics and pharmacokinetics related outcomes Exploratory outcomes: • HFMSE • Pediatric Quality of Life Inventory • CMAP • Upper Limb Module Test • Myometry • 6-minutes walk test • Assessment of caregiver experience with neuromuscular disease	• Pharmacodynamics and pharmacokinetics related outcomes Exploratory outcomes: • HFMSE • Pediatric Quality of Life Inventory • CMAP • Upper Limb Module Test • Myometry • 6-minutes walk test • Assessment of caregiver experience with neuromuscular disease	• Pharmacodynamics and pharmacokinetics related outcomes Exploratory outcomes: • HFMSE • Pediatric Quality of Life Inventory • CMAP • Upper Limb Module Test • Myometry • 6-minutes walk test • Assessment of caregiver experience with neuromuscular disease
NOTES	**Publications**	Chiriboga 2016[11] Hache 2016[14]	None	Hache 2016[14] Chiriboga 2016[11]	None

		Elsheikh 2018	Day 2018	Aragon 2018	
DESIGNS AND POPULATIONS	**Study design**	Case series of adult patients with SMA	Case series of adult patients with SMA	Case series of patients with type I SMA receiving Spinraza as part of an expanded access program	
	Locations	US	US	Australia, China, Korea, Republic of, Mexico, Netherlands, Poland, Portugal, Taiwan, Turkey, UK	
	Enrolled (N)	29	20	33	

		Elsheikh 2018	Day 2018	Aragon 2018	
Designs and Populations	**Inclusion criteria**	Unclear	Unclear	• Genetic documentation of 5q SMA homozygous gene deletion, homozygous mutation, or compound heterozygote • Onset of clinical signs and symptoms at ≤ 6 months (180 days) of age, consistent with infantile onset type I SMA • Patient whose care in the opinion of the treating physician meets, and is expected to continue to meet, the guidelines set out in the 2007 Consensus Statement for Standard of Care in SMA	
	Exclusion criteria	Unclear	Unclear	• Patient is qualified to participate in an ongoing clinical trial with nusinersen • Participation in a prior nusinersen study • Previous exposure to nusinersen • History of brain or spinal cord disease that would interfere with the LP procedures or CSF circulation • Presence of implanted shunt for the drainage of CSF or implanted CNS catheter • Previous or current participation in a clinical trial with an investigational gene therapy for SMA • Participation in a study with an investigational therapy for SMA within 6 months or five half-lives of the investigational drug, whichever is the longer, prior to the first dose of nusinersen	

		Elsheikh 2018	Day 2018	Aragon 2018	
Drugs	**Intervention**	Nusinersen — unclear dose	Nusinersen — unclear dose	Nusinersen on days 1, 15, 30, 60, and 180 with a dose: Prior to nusinersen drug approval: age dependant analogous or the preceding trials Post approval: 12 mg, independent of age	
	Comparator(s)	NA	Unclear	NA	
Duration	**Phase**				
	Run-in	Unclear	Unclear	NR	
	Double-blind	NA (treatment period of four loading doses — unclear the period)	Unclear	NA (outcomes reported at 180 days [6 months])	
	Follow-up	Unclear	Unclear	NR	
Outcomes	**Primary end point**	Not predefined — authors reported on: • Procedure tolerance • Post LP headache • Subjective change in stamina and endurance • HSFMSE • Muscle strength • 6-minutes walking test	Not predefined — authors reported on: • Procedure tolerance • Subjective patient reporting change • TUG • RULM • PFT • 6-minutes walking test	• Change from baseline in CHOP INTEND score • Change from baseline in HINE score • Change from baseline in Motor Function Measure • Changes over time were analyzed with the Friedman and McNemar tests	
	Other end points	NA	NA	NA	
Notes	**Publications**	Elsheikh 2018[8]	Day 2018[7]	Aragon 2018[30]	

ASO = antisense oligonucleotide; CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP = compound muscle action potential; CNS = central nervous system; CSF = cerebrospinal fluid; HFMSE = Hammersmith Functional Motor Scale – Expanded; HINE = Hammersmith Infant Neurological Examination; LP = lumbar puncture; NA = not applicable; NR = not reported; RULM = Revised Upper Limb Module; PT = pulmonary function test; SMA = spinal muscular atrophy; SMN = survival motor neuron; TUG = Timed Up and Go test; WHO = World Health Organization.

Source: Clinical study reports of CS1, CS2, CS10, CS12, SHINE, CS3A, ENDEAR, CHERISH, NURTURE, EMBRACE, and relevant publications as outlined in the table.[7,8,11-15,28,29,31-40]

Included Studies

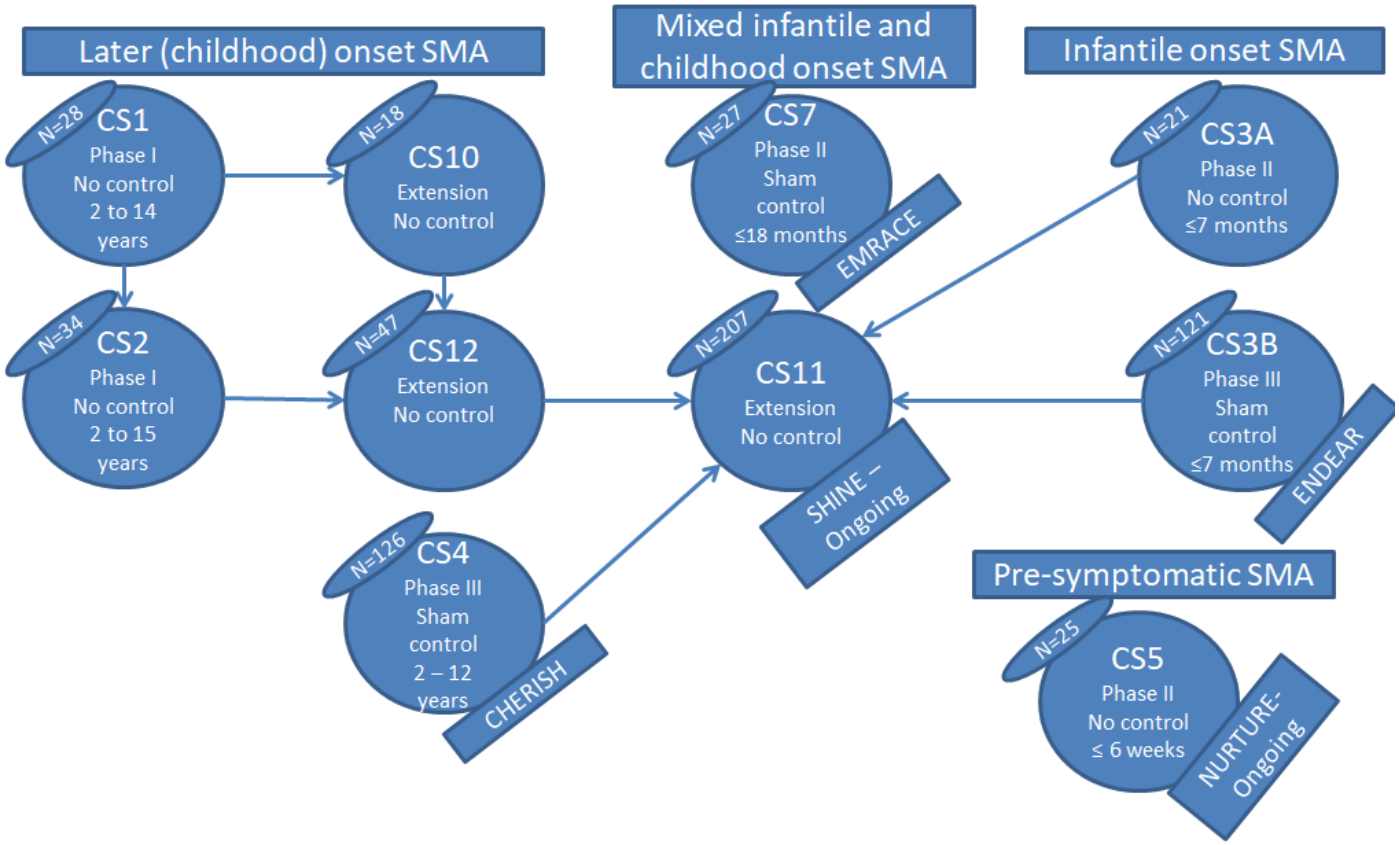
Description of Studies

A total of 15 studies were included in this report. As part of the resubmission, the manufacturer provided CADTH with 19 reports representing data from 10 Spinraza development studies, two observational studies, and one letter from a clinical centre. Of the 10 nusinersen development studies, three are randomized controlled trials (RCTs) (ENDEAR [N = 121], CHERISH [N = 126], and EMBRACE [N = 27]), four are phase I uncontrolled trials along with their extension studies (CS1 [N = 28], CS2 [N = 34], CS10 [N = 18], and CS12 [N = 47]), two are phase II uncontrolled trials (CS3A [N = 21], and NURTURE [N = 25]), and one is an extension study that included participants from all trials except EMBRACE and NURTURE (SHINE [N = 207]). Of the included studies, ENDEAR was reviewed in detail in the original nusinersen submission and will not be discussed in details in this report. A copy of the original Clinical Report discussing the ENDEAR trial is attached in Appendix 6. A flow chart of nusinersen development studies is presented in Figure 3.

The flow chart demonstrates that patients who enrolled in CS1 (phase I) subsequently were eligible to enroll in CS2 (phase I), patients who did not enroll in CS2 were eligible to participate in the CS10 extension study. Patients who enrolled in CS2 and CS10 were further eligible to participate in the CS12 extension trial. Subsequently, patients in the CS12 trial were enrolled in the ongoing SHINE extension trial (also called CS11). Similarly, patients who participated in the CS3A single arm phase II trial, in the CHERISH (also called CS4) phase III RCT, and in the ENDEAR (also called CS3B, see Appendix 6) phase III RCT were enrolled into the SHINE extension trial. The interim analysis of SHINE compares patients' outcomes to the baseline in their respective studies. As such, considering that CS1, CS2, CS10, CS12, and CS3A were single arm uncontrolled trials, only the outcomes as reported in the SHINE interim analysis are presented.

In addition to nusinersen's development studies, the manufacturer provided abstracts of poster presentations of two case series observational studies of adult patients receiving nusinersen treatment for SMA.[7,8] The manufacturer also provided a letter from a clinical centre outlining its experience in treating adult patients with nusinersen. This letter did not contain any reported data; thus, will be presented in the discussion of this report.[9] Further to the previously mentioned studies, the CDR systematic search identified three case series observational studies outlining the experience with expanded access programs in several countries for patients diagnosed with SMA. These three observational studies regarding the expanded access program focused on nusinersen treatment for patients with type I SMA but did not restrict the patients' age below seven months.

Figure 3: An Overview of Nusinersen Development Studies



SMA = spinal muscular atrophy.

Populations

Inclusion and Exclusion Criteria

Within nusinersen's primary development studies (CS1, CS2, CS3A, ENDEAR, CHERISH, NURTURE, and EMBRACE) a common inclusion criterion was a proven SMA diagnosis through genetic documentation of 5q SMA homozygous gene deletion or homozygous mutation. Beyond this criterion, these studies varied considerably in their inclusion criteria. NURTURE targeted patients who were pre-symptomatic, with two or three copies of the SMN2 gene, and who were six weeks of age or younger. CS3A targeted patients who were between 21 days and seven months of age, presented symptoms at or before six months of age, with no restriction over SMN2 gene copy number. ENDEAR (see Appendix 6) targeted similar patients as CS3A, with the added inclusion criterion of having two SMN2 gene copies. CHERISH targeted patients who were between the ages of two and 12 years old, could sit independently, and presented symptoms after six months of age. EMBRACE included patients who were not eligible for ENDEAR or CHERISH; specifically, patients with disease onset at six month or earlier but who had three SMN2 gene copies; patients with disease onset at six months or earlier but who were over seven months of age and had two SMN2 gene copies; and patients with disease onset after six months but who had two SMN gene copies. CS1 and CS2 included patients aged two to 15 years with no specification

regarding disease onset. The exclusion criteria of these studies were similar in that they excluded patients in need of ventilatory support, presence of a condition that would interfere with the nusinersen administration, and previous exposure to other investigational drugs. In addition, CHERISH excluded patients who had active gastric tube feeding.

Nusinersen's extension studies (CS10, CS12, and SHINE) shared a common inclusion criterion of satisfactory completion of the primary study. The three case series of expanded access programs had a common inclusion criterion of diagnosis of SMA type I. The German expanded access program provided more details regarding the method of determining SMA type I diagnosis, which included genetic documentation of 5q SMA and onset of symptoms before six months of age. The Italian expanded access program did not provide clear criteria for the SMA type I diagnosis, and no exclusion criteria were clearly defined. The third multinational expanded access program case series excluded patients who were previously exposed to nusinersen or other investigational products and who had a history of a medical condition that may interfere with nusinersen administration. The two case series of adult patients with SMA did not have clear inclusion and exclusion criteria beyond the description of being an adult patient with SMA — it is not clear where these patients were identified from.

Based on the population targeted by each of these studies' inclusion criteria, and considering SHINE included the results from CS1, CS2, CS10, CS12, and CS3A, the following studies can be placed into categories based on the evidence gaps identified by CDEC during its original recommendation:

- patients who are pre-symptomatic: NURTURE (also called CS5, referred to as NURTURE here after)
- patients diagnosed at later stages of disease: CHERISH (also called CS4, referred to as CHERISH here after), SHINE — later onset population (also called CS11, referred to as SHINE here after), EMBRACE (also called CS7, referred to as EMBRACE here after), Elsheikh 2018, and Day 2018
- patients with more than two copies of the SMN2 gene: CHERISH, SHINE, EMBRACE, Elsheikh 2018, and Day 2018
- patients older than seven months of age (with symptom onset before seven months of age): Pane 2018, SHINE — patients who participated in the ENDEAR control arm
- patients with SMA who require ventilation: Pechmann 2018
- patients with symptom onset at birth or within one week of birth: None.

The report will be organized to discuss each evidence gap separately. As the evidence addressing patients diagnosed at later stages of the disease and patients with more than two SMN 2 gene copies is identical, these two categories will be discussed together in this report, with separate subsections based on the age and disease onset of the enrolled patients (infantile onset, mixed infantile and early childhood onset, early childhood onset, later childhood onset, and adult patients).

Baseline Characteristics

Patients Who Are Pre-symptomatic

One study, NURTURE, enrolled 25 pre-symptomatic patients with SMA with a mean age at nusinersen first dose of [redacted]. Of these 25 patients, [redacted] had two copies of the SMN2 gene, while [redacted] had three copies of the SMN2 gene. Of the

enrolled, [redacted] were females. According to the clinical experts consulted on this review, assessment of baseline HINE Section 2 milestones reflect normal values seen in unaffected infants. Key baseline characteristics of the study population are displayed in Table 5.

Table 5: Summary of Baseline Characteristics in Studies Addressing Patients Who Are Pre-symptomatic (NURTURE)

	NURTURE (CS5) — ITT Set		
	2 SMN2 [redacted]	3 SMN2 [redacted]	Total N = 25
Demographics			
Age at first dose of study treatment, day, mean (SD)	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]
White, n (%)	[redacted]	[redacted]	[redacted]
Asian, n (%)	[redacted]	[redacted]	[redacted]
Weight (kg), median (range)	[redacted]	[redacted]	[redacted]
HINE Section 2 Characteristics			
Voluntary grasp: uses whole hand to grasp, n (%)	[redacted]	[redacted]	[redacted]
Ability to kick: unable to kick, n (%)	[redacted]	[redacted]	[redacted]
Head control: unable to maintain head upright, n (%)	[redacted]	[redacted]	[redacted]
Sitting: unable to sit, n (%)	[redacted]	[redacted]	[redacted]
Rolling: no rolling, n (%)	[redacted]	[redacted]	[redacted]
Crawling: does not lift head, n (%)	[redacted]	[redacted]	[redacted]
Standing: does not support weight, n (%)	[redacted]	[redacted]	[redacted]
Walking: no walking, n (%)	[redacted]	[redacted]	[redacted]

HINE = Hammersmith Infant Neurological Examination; ITT = intent to treat; SD = standard deviation; SMN = survival motor neuron.

Source: Clinical study report: SM201 (NURTURE). An open-label study to assess the efficacy, safety, tolerability, and pharmacokinetics of multiple doses of ISIS 396443 delivered intrathecally to subjects with genetically diagnosed and pre-symptomatic spinal muscular atrophy **[CONFIDENTIAL internal manufacturer's report]**. Mississauga (ON): Biogen Canada Inc.; 2018.

Patients Diagnosed at Later Stages of Disease / Patients With More Than Two Copies of the SMN2 Gene

Infantile Onset, Including Patients With SMN2 Gene Copy Greater Than Two: Addressing this patient population was the CS3A phase II single arm uncontrolled study, along with the extension into the SHINE study. CS3A enrolled 20 patients with a mean age at first dose of 5.0 months (standard deviation [SD] = 2.04). Of these 20 patients, 17 (85%) had two SMN2 gene copies, two (10%) had three SMN2 gene copies, and one patient was of unknown SMN2 gene copy number. Of the enrolled, eight patients (40%) were females. At baseline, these patients had a mean disease onset of three months (SD: 1.3), and were exhibiting symptoms of hypotonia (95%), limb weakness (95%), developmental motor delay (85%), respiratory symptoms including pneumonia (45%), and swallowing or feeding difficulties (45%). None of the patients required BiPAP support at baseline, while two

patients (10%) require gastric tube feeding within 30 days before first dose. Key baseline characteristics of the study population are displayed in Table 6.

Table 6: Summary of Baseline Characteristics of Studies Including Patients With More Than Two SMN2 Gene Copies — Infantile Onset (SHINE — Index Study CS3A)

	SHINE (Population of CS3A Index Study)
	Total N = 20
Demographics	
Age at first dose of study treatment, mean (SD)	5.0 (2.04) months
Female, n (%)	8 (40)
White, n (%)	16 (80)
Asian, n (%)	1 (5)
Weight (kg), median (min, max)	6.58 (5.1, 9.3)
SMN2 Copy Number	
Two copies, n (%)	17 (85)
Three copies, n (%)	2 (10)
Four copies, n (%)	0
Unknown, n (%)	1 (5)
Disease History	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Disease Symptoms	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Ventilatory Support	
On BiPAP at baseline, n (%)	0
Non-invasive ventilation > 16 hour per day, n (%)	0
Tracheostomy, n (%)	0
Feeding Support	
Gastric tube feeding within 30 days prior to first dose, n (%)	2 (10)
Nasogastric tube feeding within 30 days prior to first dose, n (%)	1 (5)
Feeding tube or gastrostomy, n (%)	NR
Patients With Motor Milestones Achieved	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

BiPAP = bi-level positive air pressure; max = maximum; min = minimum NR = not reported; SD = standard deviation; SMN = survival motor neuron.

Source: Clinical study report: ISIS 396443-CS11 (SHINE). An open-label extension study for patients with spinal muscular atrophy who previously participated in investigational studies of ISIS 396443 **[CONFIDENTIAL internal manufacturer's report]**. Mississauga (ON): Biogen Canada Inc.; 2018.

Mixed Infantile and Early Childhood Onset, Including Patients With SMN2 Gene Copy Greater Than Two: One study, EMBRACE, enrolled patients with disease onset at six month or earlier who had three SMN2 gene copies, patients with disease onset at six months or earlier who were over seven months of age and had two SMN2 gene copies, and patients with disease onset after six months but who had two SMN gene copies. The study randomized, on a 2:1 ratio, 21 patients into the nusinersen-treated group [redacted] and sham control group [redacted]

Table 7: Summary of Baseline Characteristics of Studies Including Patients With More Than Two SMN2 Gene Copies — Mixed Infantile And Childhood Onset (EMBRACE)

	EMBRACE — ITT	
	Nusinersen [redacted]	Sham Control [redacted]
Demographics		
Age at first dose of study treatment, mean (SD)	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]
White, n (%)	[redacted]	[redacted]
Asian, n (%)	[redacted]	[redacted]
Weight (kg), median (min, max)	[redacted]	[redacted]
SMN2 Copy Number		
Two copies, n (%)	[redacted]	[redacted]
Three copies, n (%)	[redacted]	[redacted]
Disease History		
Age at symptom onset, mean (SD)	[redacted]	[redacted]
Age at diagnosis, mean (SD)	[redacted]	[redacted]
Disease Symptoms		
Hypotonia, n (%)	[redacted]	[redacted]
Developmental motor delay, n (%)	[redacted]	[redacted]
Paradoxical breathing, n (%)	[redacted]	[redacted]
Pneumonia or respiratory symptoms, n (%)	[redacted]	[redacted]
Limb weakness, n (%)	[redacted]	[redacted]
Swallowing or feeding difficulties, n (%)	[redacted]	[redacted]
HINE Section 2 Characteristics		
Voluntary grasp: uses whole hand to grasp, n (%)	[redacted]	[redacted]
Ability to kick: unable to kick, n (%)	[redacted]	[redacted]
Head control: unable to maintain head upright, n (%)	[redacted]	[redacted]

	EMBRACE — ITT	
	Nusinersen [redacted]	Sham Control [redacted]
Sitting: unable to sit, n (%)	[redacted]	[redacted]
Rolling: no rolling, n (%)	[redacted]	[redacted]
Crawling: does not lift head, n (%)	[redacted]	[redacted]
Standing: does not support weight, n (%)	[redacted]	[redacted]
Walking: no walking, n (%)	[redacted]	[redacted]
Disease Support		
Use wheelchair, n (%)	[redacted]	[redacted]
Attend physiotherapy, n (%)	[redacted]	[redacted]

HINE = Hammersmith Infant Neurological Examination; ITT = intent to treat; max = maximum; min = minimum; SD = standard deviation; SMN = survival motor neuron.

Source: Clinical study report: 232SM202 (EMBRACE). A phase 2, randomized, double-blind, sham-procedure controlled study to assess the safety and tolerability and explore the efficacy of ISIS 396443 (BIIB058) administered intrathecally in subjects with spinal muscular atrophy who are not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4 **[CONFIDENTIAL internal manufacturer's report]**. Mississauga (ON): Biogen Canada Inc.; 2018.

Early Childhood Onset, Including Patients With SMN2 Gene Copy Greater Than Two: One study, CHERISH, addressed patients with disease onset beyond six months who were two to 12 years of age. Patients were randomized on a 2:1 ratio to the nusinersen group (N = 84), and to the sham control group (N = 42). The distribution of baseline characters was similar between the two groups, with the exception of an imbalance in the percentage of patients who were able to stand without support at 13% in the nusinersen group compared with 29% in the sham control group. Overall, the mean total age of patients was 3.6 years (SD: 1.6), half the participants were female, three-quarters were White, with Asians forming the next largest race group (18%). Overall, the participants had a mean age of 11.2 months (SD: 3.4) at symptom onset and a mean of 38.2 months (SD: 19.8) from disease onset until study enrolment. The majority of patients had three copies of the SMN2 gene (n = 111 [88%]). All patients were able to sit without support and 37% were able to walk with support. Key baseline characteristics of the study population are displayed in Table 8.

Table 8: Summary of Baseline Characteristics of Studies of Patients With Early Childhood Onset, Including Patients With SMN2 Gene Copy Greater Than Two (CHERISH)

	CHERISH — ITT	
	Nusinersen N = 84	Sham Control N = 42
Demographics		
Age at screening, mean (SD)	3.8 (1.6) years	3.4 (1.6) years
Age at first dose , mean (SD)	NR	NR
Female, n (%)	46 (55)	21 (50)
White, n (%)	64 (76)	30 (71)
Asian, n (%)	16 (19)	7 (17)
[redacted]	[redacted]	[redacted]
SMN2 Copy Number		
Two copies, n (%)	6 (7)	4 (10)
Three copies, n (%)	74 (88)	37 (88)
Four copies, n (%)	2 (2)	1 (2)
Unknown, n (%)	2 (2)	0

	CHERISH — ITT	
	Nusinersen N = 84	Sham Control N = 42
Disease History		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Motor Milestones Achieved		
Sat without support, n (%)	84 (100)	42 (100)
Stood without support, n (%)	11 (13)	12 (29)
Walked with support, n (%)	20 (24)	14 (33)
Walked ≥ 15 feet independently, n (%)	0	0
Disease Support		
Used a wheelchair, n (%)	[redacted]	[redacted]
Attended physical therapy, n (%)	[redacted]	[redacted]

ITT = intent to treat; NR = not reported; SD = standard deviation; SMN = survival motor neuron.

Source: Clinical study report: ISIS 396443-CS4 [CHERISH]. A phase 3, randomized, double-blind, sham-procedure controlled study to assess the clinical efficacy and safety of ISIS 396443 administered intrathecally in patients with later-onset spinal muscular atrophy **[CONFIDENTIAL internal manufacturer's report]**. Mississauga (ON): Biogen Canada Inc.; 2018.

Later Childhood Onset, Including Patients With SMN2 Gene Copy Greater Than Two: Nusinersen's phase I development studies (CS1 and CS2), along with their extensions (CS10 and CS12), and their subsequent inclusion in the SHINE study may inform on this population. The studies were single arm uncontrolled trials that enrolled a total of 56 patients with a mean age at first dose of [redacted] The need for ventilatory and feeding support were part of the exclusion criteria for the CS1 and CS2 index studies. Key baseline characteristics of the study population are displayed in Table 9.

Table 9: Summary of Baseline Characteristics of Studies of Patients With Later Childhood Onset, Including Patients With SMN2 Gene Copy Greater Than Two (CS1 and CS2 Index Studies of SHINE)

	SHINE (Pooled Population of CS1 and CS2 Index Studies)
	Total N = 56
Demographics	
Age at first dose of study treatment, mean (SD)	[redacted]
Female, n (%)	[redacted]
White, n (%)	[redacted]
Asian, n (%)	[redacted]
SMN2 Copy Number	
Two copies, n (%)	[redacted]
Three copies, n (%)	[redacted]
Four copies, n (%)	[redacted]
Unknown, n (%)	[redacted]
Disease History	
Time from diagnosis to first dose, mean (SD)	[redacted]
Time from disease onset to first dose, mean (SD)	[redacted]
Age at symptom onset, mean (SD)	[redacted]
Age at diagnosis, mean (SD)	[redacted]
Motor Milestones Achieved	
Sat without support, n (%)	[redacted]
Stood without support, n (%)	[redacted]
Walked with support, n (%)	[redacted]
Walked ≥ 15 feet independently, n (%)	[redacted]
Ventilatory Support	
On BiPAP at baseline, n (%)	[redacted]
Feeding Support	
Gastric tube feeding within 30 days prior to first dose, n (%)	[redacted]
NasoGastric tube feeding within 30 days prior to first dose, n (%)	[redacted]

BiPAP = bi-level positive air pressure; NR = not reported; SD = standard deviation; SMN = survival motor neuron.

Source: Clinical study report: ISIS 396443-CS11 (SHINE). An open-label extension study for patients with spinal muscular atrophy who previously participated in investigational studies of ISIS 396443 **[CONFIDENTIAL internal manufacturer's report]**. Mississauga (ON): Biogen Canada Inc.; 2018.

Adult Patients: Two case series observational studies were submitted by the manufacturer in the form of poster abstracts. No full text was available. Elshaeikh 2018 reported on six patients that received at least one injection; the baseline characteristics of these patients were not described. Day 2018 reported on 20 patients that received nusinersen; the abstract reports that these patients had an age range of 18 to 65 years, 75% were non-ambulatory, 57% were males, 35% required ventilator support, and 40% had spinal fusion.

Patients Diagnosed Before Seven Months of Age But Receive Treatment After Seven Months of Age

The ENDEAR extension into SHINE can offer some insight into the population of patients diagnosed before seven months of age but receive treatment after seven months of age, as the control group in ENDEAR started to receive nusinersen treatment when they transitioned

into the SHINE trial. As such, we are interested in the outcomes of these patients compared with baseline at the beginning of the extension study, SHINE (as opposed to the baseline characteristics in the original ENDEAR index study). These baseline characteristics are summarized in Table 10. [redacted]

Patients enrolled in the Aragon 2018 (N = 33) expanded access program had a median age at first dose of 21.3 months (range 8.3 to 113.1 months), were 45.5% females, and 51.5% had three SMN2 gene copies. These patients spent a median of 26.0 months from disease onset to first dose (range: 4.3 to 109.1) and were of a median age of four months when first signs of the disease manifested (range: 1.5 to 5 months). Of these patients, 51.5% required non-invasive ventilation more than 16 hours per day and 27.3% required a feeding tube or had a gastrostomy.

Patients enrolled in the Pane 2018 (N = 104) expanded access program had an age range of 0 to 19 years, 62.5% of patients had two SMN2 gene copies, and 23.1% had three SMN2 gene copies. The publication does not provide further details regarding the baseline characteristics of included patients.

Table 10: Summary of Baseline Characteristics of Patients Diagnosed Before Seven Months of Age But Who Receive Treatment After Seven Months of Age (Pane 2018, Aragon 2018, and SHINE — ENDEAR Index)

	Pane 2018	Aragon 2018	SHINE (ENDEAR Index Study [Represent Characteristics at the Start of SHINE Study])	
	N = 104	**N = 33**	**Previous Control** [redacted]	**Previous Nusinersen** [redacted]
Demographics				
Age at first dose	Range: 0 to 19 years	Median (range): 21.3 (8.3 to 113.1) months	[redacted]	[redacted]
Female, n (%)	NR	15 (45.5)	[redacted]	[redacted]
White, n (%)	NR	NR	[redacted]	[redacted]
Asian, n (%)	NR	NR	[redacted]	[redacted]
SMN2 Copy Number				
One copy, n (%)	3 (2.9)	0	[redacted]	[redacted]
Two copies, n (%)	65 (62.5)	15 (45.5)	[redacted]	[redacted]
Three copies, n (%)	24 (23.1)	17 (51.5)	[redacted]	[redacted]
Four copies, n (%)	0	0	[redacted]	[redacted]
Unknown, n (%)	12 (11.5)	0	[redacted]	[redacted]
Disease History				
Time from diagnosis to first dose	NR	NR	[redacted]	[redacted]
Time from disease onset to, first dose, or sham injection	NR	Median (range): 26.0 (4.3 to 109.1) months	[redacted]	[redacted]
Age at symptom onset	NR	Median (range): 4	[redacted]	[redacted]

	Pane 2018	Aragon 2018	SHINE (ENDEAR Index Study [Represent Characteristics at the Start of SHINE Study])	
	N = 104	N = 33	Previous Control [redacted]	Previous Nusinersen [redacted]
		(1.5 to 6) months	[redacted]	
Age at diagnosis	NR	NR	[redacted]	[redacted]
Disease Support				
Non-invasive ventilation > 16 hour per day, n (%)	NR	17 (51.5)	[redacted]	[redacted]
Tracheostomy, n (%)	NR	0	[redacted]	[redacted]
Feeding tube or gastrostomy, n (%)	NR	9 (27.3)	[redacted]	[redacted]

NR = not reported; SMN = survival motor neuron.

Source: Clinical study report: ISIS 396443-CS11 (SHINE). An open-label extension study for patients with spinal muscular atrophy who previously participated in investigational studies of ISIS 396443 **[CONFIDENTIAL internal manufacturer's report]**. Mississauga (ON): Biogen Canada Inc.; 2018.

Pane M, Palermo C, Messina S, Sansone VA, Bruno C, Catteruccia M, et al. Nusinersen in type 1 SMA infants, children and young adults: Preliminary results on motor function. Neuromuscul Disord. 2018;01:01.

Aragon-Gawinska K, Seferian AM, Daron A, Gargaun E, Vuillerot C, Cances C, et al. Nusinersen in spinal muscular atrophy type 1 patients older than 7 months: A cohort study. Neurology. 2018.

Patients With SMA Who Require Ventilation

Patients enrolled in the Pechmann 2018 (N = 61) expanded access program would fit under this subsection, where more than half of the included patients were either on non-invasive ventilation or had a tracheostomy. Patients had a mean age at first dose of 21.08 months (range 1 to 93 months), were 49.2% females, and 32.8% had three SMN2 gene copies. These patients spent a median of 2.8 months from disease onset to first dose (range: 0 to 6) and were of a median age of 2.8 months when first signs of the disease manifested (range: 0 to 6 months). Of these patients, 9.8% required non-invasive ventilation, 19.7% had a tracheostomy, and 55.7% required a feeding tube or had a gastrostomy.

Table 11: Summary of Baseline Characteristics of Patients With Spinal Muscular Atrophy Who Require Ventilation

	Pechmann, 2018
	Total N = 61
Demographics	
Age at first dose of study treatment, mean (SD)	21.1 (20.2)
Female, n (%)	30 (49.2)
White, n (%)	NR
Asian, n (%)	NR
SMN2 Copy Number	
Two copies, n (%)	38 (62.3)
Three copies, n (%)	20 (32.8)
Four copies, n (%)	0
Unknown, n (%)	3 (4.9)
Disease History	
Age at symptom onset, mean (SD)	Median (range): 2.78 (0 to 6) months

	Pechmann, 2018
	Total N = 61
Ventilatory Support	
Non-invasive ventilation > 16 hour per day, n (%)	6 (9.8)
Tracheostomy, n (%)	12 (19.7)
Feeding Support	
Feeding tube or gastrostomy, n (%)	34 (55.7)

NR = not reported; SD = standard deviation; SMN = survival motor neuron.

Source: Pechmann A, Langer T, Schorling D, Stein S, Vogt S, Schara U, et al. Evaluation of Children with SMA Type 1 Under Treatment with Nusinersen within the Expanded Access Program in Germany. J Neuromuscul Dis. 2018;5(2):135-43.

Interventions

While all of the 15 included studies reported the use of nusinersen as the active intervention, the schedule of the dose administration varied. Furthermore, three of the included studies (Pane 2018, Elsheikh 2018, and Day 2018) did not provide clear descriptions of the dose and administration schedule. Most of the phase II and III trials aimed to administer 12 mg of nusinersen in a volume of 5 mL, or a scaled volume based on age, while the phase I trials varied in dose. The schedule of administration did differ between nusinersen's development studies. Nusinersen was administered using a single intrathecal injection through lumbar puncture using a spinal anesthesia needle and a 5 mL syringe, delivered as a slow bolus at the L3/L4 spinal space (plus or minus one lumbar spine level if needed). Where a study was sham controlled, the sham procedure matched the dosage and the maintenance schedule of nusinersen treatment, which consisted of a needle prick, breaking the skin, at the site of an L3/L4 lumbar puncture. Patients were kept in the procedure room for the same duration of time as the nusinersen-treated patients, and the needle prick site was covered by the same type of bandage. The administration of both procedures was conducted by unblinded personnel in an enclosed procedure room where study investigators and parents were not allowed.

Patients in the EMBRACE trial were randomized in a 2:1 ratio to either nusinersen or sham control treatment using an interactive response technology. Randomization was stratified based on age at onset of clinical signs and symptoms consistent with SMA: younger than six months versus older than six months. Patients in the CHERISH trial were randomized in a 2:1 ratio to either nusinersen or sham control treatment; randomization was stratified based on the patient's age at screening (younger than six years old versus six years old and older).

Concomitant medication in nusinersen's development studies were allowed as necessary to address any adverse events (AEs) or to provide supportive care, as deemed necessary by the treating physician. Only experimental treatments for SMA were prohibited (e.g., salbutamol, valproate, creatine, and hydroxyurea). No descriptions of concomitant medications were provided in the observational studies.

A detailed dosage and administration schedule for each of the included studies, along with a description of the Health Canada recommended dose and administration schedule, is presented in Table 12.

Table 12: Dosage and Administration Schedule of Each of the Included Studies

Study – Arm/Index	Dose	Loading Dose				Maintenance Dose				
Health Canada–approved dosage	12 mg (5 mL)	Day 0	Day 14	Day 28	Day 63	Day 183	Day 303	Day 423	Day 543	Once every 4 months
CS1 (85 Days Planned Study Duration)										
Cohort 1	1 mg (5 mL)	Day 1	NA	NA	NA	NA	NA	NA	NA	NA
Cohort 2	3 mg (5 mL)	Day 1	NA	NA	NA	NA	NA	NA	NA	NA
Cohort 3	6 mg (5 mL)	Day 1	NA	NA	NA	NA	NA	NA	NA	NA
Cohort 4	9 mg (5 mL)	Day 1	NA	NA	NA	NA	NA	NA	NA	NA
CS10 (169 Days Planned Study Duration)										
Cohort 1	6 mg (5 mL)	Day 1	NA	NA	NA	NA	NA	NA	NA	NA
Cohort 2	9 mg (5 mL)	Day 1	NA	NA	NA	NA	NA	NA	NA	NA
CS2 (253 Days Planned Study Duration)										
Cohort 1	3 mg (5 mL)	Day 1	NA	Day 29	Day 85	NA	NA	NA	NA	NA
Cohort 2	6 mg (5 mL)	Day 1	NA	Day 29	Day 85	NA	NA	NA	NA	NA
Cohort 3	9 mg (5 mL)	Day 1	NA	NA	Day 85	NA	NA	NA	NA	NA
Cohort 4	12 mg (5 mL)	Day 1	NA	NA	Day 85	NA	NA	NA	NA	NA
CS12 (715 days planned study duration)	12 mg (5 mL)	Day 1	NA	NA	NA	Day 169	Day 351	NA	Day 533	NA
CS3A (1,352 Days Planned Study Duration)										
Cohort 1	6 mg loading and 12 mg maintenance (4 mL to 5 mL)	Day 1	Day 15	NA	Day 85	Day 253	Day 379	Day 505	Day 631	Once every 4 months
Cohort 2	12 mg (4 mL to 5 mL)	Day 1	Day 15	NA	Day 85	Day 253	Day 379	Day 505	Day 631	Once every 4 months
ENDEAR (394 Days Planned Study Duration)										
Nusinersen group	12 mg (4 mL to 5 mL)	Day 1	Day 15	Day 29	Day 64	Day 183	Day 302	NA	NA	NA
Sham control group	Sham	Day 1	Day 15	Day 29	Day 64	Day 183	Day 302	NA	NA	NA
CHERISH (456 Days Planned Study Duration)										
Nusinersen group	12 mg (5 mL)	Day 1	NA	Day 29	Day 85	Day 274	NA	NA	NA	NA
Sham control group	Sham	Day 1	NA	Day 29	Day 85	Day 274	NA	NA	NA	NA
EMBRACE (422 Days Planned Study Duration)										
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Study – Arm/Index	Dose	Loading Dose				Maintenance Dose				
NURTURE (1,820 days planned study period)	12 mg (5 mL)	Day 1	Day 15	Day 29	Day 64	Day 183	Day 302	Day 421	Day 540	Once every 4 months
SHINE (1,800 Days Planned Study Duration)										
[redacted]										
[redacted]										
[redacted]										
[redacted]										
[redacted]										
[redacted]										
Aragon 2018 (6 months observation duration)	12 mg (4 mL to 5mL)	Day 1	Day 15	Day 29	Day 64	Day 183	NA	NA	NA	NA
Pechmann 2018 (6 months observation duration)	12 mg (4 mL to 5mL)	Day 1	Day 15	Day 29	Day 64	Day 183	NA	NA	NA	NA
Pane 2018 (6 months observation duration)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Elsheikh 2018 (6 months observation duration)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Day 2018 (6 months observation duration)	[redacted]									

NA = not applicable; NR = not reported.

Source: Clinical study reports of CS1, CS2, CS10, CS12, SHINE, CS3A, ENDEAR, CHERISH, NURTURE, EMBRACE, and relevant publications.[7,8,11-15,28,29,31-40]

Outcomes

Details regarding the validity and reliability of outcomes measured are presented in Appendix 5.

a) Proportion of motor milestone responders (Section 2 of the HINE)

The proportion of HINE Section 2 responders was the first of two primary outcomes. Section 2 of the HINE scale is concerned with motor milestones and assesses eight motor milestones: head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing, and walking. Each milestone has three to five possible descriptive ratings, ranging from "not performing the task at all" to "fully demonstrating the milestone."

Although the original HINE developers did not define a quantitative scoring system for Section 2, scores for each milestone were obtained by assigning a value of zero to the absence of the activity and adding one point for each incremental rating. Specifically, a one-point increase from baseline can be achieved if an improvement took place in any of the categories of head control, rolling, sitting, crawling, standing, or walking, a two-point improvement is achieved through exhibiting the ability to kick or touch toes. Voluntary grasp was excluded from the analysis. The manufacturer indicated that it was excluded because voluntary grasp lacks movement against gravity, and many infantile patients with SMA would achieve all milestones in this category. Worsening was considered as at least a two-point decrease or a decrease to the lowest possible level, no kicking in the ability to kick category, and at least a one-point decrease for the other categories. Although a total score was not described in the original development of the tool, it is assumed by the reviewer that a total HINE score for Section 2 was calculated by scoring each milestone on an ordinal scale (with zero representing no ability) and summing the scores. The manufacturer provided the following definition for motor milestone responders:

> "A motor milestones responder was based on the motor milestones categories in Section 2 of the HINE (with the exclusion of voluntary grasp) using the assessment at the later of the scheduled assessment day visit as follows:
>
> (i) The patient demonstrated at least a 2-point increase in the motor milestones category of ability to kick or achievement of maximal score on that category (touching toes), or a 1-point increase in the motor milestones of head control, rolling, sitting, crawling, standing, or walking, AND
>
> (ii) among the 7 motor milestone categories (with the exclusion of voluntary grasp), the patient demonstrated improvement (as defined in [i]) in more categories than worsening. Note: for the category of ability to kick, similar to the definition of improvement in (i) above, worsening is defined as at least a 2-point decrease or decrease to the lowest possible score of no kicking. For the other 6 categories, worsening is defined as at least a 1-point decrease."

A minimal clinically important difference score was not specifically identified from the literature for this measure; although, the manufacturer reported that based on the natural history of SMA type I, a change in score of more than one point for any given milestone is highly unlikely in untreated patients with SMA type I.

Patients were assessed by a neurologist at the study centre; the assessment was performed at screening, and before the lumbar puncture procedure.

b) Time to death or permanent ventilation

Time to death or permanent ventilation was a secondary/exploratory outcome reported in nusinersen's development studies. Permanent ventilation was defined in the study as the need for 16 hours or more of continuous ventilatory support per day for 21 or more consecutive days, in the absence of an acute reversible event, or if the patient required tracheostomy. A patient's ventilation use was recorded daily by the caregiver and collected during study visits and weekly telephone contacts. The time to death or permanent ventilation was assessed by an adjudication committee blinded to the patient's assignment. A second definition of respiratory intervention was used in the NURTURE study, where an event was defined as either invasive or non-invasive ventilation for 6 hours or more per day continuously for seven or more consecutive days OR tracheostomy.

c) Proportion of Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease (CHOP INTEND) responders

A secondary outcome, the CHOP INTEND, was developed in infants with SMA type I and designed for use to measure motor function in infants and children with neuromuscular disorders. It is made up of 16 items, each rated 0 to 4 (no response, minimal, partial, nearly full, and complete level of response, respectively) giving a maximum total score of 64 when summed. Higher summed scores indicate better performance.

The manufacturer defined a CHOP INTEND responder as a patient with a score change from baseline of four or more points when assessed on scheduled assessment study days. A minimum clinical important difference in CHOP INTEND was not found. However, CHOP INTEND scores were studied over time in 17 patients with type I SMA over a period of up to 36 months.[41] Scores were found to decrease over time at a mean rate of 1.27 points per year.[41]

d) Change from baseline HFMSE score

The Hammersmith Functional Motor Scale was designed to measure motor function in patients with SMA type II and type III with limited mobility.[42] The Hammersmith Functional Motor Scale – Extended (HFMSE) builds upon the Hammersmith Functional Motor Scale by adding 13 items from the Gross Motor Function Measure, an instrument designed for patients with cerebral palsy and previously validated in children with SMA.[42] The HFMSE is intended for use in patients with type II and type III SMA and captures higher functioning skills.[42] It consists of 33 activities that can be scored one of three ways: 0 for unable to perform, 1 for performs with modification/adaptation, and 2 for performs without modification.[42] The item scores are summed to give a total score with a maximum of 66.[42] The higher the total score, the greater the patient's motor functioning.[42] An increase of more than two points in total score is unlikely in untreated patients with SMA types II and III.[43] Patient and caregivers consider a one-point increase meaningful.[44]

e) Survival rate

The overall survival of patients.

f) Per cent of patients not requiring permanent ventilation.

The percentage of patients who did not need permanent ventilation.

Growth parameters

Growth parameters was a tertiary/exploratory outcome in nusinersen's development studies, where trained staff would assess weight, body length (or height), arm circumference (where applicable based on age), chest circumference (where applicable based on age), and head circumference (where applicable based on age) at screening and before the lumbar puncture administration. A growth failure was generally captured through using two definitions — the first as a post-baseline weight below the fifth percentile, and the second as a weight drop crossing two or more major percentiles in six months.

g) Proportion of patients developing clinically manifested SMA

The proportion of patients developing clinically manifested SMA was an outcome in the NURTURE study. The manufacturer provided the following definition of patients considered to have developed a clinically manifested SMA: patient's weight dropped below the fifth percentile according to the World Health Organization (WHO) criteria at 13 or 24 months; patient's weight dropped two or more major weight percentiles; patient failed to demonstrate the following as assessed by WHO motor milestones, as assessed by the investigator at 13 and 24 months of age; ability to sit without support, standing with assistance, hands-and-knees crawling at 24 months of age; walking with assistance, standing alone, and walking alone; or, lastly, patients who discontinue treatment or die before the visit scheduled for 13 or 24 months of age.

h) Hospitalization

The number of hospitalizations that occurred during the study period was measured as a tertiary outcome.

i) Drug related AEs and serious adverse events (SAEs)

An AE was recorded as "treatment emergent" if it either existed before the first procedure and worsened subsequently, or if it was not present before the first procedure and subsequently appeared.

Statistical Analysis

NURTURE

NURTURE is an ongoing single arm, open-label, uncontrolled, phase II clinical trial. No clear description of the rationale of sample size was provided. No adjustment for multiple testing was described. The primary outcome measure of time to respiratory intervention or death was performed on patients with two copies of the SMN2 gene. [redacted] Other outcomes were presented with summary measures as secondary outcomes. [redacted]

EMBRACE

EMBRACE was designed as a two-part study; part one was a randomized, sham controlled study. [redacted] Statistical analysis was presented as summary measures with change from baseline associated with SDs or 95% confidence interval (CI). [redacted]

CHERISH

CHERISH was a double-blind, randomized, sham controlled study. [redacted] However, as the study was terminated early, the primary outcome was not tested again. Subsequently, a stage-wise hierarchical testing approach for secondary outcome at an alpha of 0.05 was conducted on the following:

- proportion of patients achieving a three-point or greater increase in HFMSE at 15 months
- proportion of patients achieving any new motor milestone at 15 months
- number of new motor milestones achieved at 15 months
- change from baseline in Revised Upper Limb Module (RULM) Test at 15 months
- proportion of patients achieving standing alone at 15 months
- proportion of patients achieving walking with assistance at 15 months.

The main efficacy end point of comparing the HFMSE score at 15 months from baseline between the two groups was analyzed using [redacted] Secondary and tertiary outcomes falling outside the hierarchy of testing were planned to be presented with summary measures and no formal statistical testing was conducted.

SHINE

SHINE is an ongoing, single arm, uncontrolled, extension study of CS12 (which is an extension of CS2 and CS10; CS10 in turn is an extension of CS1), CS3A, ENDEAR, and CHERISH. [redacted] Outcomes were described as summary measures at assessment day and of change from baseline. SHINE had two analyses planned, an integrated analysis that maintained the baseline values of the index studies (i.e., change from baseline was assessed on the baseline values of the original study — not the baseline values at the beginning of the extension study), and a separate analysis using baseline values starting at the enrolment in SHINE. However, as SHINE is ongoing and patient exposure in SHINE is relatively short, the manufacturer

emphasized the integrated analysis in its interim report. [redacted]

CS1, CS2, CS10, CS12, and CS3A

Please see the description for SHINE.

ENDEAR

The previous CDR report discussing ENDEAR in detail is provided in Appendix 6.

Aragon 2018

Aragon 2018 was a case series observational study. Changes in outcomes over time were analyzed using the Friedman test. In addition, analyses comparing patients with two SMN2 copies and three SMN2 copies were conducted using the Mann-Whitney test. No missing data imputation method was employed, nor any description of adjustment for potential multiple testing.

Pechmann 2018

Pechmann 2018 was a case series observational study. Summary statistics were described at baseline and assessment day with a summary measure of mean change from baseline. Regression analysis was conducted to test potential factors associated with the change in CHOP INTEND score. Missing data were handled using the last observation carried forward method.

Pane 2018

Pane 2018 was a case series observational study. No statistical analysis approach or missing data handling methods were described.

Elsheikh 2018

Elsheikh 2018 was a case series observational study. No statistical analysis approach or missing data handling methods were described.

Day 2018

Day 2018 was a case series observational study. No statistical analysis approach or missing data handling methods were described.

Analysis Populations

NURTURE

The intent-to-treat (ITT) set: Defined as all subjects who received at least one dose of nusinersen.

The efficacy set: Defined as the subset of patients in the ITT set who had either attended the targeted visit of the analysis or who would have had the opportunity to attend the visit had they not died or discontinued.

EMBRACE

Safety set: All patients who were randomized and who received at least one dose of nusinersen or sham procedure. Patients who were randomized to sham but incorrectly received nusinersen would be counted in the nusinersen group.

ITT set: All patients who were randomized and who received at least one dose of nusinersen or sham procedure. Analysis was based on randomized group.

The efficacy set: Defined as the subset of patients in the ITT set who had either attended the targeted visit of the analysis or who would have had the opportunity to attend the visit had they not died or discontinued.

CHERISH

ITT set: All patients who were randomized and who received at least one dose of nusinersen or sham procedure. Analysis was based on randomized group.

Interim efficacy set: The subset of patients in the ITT set who had the opportunity to be assessed at the day 456 visit.

Efficacy set: The subset of patients in the ITT set who had the opportunity to be assessed at the day 456 visit (i.e., month 15).

Per-protocol set: The subset of patients in the ITT set who completed at least the initial three doses of the study drug or sham procedures, had baseline and day 169 efficacy assessments, and had no significant protocol deviations that would be expected to affect efficacy assessments.

Safety set: All patients who were randomized and received at least one dose of the study drug or sham procedure.

SHINE

Safety set: All patients who were enrolled and who received at least one dose of nusinersen or underwent sham procedure during an index study or SHINE.

Efficacy set: Subset of patients in the safety set who had the opportunity to be assessed at a particular visit.

CS1, CS2, CS10, CS12, and CS3A

Please see the description for SHINE.

ENDEAR

The previous CDR report discussing ENDEAR in detail is provided in Appendix 6.

Aragon 2018

None reported.

Pechmann 2018

None reported.

Pane 2018

None reported.

Elsheikh 2018

None reported.

Day 2018

None reported.

Patient Disposition

NURTURE

[redacted]

EMBRACE

All of the 21 screened patients were enrolled in the study; 14 were randomized into the nusinersen group and seven into the sham control group. Due to early termination, only six patients (43%) in the nusinersen group completed Part 1 (assessment visit day 422) while none of the control group reached the 422 assessment visit day. One patient discontinued the study in the control group due to a fatal AE.

CHERISH

Of 179 screened patients, 126 patients were randomized into the nusinersen (N = 84) and sham control (N = 42) groups. Table 13 provides an overview of the CHERISH patient disposition.

Table 13: Patient Disposition of CHERISH Study

	CHERISH	
	Nusinersen	Sham Control
Screened, N	179	
Randomized, N (%)	84	42
Discontinued, N (%)	0	0
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

ITT = intent to treat; NR = not reported; PP = per protocol.

Source: Clinical study report: ISIS 396443-CS4 [CHERISH]. A phase 3, randomized, double-blind, sham-procedure controlled study to assess the clinical efficacy and safety of ISIS 396443 administered intrathecally in patients with later-onset spinal muscular atrophy **[CONFIDENTIAL internal manufacturer's report]**. Mississauga (ON): Biogen Canada Inc.; 2018.

SHINE

Of 142 patients who received nusinersen or sham procedure in studies CS3A and ENDEAR (infantile onset SMA), [redacted]

[redacted]

[redacted]

Source: Clinical study report: ISIS 396443-CS11 (SHINE). An open-label extension study for patients with spinal muscular atrophy who previously participated in investigational studies of ISIS 396443 **[CONFIDENTIAL internal manufacturer's report]**. Mississauga (ON): Biogen Canada Inc.; 2018.

[redacted]

[redacted]

Source: Clinical study report: ISIS 396443-CS11 (SHINE). An open-label extension study for patients with spinal muscular atrophy who previously participated in investigational studies of ISIS 396443 **[CONFIDENTIAL internal manufacturer's report]**. Mississauga (ON): Biogen Canada Inc.; 2018.

CS1, CS2, CS10, CS12, and CS3A

Please see the description for SHINE.

ENDEAR

The previous CDR report discussing ENDEAR in detail is provided in Appendix 6.

Aragon 2018

No description of the number of patients screened, dosed, and assessed was provided in the publication. Data were collected on a total of 33 patients.

Pechmann 2018

No description of the number of patients screened, dosed, and assessed was provided in the publication. Results on a total of 61 patients were reported.

Pane 2018

Of 122 eligible patients, 104 were assessed at six months after the first administration of nusinersen within the expanded access program. Of these 18 patients that were nit assessed: 10 did not receive nusinersen due to severe scoliosis, five patients withdrew their consent within three months of their first nusinersen administration, two did not have the assessment conducted, and one infant patient died. No other additional patient disposition information was available.

Elsheikh 2018

A total of 29 patients were evaluated for nusinersen treatment; of these patients, 12 received insurance approval, six were not interested, five did not complete the insurance application process, four lacked insurance, and two were denied coverage. Of the 12 patients who received insurance approval, six received at least one injection and three completed the four loading doses. No other additional patient disposition information was available.

Day 2018

[redacted]

Exposure to Study Treatments

NURTURE

[redacted]

Table 14: Exposure to Study Treatment — NURTURE

	NURTURE — ITT Set		
	2 SMN2 Copies [redacted]	3 SMN2 Copies [redacted]	Total N = 25
Number of patients dosed, N	[redacted]	[redacted]	25 (100)
Number of doses received, mean (SD)	[redacted]	[redacted]	[redacted]
Number of doses received, n (%)			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Time on study (days), mean (SD)	[redacted]	[redacted]	[redacted]
Total number of patients-years on study	[redacted]	[redacted]	[redacted]

ITT = intent to treat; SD = standard deviation; SMN = survival motor neuron.

Source: Clinical study report: SM201 (NURTURE). An open-label study to assess the efficacy, safety, tolerability, and pharmacokinetics of multiple doses of ISIS 396443 delivered intrathecally to subjects with genetically diagnosed and pre-symptomatic spinal muscular atrophy **[CONFIDENTIAL internal manufacturer's report]**. Mississauga (ON): Biogen Canada Inc.; 2018.

EMBRACE

[redacted]A summary of treatment exposure can be found in Table 15.

Table 15: Exposure to Study Treatment — EMBRACE

	EMBRACE — Safety Set	
	Control N = 7	Nusinersen N = 14
Number of patients who received nusinersen or sham, n (%)	[redacted]	[redacted]
Number of doses or sham procedures received, mean (SD)	[redacted]	[redacted]
Number of doses received or sham procedures undergone, n (%)		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Time on study (days), mean (SD)	[redacted]	[redacted]
Total number of patients-years on study	[redacted]	[redacted]

SD = standard deviation.

Source: Clinical study report: 232SM202 (EMBRACE). A phase 2, randomized, double-blind, sham-procedure controlled study to assess the safety and tolerability and explore the efficacy of ISIS 396443 (BIIB058) administered intrathecally in subjects with spinal muscular atrophy who are not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4 **[CONFIDENTIAL internal manufacturer's report]**. Mississauga (ON): Biogen Canada Inc.; 2018.

CHERISH

As of the data cut-off date, 84 (100%) of patients in the nusinersen group received at least three doses, with 83 patients (99%) receiving all four planned doses. Of the 42 patients in the sham control group, all (100%) received the four planned sham injections. A summary of treatment exposure can be found in Table 16.

Table 16: Exposure to Study Treatment — CHERISH

	CHERISH — Safety Set	
	Control N = 42	Nusinersen N = 84
Number of patients who received nusinersen or sham, n (%)	42 (100)	84 (100)
Number of doses or sham procedures received, mean (SD)	4.0 (0)	4.0 (0.1)
Number of doses received or sham procedures undergone, n (%)		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Time on study (days), mean (SD)	[redacted]	[redacted]
Total number of patients-years on study	[redacted]	[redacted]

SD = standard deviation.

Source: Clinical study report: ISIS 396443-CS4 [CHERISH]. A phase 3, randomized, double-blind, sham-procedure controlled study to assess the clinical efficacy and safety of ISIS 396443 administered intrathecally in patients with later-onset spinal muscular atrophy **[CONFIDENTIAL internal manufacturer's report]**. Mississauga (ON): Biogen Canada Inc.; 2018.

SHINE

[redacted]

[redacted] A summary of treatment exposure of infantile onset SMA can be found in Table 17.

Table 17: Exposure to Study Treatment — SHINE — Infantile Onset

	SHINE — Infantile Onset SMA — SHINE and Index Data			
	CS3A N = 20	ENDEAR — Previous Sham Control		ENDEAR — Previous Nusinersen N = 81
		ENDEAR Data N = 41	SHINE Data N = 24	
Number of patients who received nusinersen or sham, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number of doses or sham procedures received, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Total amount of nusinersen received, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Number of doses received or sham procedures undergone, n (%)				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time on study (days), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Total number of patients-years on study	[redacted]	[redacted]	[redacted]	[redacted]

SD = standard deviation.

Source: Clinical study report: ISIS 396443-CS11 (SHINE). An open-label extension study for patients with spinal muscular atrophy who previously participated in investigational studies of ISIS 396443 **[CONFIDENTIAL internal manufacturer's report]**. Mississauga (ON): Biogen Canada Inc.; 2018.

[redacted]

Table 18: Exposure to Study Treatment — SHINE — Later Onset

	SHINE — Later Onset SMA – SHINE and Index Data			
	CS1 and CS2 pooled N = 56	CHERISH — Previous Sham Control		CHERISH — Previous Nusinersen N = 84
		CHERISH data N = 42	SHINE data N = 42	
Number of patients who received nusinersen or sham, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number of doses or sham procedures received, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Total amount of nusinersen received, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Number of doses received or sham procedures undergone, n (%)				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time on study (days), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Total number of patients-years on study	[redacted]	[redacted]	[redacted]	[redacted]

SD = standard deviation.

Source: Clinical study report: ISIS 396443-CS11 (SHINE). An open-label extension study for patients with spinal muscular atrophy who previously participated in investigational studies of ISIS 396443 **[CONFIDENTIAL internal manufacturer's report]**. Mississauga (ON): Biogen Canada Inc.; 2018.

CS1, CS2, CS10, CS12, and CS3A

Please see the description for SHINE.

ENDEAR

The previous CDR report discussing ENDEAR in detail is provided in Appendix 6.

Case Series Studies: Aragon 2018, Pechmann 2018, Pane 2018, Elsheikh 2018, and Day 2018

Drug exposure not reported.

Critical Appraisal

Internal Validity

NURTURE

NURTURE is a single arm, open-label, uncontrolled, phase II clinical trial. The study aimed to assess the effect of nusinersen on pre-symptomatic patients with genetically confirmed SMA and two to three copies of SMN2 gene. The manufacturer justifies the lack of control based on the fact that patients with this genotype are almost certain to develop SMA type I or SMA type II and thus no control was necessary to measure the appearance of clinically symptomatic SMA. Using this study design precludes the ability to draw a causal inference. Furthermore, without a control group, any benefit observed cannot be attributed to nusinersen alone, where other confounding factors are potentially present. In addition, while objective clinical outcomes such as death or need for ventilation may not be overly affected by the open-label design of the study, other more subjective outcomes could potentially be biased in favour of the treatment. Standard Kaplan–Meier estimates were used to appropriately analyze survival-based outcomes and summary measures were provided for other outcomes. However, the methods used for handling missing data (beyond standard censoring in survival outcomes) were not described, although at time of the data cut-off, no patient was missing.

The current results for NURTURE represent an interim analysis results, as the study is still ongoing. However, results from interim analysis do not necessary reflect results of the final analysis and need to be considered on their own as representing a specific period of the trial.

EMBRACE

EMBRACE was a two-part phase II clinical trial. The first part was a double-blind, randomized, sham controlled trial, while the second part was an open-label extension phase. The study methods regarding randomization and treatment allocation (as described in the statistical analysis section) were well-reported and did not appear to be a potential source of bias. [redacted] The manufacturer did not provide power analysis for EMBRACE, and, despite the study design, all outcomes were considered exploratory in nature. Thus, no adjustment for multiple testing was required. [redacted]

[redacted]

EMBRACE was terminated early due to positive results from other nusinersen trials, and patients were moved into the extension phase of EMBRACE (ongoing). The early termination and the resulting interim analysis of the result may not reflect what the actual

planned results may have observed, and need to be considered on their own as representing a specific period of the trial. Also, potential for investigators to unmask patients assignment does exist: while allocation concealment was maintained, it is possible that investigators who had previous experience caring for or researching SMA could ascertain treatment assignment in patients who exhibited considerable improvements in motor milestone development that are otherwise unlikely to be observed in untreated patients. It is unclear if potential unblinding would introduce operational bias into the subsequent conduct of the study.

CHERISH

CHERISH was a randomized, sham-procedure control, double-blind, clinical trial. The study methods were generally well-reported (as described in the statistical analysis section), including the details of power analysis, randomization, allocation concealment, statistical analysis, control for multiple testing, and handling of missing data. Overall, potential issues pertaining to the internal validity of the study can be identified as relating to the following points:

1) Unequal randomization ratio

The manufacturer randomized patients in a 2:1 ratio to nusinersen or sham procedure, respectively. An ethical rationale for this approach was provided. Potential challenges that may be associated with such an allocation ratio include the need for a larger sample size to capture differences in treatment effect, and the potential of reducing the effectiveness of blinding as investigators and assessors would be aware that the probability of being allocated to active treatment is twice that of control. Based on the primary end points of the study, it appears to be adequately powered given that statistically significant differences were observed. A reduction in statistical power due to the 2:1 randomization ratio could potentially have an effect on the secondary outcomes and subgroups analyses.

2) Imbalances in the baseline patient characteristics after randomization between treatment groups

Patients that were randomized to the nusinersen treatment had longer disease duration, and fewer patients were able to stand and walk with support as compared with patients randomized into the sham control group. This may indicate that patients in the nusinersen group have a more severe illness at baseline, which can be supported by higher percentage of patients in the nusinersen group using wheelchairs than in the sham control group. The direction of the potential bias caused by these imbalances is not clear; while patients in the nusinersen group have more room to gain in the primary end point as compared with the sham control group, the disease process and nusinersen mechanism make it likely to see more benefit in less severe patients than more severe patients.

3) Potential for investigators to unmask patients assignment

While allocation concealment was maintained by including a sham procedure, there was a potential for treatment status to be unmasked post-randomization. It is possible that investigators who had previous experience caring for or researching SMA could ascertain treatment assignment in patients who exhibited considerable improvements in motor milestone development that are otherwise unlikely to be observed in untreated patients. It is unclear if potential unblinding would introduce operational bias into the subsequent conduct of the study.

4) Premature termination of the study

Studies that are early terminated commonly overestimate the benefit of an investigational drug.[45,46] In addition, other issues regarding using results of interim analysis may also appear.[45,46] However, the termination of CHERISH was at a point where the majority of patients completed the planned dosage and sham procedures, and thus may not present itself as an important source of potential bias. However, the study was only able to capture a small number of patients in the health-related QoL measure, which reduces the value of these outcomes considerably.

SHINE

SHINE is an ongoing, open-label, single arm, uncontrolled extension study that is following patients who participated in seven previous nusinersen development (CS1, CS2, CS3A, ENDEAR, CHERISH) and extension studies (CS10, CS12). As the current interim analysis of SHINE attempts to contrast the observed results with the baseline results of the first original study (index study) that a patient group moved from, handling of missing data is an important aspect to avoid the potential for overestimating the benefit due to the attrition of more severe cases (i.e., survivor bias).

The manufacturer employed several strategies to impute missing data based on the type of outcome (described in the statistical analysis section). While the outlined strategies have the potential to mitigate some of the limitations associated with missing data, consideration should be given to the long overall study period from the index study until the date of the interim analysis and the potential for unrealistic or inaccurate data imputation when using the last observation carried forward method or variations of it, considering the overall disease progression in the studied population. Also, due to the lack of control arm, we are unable to draw any association between an observed potential benefit when contrasted with baseline and nusinersen treatment. In addition, while objective clinical outcomes such as death or need for ventilation may not be overly affected by the open-label design of the study, other more subjective outcomes will most likely be biased in favour of the treatment.

CS1, CS2, CS10, CS12, and CS3A

Please see the description for SHINE.

ENDEAR

The previous CDR report discussing ENDEAR in detail is provided in Appendix 6.

Case Series Studies: Aragon 2018, Pechmann 2018, Pane 2018, Elsheikh 2018, and Day 2018

These five studies were reported as prospective, case series, observational studies. The study design is descriptive in nature and cannot draw any association between an observed potential benefit and nusinersen treatment. The value of any observed benefits as compared with baseline is limited, and can only be used for hypothesis generation.

External Validity

NURTURE

NURTURE addressed pre-symptomatic patients with SMA. NURTURE did not include any Canadian sites. In addition, considering there is no established screening program in Canada for SMA, it is unclear if the inclusion and exclusion criteria and the baseline characteristics of NURTURE are reflective of the pre-symptomatic population with SMA in Canada. However, the clinical experts consulted on this review identified that patients included in the NURTURE trial are indeed likely to develop SMA type I. NURTURE is an ongoing study and the results presented in this review are from an interim analysis; considering the lifelong duration of SMA, it is likely that the final analysis would provide more value. The outcomes described in NURTURE are, in the opinion of the clinical expert, relevant clinically in cases of siblings of patients with diagnosed SMA. Beyond the testing of siblings of patients with SMA, there is no known active screening program in Canada. Due to the single arm design of the NURTURE study and due to the lack of clear natural history data on pre-symptomatic Canadian patients, the applicability of the results of the NURTURE study to the Canadian population is uncertain.

EMBRACE

The EMBRACE study included patients that did not meet the inclusion and exclusion criteria of the ENDEAR or CHERISH studies, thus filling an important gap for the population with SMA not studied in CHERISH in ENDEAR. No Canadian sites were part of the EMBRACE study. However, due to the limitations in the internal validity of the study, external validity is thus also limited.

CHERISH

CHERISH addressed patients who are most likely to be classified as having SMA type II; more than half of the patient population (56%) were enrolled in Canada and the US. The clinical experts consulted on this review identified the inclusion and exclusion criteria as appropriate and that the baseline characteristics represent patients that are commonly categorized as having SMA type II. A limitation to the external validity of the results of CHERISH is the difference in the dosage schedule from that approved by Health Canada. Health Canada recommends four loading doses followed by maintenance doses at four-month intervals; while the dosage regimen in CHERISH included three loading doses followed by a maintenance dose after six months. It is unclear to what extent this would affect the generalizability of the CHERISH findings. The clinical expert consulted on this

review does not believe the difference is significant enough to cause concern. A second limitation is the uncommon clinical practice use of the primary end point reported in CHERISH (HFMSE).

SHINE

SHINE as an extension study provides value in addressing potential safety issues and maintaining observed benefits in the index studies. As the study is ongoing, the main interim analysis descriptively measured the mean changes of the outcomes from the baseline index study values. Also, the inclusion of patients who participated in dose-finding studies resulted in a very heterogeneous population in terms of drug exposure.

CS1, CS2, CS10, CS12, and CS3A

Please see the description for SHINE.

ENDEAR

The previous CDR report discussing ENDEAR in detail is provided in Appendix 6.

Aragon 2018

As part of an expanded access program, it is unclear how patients were selected and assigned to treatment. Aragon 2018 reported characteristics of age, gender, and disease duration. It is not clear how this population is similar or not to a Canadian population, considering that the study did not include any Canadian sites.

Pechmann 2018

As part of an expanded access program, it is unclear how patients were selected and assigned to treatment. Pechmann 2018 reported characteristics of age, gender, and disease duration. It is not clear how this population is similar or not to a Canadian population, considering that the study did not include any Canadian sites.

Pane 2018

No description of baseline characteristics was provided in Pane 2018. The nature of the study as part of an expanded access program also does not provide relevant information on selection and treatment allocation. As such, there is insufficient information to assess the similarity of the populations studied in Pane 2018 to a Canadian population.

Elsheikh 2018

As this was an abstract poster presentation of a descriptive observational study, there was insufficient information to be able to assess the population described, the methods of selecting said population, or the method of study conduct. As such, the generalizability of the results is unclear.

Day 2018

As this was an abstract poster presentation of a descriptive observational study, there was insufficient information to be able to assess the population described, the methods of selecting said population, or the method of study conduct. As such, the generalizability of the results is unclear.

Efficacy

Only those efficacy outcomes identified in the review protocol (Table 3) are reported as follows.

Patients Who Are Pre-symptomatic

Addressing this population is one study, NURTURE. An overview of the outcomes results is presented in Table 19.

Time to Death or Respiratory Intervention

[redacted]

Hammersmith Infant Neurological Examination Motor Milestones

[redacted]

Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders Scores

[redacted]

World Health Organization Motor Milestones

[redacted]

Growth Failure

[redacted]

Patients Manifesting Spinal Muscular Atrophy Symptoms

[redacted]

Table 19: Summary of Efficacy Outcomes in Studies Addressing Patients Who Are Pre-symptomatic (NURTURE)

	NURTURE (CS5) — ITT Set		
Outcome	**2 SMN2** [redacted]	**3 SMN2** [redacted]	**Total N = 25**
Time to Death or Respiratory Intervention (Primary Outcome)			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
HINE Score			
[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
CHOP INTEND			
[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
WHO Motor Milestones			
[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Growth Failure			
[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Patients Manifesting SMA Symptoms			
[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Outcome	NURTURE (CS5) — ITT Set		
	2 SMN2 [redacted]	3 SMN2 [redacted]	Total N = 25
[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE = Hammersmith Infant Neurological Examination; ITT = intention-to-treat; SMA = spinal muscular atrophy; SMN = survival motor neuron; WHO = World Health Organization.

Source: Clinical study report: SM201 (NURTURE). An open-label study to assess the efficacy, safety, tolerability, and pharmacokinetics of multiple doses of ISIS 396443 delivered intrathecally to subjects with genetically diagnosed and pre-symptomatic spinal muscular atrophy **[CONFIDENTIAL internal manufacturer's report]**. Mississauga (ON): Biogen Canada Inc.; 2018.

Patients With Infantile Onset SMA Including Patients With SMN2 Gene Copy Greater Than Two

Addressing this population is one study, SHINE — CS3A index. An overview of the outcomes results is presented in Table 20.

Time to Death or Permanent Ventilation

[redacted] The median time to death or permanent ventilation could not be calculated. All of these events occurred during the index CS3A study period.

Hammersmith Infant Neurological Examination Section 2 Score

At last observed visit, [redacted]

Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders Score

[redacted]

Table 20: Summary of Efficacy Outcomes in Studies Addressing Patients With Infantile Onset SMA, Including Patients With SMN2 Gene Copy Greater Than Two

Outcome	SHINE (Population of CS3A Index Study)
	Total [redacted]
Time to Death or Permanent Ventilation	
Number of patients who died or required permanent ventilation, n (%)	[redacted]
Time (weeks) to death or permanent ventilation	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
HINE-2 Score	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CHOP INTEND Score	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE = Hammersmith Infant Neurological Examination; SMA = spinal muscular atrophy; SMN = survival motor neuron.

Source: Clinical study report: ISIS 396443-CS11 (SHINE). An open-label extension study for patients with spinal muscular atrophy who previously participated in investigational studies of ISIS 396443 **[CONFIDENTIAL internal manufacturer's report]**. Mississauga (ON): Biogen Canada Inc.; 2018.

Patients With Mixed Infantile and Early Childhood Onset, Including Patients With SMN2 Gene Copy Greater Than Two

Addressing this population is one study, EMBRACE. An overview of the outcomes results is presented in Table 21.

Ventilation Use — Number of Hours Per Day

[redacted]

Hammersmith Infant Neurological Examination Section 2 Score

[redacted]

Time to Death or Permanent Ventilation

[redacted]

Table 21: Summary of Efficacy Outcomes in Studies Addressing Patients With Mixed Infantile and Early Childhood Onset, Including Patients With SMN2 Gene Copy Greater Than Two

Outcome	EMBRACE — ITT Set	
	Sham Control [redacted]	Nusinersen [redacted]
Ventilation Use — Number of Hours Per Day		
[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
HINE-2 Score		
[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Time to Death or Permanent Ventilation		
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

HINE = Hammersmith Infant Neurological Examination; ITT = interntion-to-treat; SMA = spinal muscular atrophy; SMN = survival motor neuron.

Source: Clinical study report: 232SM202 (EMBRACE). A phase 2, randomized, double-blind, sham-procedure controlled study to assess the safety and tolerability and explore the efficacy of ISIS 396443 (BIIB058) administered intrathecally in subjects with spinal muscular atrophy who are not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4 **[CONFIDENTIAL internal manufacturer's report]**. Mississauga (ON): Biogen Canada Inc.; 2018.

Patients With Early Childhood SMA Onset, Including Patients With SMN2 Gene Copy Greater Than Two

Addressing this population is one study: CHERISH. An overview of the outcomes results is presented in Table 22.

HFMSE: Change From Baseline to Month 15 (Primary Outcome Main Analysis)

The first primary outcome, the change in HFMSE score from baseline to month 15, was analyzed based on the ITT set. There was a statistically significant difference between groups as patients in the nusinersen group exhibited overall improvements in HFMSE score compared with an overall decline in the HFMSE score in patients in the sham control group (least squares mean difference = 5.9 [95% CI, 3.7 to 8.1]). All conducted sensitivity analyses showed similar results to the base case.

HFMSE Responders (Three Points or More Increase) at 15 Months

HFMSE responders was the first secondary outcome to be tested in the stage-wise hierarchal approach for controlling multiple testing in secondary end points. A responder was any patients who gained more than three points. More than half of the patients in the nusinersen group were deemed responders (56.8%) compared with 26.3% in the sham control group. Thus, the result shows a statistically significant difference of 30.5% (95% CI, 12.74 to 48.31).

Proportion of Patients Achieving New Motor Milestones at 15 Months

This was the second end point on the stage-wise hierarchal testing approach. While there were a numerically higher number of patients in the nusinersen group who achieved a new motor milestone (13 patients [19.7%]) compared with patients enrolled in the sham control group (two patients [5.9]), the statistical comparison did not show a statistically significant difference (13.8% [95% CI, –6.64 to 34.17]). As such, all subsequent end points are outside the hierarchy of testing and considered inconclusive as any reported *P* value is not adjusted for multiple testing (i.e., nominal in nature).

Number of New Motor Milestones Achieved at 15 Months

Overall, patients in the nusinersen group had a mean of 0.2 new motor milestones achieved (95% CI, 0.1 to 0.3) compared with a mean of –0.2 in the sham control group (95% CI, –0.4 to 0). This outcome falls outside of the hierarchal testing approach and thus the *P* value in not adjusted for multiple testing.

Change From Baseline in Revised Upper Limb Module Test at 15 Months

Patients in the nusinersen group exhibited a mean improvement of 4.2 (95% CI, 3.4 to 5.0) from baseline in the outcome of RULM test at 15 months compared with a mean improvement of 0.5 (95% CI, –0.6 to 1.6) from baseline in the sham control group. This outcome falls outside of the hierarchal testing approach and thus the *P* value in not adjusted for multiple testing.

Proportion of Patients Achieving Standing Alone at 15 Months

One patient was able to achieve this outcome in the nusinersen group. Similarly, one patient was able to demonstrate this outcome in the sham control group.

Proportion of Patients Achieving Walking With Assistance at 15 Months

One patient was able to achieve this outcome in the nusinersen group. No patient was able to demonstrate this outcome in the sham control group.

[redacted]

Table 22: Summary of Efficacy Outcomes in Studies Addressing Patients With Early Childhood SMA Onset, Including Patients With SMN2 Gene Copy Greater Than Two

Outcome	CHERISH – ITT Set	
	Sham Control N = 42	Nusinersen N = 84
HFMSE: Change From Baseline to Month 15 (Primary Outcome Main Analysis)		
Number of patients with observed value, n (%)	34 (81)	66 (79)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Change in HFMSE, least squares mean (95% CI)	–1.9 (–3.8 to 0.0)	4.0 (2.9 to 5.1)
Between-groups difference, least squares mean difference (95% CI)	**5.9 (3.7 to 8.1)**	
P value	**< 0.0001**	
HFMSE responders (≥ 3 points increase) at 15 months		
Number of patients assessed, n (%)	34 (81)	66 (79)
[redacted]	[redacted]	[redacted]
Between-groups difference in proportion, % (95% CI)	**30.5 (12.74 to 48.31)**	
[redacted]	[redacted]	
[redacted]	[redacted]	
Proportion of patients achieving new motor milestones at 15 months		

Outcome	CHERISH – ITT Set	
	Sham Control N = 42	Nusinersen N = 84
Number of patients assessed, n (%)	34 (81)	66 (79)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
Number of new motor milestones achieved at 15 months		
Number of patients assessed, n (%)	34 (81)	66 (79)
Number of new motor milestones achieved, least square mean (95% CI)	–0.2 (–0.4 to 0)	0.2 (0.1 to 0.3)
Between-groups difference, least squares mean difference (95% CI)	0.4 (0.2 to 0.7)	
P value (unadjusted for multiple testing)	0.0001	
Change From Baseline in Revised Upper Limb Module Test at 15 Months		
Number of patients assessed, n (%)	42 (100)	84 (100)
[redacted]	[redacted]	[redacted]
Change from baseline, least squares mean difference (95% CI)	0.5 (–0.6 to 1.6)	4.2 (3.4 to 5.0)
Between-groups difference, least squares mean difference (95% CI)	3.7 (2.3 to 5.0)	
P value (unadjusted for multiple testing)	0.0000001	
Proportion of Patients Achieving Standing Alone at 15 Months		
Number of patients assessed, n (%)	34 (81)	66 (79)
[redacted]	[redacted]	[redacted]
Between-groups difference in proportion, % (95% CI)	–1.4 (–21.8 to 19.3)	
P value (unadjusted for multiple testing)	> 0.9999	
Proportion of Patients Achieving Walking With Assistance at 15 Months		
Number of patients assessed, n (%)	34 (81)	66 (79)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
Change From Baseline in PedsQL (Total Score — Patient Assessment) at 15 Months		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
Change From Baseline in PedsQL (Total Score – Parent Assessment) at 15 Months		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
Change From Baseline in ACEND (Total Score) at 15 Months		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	

Outcome	CHERISH – ITT Set	
	Sham Control N = 42	Nusinersen N = 84
Hospitalization		
[redacted]		

ACEND = Assessment of Caregiver Experience in Neuromuscular Disease ;CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CI = confidence interval; HFMSE = Hammersmith Functional Motor Scale – Expanded; HINE = Hammersmith Infant Neurological Examination; ITT = intention-to-treat; PedsQL = Pediatric Quality of Life Inventory; RULM = Revised Upper Limb Module; SAE = serious adverse event; SMA = spinal muscular atrophy; SMN = survival motor neuron; WDEAs = withdrawal due to adverse events; WHO = World Health Organization.

Source: Clinical study report: ISIS 396443-CS4 [CHERISH]. A phase 3, randomized, double-blind, sham-procedure controlled study to assess the clinical efficacy and safety of ISIS 396443 administered intrathecally in patients with later-onset spinal muscular atrophy **[CONFIDENTIAL internal manufacturer's report]**. Mississauga (ON): Biogen Canada Inc.; 2018.

Patients With Later Childhood Onset, Including Patients With SMN2 Gene Copy Greater Than Two

Addressing this population is one study: SHINE (index CS1, CS2, CS10, and CS12). Results were reported separately for patients who were designated as SMA type II and patients who were designated as SMA type III. An overview of the outcomes results is presented in Table 23.

Hammersmith Functional Motor Scale – Expanded: Change From Baseline

At last observable visit, [redacted] This is an exploratory descriptive outcome and no comparative statistical testing was conducted.

Change From Baseline in Upper Limb Module Test

[redacted] This is an exploratory descriptive outcome and no comparative statistical testing was conducted.

Change From Baseline in Six-Minute Walk Test

[redacted]This is an exploratory descriptive outcome and no comparative statistical testing was conducted.

Table 23: Summary of Efficacy Outcomes in studies Addressing Patients With Later Childhood Onset, Including Patients With SMN2 Gene Copy Greater Than Two

Outcome	SHINE (Patients Previously Participating in CS12)	
	Designated as Type II SMA	Designated as Type III SMA
HFMSE: Change From Baseline		
Assessment day	Last Observed Visit	
Number of patients assessed	[redacted]	[redacted]
Baseline HFMSE score, mean (SD)	[redacted]	[redacted]
Assessment day HFMSE score, mean (SD)	[redacted]	[redacted]
Change from baseline, mean (SD)	[redacted]	[redacted]
HFMSE responders, n (%)	[redacted]	[redacted]
Change From Baseline in Upper Limb Module Test		
Assessment day	Last Observed Visit	
Number of patients with baseline value	[redacted]	[redacted]
Number of patients assessed	[redacted]	[redacted]
Baseline score, mean (SD)	[redacted]	[redacted]
Assessment day score, mean (SD)	[redacted]	[redacted]
Change from baseline, mean (SD)	[redacted]	[redacted]
Change From Baseline in Six-Minute Walk Test		
Assessment day	Last Observed Visit	
Number of patients with baseline value	[redacted]	[redacted]
Number of patients assessed	[redacted]	[redacted]
Baseline score, mean (SD)	[redacted]	[redacted]
Assessment day score, mean (SD)	[redacted]	[redacted]
Change from baseline, mean (95% CI)	[redacted]	[redacted]

CI = confidence interval; HFMSE = Hammersmith Functional Motor Scale – Expanded; SD = standard deviation; SMA = spinal muscular atrophy; SMN = survival motor neuron.

Source: Clinical study report: ISIS 396443-CS11 (SHINE). An open-label extension study for patients with spinal muscular atrophy who previously participated in investigational studies of ISIS 396443 **[CONFIDENTIAL internal manufacturer's report]**. Mississauga (ON): Biogen Canada Inc.; 2018.

Adult Patients

Two case series observational studies poster abstracts address this patient population. Unfortunately, no explicit results were reported for the included patients. Elsheikh 2018 observed that three patients reported subjective improvement in stamina and endurance, one patient's HSFMSE score did not improve, one patient's HSFMSE score improved from 31 to 34, and one patient had an increase of 25 metres in the six-minute walk test. However, the time frame of these improvements was not provided. Day 2018 reported [redacted]Similar to Elsheikh 2018, the time frame of these improvements was not reported.

Patients Diagnosed Before Seven Months of Age But Receive Treatment After Seven Months of Age

Addressing this population are three studies: SHINE (ENDEAR index, reported against the baseline at the start of SHINE), Pane 2018, and Aragon 2018. An overview of the outcomes results is presented in Table 24.

Time to Death or Permanent Ventilation

This outcome was only reported in the SHINE — ENDEAR index study. [redacted] This outcome was not reported in the Pane 2018 and Aragon 2018 studies.

Hammersmith Infant Neurological Examination Section 2 Score

In SHINE (ENDEAR index [redacted] Aragon 2018 reports a median HINE score of 3.5 (range: 0 to 11) at six months contrasted with the baseline median value of 1 (range 0 to 6). Pane 2018 reported that the mean change in HINE score was 1.3 (SD: 2.2).

Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders Score

In SHINE (ENDEAR index), at last observed visit, [redacted] Aragon 2018 reports a median score of 35 (range: 19 to 51) at six months contrasted with the baseline median value of 31.5 (range: 6 to 45). Pane 2018 did not provide a summary measure for this outcome; instead, they reported that the CHOP INTEND changes ranged between –7 and 27 points.

Table 24: Summary of Efficacy Outcomes in Studies Addressing Patients Diagnosed Before Seven Months of Age But Who Received Treatment After Seven Months of Age

	Pane 2018	Aragon 2018	[redacted]	
	N = 104	**N = 33**	[redacted]	[redacted]
Time to Death or Permanent Ventilation				
Number of patients who required permanent ventilation at baseline, n (%)	NR	NR	[redacted]	[redacted]
Number of evaluable patients, n (%)	NR	NR	[redacted]	[redacted]

	Pane 2018	Aragon 2018	[redacted]	
Number of patients who died or required permanent ventilation, n (%)	NR	NR		
Number of patients who died	NR	NR		
Time (weeks) to death or permanent ventilation	NR	NR		
5th percentile	NR	NR		
10th percentile	NR	NR		
25th percentile	NR	NR		
50th percentile — median (95%CI)	NR	NR		
75th percentile	NR	NR		
90th percentile	NR	NR		
HINE-2 Score				
Assessment time point (study day)	6 months	6 months		
Number of patients at assessment, N	104	30		
Baseline mean of score, mean (SD)	2.1 (3.07)	Median 1, range 0 to 6		
Assessment visit mean score, mean (SD)	NR	Median 3.5, range 0 to 11		
Change from baseline, mean (SD)	1.3 (2.18)	NR		
HINE-2 Motor Milestone Responders				
Assessment time point (study day)	NR	NR		
Number of patients, N	NR	NR		
Motor milestone responders, N (%)	NR	NR		
CHOP INTEND Score				
Assessment time point (study day)	6 months	6 months		
Number of patients assessment, N	104	22		
Baseline mean score, mean (SD)	15.1 (13.53)	Median 31.5, range 6 to 45		
Assessment visit mean score, mean (SD)	NR	Median 35, range 19 to 51		
Change from baseline, mean (SD)	4.5 (5.8)	NR		

CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CI = confidence interval; HINE = Hammersmith Infant Neurological Examination; NR = not reported.

Source: Clinical study report: ISIS 396443-CS11 (SHINE). An open-label extension study for patients with spinal muscular atrophy who previously participated in investigational studies of ISIS 396443 [CONFIDENTIAL internal manufacturer's report]. Mississauga (ON): Biogen Canada Inc.; 2018.

Pane M, Palermo C, Messina S, Sansone VA, Bruno C, Catteruccia M, et al. Nusinersen in type 1 SMA infants, children and young adults: Preliminary results on motor function. Neuromuscul Disord. 2018;01:01.

Aragon-Gawinska K, Seferian AM, Daron A, Gargaun E, Vuillerot C, Cances C, et al. Nusinersen in spinal muscular atrophy type 1 patients older than 7 months: A cohort study. Neurology. 2018.

Patients With Spinal Muscular Atrophy Who Require Ventilation

One study can inform this patient population: Pechmann 2018.

Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders Score

At six months after nusinersen treatment, Pechmann 2018 reports a mean change from baseline of 9.0 (SD: 8.0) points — starting from a mean baseline value of 22.3 to a mean value at assessment date of 31.2 (SD: 16.2). In a subgroup of patients that started the study

requiring permanent ventilation (18 patients [30%]), the mean change in the CHOP INTEND score from baseline was 5.6 points (SD: 7.5).

Hammersmith Infant Neurological Examination Section 2 Score

At six months after nusinersen treatment, Pechmann 2018 reports a mean change from baseline of 1.4 (SD: 2.1) points — starting from a mean baseline value of 0.8 to a mean value at assessment date of 2.5 (SD: 3.3). These results were not reported in the subgroup of patients that started the study requiring permanent ventilation.

Ventilator Support

At the beginning of the study, 26 patients (43%) did not require ventilation; at six months, 19 patients (31%) did not require ventilation. Non-invasive ventilation less than 16 hours per day was required by 17 patients at the start and at the end of the study (28%). The number of patient requiring ventilation for more than 16 hours per day or who required a tracheostomy increased from 18 (30%) at the beginning of the study to 25 (41%) at the end of the study.

Table 25: Summary of Efficacy Outcomes in Studies Addressing Patients With Spinal Muscular Atrophy Who Require Ventilation

	Pechmann, 2018
	Total N = 61
CHOP INTEND Score — Overall Population	
Assessment time point	6 months
Number of patients assessed, n (%)	61 (100)
Baseline mean score, mean (SD)	22.3 (NR)
Assessment visit mean score, mean (SD)	31.2 (16.2)
Change from baseline, mean (SD)	9.0 (8.0)
CHOP INTEND Score — Patients Requiring Permanent Ventilation	
Assessment time point	6 months
Number of patients assessed, n (%)	18 (30)
Baseline mean score, mean (SD)	9.4 (9.1)
Assessment visit mean score, mean (SD)	NR
Change from baseline, mean (SD)	5.6 (7.5)
HINE-2 Score	
Assessment time point (study day)	6 months
Number of patients assessed, n (%)	61 (100)
Baseline mean of score, mean (SD)	0.8 (NR)
Assessment visit mean score, mean (SD)	2.5 (3.3)
Change from baseline, mean (SD)	1.4 (2.1)
Motor milestone responders, n (%)	21 (34.4)
Ventilator Support	
No support	
At baseline, n (%)	26 (43)
After 6 months, n (%)	19 (31)
Non-invasive ventilation (< 16 hours per day)	
At baseline, n (%)	17 (28)
After 6 months, n (%)	17 (28)

	Pechmann, 2018
	Total N = 61
Non-invasive ventilation (> 16 hours per day) or tracheostomy	
At baseline, n (%)	18 (30)
After 6 months, n (%)	25 (41)

CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE = Hammersmith Infant Neurological Examination; NR = not reported; SD = standard deviation; SMA = spinal muscular atrophy.

Source: Pechmann A, Langer T, Schorling D, Stein S, Vogt S, Schara U, et al. Evaluation of Children with SMA Type 1 Under Treatment with Nusinersen within the Expanded Access Program in Germany. J Neuromuscul Dis. 2018;5(2):135-43.

Harms

Only those harms identified in the review protocol are reported as follows (see 2.2.1, Protocol). See Table 26 for detailed harms data.

NURTURE

[redacted]

Table 26: Harms — NURTURE

	NURTURE — Safety Set N = 25
AEs	**Nusinersen**
Subjects with > 0 AEs, N (%)	[redacted]
Most common AEs[a]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
SAEs	
Subjects with > 0 SAEs, N (%)	[redacted]
Most common SAEs[b]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
WDAEs	
WDAEs, N (%)	[redacted]
Deaths	
Number of deaths, N (%)	[redacted]
Notable Harms	

	NURTURE — Safety Set N = 25
AEs related to lumbar puncture, n (%)	[redacted]
Most common reasons	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

AE = adverse events; SAE = serious adverse events; WDAE = withdrawal due to adverse events.

Source: Clinical study report: SM201 (NURTURE). An open-label study to assess the efficacy, safety, tolerability, and pharmacokinetics of multiple doses of ISIS 396443 delivered intrathecally to subjects with genetically diagnosed and pre-symptomatic spinal muscular atrophy [CONFIDENTIAL internal manufacturer's report]. Mississauga (ON): Biogen Canada Inc.; 2018.

[a] Frequency > 10%.

[b] Frequency > 1%.

EMBRACE

[redacted]

Table 27: Harms — EMBRACE

	EMBRACE — Safety Set	
AEs	**Control (N = 7)**	**Nusinersen (N = 14)**
Subjects with > 0 AEs, N (%)	[redacted]	[redacted]
Most common AEs[a]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
SAEs		
Subjects with > 0 SAEs, N (%)	[redacted]	[redacted]
Most common SAEs[b]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

	EMBRACE — Safety Set	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
WDAEs		
WDAEs, N (%)	[redacted]	[redacted]
Deaths		
Number of deaths, N (%)	[redacted]	[redacted]
Most common reasons		
[redacted]	[redacted]	[redacted]
Notable Harms		
AEs related to lumbar puncture, n (%)	[redacted]	[redacted]
Most common reasons		

AE = adverse events; SAE = serious adverse events; WDAE = withdrawal due to adverse events.

Source: Clinical study report: 232SM202 (EMBRACE). A phase 2, randomized, double-blind, sham-procedure controlled study to assess the safety and tolerability and explore the efficacy of ISIS 396443 (BIIB058) administered intrathecally in subjects with spinal muscular atrophy who are not eligible to participate in the clinical studies ISIS 396443-CS3B or ISIS 396443-CS4 **[CONFIDENTIAL internal manufacturer's report]**. Mississauga (ON): Biogen Canada Inc.; 2018.

[a] Frequency > 10%.

[b] Frequency > 1%.

CHERISH

Adverse Events

A total of 78 patients (93%) in the nusinersen group and a total of 42 patients (100%) in the sham control group experienced at least one AE. AEs related to upper respiratory tract infection were the most common in both groups.

Serious Adverse Events

A total of 14 patients (17%) in the nusinersen group and 12 patients (29%) in the sham control group experienced at least one SAE. Pneumonia as an SAE was more frequent in the sham control group (14%) than in the nusinersen group (2%).

Withdrawals Due to Adverse Events

No withdrawals due to AEs were reported.

Mortality

No deaths were reported.

Notable Harms

AEs deemed to be related to lumbar puncture were not reported. However, one patient experiences a post lumbar puncture syndrome, which was classified as an SAE.

Table 28: Harms — CHERISH

	CHERISH — Safety Set	
AEs	**Control (N = 42)**	**Nusinersen (N = 84)**
Patiens with > 0 AEs, N (%)	42 (100)	78 (93)
Most common AEs[a]		
Upper respiratory tract infection	19 (45)	25 (30)
Nasopharyngitis	15 (36)	20 (24)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Pyrexia	15 (36)	36 (43)
Cough	9 (21)	21 (25)
[redacted]	[redacted]	[redacted]
Vomiting	5 (12)	24 (29)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Back pain	0	21 (25)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Headache	3 (7)	24 (29)
SAEs		
Patients with > 0 SAEs, N (%)	12 (29)	14 (17)
Most common SAEs[b]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Pneumonia	6 (14)	2 (2)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Influenza	2 (5)	0
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

	CHERISH — Safety Set	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Respiratory distress	2 (5)	2 (2)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Faecaloma	2 (5)	0
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
WDAEs		
WDAEs, N (%)	[redacted]	[redacted]
Deaths		
Number of deaths, N (%)	[redacted]	[redacted]
Notable Harms		
AEs related to lumbar puncture, n (%)	[redacted]	[redacted]
Most common reasons		

AE = adverse events; SAE = serious adverse events; WDAE = withdrawal due to adverse events.

Source: Clinical study report: ISIS 396443-CS4 [CHERISH]. A phase 3, randomized, double-blind, sham-procedure controlled study to assess the clinical efficacy and safety of ISIS 396443 administered intrathecally in patients with later-onset spinal muscular atrophy [CONFIDENTIAL internal manufacturer's report]. Mississauga (ON): Biogen Canada Inc.; 2018.

[a] Frequency > 10%.

[b] Frequency > 1%.

SHINE

[redacted]

[redacted]

Table 29: Harms — SHINE

	SHINE			
	SHINE (CS3A Index) Safety Data	SHINE (ENDEAR Index Study [Data Represent Time on SHINE Only])		SHINE (CS1 and CS2) Safety Data
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with > 0 AEs, N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Most common AEs[a]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	SHINE			
	SHINE (CS3A Index) Safety Data	SHINE (ENDEAR Index Study [Data Represent Time on SHINE Only])		SHINE (CS1 and CS2) Safety Data
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	SHINE			
	SHINE (CS3A Index) Safety Data	SHINE (ENDEAR Index Study [Data Represent Time on SHINE Only])		SHINE (CS1 and CS2) Safety Data
[redacted]				
SAEs				
Patients with > 0 SAEs, N (%)				
Most common SAEs[a]				

	SHINE			
	SHINE (CS3A Index) Safety Data	SHINE (ENDEAR Index Study [Data Represent Time on SHINE Only])		SHINE (CS1 and CS2) Safety Data
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	SHINE			
	SHINE (CS3A Index) Safety Data	SHINE (ENDEAR Index Study [Data Represent Time on SHINE Only])		SHINE (CS1 and CS2) Safety Data
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WDAEs				
WDAEs, N (%)	4 (20)	2 (8)	4 (6)	0
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deaths				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	SHINE			
	SHINE (CS3A Index) Safety Data	SHINE (ENDEAR Index Study [Data Represent Time on SHINE Only])		SHINE (CS1 and CS2) Safety Data
[redacted]				
Notable Harms				
[redacted]				

AE = adverse events; SAE = serious adverse events; WDAE = withdrawal due to adverse events.

Source: Clinical study report: ISIS 396443-CS11 (SHINE). An open-label extension study for patients with spinal muscular atrophy who previously participated in investigational studies of ISIS 396443 [CONFIDENTIAL internal manufacturer's report]. Mississauga (ON): Biogen Canada Inc.; 2018.

[a] Frequency > 10%.

[b] Frequency > 1%.

CS1, CS2, CS10, CS12, and CS3B

Please see SHINE study.

ENDEAR

The previous CDR report discussing ENDEAR in detail is provided in Appendix 6.

Observational Studies

The included observational case series studies provided limited information regarding harms demonstrated in enrolled patients. Aagon 2018, Day 2018, and Elsheikh 2018 did not provide any relevant information. Pane 2018 reported that one patient died in the study due to complication arising from a neonatal onset SMA. Pechmann 2018 did not report on the number of patients experiencing at least one AE. However, Pechmann reported that the total number of AEs was 53, of which, 29 (54.7%) were considered SAEs. Pechmann 2018 reported that respiratory tract infection constituted more than half of the reported AEs (31 [58.5%]) and that acute respiratory failure was the next most common AE (8 [15.1%]).

Table 30: Harms

	Aragon 2018	Day 2018	Elsheikh 2018	Pane 2018	Pechmann 2018
	Nusinersen N = 33	Nusinersen N = 20	Nusinersen N = 29	Nusinersen N = 104	Nusinersen N = 61
AEs					
Patients with > 0 AEs, N (%)	NR	NR	NR	NR	NR
SAEs					
Patients with > 0 SAEs, N (%)	NR	NR	NR	NR	NR
WDAEs					
WDAEs, N (%)	NR	NR	NR	NR	NR
Deaths					
Number of deaths, N (%)	NR	NR	NR	1	1
Notable Harms					
AEs related to lumbar puncture, n (%)	NR	NR	NR	NR	NR

AE = adverse events; NR = not reported; SAE = serious adverse events; WDAE = withdrawal due to adverse events.

Source: Aragon-Gawinska K, Seferian AM, Daron A, Gargaun E, Vuillerot C, Cances C, et al. Nusinersen in spinal muscular atrophy type 1 patients older than 7 months: A cohort study. Neurology. 2018.

Day J, Wolford C, MacPherson C, Martens W, McDermott M, Darras B, et al. Nusinersen efficacy in adults with spinal muscular atrophy. American Academy of Neurology Annual Meeting; April 21-27th; Los Angeles (CA)2018.

Elsheikh B, Arnold W, Mezache L, Kissel J. Nusinersen treatment for adults with Spinal Muscular Atrophy; a single center experience (S46.006). Neurology. 2018;90 (15 Supplement).

Pane M, Palermo C, Messina S, Sansone VA, Bruno C, Catteruccia M, et al. Nusinersen in type 1 SMA infants, children and young adults: Preliminary results on motor function. Neuromuscul Disord. 2018;01:01.

Pechmann A, Langer T, Schorling D, Stein S, Vogt S, Schara U, et al. Evaluation of Children with SMA Type 1 Under Treatment with Nusinersen within the Expanded Access Program in Germany. J Neuromuscul Dis. 2018;5(2):135-43.

Discussion

Summary of Available Evidence

A total of 15 studies were included in this review in accordance with the review protocol: two randomized controlled design trials, (CHERISH [N = 106], and ENDEAR [N = 121]); two phase I single arm trials (CS1 [N = 28], CS 2 [N = 34]); three phase II trials where two were single arm studies (CS3A [N = 21], CS5 [N = 25]) and one was a randomized controlled trial (CS7 [N = 27]); three extension studies (CS 10 [N = 18], CS12 [N = 12], and SHINE [N = 207]); and five observational case series (Pechmann 2018 [N = 61], Pane 2018 [N = 122], Aragon 2018 [N = 33], Elsheikh 2018 [N = 29], and Day 2018 [N = 20]).

ENDEAR was included and reviewed in detail in the original nusinersen submission (see Appendix 6) and CDEC provided the original recommendation based on ENDEAR. As such, results from ENDEAR were not repeated here. Patients from CS1 moved into the extension study of CS10, where they subsequently moved into the extension study of CS12 where patients from CS2 also moved. Eventually, patients in CS12 were enrolled in the SHINE extension study; thus, only results from SHINE contrasted with the baseline characteristics of the index study were reported in this review. SHINE also included patients from CS3A, which was a single arm trial; thus, only results from SHINE contrasted with the baseline characteristics of CS3A were presented in this review. While patients in CHERISH also ended up in the SHINE extension study, as CHERISH was a controlled trial, results from the controlled part were reported and, subsequently, results from the SHINE extension study were also reported with baseline characteristics at the time of SHINE enrolment. Of the five case series observational studies, two were in poster abstract form submitted by the manufacturer and did not provide proper quantitative assessment of the studied patients; the other three were case series describing the experience with treating patients diagnosed as SMA type I through an expanded access program.

An additional letter from a medical centre was provided by the manufacturer outlying the experience of the centre in treating adult patients who are diagnosed with SMA. The letter did not follow a study design and it did not report in quantitative information regarding the efficacy of nusinersen.

Interpretation of Results

Efficacy

Patients Who Are Pre-symptomatic

Addressing this evidence gap is a phase II, ongoing, single arm, uncontrolled trial, NURTURE. [redacted]

[redacted]

Informally contrasting the interim results to a median survival age of 13.6 months in the SMA type I natural history studies and the positive development results to the rapid decline in natural history trials would show a considerable benefit for patients with a genetic diagnosis of SMA and two to three SMN2 gene copies. In addition, the positive results from the ENDEAR trial on patients with SMA type I with two SMN2 gene copies may further support the hypothesis of beneficial effects of nusinersen on pre-symptomatic patients. However, since NURTURE is a single arm trial, the lack of control impedes our ability to determine the extent of the findings attributed to nusinersen. Any comparison to baseline values cannot rule out the potential effect of confounding factors and systematic biases. In addition, since patients were pre-symptomatic, and considering the deteriorating nature of the disease and the mechanism of action of nusinersen, any attempt at an informal comparison against studies of patients with SMA type I is likely to lead to overestimation of the effect. Such informal comparison assumes that patients in the NURTURE would have progressed to SMA type I and that they would have followed the same course as patients who have been already diagnosed with SMA type I; we do not know if patients in the NURTURE trial would have progressed to develop SMA type I. Overall, despite encouraging results in this single arm trial, the outcomes should be considered along with the limitations associated with exploratory descriptive results and have limited generalizability.

Patients With Infantile Onset SMA, Including Patients With SMN2 Gene Copy Greater Than Two

Addressing this evidence gap is a phase II, single arm, uncontrolled trial, CS3A, along with the extension study part within SHINE. CS3A enrolled 20 patients with a mean age at first dose of 5.0 months (SD: 2.04). Of these 20 patients, 17 (85%) had two SMN2 gene copies, two (10%) had three SMN2 gene copies, and one patient was of unknown SMN2 gene copy number. As the extension study is still ongoing, the interim analysis covers the results at a point where patients spent an average of approximately 2.7 years between the original CS3A trial and the SHINE extension part.

The interim analysis reports that a total of nine patients (45%) had died or required permanent ventilation. The median time to death or permanent ventilation could not be calculated. However, the lower CI of the 50th percentile was 27.6 weeks. All of these events occurred during the index CS3A study period. Patients showed a mean increase of 7.8 points in HINE score over the baseline score registered at the beginning of the CS3A trial. While no formal minimal clinically important difference definition of the HINE has been found in our search, it is reported in the literature that an increase of more than one point is highly unlikely in patients diagnosed with SMA type 1 (see Appendix 5). The improvement in motor development is further supported by a mean increase of 13.4 points over baseline score in the CHOP INTEND tool.

A potentially important source of bias in these outcomes (and all other outcomes contrasting SHINE with the baseline characteristics of the index studies) is bias due to drop-outs and missing data. [redacted] While all of these patients died during the CS3A and would be captured in a survival analysis, other outcomes, including the HINE, could potentially be biased with unclear direction. Also, since this was a single arm trial, any comparison to baseline values cannot rule out the role of confounding factors and systematic biases. Although, as this is an infantile onset population, the positive results demonstrated in the ENDEAR trial and the deterioration noted in natural history studies can serve in an informal way to attribute the benefits observed over baseline to nusinersen treatment. However, although this trial included patients with three copies of the SMN2 gene, the proportion of these patients was low (10%); with this low percentage of patients with three SMN2 copies, this study cannot address the evidence gap regarding the efficacy of nusinersen in a population of infantile onset SMA with three copies of the SMN2 gene. Overall, generalizability of the results to the patient population with SMA is limited and the outcome should be considered along with the limitations associated with exploratory descriptive results.

Patients With Mixed Infantile and Early Childhood Onset, Including Patients With SMN2 Gene Copy Greater Than Two

Addressing this evidence gap is one phase II, randomized, sham controlled, trial, EMBRACE; the study had an overall exploratory design with no pre-planned statistical comparison. The trial was made to include patients who did not meet the inclusion criteria of ENDEAR or CHERISH. [redacted]

The interpretation of these results shows that patients who enrolled in the nusinersen group showed a mean increase in usage of daily ventilation but also showed a marked mean increase in total HINE score. Considering the severe imbalances in the baseline characteristics, the small sample size, and the exploratory nature of the trial, the results should be treated for each group on their own and considered along with the limitations associated with exploratory descriptive results, and would have limited generalizability.

Patients With Early Childhood SMA Onset, Including Patients With SMN2 Gene Copy Greater Than Two

Addressing this evidence gap is one phase III, randomized, sham controlled, trial, CHERISH. Patients were randomized on a 2:1 ratio to the nusinersen group (N = 84), and to the sham control group (N = 42). Overall, the participants had a mean age of 11.2 months (SD: 3.4) at symptom onset and a mean of 38.2 months (SD: 19.8) from disease onset until

study enrolment. The majority of patients had three copies of the SMN2 gene (n = 111 [88%]). The first primary outcome, the change in HFMSE score from baseline to month 15, demonstrated a statistically significant difference between groups as patients in the nusinersen group exhibited overall improvements in HFMSE score compared with an overall decline in the HFMSE score in patients in the sham control group (least squares mean difference = 5.9 [95% CI, 3.7 to 8.1]). The magnitude of difference is larger than two points, which is reported as an unlikely improvement to be seen in patients with SMA types II or III, also considering that parents have identified a one-point change in this scale as meaningful. Several sensitivity analyses were conducted, largely to test for different approaches in handling of missing data and protocol violations; all of these analyses showed similar results to the base case. The improvement seen in the primary outcome is further supported by a statistically significant difference in the proportion of HFMSE responders (increase of three points or more) at 15 months, where more than half of the patients in the nusinersen group were deemed responders (56.8%) compared with 26.3% in the sham control group, showing a statistically significant difference of 30.5% (95% CI, 12.74 to 48.31). The second secondary outcome in the CHERISH statistical hierarchy, the proportion of patients achieving new motor milestones at 15 months, failed to achieve statistical significance, thus all the remaining outcomes reported in CHERISH fall outside the hierarchy of testing and are considered inconclusive, and any reported *P* value is not adjusted for multiple testing (i.e., is nominal in nature).

Other exploratory outcomes do support the beneficial effect seen in the primary outcome, the change from baseline in the RULM test at 15 months, and in the [redacted]

It is noted, however, that the results of the outcomes that involve capturing large and important milestones were numerically small. Two patients were able to stand alone at 15 months, one in each group, and only one patient was able to walk with assistance (nusinersen group). However, considering the sample size was not powered to capture these outcomes, and that the 2:1 randomization also led to a reduction in the power of a given sample size, any interpretation of the results that did not show statistical significance is not possible.

The main limitation of the CHERISH study lies in the decreased ability to generalize the results due to the intervention being administered on a schedule different from the one indicated by Health Canada. In CHERISH, there was one less loading dose and the maintenance dose was administered six months after the last loading dose; this contrasted the indicated four loading doses and maintenance dose after four months, as indicated by Health Canada. As such, it is unclear if a similar population under Health Canada's indicated dosage regimen would demonstrate similar benefits to those seen in CHERISH. The clinical experts consulted on this review do not expect that this difference in dosage regimen is clinically meaningful.

Patients With Later Childhood Onset, Including Patients With SMN2 Gene Copy Greater Than Two

Addressing this evidence gap are two phase I, single arm, uncontrolled trial, CS1 and CS2; and two extension studies, CS10 and CS12; which all ended up in the SHINE extension study as one pooled study. The studies enrolled a total of 56 patients [redacted]

[redacted]

These were all exploratory descriptive outcomes and no comparative statistical testing was conducted.

A potentially important source of bias in these outcomes (and all other outcomes contrasting SHINE with the baseline characteristics of the index studies) is survivor bias. [redacted] While the manufacturer did attempt to use varying methods of data imputation based on several scenarios of missing data, the long duration of the study period and the deteriorating nature of the disease may lead to overestimation. In addition, patients enrolled in these trials received nusinersen in varying dosages and regimens that differ substantially from the Health Canada–approved indication. Also, since this was a single arm trial, generalizability of the results is very limited. Any comparison to baseline values cannot rule out the role of chance, confounding factors, and systematic biases. With no other randomized trial of similar population and no clear natural history trials, even informal inference regarding the generalizability of these results is difficult to make. Overall, generalizability of the results to the patient population with SMA is limited and the outcome should be considered along with the limitations associated with exploratory descriptive results.

Adult Patients

While two observational case series studies and a letter of the experience of a medical centre in this patient population were submitted as potential information to address this evidence gap, none of these resources provided meaningful quality evidence to allow any interpretation of the potential benefits of nusinersen for treating adult patients with SMA. This population remains a strong evidence gap and requires more studies to address the question of clinical efficacy in treating the adult population.

Patients Diagnosed Before Seven Months of Age But Who Receive Treatment After Seven Months of Age

Addressing this patient population are two observational case series (Aragon 2018 and Pane 2018) and the extension part of ENDEAR within SHINE. Specifically, patients who were randomized in ENDEAR into the sham control group and subsequently received nusinersen in the extension phase can provide insights in this population. [redacted]

Patients enrolled in the Aragon 2018 (N = 33) expanded access program had a median age at first dose of 21.3 months (range: 8.3 to 113.1 months), were 45.5% females, and 51.5% had three SMN2 gene copies. These patients spent a median of 26.0 months from disease onset to first dose (range: 4.3 to 109.1) and were of a median age of four months when first signs of the disease manifested (range: 1.5 to 5 months). Of these patients, 51.5% required non-invasive ventilation more than 16 hours per day and 27.3% required a feeding tube or had a gastrostomy. Patients enrolled in the Pane 2018 (N = 104) expanded access program had an age range of 0 to 19 years, 62.5% of patients had two SMN2 gene copies, and 23.1% had three SMN2 gene copies.

[redacted] Aragon 2018 reports a median HINE score of 3.5 (range: 0 to 11) at six months contrasted with the baseline median value of 1 (range 0 to 6). Pane 2018 reported that the mean change in HINE score was 1.3 (SD: 2.2). [redacted] Aragon 2018 reports a median score of 35 (range: 19 to 51) at six months contrasted with the baseline median value of 31.5 (range: 6 to 45). Pane 2018 did not provide a summary measure for this outcome; instead, they reported that the CHOP INTEND changes ranged between –7 and 27 points.

When contrasting the results of this patient population with that of ENDEAR, the numerical magnitude of gain is relatively smaller in patients that begin treatment after seven months of age. Also, the improvement seen in patients who were already in nusinersen, while maintained, did not increase nearly as substantially as demonstrated in the ENDEAR trial. This may be due to the ceiling effect in the HINE and CHOP INTEND tools, or could potentially be due to a plateauing of effect of the benefits of nusinersen. These observations are based on an informal contrast of the results from ENDEAR and the extension phase of

ENDEAR in the SHINE study. As such, it carries no statistical inference and does not provide strong evidence regarding the magnitude of benefit in patients treated after seven months compared with patients treated before seven months of age. The two non-comparative case series studies may serve as supporting evidence of the benefits observed in the SHINE results. However, all three studies are non-comparative in nature and any comparison to baseline values cannot rule out the role of chance, confounding factors, and systematic biases. As such, these outcomes should be treated with the same limitations as a descriptive exploratory outcome, with limited generalizability.

Patients With SMA Who Require Ventilation

Addressing this patient population is one observational case series. More than half of the patients enrolled in the Pechmann 2018 (N = 61) expanded access program required either non-invasive ventilation or a tracheostomy. Patients had a median age at first dose of 2.8 months (range: 0 to 6 months), were 49.2% females, and 32.8% had three SMN2 gene copies. These patients spent a median of 2.8 months from disease onset to first dose (range: 0 to 6) and were of a median age of 2.8 months when the first signs of the disease manifested (range: 0 to 6 months).

At six months after nusinersen treatment, Pechmann 2018 reports a CHOP INTEND mean change from baseline of 9.0 (SD: 8.0) points — starting from a mean baseline value of 22.3 to a mean value at assessment date of 31.2 (SD: 16.2). In a subgroup of patients that started the study requiring permanent ventilation (18 patients [30%]), the mean change in the CHOP INTEND score from baseline was 5.6 points (SD: 7.5). Further, Pechmann 2018 reports a HINE mean change from baseline of 1.4 (SD 2.1) points — starting from a mean baseline value of 0.8 to a mean value at assessment date of 2.5 (SD: 3.3). These results were not reported in the subgroup of patients that started the study requiring permanent ventilation. Ventilation use saw an increase in the proportion of patients requiring more than 16 hours per day of ventilation or tracheostomy, from 30% at baseline to 41% at the end of the study, while the proportion of patients who did not require ventilation decreased from 43% at baseline to 31% at the end of the study.

The results from Pechmann are descriptive and suffer from the many limitations associated with descriptive results from observational studies. It is not possible to assign any of the outcomes observed as solely due to the effect of nusinersen, and any comparison to baseline values cannot rule out the role of chance, confounding factors, and systematic biases. However, the outcomes reported are, overall, in the same direction as reported in the ENDEAR trial. It is noted, however, that, numerically, patients on permanent ventilation gained considerably less than those who did not need ventilation. While an increase in the ventilation requirement was also reported, a number of patients in the endear trial treated with nusinersen also required ventilation. Without a comparative group, we cannot assess the impact of nusinersen on patients with SMA who require ventilation.

Overview of All Spinal Muscular Atrophy Population

While there is a large number of studies that can provide insight into the clinical benefit of nusinersen in patients with SMA, only two are to be considered higher-quality evidence: ENDEAR and CHERISH. Together these studies cover infantile onset patients with SMA who are seven months of age or younger (ENDEAR) and early childhood onset patients with SMA who are 12 years of age or younger (CHERISH). There is a population of patients with SMA that exist between these two studies in the form of infantile onset patients with SMA who are older than seven months by the time of treatment initiation. Evidence addressing

this in-between population comes from an extension study and two case series studies with results that are descriptive in nature and cannot be generalized. However, considering the abundance of natural history data on patients with SMA type I, these three studies may suggest a beneficial effect that is unlikely to be seen in untreated patients. However, such informal inferences are commonly associates with overestimation of the treatment effect.

The benefits of nusinersen in patients with SMA who are older than 12 years or have SMA onset at a later time in their childhood is not as clear as the other two population addressed by ENDEAR and CHERISH. No comparative evidence exists in this population and the extension study data that may provide some insights have several limitations. A larger evidence gap still exist in adult patients with SMA where there is no satisfactory clinical evidence to provide insight into the potential clinical benefits of nusinersen beyond subjective reporting of individual patients experiences. Considering that the last two population with SMA also have the largest heterogeneity in disease presentation and progression, it is not possible to generalize the results reported in ENDEAR and CHERISH into them, and basic questions regarding the existence of a beneficial effect of nusinersen beyond placebo and other confounders exist.

A persisting evidence gap is the clinical effect of nusinersen on the respiratory function and ventilation status of patients who are already on permanent ventilation by the time they receive nusinersen. The only available evidence is in the form of half the population of a case series study, where patients who were on permanent ventilation showed a smaller numerical improvement in CHOP INTEND than patients who did not require permanent ventilation. The study also described a higher proportion of patients on permanent ventilation at the end of the study than at the beginning. None of the manufacturer trials allowed the inclusion of patients who require permanent ventilation. The mechanism of action of nusinersen, where the over expression of the SMN2 gene help maintain existing motor neuron but would not have an effect on the already damaged motor neuron, may suggest that any effect of nusinersen on pulmonary function of patients who require permanent ventilation is potentially small. This also observed in the infantile onset studies where, despite treatment with nusinersen, a proportion of patients ended up requiring permanent ventilation. Based on the present level of evidence, and the consideration of the mechanism of action of nusinersen, any potential beneficial effect of nusinersen on patients that require permanent ventilation by the time of treatment initiation is unknown.

Harms

Throughout all the manufacturer-provided trials, the most common AEs are related to infections and/or respiratory problems, two common complications of SMA. A number of AEs related to the lumbar puncture procedure were also frequently reported in several trials. The Health Canada product monograph suggests that the majority of the reported AEs are related to the disease process or the lumbar puncture procedure.[25] The included observational studies do not provide sufficient reporting of harms in their respective case series.

Potential Place in Therapy

The following is based on information and opinions provided by the clinical experts consulted by CDR for the purpose of this review.

SMA results in the irreversible loss of motor neurons and motor nerves. The loss of these nerves causes skeletal muscles to become progressively weaker, giving rise to swallowing

problems and breathing difficulties and/or weakness of the limbs and trunk. A natural history study using a specialized neurophysiological technique called motor unit number estimation has found that there is a relatively rapid loss of motor neurons early in the course of the disease followed by a more gradual decline.[10] As children's muscle fibres undergo an increase in size over the first few years of life (a process known as physiological hypertrophy), any intervention to prevent the irreversible loss of motor neurons and consequently allow muscle fibres the potential for more normal development is advantageous; consequently, the optimal time for intervention is early in the course of the disease before rapid and irreversible loss of motor neurons has occurred. While early diagnosis of SMA and treatment is important in all patients, it is particularly important in patients with type I and type II SMA, as these patients will develop move severe SMA symptoms more rapidly than other types of patients with SMA.

SMA is diagnosed in Canada via genetic testing. Initial testing evaluates for the homozygous 5q deletion within the SMN1 gene, which identifies 95% of cases. If negative, SMN1 gene sequencing will be performed as a second step. Nerve conduction studies and electromyography is performed in some patients; however, even when evidence of a motor neuropathy is identified on this study, it is followed up with confirmatory genetic testing.

Motor function is the most important aspect of the disease that affects patients' QoL; deterioration of motor function leads to loss of ambulation, difficulties in verbal communication, and inability to handle secretions. Deterioration of respiratory function is a critical aspect that may lead to severe and life-threatening complications. In patients who lose ambulation, maintaining function in the upper limbs becomes important.

Current standard of care practice for patients with genetically confirmed SMA includes surveillance and anticipatory management of symptoms. Patients with SMA receive monitoring for 1) growth, gastrointestinal function, and nutrition; 2) respiratory complications; and 3) orthopaedic complications (i.e., scoliosis and/or contractures).

Anticipatory management of respiratory complications is particularly important for children with SMA type I and type II because these patients are at high risk of having a weak cough with impaired clearance of airway secretions, nocturnal hypoventilation, and recurrent pulmonary infections. Patients who are diagnosed with SMA type II usually fail to achieve new motor milestones; thus, the most impactful outcome for these patients is achieving and maintaining new motor milestones. Consequently, assessment of respiratory function and motor function, through the achievement of major milestones, are key outcomes to assess disease progression in patients with type I and type II SMA. This standard of care is not expected to change with emerging therapies; however, it is hoped that the progression and complications of this disease would be ameliorated by a treatment that delayed the progression of disease.

Patients with SMA type III make up approximately 10% to 20% of all patients with SMA. These patients typically have developed the ability to walk, but this milestone can be lost as the disease progresses. Patients who manifest the disease shortly after achieving the milestone of walking and who may have a fewer number of SMN2 genes are more likely to lose their ability to walk. Early treatment of patients with SMA type III, particularly young patients with apparent rapid disease progression, would have the theoretical potential of preventing loss of ambulation with the significant gain of independence and avoidance of numerous medical complications that can result in non-ambulatory patients. Because patients with type III SMA usually lose motor milestones, maintaining motor milestones such as walking is an important outcome for these patients.

Adult patients with SMA are typically either patients with SMA type III who have reached adulthood, or are patients diagnosed as SMA type IV where symptoms manifested after reaching adulthood. Patients with SMA type III who have reached adulthood make up a larger group of the adult patients with SMA seen in clinical practice than patients with type IV SMA. Of patients with SMA type III who reach adulthood and are able to walk, risk of falls, ability to use stairs, and the distance they are able to walk before feeling fatigued are the most common issues reported in the clinic. Thus, an assessment of the distance patients are able to walk is commonly used in clinical practice to assess disease progression. If a patient loses the ability to walk, maintaining upper limb function to allow use of a wheelchair becomes an important outcome.

According to the clinical experts consulted for this review, nusinersen would be beneficial to all infants with SMA type I, regardless of SMN2 gene copy number. Based on the available clinical data, the mechanism of action of nusinersen, and clinical experience, the two most important factors in determining an optimal response to treatment with nusinersen are time since symptom onset and the age of the patient; this is due to the fact that motor neuron deterioration is irreversible and early intervention is essential to prevent deterioration of motor function. The shorter the duration since symptom onset, the younger the patient, and the more severe the prognosis (based on genetic testing), the higher the likelihood of observing a clinically meaningful response to treatment with a drug such as nusinersen. Clinical experts believe that an assessment of whether patients have responded to treatment should be carried out approximately 18 months after the initiation of the first dose of nusinersen, when patients are expected to have gained and maintained new motor milestones.

In adults with SMA (including type IV and type III who reach adulthood), it is unclear what the potential benefits of treatment with a drug such as nusinersen would be, as clinical experience and natural history data indicate a plateau of the disease progression in the adult population. It is also unknown which adult patients with SMA are likely to respond to treatment. Progression of SMA in adult patients is slow, and signs of progression may become clinically detectable only every five years. As such, if an adult patient were to be treated with nusinersen, it is unlikely to observe the effects of the treatment as quickly as in a younger population where the disease progression is much faster. Potentially, assessment of the response of treatment may be conducted after five years of treatment, when the signs of disease progression usually manifest.

Implementation of nusinersen treatment may present some challenges. Patients with potential spinal deformity would likely require a radiographic guided lumbar puncture. While access to radiographic services may not be very challenging in the pediatric population, adults may be deferred frequently due to the use of these services for urgent stroke management. In addition, the most appropriate site at which treatment should be administered requires further discussion to take into account the needs of patients who may live in areas that are not in close proximity to a tertiary medical facility. Ideally, assessment of motor function should be conducted by a physiotherapist before every injection, which takes place approximately every four months; this might not be feasible due to the length of time such assessments would take and the busy schedule of physiotherapists.

Because pre-symptomatic treatment with nusinersen offers the greatest potential for preventing irreversible loss of motor neurons, physicians and public health agencies must consider what can be done to ensure early diagnosis, including the potential for incorporating SMA into provincial newborn screening programs. The potential benefit of pre-

symptomatic treatment is especially important for infants with two copies of the SMN2 gene, who are most likely to develop SMA type I.

Conclusions

Higher-quality evidence assessing the clinical efficacy of nusinersen in the population with SMA is present in the ENDEAR and CHERISH studies. The ENDEAR study was reviewed in the original submission and was used as the basis of the original CDEC recommendation. CHERISH demonstrated a statistically significant, and potentially clinically meaningful, change in the HFMSE score from baseline in the nusinersen group when compared with the sham control group. The result of this primary outcome was further supported by a statistically significant secondary outcome of HFMSE responders and by the exploratory outcomes of change in RULM, PedsQL (parent, total score), and hospitalization. Exploratory outcomes were not adjusted for multiple testing. The main limitation in CHERISH is the dosage schedule of nusinersen not matching Health Canada's approved schedule, which reduces the generalizability of the results. One ongoing single arm study, NURTURE, addressed SMA pre-symptomatic patients with two or three SMN2 gene copies, and was available for inclusion; [redacted]. However, due to the lack of a control group we are unable to determine the extent of benefit attributed to nusinersen treatment. Also, due the potential variability in disease progression of pre-symptomatic patients, the drug protective mechanism of action, and the deteriorating nature of the condition, the informal contrast of findings from pre-symptomatic patients with SMA type I natural history is likely to overestimate the effect due to the assumption that all patients in NURTURE would have progressed to develop SMA type I. Studies addressing the older patient population with later SMA onset (likely to be considered as SMA type III) were single arm descriptive studies. While these studies do show an improvement in motor development and function, considering the heterogeneity of the disease presentation and progression in this population, the results from the single arm studies do not provide high-quality evidence of the magnitude of the benefit of nusinersen beyond potential confounders, expectation bias, and other systematic biases. Studies addressing the adult population with SMA do not provide informative evidence due to the limitations associated in the design, conduct, and reporting of these studies. The lack of a control in the single arm studies limits the generalizability of the results, and an informal contrast with the natural history of patients with SMA is highly susceptible to overestimation of the treatment effect. No sufficient evidence exists to address the potential beneficial effect of nusinersen in patients with SMA who require permanent ventilation at treatment initiation.

The collective evidence suggests that harms associated with nusinersen are largely related to the disease progression and the complications that may arise due to the lumbar puncture administration of nusinersen.

Appendix 1: Patient Input Summary

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Groups Supplying Input

One submission was prepared jointly by the Canadian Organization for Rare Disorders (CORD) and Cure SMA Canada, both registered charities. CORD advocates on behalf of those with rare disorders and provides support to patient groups. Cure SMA Canada provides support to those affected by spinal muscular atrophy (SMA) and provides information and resources to families, communities, and health professionals. A second submission was prepared by Muscular Dystrophy Canada (MDC), a national, non-profit organization that provides support to Canadians affected by neuromuscular disorders by helping them navigate systems; access resources; and providing information, funding, and education. In the past two years, CORD and Cure SMA Canada have received between $10,000 and $50,000 in funding from Biogen, while MDC has received funding between $0 and $5,000 from Biogen. No other conflicts of interest were declared.

2. Condition-Related Information

The joint submission of CORD and Cure SMA Canada was based on the results of one focus group, four interviews, and a survey from the original submission, as well as from semi-structured interviews (conducted in August 2018) of 11 families of patients with Spinraza experience for this submission (CADTH is unsure of how these families were identified). Most of the respondents from the original submission were caregivers and family members, while the 11 families that were interviewed had patients with a range of SMA types (three were classified as type I, four were classified as type II, three were classified as type III, and one patient was an individual who had started Spinraza at birth and had no symptoms of SMA at one year of age [SMA type not confirmed]). In order to ascertain the perspective of patients with SMA for this submission, MDC Neuromuscular Service Specialists conducted interviews (in person or by telephone) with 265 caregivers and 125 patients living with SMA between July 23 and August 14, 2018 (all SMA types were represented). The remainder of this appendix is based on information gathered through these sources.

SMA affects patients with widely ranging degrees of severity depending on age of onset. SMA type I presents by the age of six months and is the most common genetic cause of infant mortality. In SMA type II, age of onset is six to 18 months and patients have delayed motor milestones, respiratory issues, and the possibly of a shortened life expectancy. Patients with SMA type III are those with onset from 18 months to 18 years of age and they experience muscle weakness. SMA type IV is adult onset with varying degrees of muscle weakness. Common to all types of SMA is a progressive decline in muscle function.

Reactions to receiving an SMA diagnosis are overwhelmingly negative, with feelings of despair and frustration over the lack of effective treatments for SMA. The survey found significant proportions of respondents with major problems or inability in each of the following areas: walking, muscle strength (lack of weakness, pain, or fatigue), fine motor skills, (deep) breathing, and swallowing or feeding. Inability to walk means relying on wheelchairs and other mobility aids and dealing with associated barriers. Assistance may be required to transfer to and from mobility aids. Those who can walk with assistance may not be able to get up, use the stairs, bathe, or use the toilet independently. Young patients also miss out on typical childhood experiences such as using the playground. In more severe

cases, patients cannot execute basic movements such as sitting up and require help with needs such as transfers as well as positioning in wheelchairs and in beds. One parent of a patient with type III SMA noted their son “is currently walking for short distances, and is gradually losing his mobility. He will soon spend most of his time in a motorized wheelchair.” Of their son with type II SMA, one parent said, “it affects most aspects of our life. He requires daily care giving from getting dressed and eating to toileting and bathing. I’m a single mother and he’s in my care the majority of the time, so these responsibilities are placed on me. I’ve had to give up my full time job as the demands of caring for him are great.” Loss of independence and reliance on assistance for daily care tasks leads to extra time and difficulty in navigating situations that would be simple for others. Difficulty in swallowing may necessitate use of a feeding tube and difficulty in breathing maybe lead to reliance on mechanical ventilation during nights or around the clock. The parent of an adult patient with SMA type III stated, “Quality of life is different for everyone. Improved quality of life for my son could mean lifting a glass to his mouth, rolling over in bed, or toileting himself unaided. Improved quality of life (QoL) could mean taking a deeper breath or holding his girlfriend in his arms.” For young adults, all of these difficulties present barriers to moving away from home, finding work, and being independent. There is also awareness of the burden placed on family members.

Progressive, life-changing loss of motor function and abilities has devastating effects, with changes such as “walking to standing to power chair in 5 years” and losing the ability to perform daily hygiene tasks or even breathe and swallow independently. There is great frustration over this progressive decline for adults and children alike, with one patient calling it “the hardest part.” One young adult confined to a wheelchair expressed expectations of further decline and not being able to achieve milestones in the future such as home or car ownership or having children. In extreme cases, patients with SMA may have no choice but to reside in a long-term care facility, which can lead to further mental health issues (such as depression and anxiety). In some circumstances, some long-term care facilities are not able to accommodate these complex care situations, leaving the patient and family at a loss.

The lives of families and caregivers of patients with SMA are profoundly affected, with one parent stating, “SMA is all encompassing.” A lot of time and physical support goes into caring for a patient with SMA and often a family member has to reduce or leave employment to accommodate appointments and provide constant monitoring and assistance. Physical care can be complex and tough on the body (e.g., transfers). Patients are vulnerable to illness, leading to difficulty and anxiety associated with going out in public, attending social functions, and travelling, all of which have an isolating effect on families. As one parent stated, SMA “impacts every aspect of daily living as much for the person affected than to the parents/caregiver. Whether it be a need in a physical task such as transfers, picking up/holding items, eating, toileting or assuring exercising/stretching time, making sure they spend time in a standing position or that their posture is protected and well-adjusted to prevent quick progression of scoliosis and hip dysplasia, there is always something to assist with or worry about. This is without mentioning controlling the common colds to avoid potential life threating lung infections, cough assist machines to help normal lung function and Bi-PAP machines at nighttime to promote a good night sleep and a healthy oxygen and CO_2 flow.” The progression in paralysis and loss of function has a psychological and emotional impact on families, with one parent describing it as “frustrating and heartbreaking to witness.” Caregivers struggle with fear of the unknown and burnout. There is also the financial burden of out-of-pocket costs, as well as difficulties in securing insurance coverage and government funding. Families are the main caregivers out of necessity because outside resources are lacking.

3. Current Therapy-Related Information

Treatments for SMA include mobility aids, breathing support, spinal treatment, feeding tubes, physiotherapy, removal of tonsils and adenoids, and medications. Despite some improvements to QoL with some of the aforementioned treatments, patients and caregivers are well aware that current care only helps with symptoms and does not treat SMA itself or stop its progression.

Parents of infants with type I SMA would like to see treatment that improves breathing as well as ability to feed and perform small movements like rolling over. Parents in general would like a treatment that reduces pain, controls loss of mobility, improves muscle function, and allows their children to continue performing activities such as independent daily self-care (feeding, operating a wheelchair, writing, toileting, bathing) for as long as possible. Patients themselves place importance on slowing the disease progression and maintaining independence that would allow them to continue with school or work.

4. Expectations and Experience About the Drug Being Reviewed

In patients without Spinraza experience, there is hope that Spinraza will improve overall QoL, maintain or restore respiratory function and muscle strength and movement, slow or stop disease progression, and lessen dependence on others. Those newly diagnosed hope it will prevent symptoms from manifesting. Interviewees felt that Spinraza could prevent the irreversible loss of motor neurons, reducing the risk of losing mobility and ability to perform self-care tasks, and the risk of requiring respiratory support.

In patients who had some experience with Spinraza (between seven months and three years) from the 11 families interviewed by CORD and Cure SMA Canada, all respondents observed significant improvements that demonstrated improvements in functioning, QoL, and family impact. Six of these patients had obtained access to Spinraza through clinical trials, three patients had access through workplace private insurance plans, and two of the patients privately funded their access. Some variability in response was noted by the interviewees that were dependent on the SMA type; however, all patients (regardless of SMA type) experienced improvements in functioning. This translated into improved participation in daily living activities, school performance, and better QoL for patients and their families.

Type I SMA

Based on the parent reports, patients with SMA type I experienced varied but noticeable improvements in core physical abilities, namely, sitting, rolling over, standing, using a walker, and walking. One parent stated, “She is now able to sit in a chair without choking,” for a child who never experienced sitting, while another parent noted that her son who had been on Spinraza for almost three years and who had experienced significant loss of function “now can sit independently for two minutes at a time, can sit in power chair for 3 hours at a time, can talk, holds his own head up, can lift his legs.” There were also improvements observed in terms of breathing, eating, and talking in patients with type I SMA on Spinraza. The ability to be off a ventilator for even some period of time was observed by some parents of children with type I SMA, with one parent stating, “She is no longer ventilated 24 hours and can breathe on her own for half an hour at time, so we can do daily activities like get dressed or transfer.” Another parent of a child who was unable to breathe or sit independently on her own noted that upon receiving Spinraza, “she drives a manual wheelchair around and can go swimming.” One 18-year-old patient who used to use a

microphone was able to project his voice loud enough to be heard with Spinraza treatment. In addition to the aforementioned, an increase in motor function was observed, especially in relation to hand and finger movement. Said the mom of a child with type I SMA who had lost the ability to use her hands, “She can hold a marker and now won’t stop colouring; she is also learning sign language,” while the priority to maintain function in one 18-year-old boy’s three usable fingers was maintained: “He enjoys using his computer and has better stamina and control with his fingers so will be on the computer for a few hours a day without becoming tired. This is important since he is starting college in the fall.” Improvements in illness and recovery, followed by less hospitalizations, were also observed, as evidenced by one mother, “She went from three to four illnesses a year lasting three to four weeks to now just one lasting two to three days.” Improvements in family impact were noted by one parent whose unaffected sibling was experiencing severe depression and anxiety due to his perceived lack of attention and care. Once his sister started receiving Spinraza, she noted, “With less hospitalization, there has been a 360-change in [brother] … significantly happier, helps in his sister’s care.” In terms of positive social and health system impact, one mother stated, “Small functional improvements (example that patient can cough on her own) can eliminate health care spending in the long run; since receiving therapy, hospital visit duration and number of visits has declined significantly; (example, one-night stay versus multiple weeks/months); now receiving care at outpatient clinic rather than the hospital ICU.”

Type II SMA

Improvements were observed in physical/motor activities, breathing, eating, talking, illness and recovery, and with regard to the impact on families and the social and health systems in patients classified as having type II SMA who were receiving Spinraza. Some parents observed pronounced improvements in physical function, with one mother stating that her five-year-old child who had been on Spinraza for three years and who “could never do 4-point crawl but could only do ‘commando crawl,’” had stopped moving her legs and had stopped rolling; “she is walking with a walker and some supports.” Another parent whose six-year-old child had been on treatment for about 10 months stated, “Since treatment she has gained the ability to fully undress and dress herself (‘which is amazing’); she can get from her bed into her wheelchair on her own and doesn’t need help with small tasks such as removing marker lids; she is playing the piano again (she lost the ability to play with both hands just before sixth birthday); and she can get off the toilet on her own.” Breathing and swallowing were both notably improved in these patients. In addition, one parent noted that, “A few weeks ago she called for me in her sleep; she had rolled over in her bed and got herself tangled up in her blanket. She hadn’t rolled over since she was 8 months old, and the strength of her voice … was significant.” Patients with type II SMA were also observed to be able to better fend off illness, with one parent stating, “this is the first winter he was not hospitalized; from two to three respiratory visits a year versus none this year.” In addition, some parents were able to increase their days of employment and increase family travel time due to the increasing abilities of their children and their increased confidence in their children’s abilities.

Type III SMA

Improvements levels of independence were observed in patients with type III SMA, particularly in terms of being able to get up, walk around, and having more energy. As one parent stated, “Now he is able to get up on his own from the ground independently and can now walk upstairs (slowly),” while another parent noted, “She still falls but is able to walk around and not get tired or be carried.” The parent of a 17-year-old with type III SMA who

had a spinal fusion at 13 and lost the ability to walk stated that her child “now can balance [standing] and can lift arms above head; is doing weightlifting and biking.” The importance of improvements in independence and confidence cannot be emphasized enough for not only the patients but for their families, as one parent stated, “She can get from her bed into her wheelchair on her own …and start getting ready … without assistance. I cannot emphasize enough what a huge impact this has on the family.” The mother of one 17-year-old additionally said, “If you are in university/school and your goal is to keep your fingers strong so that you can continue attending school then that is just as important as a 12-year old needing to continue to walk.” Improvements in strength, confidence, stamina, and eating have also been observed. As one parent stated about her daughter, “She is not as tired in the afternoons/early evening, more ability to eat meals; stays up at night to watch a movie after dinner.” One older patient themselves also noted that their strength is slowly improving.

Most parents indicated very few side effects, if any, related to the drug or its administration. The most common side effects were constipation and headache. Once problems associated with injections were solved (e.g., fasting, lack of sedation), subsequent injections went well. Side effects and anxiety were mentioned with lumbar puncture but were considered manageable. Challenges associated with treatment include obtaining access, travelling with a patient with complex care needs, and the time off work and costs associated with travelling.

4. Additional Information

Common concerns expressed with the current access to Spinraza include affordability, restriction of availability to SMA type I, difficulty in travel, difficulty in navigating the process, and access in rural areas. In addition, there are concerns that the treatment is not considered urgent for patients with types II and III SMA when, in fact, there can be just as urgent a need in these patients.

The following were the responses of the interviewees when they were asked if Spinraza should be stopped in cases where the clinical team has decided that treatment was not working in the patient:

- “This is a tricky one to answer because [others] may not be seeing progress but [the child] may not be declining either; I feel like the physio test and the nerve test are all good examples but they do not [tell everything].”
- “The last time [son] received his [drug trial] in July, he didn’t do very well because he was agitated, frustrated, had just had a blood test so the results didn’t show how he was actually doing. It was not an accurate representation of real world situation and ability.”
- “It needs to be taken into consideration that these are kids and they aren’t going to do exactly what you want, so the testing is not going to be perfect or accurate. I know it’s not perfect for my son anyway.”

Appendix 2: Literature Search Strategy

1.1 Medline Search

(Spinraza* or Nusinersen or ASO-10-27 or ASO1027 or ISIS 396443 or ISIS396443 or ISIS SMN?Rx? or ISISSMN?Rx? or IONIS SMN?Rx? or IONISSMN?Rx? or 5Z9SP3X666).ti,ab,kf,ot,hw,rn,nm.

1.2 Embase Search

*nusinersen/

OR

(Spinraza* or Nusinersen or ASO-10-27 or ASO1027 or ISIS 396443 or ISIS396443 or ISIS SMN?Rx? or ISISSMN?Rx? or IONIS SMN?Rx? or IONISSMN?Rx?).ti,ab,kw,dq.

1.3 Medline, Embase Search History (128)

Database(s): **Embase** 1974 to 2018 August 21**, Ovid MEDLINE(R) ALL** 1946 to August 21, 2018 Search Strategy:

#	Searches	Results
1	(Spinraza* or Nusinersen or ASO-10-27 or ASO1027 or ISIS 396443 or ISIS396443 or ISIS SMN?Rx? or ISISSMN?Rx? or IONIS SMN?Rx? or IONISSMN?Rx? or 5Z9SP3X666).ti,ab,kf,ot,hw,rn,nm.	348
2	1 use medall	104
3	*nusinersen/	97
4	(Spinraza* or Nusinersen or ASO-10-27 or ASO1027 or ISIS 396443 or ISIS396443 or ISIS SMN?Rx? or ISISSMN?Rx? or IONIS SMN?Rx? or IONISSMN?Rx?).ti,ab,kw,dq.	269
5	3 or 4	277
6	5 use oemezd	177
7	6 not conference abstract.pt.	107
8	2 or 7	211
9	remove duplicates from 8	128

1.4 PubMed Search

“nusinersen” [Supplementary Concept]

OR

Spinraza*[tiab] OR Nusinersen[tiab] OR ASO-10-27[tiab] OR ASO1027[tiab] OR ISIS 396443[tiab] OR ISIS396443[tiab] OR ISIS SMNRx[tiab] OR ISISSMNRx[tiab] OR IONIS SMNRx[tiab] OR IONISSMNRx[tiab] OR 5Z9SP3X666

1.5 PubMed Search History (10)

Search	Query	Items found
#5	Search **(#3 AND #4)**	10
#4	Search **publisher[sb]**	534,617
#3	Search **(#1 OR #2)**	102
#2	Search **(Spinraza*[tiab] OR Nusinersen[tiab] OR ASO-10-27[tiab] OR ASO1027[tiab] OR ISIS 396443[tiab] OR ISIS396443[tiab] OR ISIS SMNRx[tiab] OR ISISSMNRx[tiab] OR IONIS SMNRx[tiab] OR IONISSMNRx[tiab] OR 5Z9SP3X666)**	97
#1	Search **"nusinersen" [Supplementary Concept]**	33

Appendix 3: Excluded Studies

Table 31: Excluded Studies

Reference	Reason for Exclusion
Farrar 2018[47]	Outcome
Luu 2017[48]	Outcome
Pechmann 2018[49]	Outcome

CADTH

Appendix 4: Previous Spinraza CADTH Canadian Drug Expert Committee Recommendation

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(FINAL)

Nusinersen (Spinraza — Biogen Canada Inc.)
Indication: Treatment of 5q Spinal Muscular Atrophy

RECOMMENDATION:

The CADTH Canadian Drug Expert Committee (CDEC) recommends that nusinersen be reimbursed for the treatment of 5q Spinal Muscular Atrophy (SMA), if the following criteria and conditions are met:

Criteria:

- Genetic documentation of 5q SMA homozygous gene deletion, homozygous mutation, or compound heterozygote.
- Genetic documentation of two copies of the survival motor neuron 2 (SMN2) gene.
- Disease duration less than 26 weeks with onset of clinical signs and symptoms consistent with SMA after the first week after birth and on or before 7 months of age.
- Patient is not currently requiring permanent invasive ventilation.
- Treatment should be discontinued if, prior to the fifth dose or every subsequent dose of nusinersen:
  - there is no demonstrated maintenance of motor milestone function (as assessed using the Hammersmith Infant Neurological Examination [HINE] Section 2); or
  - there is no demonstrated improvement in motor milestone function (as assessed using the HINE Section 2); or
  - if permanent invasive ventilation is required.

Conditions:

- Substantial reduction in price.
- Under the care of a specialist with experience in the diagnosis and management of SMA.
- Collection of real-world evidence on the use of nusinersen for the treatment of SMA.

CADTH

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

NUSINERSEN (SPINRAZA — BIOGEN CANADA INC.)

Indication: Treatment of 5q Spinal Muscular Atrophy

Recommendation

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- Genetic documentation of 5q SMA homozygous gene deletion, homozygous mutation, or compound heterozygote.
- Genetic documentation of two copies of the survival motor neuron 2 (SMN2) gene.
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- Patient is not currently requiring permanent invasive ventilation.
- Treatment should be discontinued if, prior to the fifth dose or every subsequent dose of nusinersen:
  - there is no demonstrated maintenance of motor milestone function (as assessed using the Hammersmith Infant Neurological Examination [HINE] Section 2); or
  - there is no demonstrated improvement in motor milestone function (as assessed using the HINE Section 2); or
  - if permanent invasive ventilation is required.

Conditions

- Substantial reduction in price.
- Under the care of a specialist with experience in the diagnosis and management of SMA.
- Collection of real-world evidence on the use of nusinersen for the treatment of SMA.

Reasons for the Recommendation

1. In one randomized, double-blind, sham controlled, phase III clinical trial (ENDEAR, N = 121), patients up to seven months of age with diagnosed infantile-onset SMA (duration of disease 0 to 26 weeks) and two copies of the SMN2 gene, had improved motor milestone development with nusinersen compared with sham procedure (between-group difference in the percentage of HINE Section 2 responders of 50.7% [95% CI, 31.8% to 66.5%]), and a lower risk of death or permanent ventilation (39% versus 68%, hazard ratio 0.53 [95% CI, 0.32 to 0.89]). Patients were not eligible for inclusion in the ENDEAR trial if they had signs and symptoms of SMA present at birth or within the first week after birth. No patients in the ENDEAR study required permanent ventilation at baseline.
2. SMA is a rare, genetic, life-threatening, and seriously debilitating neuromuscular disorder that has a heavy burden on caregivers and the health care system. There is an absence of clinically effective drug and non-drug alternative treatments.
3. Based on clinical expert opinion and in consideration of prioritizing patients most likely to benefit from nusinersen, use of nusinersen should be preferentially directed toward patients with SMA who have demonstrated objective improvement in motor outcomes and deferral of permanent mechanical ventilation. In the ENDEAR trial, 36 out of 73 patients (49%) receiving nusinersen were not considered motor milestone responders, and 18 out of 80 (23%) required permanent ventilation.
4. CADTH Common Drug Review (CDR) reanalysis of a cost-utility model submitted by the manufacturer found that nusinersen was unlikely to be cost-effective at the submitted price, with costs per quality-adjusted life-year (QALY) of $9.2 million for SMA type I and $24.4 million for SMA type II. Results for SMA type III were uncertain due to lack of appropriate clinical data, but were estimated at $7.4 million per QALY. Under a scenario of a 95% price reduction for nusinersen, incremental cost-utility ratios (ICURs) still exceed $400,000 per QALY.

Of Note

- CDEC noted that the clinical trial meeting the inclusion criteria of the CDR systematic review focused only on one subset of SMA patients (patients likely to develop SMA type I). There was insufficient evidence regarding the efficacy and safety of

nusinersen in other patient populations, including patients with symptom onset at birth or within one week of birth, patients with advanced SMA who require ventilation, patients older than seven months of age, patients with more than two copies of the SMN2 gene, patients diagnosed at later stages of disease, and patients who are pre-symptomatic. The clinical and cost-effectiveness of treatment with nusinersen in such scenarios is unknown, and there is a lack of data to assess the efficacy and safety of continued use of nusinersen over the long term, regardless of patient population.

- Given that some patients do not respond to treatment with nusinersen, CDEC discussed the importance of criteria to allow for the assessment of whether to continue treating a patient with nusinersen after a specified duration of time. The committee recognized that maintenance of motor function may be considered a meaningful response to treatment in some patients, whereas an improvement in motor functioning may be desirable in others. CDEC recognized that motor function **or** the need for permanent invasive ventilation may necessitate a decision to discontinue treatment with nusinersen. The committee noted that there are several reasons for, and types of, respiratory support (e.g., invasive or non-invasive ventilation, nighttime versus daytime ventilation), and considered that patients requiring a permanent, invasive form of ventilation should be discontinued from treatment with nusinersen given that ventilation is unlikely to be reversible and there is no evidence that nusinersen is efficacious in such patients. A minimum of six months of treatment with nusinersen was considered by the committee to be a sufficient duration to assess the appropriateness of continuing a patient on nusinersen based on their response to treatment. At six months, patients would be old enough for the treating physician to perform an assessment of motor function, and the timing would equate to the approximate timing of administration of the fifth dose of nusinersen according to the Health Canada – approved recommended dosing regimen. No patients in the ENDEAR trial required permanent ventilation at baseline, and as a co-primary efficacy end point in the trial, permanent ventilation was defined as the need for 16 hours or more of continuous ventilatory support per day for 21 or more consecutive days, in the absence of an acute reversible event, or if the patient required tracheostomy.

Discussion Points

- CDEC discussed the challenge of recommending reimbursement criteria for nusinersen on the basis of SMA subtype (i.e., SMA type I, II, III, or IV) considering that there is overlap between SMA subtypes on some criteria, and that the achievement of major motor milestones such as sitting or walking independently is both a goal of treatment and a criterion used for classifying patients. SMA subtype is a classification that is often applied retrospectively, and the committee considered the clinical features of SMA (i.e., SMN2 copy number, disease duration, age of onset of clinical signs and symptoms) as more informative for reimbursement recommendations.
- CDEC noted that one phase III randomized, sham-controlled trial (CHERISH, N = 126) was conducted that included patients aged 2 to 12 years, who had onset of clinical signs and symptoms consistent with SMA at >6 months of age, and who could sit independently but had never had the ability to walk independently. Nusinersen was administered as three loading doses (Days 1, 29, and 85) and one maintenance dose at day 274, an administration schedule that differed from the Health Canada – approved recommended dosing schedule. Although the results of this trial demonstrated that nusinersen-treated patients exhibited a statistically significant gain in motor function compared with patients in the sham control group, there was no evidence to confirm that similar efficacy and safety results would be found if nusinersen was given at the Health Canada–approved recommended dosing regimen in this patient population.
- CDEC discussed the exploratory subgroup analysis in the ENDEAR trial that reported efficacy results for patients with a disease duration of less than and equal to 12 weeks, the median of the study population, and those patients with a disease duration greater than 12 weeks. The results of these subgroup analyses were suggestive of preferential responses in patients treated earlier in the course of their disease, and were supported by clinical experts consulted by CADTH who noted that treating early in the disease, specifically for patients who are likely to develop SMA type I, is important. CDEC noted that the variability between practice centres, including urban and rural centres, and the availability of specialists, may impact the timing of diagnosis, as many patients who are likely to develop SMA type I appear normal at birth. Newborn screening programs that include screening for SMA may allow patients to be identified early; late diagnosis is often associated with the need for respiratory support.

Background

Nusinersen has a Health Canada–approved indication for the treatment of patients with 5q SMA. Nusinersen is an antisense oligonucleotide that is administered via intrathecal injection by lumbar puncture. The Health Canada–approved dosage is a 5 mL solution containing 12 mg of nusinersen, with a regimen of four loading doses at day 0, day 14, day 28, and day 63, and subsequent maintenance doses every four months.

Summary of CDEC Considerations

The committee considered the following information prepared by the CDR: a systematic review of randomized controlled trials (RCTs) of nusinersen and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from clinical experts with experience treating patients with SMA, and patient group-submitted information about outcomes and issues important to patients and caregivers who are affected by SMA.

Patient Input Information

Three patient groups (Muscular Dystrophy Canada [MDC], the Canadian Organization for Rare Disorders [CORD], and Cure SMA Canada) responded to the call for patient input for this CDR review in the form of one submission from MDC and a joint submission from CORD and Cure SMA Canada. Information for the MDC submission was gathered through interviews with 123 SMA patients and 350 caregivers. Information for the initial CORD and Cure SMA Canada submission was gathered from one focus group, four structured interviews, and 247 responses to an online survey. The following is a summary of key input from the perspective of the patient groups:

- The majority of respondents (60%) were considered SMA type II, and reported, most commonly, not being able to walk, suffering from major muscle weakness, pain and fatigue, difficulty with fine motor skills, deep breathing, swallowing, and feeding as part of living with the disease.
- The level of disability caused by SMA places a significant and impactful burden on families and caregivers of patients suffering from the disease. The time and physical support required by patients have substantial financial, psychological, and emotional consequences on families and caregivers.
- Until nusinersen there was no available treatment for SMA. A variety of supportive therapies (e.g., mechanical aids, rehabilitation services, or supportive medications) have typically been used to manage the symptoms, however, patients would still continue to deteriorate on these therapies.
- Patients would like a treatment that would help them regain some range of motion, slow the deterioration process, maintain muscle strength, reduce their dependency on others, decrease respiratory issues, and provide an overall improved quality of life.
- Patients that received nusinersen indicated positive experiences, improvements in muscle strength, and better respiratory function. The greatest concerns expressed by both groups related to access to the drug (i.e., affordability, complex administrative procedures, and the travel required to obtain treatment).

Clinical Trials

The CDR systematic review included one phase III multi-centre, randomized, double-blind, sham- controlled study (ENDEAR; N = 121). The ENDEAR study recruited patients up to 7 months of age with infantile-onset SMA with documented 5q SMA homozygous gene deletion, homozygous mutation, or compound heterozygote, and two copies of the SMN2 gene. The study excluded patients who had signs or symptoms of SMA at birth or within the first week after birth, patients with hypoxemia, and patients that had a condition that would interfere with the lumbar puncture procedures. Patients enrolled in the ENDEAR trial were randomized in a 2:1 ratio to receive 5 mL intrathecal solution containing 12 mg of nusinersen (n = 81) or to undergo sham procedure (n = 40). The administration of nusinersen and the sham procedure were conducted on study days 1, 15, 29, 64, 183, and 302. The ENDEAR study assessed two co-primary outcomes: motor milestone responders according to the HINE Section 2 tool, and time to death or

permanent ventilation. Originally, the duration of the ENDEAR study was planned to be 13 months. However, the study was concluded early (approximately 6 months after the last patient enrolled) due to positive results in the pre-planned interim analysis.

At the time of the final analysis, 33% of patients in the nusinersen group had completed the follow-up period and 66% had received at least five doses of nusinersen.

The main limitation of ENDEAR was the early termination of the trial which resulted in a loss of data and a shorter time period to assess the efficacy and safety of nusinersen. These two factors may have also contributed to a lack of statistical power necessary to capture differences in the secondary outcomes and subgroup analyses. The use of a non-intention-to-treat (non-ITT) population for the primary analysis, the lack of appropriate control for multiple statistical testing, and the potential for inadvertent unbinding of the investigator were additional limitations that may have had an impact on the interval validity of the ENDEAR trial.

Additional studies assessing the efficacy of nusinersen that did not meet the inclusion criteria of the CDR systematic review included two phase II, single arm trials (NURTURE and CS3A) and one phase III RCT (CHERISH). NURTURE (ongoing, N = 20) was a phase II, single arm trial for patients with pre-symptomatic SMA who had two or three copies of the SMN2 gene, CS3A (ongoing, N = 21) was a phase II, single arm trial in patients with symptoms suggestive of SMA type I, and CHERISH (N = 126) was a phase III randomized, sham- controlled trial for patients with symptoms suggestive of SMA type II. These studies were excluded due to study design (NURTURE and CS3A), and due to a dosing regimen that did not match the Health Canada–approved regimen (CHERISH and CS3A). Two other studies not considered in the CDR clinical review included CS2 and CS12. CS2 was a phase I, open-label, dose-escalation study aimed to assess the pharmacodynamics and pharmacokinetics of multiple nusinersen doses. CS12 was an open-label, single arm, extension study of patients who had completed one of two phase I trials. The primary aim of CS12 was to report on tolerability and clinical laboratory parameter changes during the study. These two studies were not included in the CDR review due to their study design, differences in dosing and administration regimen, and lack of relevant primary outcomes.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the committee discussed the following:

- Motor function-related outcomes: This was presented in the ENDEAR study through the first co-primary outcome of proportion of motor milestone responders (Section 2 of the HINE). A responder was defined as: “(i) The patient demonstrated at least a 2-point increase in the motor milestone category of ability to kick or achievement of maximal score for that category (touching toes), or a 1-point increase in the motor milestones of head control, rolling, sitting, crawling, standing, or walking, AND (ii) among the seven motor milestone categories (with the exclusion of voluntary grasp), the patient demonstrated improvement (as defined in [i]) in more categories than worsening.” Additional related secondary outcome reported in the ENDEAR was the proportion of Children’s Hospital of Philadelphia Infant Test for Neuromuscular Disease (CHOP INTEND) responders, in which a responder was defined as a patient with a score change from baseline of 4 or greater points when assessed on study days 183, 302,
or 394.
- Respiratory and survival-related outcomes: This was presented in the ENDEAR study through the second co-primary outcome of time to death or permanent ventilation. In addition, two related secondary outcomes of survival rate and the percentage of patients not requiring permanent ventilation were assessed. The ENDEAR study defined the outcome of permanent ventilation as “the need for 16 hours or more of continuous ventilatory support per day for 21 or more consecutive days, in the absence of an acute reversible event”, or if the patient required tracheostomy.

No health-related quality of life or caregiver burden measures were assessed in the ENDEAR study.

Efficacy

The final efficacy analysis demonstrated a statistically significant difference in the proportion of HINE Section 2 motor milestone responders between the nusinersen treatment group and the sham procedure control group where 37 patients out of 73 in the nusinersen group (51%) compared with 0 patients out of 37 in the sham procedure control group were classified as responders (difference in percentage = 50.7, 95% CI, 31.8 to 66.5). The captured improvement in motor milestones of patients was also supported by a second motor milestone measure, the CHOP INTEND, where 71% of the patients allocated to nusinersen treatment achieved an improvement of 4 or more points on the CHOP INTEND scale as compared with 3% in the sham procedure control

group (percentage difference = 68.53, 95% CI, 51.27 to 81.99). The definition of treatment responders has been noted in the Health Canada Reviewer Report to be broad in that it captures many patients with minimal improvement, and treats those patients in a similar way to those who gained more significant improvements.

The second co-primary composite outcome in the ENDEAR study – time to death or permanent ventilation – indicated that 31 patients (39%) in the nusinersen group died or required permanent ventilation versus 28 patients (68%) in the sham procedure group during a period of roughly approximately 13 months (hazard ratio (HR) = 0.53, 95% CI, 0.32 to 0.89). When each event (death, and permanent ventilation) was analyzed as a separate outcome, the results indicated a statistically significant difference between nusinersen group and the sham procedure in overall survival (HR = 0.37, 95% CI, 0.18 to 0.77), but not in time to permanent ventilation (HR = 0.66, 95% CI, 0.32 to 1.37).

An exploratory subgroup analysis based on the median disease duration of 12 weeks (less than and equal to 12 weeks, and greater than 12 weeks) found a statistically significant difference between nusinersen and sham-treated patients for HINE Section 2 motor milestone responders in both groups. For time to death or permanent ventilation, the subgroup analysis based on median disease duration showed statistically significant differences compared with the sham procedure group in the subgroup below the median disease duration (HR = 0.24, 95% CI, 0.10 to 0.58) but failed to show statistically significant differences in the subgroup over the disease median duration (HR = 0.84, 95% CI, 0.43 to 1.67). However, due to the non-significance of a prior outcome in the stage-wise hierarchical strategy, (percentage of patients not requiring permanent ventilation) all subgroup analyses are considered exploratory.

Harms (Safety and Tolerability)

- Adverse events were reported in 96% of patients in the nusinersen group and 98% in the sham control group. Most adverse events and serious adverse events were related to infections and respiratory related complications. None of the adverse events were considered related to the study treatment by the study investigators.
- A lower percentage of patients in the nusinersen group had a serious adverse event compared with the sham control group (nusinersen versus control: 76% versus 95%).
- All withdrawals due to adverse events were due to the death of the patient. There were numerically fewer withdrawals due to adverse events in the nusinersen group (16%) versus the control group (39%).
- There were 16 deaths (39%) reported in the control group versus 13 deaths (16%) reported in the nusinersen group. Deaths attributed to respiratory, thoracic, and mediastinal disorders were the highest proportion in both groups (9% in the nusinersen group and 29% in the control group).
- Vomiting was noted in the nusinersen group as related to the lumbar puncture procedure (5% in nusinersen group, 0% in the control group). Two patients (3%) in the nusinersen treatment arm were reported as having an adverse effect related to renal and urinary disorders, compared with one patient (2%) in the control group.

Cost and Cost-Effectiveness

Nusinersen is available as a single-use solution in a 5 mL vial size (12 mg) at a marketed price of $118,000 per vial. 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 4 months. The annual cost of treatment with nusinersen in the first year is $708,000 and decreases to $354,000 for maintenance treatment (3 doses) in subsequent years.

The manufacturer submitted three cost-utility analyses for SMA type I, II, and III. 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. The analyses were conducted form the health care system perspective, with costs and outcomes discounted at 1.5% per annum.

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. 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. 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. 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. Subsequent probabilities were based on assumptions. For RWC, patients were assumed to maintain ambulatory status.

The manufacturer reported ICURs for nusinersen compared with RWC as follows: for SMA type I, $665,570 per QALY; for SMA type II, $2.1 million per QALY; and, for SMA type III, $2.9 million per QALY. The manufacturer indicated the probability that nusinersen was cost-effective assuming a willingness to pay of $300,000 per QALY was 0% for all SMA types.

CDR identified the following primary limitations with the manufacturer's economic model:

- In the design of the economic model for SMA type I and II, health 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.
- 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. A number of issues were identified with these approaches, including that the valuation process was not appropriate, and that 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.
- A clinical expert consulted by CDR for this review raised a number of concerns regarding the clinical trial data for nusinersen that limit the inferences and generalizations that can be made from the economic evaluation. For example, the population that may receive nusinersen is not reflected in the clinical trials and there is a lack of comparative clinical trial data for SMA type III. While analyses were conducted by SMA type (i.e., for types I and II), further stratified analysis by clinical features would be desirable.

CDR was able to conduct reanalysis to address the limitations identified regarding: choice of utility values, 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. 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 remained 0%.

CDEC Members

Dr. James Silvius (Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

November 15, 2017 Meeting

Regrets

None

Conflicts of Interest

None

Appendix 5: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- Hammersmith Infant Neuromuscular Examination (HINE) Section 2: Motor Milestones
- World Health Organization (WHO) motor milestones
- Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)
- Hammersmith Functional Motor Scale – Expanded (HFMSE)
- Revised Upper Limb Module (RULM)
- Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core Scales and 3.0 Neuromuscular Module
- Assessment of Caregiver Experience in Neuromuscular Disease (ACEND).

Findings

Hammersmith Infant Neuromuscular Examination Section 2: Motor Milestones

The HINE was based on a previous neurologic assessment and is meant for use in infants between two and 24 months of age.[50] It contains three sections that assess neurologic signs (section 1), development of motor function (section 2), and state of behaviour (section 3). The items in sections 1 and 3 can be assigned scores on an ordinal scale based on descriptive ratings and the scores can be summed to give section scores. Section 2 is composed of eight milestones: head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing, and walking.[50] Each milestone has three to five possible descriptive ratings, ranging from not performing the task at all to fully demonstrating the milestone.[50] The items can be either reported by the caretaker or observed by the examiner,[50] though information regarding inter-rater reliability between caretakers and examiners was not found. Unlike the other sections of the HINE, the Motor Milestones are age-dependent and are not intended to produce a total score.[50] Rating distributions are available for normal infants aged 12 months and 18 months for sections 1 and 2.[50]

For most individual ratings for each motor milestone in section 2, a typical age of achievement in normal infants is provided:[50]

Head control:

- Unable to maintain head upright, normal at < 3 months
- Wobbles, normal at 4 months
- All the time maintained upright, normal at 5 months

Sitting:

- Cannot sit
- With support, normal at 4 months
- Props, normal at 6 months

- Stable sit, normal at 7 months
- Pivots, normal at 10 months

Voluntary grasp:

- No grasp
- Uses whole hand
- Index finger and thumb but immature grasp
- Pincer grasp

Ability to kick (in supine):

- No kicking
- Horizontally; legs do not lift
- Upward (vertically), normal at 3 months
- Touches leg, normal at 4 to 5 months
- Touches toes, normal at 5 to 6 months

Rolling:

- No rolling
- Rolling to side, normal at 4 months
- Prone to supine or supine to prone, normal at 6 months
- Supine to prone and prone to supine, normal at 7 months

Crawling:

- Does not lift head
- On elbow, normal at 3 months
- On outstretched hand, normal at 4 to 5 months
- Crawling flat on abdomen, normal at 8 months
- Crawling on hands and knees, normal at 10 months

Standing:

- Does not support weight
- Supports weight, normal at 4 to 5 months
- Stands with support, normal at 8 months
- Stands unaided, normal at 12 months

Walking:

- Bouncing, normal at 6 months
- Cruising (walks holding on), normal at 11 months
- Walking, normal at 15 months

Natural history for the HINE section 2 assessment was examined in infants with type I spinal muscular atrophy (SMA) with disease onset between one and eight months of age.[20] Over a period of about four years, retrospective data from patients were analyzed if the patients received at least two assessments occurring every two to three months until 12 months of age and every six months thereafter.[20] Although the original HINE developers did

not define a quantitative scoring system for section 2, scores for each milestone were obtained by assigning a value of 0 to the absence of the activity and adding one point for each incremental rating.[20] All patients with SMA type Ia (disease onset at birth, n = 7) had a score of 0 for every milestone at every assessment.[20] The highest score on any item was 1 and, with the exception of one infant improving from 0 to 1 on ability to kick, none of the infants' scores improved over time.[20] Infants with SMA type Ib (disease onset before three months of age, n = 24) had a score of 1 for at least one assessment for the following milestones: head control (n = 11), voluntary grasp (n = 17), and ability to kick (n = 13).[20] Both infants with SMA type Ic (disease onset between three and six months of age) maintained a score of 1 for head control, voluntary grasp, and ability to kick.[20] The results imply that a score of more than 1 on any milestone is not expected in patients with SMA type I.

Reliability and convergent validity of the HINE section 2 in SMA type I were assessed in patients enrolled in the CS3A trial who were administered nusinersen.[51] Although not described, it is assumed that a total HINE score for section 2 was calculated by scoring each milestone on an ordinal scale (with 0 representing no ability) and summing the scores. Assessments within 14 days of each other demonstrated a test-retest reliability that was above 0.7[52] and therefore adequate (Pearson correlation coefficient $r = 0.987$; $P < 0.0001$; n = 19).[51] Change in the HINE section 2 score from baseline (1 to 7 months of age) to last assessment (5 to 39 months of age) was moderately correlated with change in the CHOP INTEND score ($r = 0.691$; $P = 0.001$) and ulnar compound muscle action potential (CMAP) amplitude ($r = 0.511$; $P = 0.025$).[51] In another, hypotheses on the strength of correlations with CHOP INTEND and CMAP were not given.[51] Incremental improvements in individual items were observed in 16 of the 19 infants and were spread out across all the milestones, suggesting responsiveness to intervention with nusinersen; however, no responsiveness statistics were calculated, nor was the relative responsiveness of the HINE versus the CHOP INTEND score or ulnar CMAP amplitude.[51]

World Health Organization Motor Milestones

The WHO motor milestones are a set of six milestones considered to be universal and fundamental to acquiring the ability to walk independently.[53] The milestones are sitting without support, standing with assistance, hands-and-knees crawling, walking with assistance, standing alone, and walking alone.[53] Children will typically progress sequentially through this order of milestones with the exception of crawling.[53] An international study conducted in Ghana, India, Norway, Oman, and the US recorded ages of achievement of each milestone in healthy children between four and 24 months of age, providing windows of achievement representing the first to 99th percentiles as follows:[53]

- sitting without support: 3.8 months to 9.2 months
- standing without assistance: 4.8 months to 11.4 months
- hands-and-knees crawling: 5.2 months to 13.5 months
- walking with assistance: 5.9 months to 13.7 months
- standing alone: 6.9 months to 16.9 months
- walking alone: 8.2 months to 17.6 months.

Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders

The CHOP INTEND was developed in infants with SMA type I and designed to measure motor function in infants and children with neuromuscular disorders having an infant's repertoire of motor skills.[54] It is well tolerated by infants in the target population[54,55] and can be administered to patients on non-invasive or invasive ventilation.[41] It is made up of 16 items, each is rated between 0 and 4 (no response, minimal, partial, nearly full, and complete level of response, respectively), giving a maximum total score of 64 when summed.[54] A higher score indicates more advanced motor development.[54] An initial pool of items, consisting of newly designed items and items taken from two previous motor scales, was evaluated in 26 infants with type I SMA.[54] The study investigators examined all items for clinical utility and redundancy while statistics describing score distributions and internal consistency (Cronbach's alpha) guided item selection.[54] An expert panel selected and edited the final item set.[54]

Intra-rater reliability assessed by a single evaluator over a two-month period in nine infants with type I SMA was acceptable according to the 0.7 threshold[52] (intraclass correlation coefficient (ICC) [3, 1] = 0.96).[54] In another trial where examiners were extensively trained on the administration and interpretation of the CHOP INTEND (in two global phase III clinical trials that examined nusinersen in patients with SMA 1), the intra-rater reliability was also acceptable according to the 0.7 threshold (ICC [1, 1] = 0.895 and by video review was ICC [1, 1] = 0.951).[56] Inter-rater reliability assessed by multiple evaluators reviewing video footage of a single evaluator was also acceptable in both infants with neuromuscular diseases (ICC [3, 4] = 0.98) and typically developing infants (ICC [3, 5] = 0.93).[54]

Construct validity of the CHOP INTEND was established using known group comparisons in a separate study in 27 patients with type IB and IC SMA (mean age of four years, age range of 3.8 to 260 months).[55] CHOP INTEND score had moderate negative associations with age (Pearson correlation coefficient $r = –0.51$; $P = 0.007$) and months since symptom onset ($r = –0.49$; $P = 0.005$).[55] Patients on non-invasive ventilation with bi-level positive air pressure (BiPAP) had lower scores than patients not requiring BiPAP (15.2 ± 10.2 versus 31.2 ± 4.2; $P < 0.001$).[55] There were no significant correlations with electrophysiological measures.[55] A separate study established convergent validity by examining motor function outcomes in 23 infants with type I SMA and 14 healthy control infants.[57] CHOP INTEND scores were compared between groups and against the Test of Infant Motor Performance Screening Items, an instrument previously validated in patients with type I SMA.[57] A hypothesis was not provided regarding the strength of the correlation between the two measures. The mean CHOP INTEND score was significantly lower in infants with SMA compared with the control group (21.4 ± 9.6 versus 50.1 ± 10.2; $P < 0.01$).[57] In both groups, there was a strong ($r > 0.80$) positive association between CHOP INTEND and Test of Infant Motor Performance Screening Items scores (SMA group: $r = 0.855$, $P < 0.0001$, n = 22; control group: $r = 0.839$, $P = 0.005$, n = 9).[57] Additionally CHOP INTEND scores were studied over time in 17 patients with type I SMA over a period of up to 36 months.[41] Scores were found to decrease over time at a mean rate of 1.27 points per year.[41] A minimal clinically important difference (MCID) was not found for the CHOP INTEND score.

Hammersmith Functional Motor Scale – Expanded

The Hammersmith Functional Motor Scale was designed to measure motor function in SMA type II and III patients with limited mobility.[42] The HFMSE builds upon the Hammersmith Functional Motor Scale by adding 13 items from the Gross Motor Function Measure (GMFM), an instrument designed for patients with cerebral palsy and previously validated in children with SMA.[42] The HFMSE is intended for use in patients with types II and III SMA and captures higher functioning skills.[42] It consists of 33 activities that can be scored one of three ways: 0 for unable to perform, 1 for performs with modification/adaptation, and 2 for performs without modification.[42] The item scores are summed to give a total score with a maximum of 66.[42] The higher the total score, the greater the patient's motor functioning.[42]

Clinical evaluators deemed the items added from the GMFM to be clinically meaningful, and focus groups and interviews established content validity of all of the HFMSE items.[44,58] Focus groups with caregivers (n = 30) and patients (n = 25) of SMA types II and III were able to relate each item to at least one relevant activity of daily living.[58] A similar sample of patients and caregivers indicated in focus groups and interviews that the items on HFMSE were relevant to their life and that improvements in any of the items would translate to greater independence.[44]

Construct validity was assessed using both convergent validity and known group comparisons in two studies in patients with types II and III SMA and ages ranging from two to 45 years.[42,59] Hypotheses regarding the strength of correlations with other measures were not stated. HFMSE score had strong (Spearman rank correlation coefficient $\rho > 0.80$) positive associations with the GMFM (both with and without the items that were added to the HFMSE), as well as a simple,10-point functional rating score ranging from "unable to sit" to "age-appropriate in motor skills" (ρ ranging from 0.88 to 0.98).[42,59] Further convergent validity was established through positive correlations with forced vital capacity as a percentage of predicted normal value ($\rho = 0.98$), knee flexion and extension strength (Pearson correlation coefficient $r = 0.74$ for both), and elbow flexion strength ($r = 0.77$).[59] Known group comparisons showed significant differences in median HFMSE score between those receiving BiPAP for less than and greater than eight hours per day (23 versus 3; $P < 0.0001$), those who are able and unable to walk (52 versus 8; $P < 0.0001$), and those who have type II and III SMA (49 versus 8; $P < 0.0001$).[59] There were also significant differences in median scores between patients with different survival of motor neuron 2 copy numbers (Kruskal-Wallis test: $P = 0.0007$).[59]

In one trial where examiners were extensively trained on the administration and interpretation of the HFMSE (in two global phase III clinical trials that examined nusinersen in patients with SMA 1), the intra-rater reliability was acceptable according to the 0.7 threshold (ICC [1, 1] = 0.0.959 and by video review, with ICC [1,1] ranging between 0.987 and 0.994).[56]

Reliability and change over time were also studied. The HFMSE demonstrated adequate test-retest reliability when administered two months apart in patients with SMA types II and III (ICC = 0.98).[59] A natural history study measured HFMSE score over time in patients with SMA types II and III (n = 268; age range of 2.5 to 55.5 years).[43] More than 75% of the patients had a change in score from baseline to 12 months of –2 to +2 points.[43] Only 7.84% experienced an increase of more than 2 points, and this was most likely to occur in children below 5 years of age.[43] Focus groups and interviews with patients, parents, and clinicians representing SMA types I to III revealed that increases in the HFMSE scale as little as 1

point would represent meaningful change and that the scale increments may not be sensitive enough to capture small functional changes that are noticeable to patients.[44]

Revised Upper Limb Module

The original Upper Limb Module was designed to capture upper limb function in non-ambulatory patients with SMA, especially in young children, and was previously validated in this population.[60] Due to ceiling effects, it was revised and renamed to the RULM. Some items in the RULM were incorporated from other upper limb scales, particularly the Performance of Upper Limb scale for Duchenne muscular dystrophy.[60] The RULM is well tolerated, even in young children, with a test duration of five to 20 minutes.[60] It consists of 19 items reflecting different functional domains that are graded on a three-point scale.[60] With the exception of one activity with a binary score, the possible scores are 0 (unable), 1 (able, with modification), and 2 (able, no difficulty), giving a maximum total score of 38. The patient chooses one arm with which to perform the tasks.[60]

Adequate inter-rater reliability was established using three video assessments of the RULM that were evaluated by 17 physiotherapists (ICC = 0.928).[60] Rasch analysis was conducted on RULM assessments of 134 ambulatory and non-ambulatory patients with SMA aged 2 to 52 years (median age of 9 years). Item and person locations revealed no floor or ceiling effects and only small gaps in measurement accuracy.[60] The threshold map indicated that response categories for each item functioned as intended.[60] The Person Separation Index, an indicator analogous to Cronbach's alpha that assesses the ability of a set of items to separate the sample,[61] demonstrated adequate internal consistency reliability (0.954).[60] Indicators of fit demonstrated that the observed data overall did not differ from the expected responses as predicted by the Rasch model and that total RULM score is a suitable measurement of a single concept.[60,61] Two pairs of items had correlated residuals, but their presence did not inflate the Person Separation Index. Scale performance did not differ between genders, though it was not tested for groups expected to score differently.[60] In another trial where examiners were extensively trained on the administration and interpretation of the RULM (in two global phase III clinical trials that examined nusinersen in patients with SMA 1), the intra-rater reliability was acceptable according to the 0.7 threshold (ICC [1, 1] = 0.0.948 and by video review, with ICC [1,1] ranging between 0.966 and 0.990).[56]

Associations with other measures of motor function, test-retest reliability, and an MCID were not found for the RULM.

Pediatric Quality of Life Inventory 4.0 Generic Core Scales and 3.0 Neuromuscular Module

The PedsQL Generic Core Scales are intended to be administered in both healthy and patient pediatric populations and, together with disease-specific modules, measure pediatric health-related quality of life (HRQoL).[62] Both the Generic Core Scales and Neuromuscular Module are available in formats for child self-report and parent proxy-report for those aged 5 to 7, 8 to 12, and 13 to 18, along with a parent proxy-report format for those aged 2 to 4.[62] Each item is scored on a five-point Likert scale (three-point scale for ages 2 to 4), with each score linearly transformed to a scale of 0 to 100.[62] To generate domain and total scores, the transformed item scores are summed and then divided by the number of items.[62] The Psychosocial Health Summary Score is the sum of the items in the Emotional, Social, and School Functioning Scales.[62] Higher scores indicate better

HRQoL.[62] The Generic Core Scales consist of the following scales: Physical Functioning (8 items), Emotional Functioning (5 items), Social Functioning (5 items), and School Functioning (5 items).[62] The Neuromuscular Module has the following scales: About My/My Child's Neuromuscular Disease (17 items), Communication (3 items), and About Our Family Resources (5 items).[62] The Communication and About Our Family Resources scales are not available for the 5- to 7-year-old format due to insufficient consistency.[62]

The Neuromuscular Module was developed particularly for SMA and Duchenne muscular dystrophy using literature, feedback from health care providers, and focus groups consisting of patients and family members of patients.[62] It was validated in a pool of 176 children with SMA (average age of 8.53 years) across multiple centres in North America.[62] Internal consistency was acceptable (Cronbach's alpha ≥ 0.7[52]) in all the scale and summary scores for all formats of the Generic Core Scales (0.64 to 0.86) and Neuromuscular Module (0.77 to 0.91) except for Social Functioning on the self- and proxy-report formats and Emotional and School Functioning on the self-report format.[62]

Construct validity for the Generic Core Scales was established using the known-groups method in patients with SMA and a healthy children sample derived from previous data.[62] The scale and summary scores were higher in healthy children with mostly large effect sizes (range: 0.74 to 3.26).[62] The Physical Functioning scale related to mobility status with scores increasing from non-sitter to sitter to walker.[62] In the Neuromuscular Module, scores for About My Neuromuscular Disease for both formats and Total Score and About Our Family Resources for proxy-report increased with greater mobility.[62]

Test-retest reliability was determined in a set of 60 patients with SMA with an average of 29.85 days between assessments.[62] There was a wide range in agreement in all the Generic Core Scales (ICC range: 0.72 to 0.84 for self-report, 0.34 to 0.79 for proxy-report) and Neuromuscular Module (ICC range: 0.58 to 0.84 for self-report, 0.82 to 0.90 for parent-report) scales in the self- and proxy-report formats, with the exception of Physical Health in the Generic Core Scales on the parent proxy-report format (ICC = 0.34).[62] The summary scores had adequate test-retest reliability except for the proxy-report total score for the Generic Core Scales.[62] Similar results for the Neuromuscular Module scales and total score were obtained in a separate set of 33 patients with SMA (ICC range: 0.73 to 0.84).[63]

Inter-rater reliability between child self-report and parent proxy-report was determined for the scale and summary scores.[62] Parent-child agreement ranged from poor to moderate for the Generic Core scales (ICC range: 0.36 to 0.44) and Neuromuscular Module scales (ICC range: 0.33 to 0.48).[62]

For the total score of the Generic Core Scales in the general pediatric population, the MCIDs calculated from the score distributions were 4.4 for the self-report format and 4.5 for the proxy-report format.[64] A clear MCID was not found for the SMA population.

Assessment of Caregiver Experience in Neuromuscular Disease

The ACEND is a self-administered instrument for assessing caregiver impact on parents raising children severely affected by neuromuscular disease.[65] Higher scores in the ACEND represent less intense caregiving impact.[65] There are two domains: Physical Impact with the four subdomains of Feeding/Grooming/Dressing (6 items), Sitting/Play (5 items), Transfers (5 items), and Mobility (7 items); and General Caregiver Impact with the three subdomains of Time (4 items), Emotion (9 items), and Finance (5 items).[65] Physical Impact items are scored on a six-point ordinal scale and the General Caregiver Impact items are

scored on a five-point scale.[65] These scores are used to generate domain and total scores standardized to a range of 0 to 100.[65]

Some items for the ACEND were taken from previous instruments and new items were developed with a panel of experts, which included orthopaedic surgeons, physical therapists, and parents of patients.[65] A total of 46 caregivers of children with moderate-to-severe neuromuscular disease were administered the ACEND survey and asked to rate clarity and relevance of the items.[65] All items were considered clear and relevant by the caregivers.[65] Each domain was assessed for consistency and some items may be redundant as they had high inter-item and item-total correlations.[65]

Patients were also classified according to the Gross Motor Function Classification System (GMFCS) to assess convergent validity and floor and ceiling effects of the ACEND.[65] All patients belonged to GMFCS levels III, IV, or V, implying inability to walk without mobility devices.[65] All of the total and subdomain scores decreased significantly with increasing GMFCS level (decreasing motor function), with the exception of the Finance subdomain.[65] Score distributions across GMFCS levels indicated floor or ceiling effects in all the Physical Impact subdomains and ceiling effects in two of the three General Caregiver Impact subdomains.[65] Item distributions were considered to be adequate aside from some items in the Transfers and Mobility subdomains.[65]

The ACEND was administered to caregivers of children aged 3 to 25 years with cerebral palsy at GMFCS levels IV and V undergoing orthopaedic hip or spine surgery.[66] Although there was an increase in HRQoL as measured by a different instrument from pre-surgery to 12 months post-surgery, the ACEND was not sensitive to this increase (n = 44).[66] However, a multivariable model found time to be a significant predictor of ACEND total score.[66] An MCID was not found for the ACEND score and it has yet to be assessed in the SMA population.

Table 32: Validity and Minimal Clinically Important Differences of Outcome Measures

Instrument	Type	Evidence of Validity	MCID	References
HINE Section 2: Motor Milestones	A set of 8 motor milestones to assess development between the ages of 2 and 24 months, with a 3- to 5-point ordinal scale for each milestone	Yes	A score of > 1 point for any given milestone is highly unlikely in untreated patients with SMA type I[20]	Haataja 1999,[50] De Sanctis 2016,[20] Bishop 2017[51]
WHO Motor Milestones	A set of 6 motor milestones with age windows of achievement of each milestone provided for normal infants	Unknown in SMA	Unknown	WHO Multicentre Growth Reference Study Group 2006[53]
CHOP INTEND	A set of 16 tasks to measure motor development in infants and children with neuromuscular disorders, with a 5-point ordinal scale for each item	Yes	Unknown	Glanzman 2010,[54] Glanzman 2011,[55] Finkel 2014,[41] Kolb 2016[57]
HFMSE	A set of 33 tasks to measure motor function in patients with SMA types II and III with limited mobility, with a 3-point ordinal scale for each item	Yes	An increase of > 2 points in total score is unlikely in untreated patients with SMA types II and III.[43] Patient and caregivers consider a 1-point	O'Hagen 2007,[42] Glanzman 2011,[59] Mercuri 2016,[43] McGraw 2017,[44] Pera 2017[58]

Instrument	Type	Evidence of Validity	MCID	References
			increase meaningful[44]	
RULM	A set of 19 tasks to measure motor function in non-ambulatory patients with SMA, with a 3-point ordinal scale for each item	Yes (with limitations)	Unknown	Mazzone 2017[60]
PedsQL 4.0 Generic Core Scales and 3.0 Neuromuscular Module	Surveys consisting of 23 and 25 items for measuring health-related quality of life in healthy and patient pediatric populations, with a 5-point Likert scale for each item	Yes (with limitations)	Generic Core Scales in the general pediatric population: 4.4 points for self-report and 4.5 points for proxy-report Neuromuscular Module: unknown	Iannaccone 2003,[63] Varni 2003,[64] Iannoccone 2009[62]
ACEND	A 41-item survey for assessing caregiver impact on parents raising children severely affected by neuromuscular disease, with a 5- or 6-point ordinal scale for each item	Neuromuscular disease: yes (with limitations) SMA: unknown	Unknown	Matsumoto 2011,[65] DiFazio 2016[66]

ACEND = Assessment of Caregiver Experience in Neuromuscular Disease; CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HFMSE = Hammersmith Functional Motor Scale – Expanded; HINE = Hammersmith Infant Neuromuscular Examination; MCID = minimal clinically important difference; PedsQL = Pediatric Quality of Life Inventory; RULM = Revised Upper Limb Module; SMA = spinal muscular atrophy; WHO = World Health Organization.

Conclusion

The HINE Section 2: Motor Milestones and WHO motor milestones provide information on normal, healthy infant motor development and can be used to identify abnormalities in attainment of motor milestones.[41,50] A score can be calculated from the HINE Motor Milestones that has excellent test-retest reliability.[51] Change in the score moderately correlates with change in other measures of motor function in patients with type I SMA receiving nusinersen.[51] Natural history in patients with type I SMA strongly suggests that an improvement greater than one point in any milestone is highly unlikely.[20]

Functional motor scales designed to assess function in patients with SMA were also used in nusinersen trials. All of the motor function scales were well tolerated in their intended populations and were developed with input from experts in neuromuscular disease. The CHOP INTEND is a set of activities assessing motor function in infants and children with neuromuscular disorders.[54] It has excellent intra-rater and inter-rater reliability[62] and its construct validity has been demonstrated in patients with type I SMA.[55,57] The HFMSE is a motor function assessment appropriate for use in patients with more advanced SMA with limited mobility.[42] In patients with types II and III SMA, both test-retest reliability[59] and construct validity are excellent.[42,59] Longitudinal data shows that more than 75% of patients with type II and III SMA experience a change in HFMSE score from –2 and +2 over the course of a year.[43] Patient and caregivers have indicated that the items in the HFMSE are relevant[44,58] and that an improvement of one point would be meaningful.[44] The RULM is an improved version of the Upper Limb Module and is designed to measure motor function of the upper limbs in patients with non-ambulatory SMA.[60] It has excellent inter-rater reliability in patients with ambulatory and non-ambulatory SMA aged 2 years and up. According to Rasch analysis, the RULM measures a single concept, separates the sample well, and has no issues with floor effects, ceiling effects, or item dependence[60] Test-retest reliability and associations with other measures of motor function were not found for the RULM. MCIDs

were not found for any of the scales. A potential limitation of functional scales is that their scores can be affected by developmental maturation in children who gain or regain abilities after adapting to their strength limitations.[18]

The PedsQL 4.0 Generic Core Scales and 3.0 Neuromuscular Module are surveys for assessing quality of life in pediatric patients, each with multiple scales and child self-report and parent proxy-report formats.[62] There are limitations in the agreement between the self-report and proxy-report formats for all of the scales and the test-retest reliability for some of the scales.[62] Due to insufficient internal consistency, some of the Generic Core Scales should only be used for descriptive analyses.[62] Scale and summary scores differ between healthy children and patients with SMA and the Physical Functioning scale and Neuromuscular Module correlate well with mobility status.[62] MCIDs of 4.4 and 4.5 for the self-report and proxy-report formats are indicated for the Generic Core Scales total score in the general pediatric population.[64] An MCID was not found for the Generic Core Scales or Neuromuscular Module in the SMA population.

The ACEND is a survey for assessing caregiver impact on parents raising children with neuromuscular disease.[47] Caregivers indicated that all items are clear and relevant.[47] All of the domain and subdomain scores (except for Finance) demonstrated convergent validity with the gross motor function classification system in a population with various neuromuscular disorders.4[7] Test-retest reliability was not[47] and there may be issues with item redundancy,[47] ceiling and floor effects,[47] and responsiveness.[48] An MCID was not found for the ACEND score and the ACEND has yet to be assessed in the SMA population.

Appendix 6: CADTH Common Drug Review of Original Spinraza Submission

Executive Summary

Introduction

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. Neurological studies indicate that the disease causes a rapid and irreversible degeneration of motor neurons; the rate of motor neuron degeneration has been reported to plateau with time. 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.[3,4] While deletion or mutation of the SMN1 gene results in SMN protein deficiency (which is essential for the development of motor neurons), the SMN2 gene produces a relatively small amount of functional SMN protein and SMN2 copy number modulates the severity of the disease. 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. Incidence and prevalence estimates in Canada are not well described in the literature. However, the manufacturer of nusinersen provided Canadian figures of an annualized estimate of new cases of SMA in Canada at 37.2 new cases per year. Four clinical subtypes of SMA are described; SMA type I makes up 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, with life expectancy improved by aggressive supportive care; SMA type III makes up about 10% to 20% of SMA cases and presents between 18 months of age and early 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, 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.

Aside from the reviewed drug, there are currently no treatments available for SMA. Standards of practice revolve around supportive care, addressing the symptoms of the disease, and attempting to improve quality of life. Nusinersen (Spinraza) is indicated for the treatment of 5q Spinal Muscular Atrophy (SMA). It is an antisense oligonucleotide that increases the proportion of exon 7 inclusion in SMN2 messenger ribonucleic acid transcripts made, through binding to a specific site in the SMN2 pre-messenger ribonucleic acid. This leads to the translation of a specific site in the SMN2 pre-messenger ribonucleic acid into functional full length SMN protein. Nusinersen is administered intrathecally by lumbar puncture in a 5 mL solution containing 12 mg of nusinersen. It is given in a regimen of four loading doses at day 0, day 14, day 28, and day 63, with subsequent maintenance doses at a four months frequency.

Results and Interpretation

Included Studies

One phase III randomized, sham-procedure controlled, trial met the inclusion criteria for the CDR systematic review. The ENDEAR study (also known as CS3B) was a randomized, double-blind, sham-procedure control, multicentre study. One-hundred and twenty-one patients were randomized at a ratio of 2 to 1 to nusinersen (n = 80) or sham procedure (n = 41) arms. The study was designed to last for 13 months, with the double-blind treatment period lasting for 10 months and 3 months of follow-up. However, the double-blind period was concluded early after the results of the pre-specified interim analysis (6 months) suggested positive results. Two primary endpoints were assessed: proportion of HINE Section 2 responders, and time to death or permanent ventilation.

The main limitation of the ENDEAR study was the early termination of the study which caused loss of data and a shorter time period to assess the efficacy and safety of nusinersen. These two factors may have also contributed to a lack of statistical power necessary to capture differences in the secondary outcomes and subgroup analyses. The use of a non-ITT population for the primary analysis, the lack of appropriate control for multiple statistical testing and the potential for inadvertent unbinding of the investigator were additional limitations that may have had an impact on the interval validity of the ENDEAR trial. The external validity of the trial was limited by the inability to generalize the results to patients with infantile-onset SMA who had disease durations of more than 26 weeks, especially when considering the rapid and irreversible loss of motor function early in the disease course; further, patients with infantile-onset SMA who have three copies of the SMN 2 gene are not represented in the ENDEAR study, these patients may show varying degree of disease presentation and can fall into either a SMA type I or II categories..

Efficacy

The final analysis demonstrated that the difference in the proportion of HINE 2 motor milestone responders favoured the nusinersen treatment group over the sham procedure control group (difference in percentage = 50.7, 95% CI 31.8 to 66.5, p-value <0.0001). This indicated that almost half of the patients in the nusinersen group were able to exhibit more improvements than worsening in the milestones outlined in the HINE section 2, with the exception of voluntary grasp. Several sensitivity analyses using different definition of responders and different analysis sets support the primary analysis. When analyzing this outcome in subgroups of patients that had a disease duration 12 weeks or less and patients with disease duration of more than 12 weeks, a statistically significant difference was found in both groups. However, results of the subgroup analyses are considered exploratory as these were outside of the stage-wise hierarchical strategy and, therefore, not adjusted for multiplicity. The captured improvements in motor milestones of patients was also supported by a second motor milestone measure, the CHOP INTEND, where 71% of the patients allocated to nusinersen treatment achieved an improvement of 4 or more points on the CHOP INTEND scale as compared to 3% in the sham procedure control group (percentage difference = 68.53, 95% CI 51.27 to 81.99). The main analysis of the second primary outcome, time to death or permanent ventilation, indicated that 39% of patients in the nusinersen group died or required permanent ventilation compared with 68% of patients in the sham procedure group during the analysis period (Hazard ratio = 0.53, 95%CI 0.32 to 0.89). Median survival time was unavailable for the nusinersen group, as an insufficient number of patients had completed the full trial. Median survival time for the sham group

was 22.6 weeks (95% CI 13.6 to 31.3). A subgroup analysis based on the median disease duration (less than and equal to 12 weeks, greater than 12 weeks), showed statistically significant differences compared to the sham procedure group for the subgroup of patients with disease duration less than and equal to 12 weeks (HR = 0.24, 95%CI 0.10 to 0.58) but failed to show statistically significant differences for the subgroup of patients with median disease duration of greater than 12weeks (HR = 0.84, 95%CI 0.43 to 1.67). Moreover, when broken down to each event type separately, the results indicate a statistically significant difference between nusinersen group and the sham procedure in overall survival (HR = 0.37, 95% CI 0.18 to 0.77), but not in time until permanent ventilation (HR = 0.66, 95% CI 0.32 to 1.37).

Efficacy results from the supportive evidence is limited due to either study design (single arm, non-comparative, descriptive, or phase II), or the use of a treatment regimen and/or dose that was not approved by Health Canada, or a combination of both factors. [redacted] Study CS3A indicated that patients with infantile onset symptomatic SMA show improvement in motor milestone development while treated with nusinersen; two patients (13%) died in the period of the study (728 days). In the CHERISH trial, nusinersen-treated patients with childhood onset SMA exhibited a statistically significant gain in motor function compared to patients in the sham control group.

Harms

Adverse events were reported in 96% of patients in the nusinersen group and 98% in the sham control group. Most adverse events and serious adverse events were related to infections and respiratory related complications. A number of patients (5%) in the nusinersen arm experienced vomiting, while none in the sham group did. A lower percentage of SAEs was reported in the nusinersen arm (76%) than in the sham-procedure arm (95%). Withdrawals due to adverse events were reported in 16% of nusinersen-treated patients and 39% of patients in the sham control group; all withdrawals due to adverse events were due to the death of the patient. Causes of death related to respiratory failure or arrest represented over half of the cases. Extension and long-term safety data studies have reported a similar safety profile.

Potential Place in Therapy[1]

Spinal muscular atrophy (SMA) results in the irreversible loss of motor neurons and motor nerves. The loss of these nerves causes skeletal muscles to become progressively weaker giving rise to swallowing problems and breathing difficulties and/or weakness of the limbs and trunk. A natural history study using a specialized neurophysiological technique called motor unit number estimation (MUNE) has found that there is a relatively rapid loss of motor neurons early in the course of the disease followed by a more gradual decline.[18] As such, the optimal time for intervention is early in the course of the disease before this rapid andirreversible loss of motor neurons has occurred.

Spinal muscular atrophy is diagnosed in Canada via genetic testing. Initial testing evaluates for the homozygous 5q deletion within the survival motor neuron 1 gene (SMN1) which identifies 95% of cases. If negative, SMN1 gene sequencing will be performed as a second step. Nerve conduction studies and electromyography (EMG) is performed in a subset of

[1] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

patients, however even when evidence of a motor neuronopathy is identified on this study it is followed up with confirmatory genetic testing.

Current standard of care practice for patients with confirmed SMA include surveillance and anticipatory management ensuring that patients receive monitoring of: 1) growth, gastrointestinal function and nutrition; 2) respiratory complications and; 3) orthopedic complications (i.e. scoliosis and/or contractures).[27] Anticipatory management of respiratory complications are particularly important for children with SMA type I and II since these patients are at high risk of having a weak cough with impaired clearance of airway secretions; nocturnal hypoventilation and; recurrent pulmonary infections. This standard of care is not expected to change with emerging therapies, however it is hoped that the progression and complications of this disease may be lessened.

Nusinersen is the only Health Canada-approved treatment that is available for children with SMA. Treatment is administered via intrathecal injection and has been shown to be safe in several clinical trials.[67,68] There is convincing evidence that nusinersen is effective for children with SMA type I. This includes both early, asymptomatic infants with SMA type I (NURTURE study) and young (< 7 months old) symptomatic infants with SMA type I (ENDEAR study).[67,68] Treated infants show improved survival (compared to natural history data) as well as improvement in their gross motor development as measured by the Hammersmith Infant Neurological Exam (HINE). Clinical improvement was even more pronounced when infants were treated earlier, particularly when pre-symptomatic.[67] According to the clinical expert consulted for this review, given these results, nusinersen should be available for all Canadian infants with SMA type I. Knowing that pre-symptomatic treatment with nusinersen offers the greatest potential for preventing irreversible loss of motor neurons, physicians and public health agencies must consider what can be done to ensure early diagnosis including the potential for including SMA into provincial newborn screening programs.

Nusinersen has also demonstrated efficacy for children (aged 2 to 12 years old) with SMA type II (CHERISH study). The interim results of a placebo-controlled trial identified children to show an improvement in motor strength and function as measured by the Hammersmith Functional Motor Scale Expanded (HFMSE). Since children's muscle fibres undergo an increase in size over the first few years of life, a process known as physiological hypertrophy, any intervention to prevent the irreversible loss of motor neurons and consequently, allow muscle fibres the potential to more normal development is advantageous. Early recognition and treatment is also important in this group. Although nusinersen has not been well studied in children with SMA type III, it would be predicted that children in this group would have a greater potential for increasing SMN protein, if treated early in the course of their disease. Patients with SMA type III comprise about 10-20% all patients with SMA. These children have had the ability to walk at some point although this can be lost as the disease progresses. Early treatment of patients with SMA type III, particularly young patients with apparent rapid disease progression would have the theoretical potential of preventing loss of ambulation with the significant gain of independence and avoidance of numerous medical complications that can result in non-ambulatory patients.

Conclusions

One randomized, double-blind, sham controlled, trial (ENDEAR, N = 121) met the inclusion criteria of the CDR systematic review. Patients included in the ENDEAR trial had a confirmed diagnosis of SMA, were less than seven months or age, had only two copies of the SMN2 gene, had a disease duration of no more than 25.86 weeks, and were most likely to develop SMA type I. Patients were randomized in a 2:1 ratio to nusinersen treatment or a sham control group. Patients were to receive ten months of treatment and have an additional three months of follow-up, however, the ENDEAR trial was concluded early based on positive results from a pre-planned interim analysis. There were statistically significant differences between the two groups, in favour of the nusinersen group, for both co-primary endpoints in the ENDEAR trial: the proportion of motor milestone responders as assessed by the HINE Section 2 tool and the time to death or permanent ventilation. No adverse events in the ENDEAR trial were considered by the study investigators to be related to the study treatment. The percentage of patients experiencing a SAEs and WDAEs were lower in the nusinersen treatment group versus the sham procedure arm. The main limitations of the ENDEAR trial was the early termination of the study which caused loss of data and a shorter time period to assess the efficacy and safety of nusinersen, and the inability to generalize the results to patients with infantile-onset SMA who had disease durations of more than 26 weeks.

Supportive evidence from two phase II trials (NURTURE, CS3A), one phase III trial (CHERISH), and two extension and long-term safety studies provided additional safety and efficacy data for patients who are likely to develop SMA type I and II. [redacted] while in the CHERISH trial, nusinersen-treated patients with childhood onset SMA experienced a statistically significant gain in motor function compared to patients in the sham control group. No new safety signals were identified in any of the supporting studies. These studies, however, were limited due to study design (single arm, non-comparative, descriptive, or phase II), and/or the use of a treatment regimen or dose that was not approved by Health Canada.

Table 1: Summary of Results

	ENDEAR	
HINE section 2 Motor Milestone Responders	**Nusinersen**	**Control**
Number of patients, N	73	37
Motor milestone responders*, N (%)	37 (51)	0
Difference in percentages (95%CI)	50.7 (31.8, 66.5)	
p-value	<0.0001	
Time to death or permanent ventilation		
Number of patients, N	80	41
Number of patients who died or required permanent ventilation, n (%)	31 (39)	28 (68)
Estimated proportion of patients who died or required permanent ventilation by:		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Hazard ratio (95%CI)	0.53 (0.32 to 0.89)	
p-value	0.0164	
Serious adverse events		
Number of patients, N	80	41
Patients with > 0 SAEs, N (%)	61 (76)	39 (95)
Respiratory distress	21 (26)	8 (20)
Respiratory failure	20 (25)	16 (39)
Pneumonia	19 (24)	5 (12)
Atelectasis	14 (18)	4 (10)
Acute respiratory failure	11 (14)	9 (22)
Pneumonia aspiration	8 (10)	5 (12)
Rhinovirus infection	7 (9)	2 (5)
Respiratory tract infection	6 (8)	1 (2)
Cardiorespiratory arrest	5 (6)	5 (12)
Respiratory arrest	5 (6)	4 (10)
Viral infection	5 (6)	1 (2)

95%CI = 95% confidence interval Abbreviations must be listed under the table in alphabetical order. For example, CI = confidence interval; OR = odds ratio.

* definition of a motor responder was: i) The patient demonstrated at least a 2-point increase in the motor milestones category of ability to kick or achievement of maximal score on that category (touching toes), or a 1-point increase in the motor milestones of head control, rolling, sitting, crawling, standing, or walking, AND (ii) among the 7 motor milestone categories (with the exclusion of voluntary grasp), the patient demonstrated improvement (as defined in [i]) in more categories than worsening.

Introduction

Disease Prevalence and Incidence

Spinal muscular atrophy (SMA) is a severe neuromuscular disease and is the leading genetic cause of infant death.[2,16] It is characterized by the degeneration of alpha motor neurons in the anterior horn of the spinal cord, leading to progressive muscle weakness.[2] Neurological studies indicate that the disease causes a rapid and irreversible degeneration of motor neurons, the rate of motor neuron degeneration has been reported to plateau with time.[18] 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.[3,4] SMN protein is essential for the development of motor neurons, and while deletion or mutation of the SMN1 gene results in SMN protein deficiency, the SMN2 gene produces a relatively small amount of functional SMN protein and SMN2 copy number modulates the severity of the disease.[1-3,16] SMA is a rare disease and estimates of its incidence and prevalence vary between studies. Most of these studies relied on clinical rather than genetic diagnosis and were often performed in small cohorts based in Europe.[4] The incidence of SMA is often cited as being approximately 10 in 100,000 live births.[4] One recent review found estimates ranging from 5.0 to 24 in 100,000 births.[4] Prevalence is estimated to be approximately one to two in 100,000 persons[4] and is affected by the drastically shortened life expectancy in the most common type of SMA. Incidence and prevalence estimates in Canada are not well described in the literature. However, the manufacturer of nusinersen provided Canadian estimate figures based on the average of three published studies of live birth incident rates in the United States, Sweden, and Poland,[69-71] The manufacturer approximated the annualized estimate of new cases of all SMA subtypes in Canada at 37.2 new cases per year; with the highest estimate of new cases in the province of Ontario at 13.9 new cases per year, second is the province of Quebec at 8.2 cases per year, third is the province of Alberta at 5.5 cases per year, and fourth is the province of British Columbia at 4.2 new cases per year, the rest of the provinces had an estimate of less than two cases per year.[72]

The disease first manifests in various ways, depending on age of onset. Infants present with severe hypotonia and feeding difficulties while later onset in young children may appear as difficulty with stairs and frequent falls.[17] Adult onset SMA presents as mild proximal muscle weakness.[2] Genetic testing gives a definitive diagnosis for 5q SMA and the first step is to test for SMN 1 gene deletion.[1] If homozygous SMN1 deletion is not found, sequencing of the SMN1 coding region may identify a causative mutation [1]. Genetic testing of the SMN2 gene can shed light on the potential subtype of SMA, as described below.

SMA is divided into four clinical subtypes (See Appendix 7 for an overview of the disease natural history):

Type I: These patients show symptoms before 6 months of age, never achieve the motor milestone of sitting, and generally do not survive past two years of age due to respiratory failure [1-3,16]. SMA Type I is the most common type of SMA, accounting for about 60% of SMA diagnosed.[4] The manufacturer approximated the annualized estimate of new cases of SMA type I to be 22.9 new cases per year nationally.[72] Almost all SMA Type I patients have two or three copies of SMN2, giving rise to a broad range of phenotypes.[6] Achievement of the motor milestone of sitting independently may cause a patient who was classified as SMA type I to be reclassified as SMA type II.[6,18] Additional subtypes of IA, IB, and IC have been proposed based on age of onset with IA being the earliest and most severe subtype.

SMA Type 0 is sometimes included in classification systems and presents in neonates as joint contractures, severe weakness and hypotonia, respiratory insufficiency, and a life expectancy of less than six months.[3,16]

Type II: Patients with Type II SMA achieve the milestone of sitting unsupported, but never walk independently. The manufacturer approximated the annualized estimate of new cases of SMA type II to be 10.5 new cases per year nationally.[72] Symptoms generally appear between 6 to 18 months after birth and most patients will survive past the age of 25,[16,17] with life expectancy improved by aggressive supportive care.[17] Type II patients represent about 20% to 30% of SMA cases[4] and most SMA Type II patients have three copies of SMN2.[6] In addition to the inability to walk independently, common symptoms are fine tremors of the upper extremities, tongue fasciculation, joint contractures, and scoliosis.[1,3,17]

Type III: Type III SMA makes up about 10% to 20% of SMA cases[4] 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.[17] Most Type III patients have three of four copies of SMN2.[6] An age of onset prior to 3 years is associated with estimated probabilities of 73%, 44%, and 34% of walking 10, 20, and 40 years after onset.[22] In those with age of onset after 3 years, the estimated probabilities are 97%, 89%, and 67% for walking 10, 20, and 40 years after onset.[22] SMA type III patients have little or no respiratory weakness.[3] Ambulatory patients may exhibit abnormal gait characteristics due to proximal weakness[17] while patients who lose the ability to walk often develop scoliosis.[1]

Type IV: A very small proportion of SMA cases are Type IV or adult onset SMA, 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.[1]

Patient input for this review described the diagnosis of a child with SMA as having a devastating effect. The feeling of hopelessness and despair in the face of a progressive and severe illness is especially pronounced, considering the absence of effective therapies. Young patients miss out on typical childhood experiences such as using the playground. In more severe cases, patients cannot execute basic movements such as sitting up and require help with needs such as transfers as well as positioning in wheelchair and in bed. In the most severe cases of infantile-onset SMA, the condition worsens over time and the patient passes away before reaching their second birthday.

Standards of Therapy

Aside from the reviewed drug, there are currently no treatments available for SMA. Standards of practice involve best supportive care, addressing the symptoms of the disease, and attempting to improve quality of life. Respiratory management is essential for all children with Type I SMA and some with Type II. Non-invasive ventilation with BiPAP can help with disordered breathing at night time and can be used during the day as needed for hypercapnia.[3] Secretion mobilization is also important in patients with weak cough and this can be achieved with postural drainage, assisted coughing, and oral suction.[1,16] When non-invasive ventilation is no longer sufficient, tracheostomy and permanent, invasive ventilation is an option. However, there is no consensus in guidelines regarding the suitability of this intervention and its use remains a choice for the family.[16,17] In patients with difficulty chewing and swallowing, changing food consistency can help with feeding and reduce risk of aspiration. A gastrostomy tube can also be placed, though there is no consensus on when this should occur.[17]

For gross motor function, management strategies include mobility aids, bracing, and physical therapy. Patients able to bear weight may make use of a standing frame or ankle-foot orthoses and physical activity such as swimming can increase stamina.[17] Manual and motorized wheelchairs provide mobility to those who can use them. Scoliosis is very common in non-ambulatory patients with SMA Type II and III, and can be corrected with surgery.[17] Bracing, seating modification, and physical therapy may slow scoliosis progression in a child until they can undergo surgery.[16]

Drug

Nusinersen (Spinraza) is indicated for the treatment of 5q Spinal Muscular Atrophy (SMA). It is an antisense oligonucleotide that increases the proportion of exon 7 inclusion in SMN2 messenger ribonucleic acid transcripts made, through binding to a specific site in the SMN2 pre-messenger ribonucleic acid. This leads to the translation of the messenger ribonucleic acid into functional full-length SMN protein. Nusinersen is administered via intrathecal injection by lumbar puncture in a 5 mL solution containing 12 mg of nusinersen. It is given in a regimen of four loading doses at day 0, day 14, day 28, and day 63, with subsequent maintenance doses at a frequency of every four months.[68]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of nusinersen for the treatment of patients with 5q Spinal Muscular Atrophy (SMA).

Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase III studies were also eligible for inclusion based on the selection criteria presented in Table 2.

Table 2: Inclusion criteria for the systematic review

Patient Population	Patients with 5q Spinal Muscular Atrophy (SMA) Subgroups: SMA type (Type I, II, III, and IV) Disease duration
Intervention	Nusinersen 12 mg (5 mL) via intrathecal administration by lumbar puncture in four loading doses at day 0, day 14, day 28, and day 63, with subsequent maintenance doses at a frequency of every four months.
Comparators	• Best supportive care • Placebo or sham • No treatment
Outcomes	**Key efficacy outcomes:** Motor function related outcomes: • Assessment of muscle strength and/or mobility using a validated scale* • Assessment of gross and fine motor skills development in pediatric population using a validated scale Respiratory related outcomes: • Assessment of pulmonary function * Survival related outcomes: • Overall survival • Event-free survival (e.g. invasive ventilation, hospitalization) Patient reported outcomes: • Health-related quality of life using a validated scale* • Assessment of symptoms severity using a validated scale* **Other efficacy outcomes:** • Caregiver burden • Use of respiratory or ventilatory assist devices • The need for enteral or parenteral feeding* • Weight percentile in pediatric population • Hospitalization **Harms outcomes:** • Adverse events, serious adverse events, withdrawals due to adverse events, mortality • Adverse events of special interest: serious infection, serious respiratory infection, respiratory complication related to drug anesthesia, lumbar puncture related adverse events (e.g. bleeding, brainstem herniation, meningitis, pain post lumbar puncture), coagulation abnormalities, renal toxicity.
Study Design	Published and unpublished phase 3 randomized controlled trials

* These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

The literature search was performed by an information specialist using a peer-reviewed search strategy. Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Spinraza and Nusinersen

No Methodological filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year

or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on July 27, 2017. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on November 15, 2017. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (https://www.cadth.ca/grey-matters): Health Technology Assessment Agencies; Health Economics; Clinical Practice Guidelines; Drug and Device Regulatory Approvals; Advisories and Warnings; Drug Class Reviews; Databases (free); Internet Search. Google and other Internet search engines were used to search for additional web-based materials, including conference abstracts. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table; excluded studies (with reasons) are presented in Appendix 3.

Results

Findings from the Literature

A total of 60 studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 3 and described in Section 3.2. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

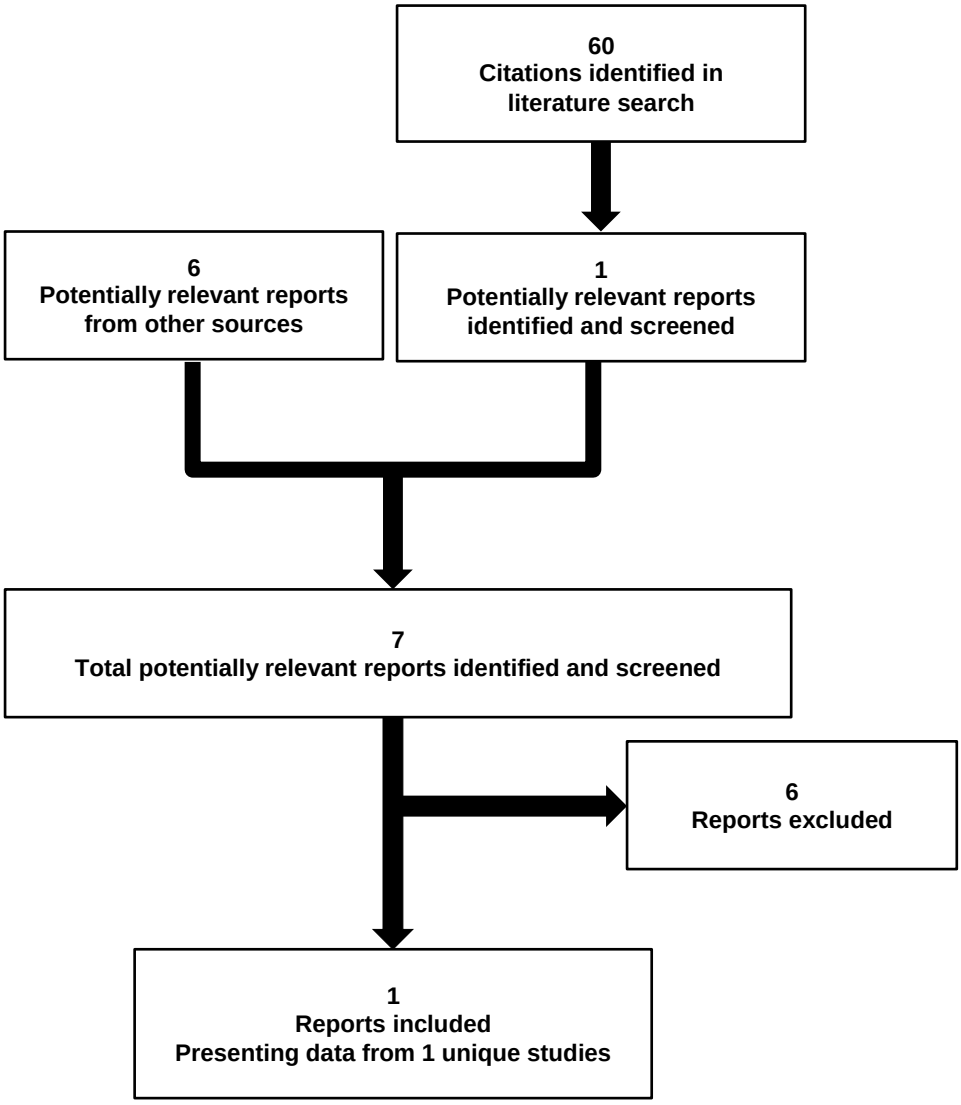


Table 3: Details of Included Study

		ENDEAR (CS3B)
Designs & Populations	**Study Design**	Phase III, randomized, double-blind, sham-procedure controlled, multicentre trial
	Locations	North America (Canada and United States), Europe, Asia-Pacific region
	Enrolled (N)	121
	Inclusion Criteria	• Genetic documentation of 5q SMA homozygous gene deletion, homozygous mutation, or compound heterozygote • Genetic documentation of 2 copies of SMN2 • Onset of clinical signs and symptoms consistent with SMA at ≤6 months (180 days) of age. • Males and females ≤7 months (210 days) of age at Screening • Patients were the product of a pregnancy of 37 to 41 weeks gestation
	Exclusion Criteria	• Hypoxemia • Signs or symptoms of SMA present at birth or within the first week after birth • History of or active condition that would interfere with lumbar puncture or assessment of study • Treatment with an investigational drug given for the treatment of SMA (e.g., oral albuterol/salbutamol, riluzole, carnitine, sodium phenylbutyrate, valproate, hydroxyurea, etc.), biological agent, or device within 30 days prior to screening or anytime during the study. Any history of gene therapy, prior ASO treatment, or cell transplantation
Drugs	**Intervention**	12-mg (in a 5 mL solution) scaled equivalent dose based on CSF volume scaling of nusinersen administered via intrathecal injection by lumbar puncture on Days 1, 15, 29, 64, 183, and 302
	Comparator(s)	Sham procedure on Days 1, 15, 29, 64, 183, and 302
Duration	Screening	21 days
	Double blind treatment period	10 months
	Follow-up	3 months
Outcomes	**Primary End Point**	• Proportion of HINE Section 2 motor milestone responders • Time to death or permanent ventilation
	Other End Points	• Proportion of CHOP INTEND responders • Survival rate • Proportion ventilation free • Growth parameters • Hospitalization
Notes	**Publications**	"None"

Abbreviations: CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HFMSE = Hammersmith Functional Motor Scale – Expanded; HINE = Hammersmith Infant Neurological Examination; RULM = Revised Upper Limb Module; SAE = serious adverse event; SMA = spinal muscular atrophy; SMN = survival motor neuron; WHO = World Health Organization.

Source: Clinical study report: ISIS 396443-CS3B.[73]

Included Studies

Description of studies

One phase III randomized, sham-procedure controlled, trial met the inclusion criteria in the CDR review protocol. The ENDEAR study (also known as CS3B) was a phase III randomized, double-blind, sham-procedure control, multicentre study, that included Canadian sites. Subsequent to screening assessment, patients were randomized on a 2:1 ratio to nusinersen or sham, respectively, using an interactive voice/ web response system. The unequal randomization ratio was justified on ethical basis.[72,73] The randomization was based on a permuted block schedule and was stratified for disease duration (defined as the age of the patient at screening minus age at symptom onset) at 12 or less weeks or more than 12 weeks. To maintain blinding, dedicated study personnel administered the injection in an unblinded fashion in a dedicated room where key study personnel (i.e., the principal investigator, study coordinator, or outcomes assessors) were not present. The sham procedure consisted of a needle prick to the target area where the treatment would be administered, covered with the same type of bandage, and patients kept in the procedure room for the same amount of time. The sham kits were packed in a blinded fashion and contained an artificial cerebrospinal fluid to simulate the cerebrospinal fluid samples collected in nusinersen-treated patients.[72] The study was designed to last for 13 months, with the double-blind treatment period lasting for 10 months and 3 months of follow-up. However, the double-blind period was concluded early due to the positive results after the results were assessed at the pre-specified interim analysis (6 months). After this early termination, all patients were to receive nusinersen afterward. One primary endpoint (proportion of HINE Section 2 responders) was assessed at the pre-specified interim analysis. Subsequent to the decision to terminate the study early, the final analysis of the two primary outcomes, proportion of HINE Section 2 responders, and time to death or permanent ventilation was conducted.

Populations

Inclusion and exclusion criteria

Patients included in the ENDEAR study were genetically documented with 5q SMA homozygous gene deletion, homozygous mutation, or compound heterozygote; had only two copies of the SMN2 gene, and were younger than 7 months of age. These inclusion criteria were intended to enroll patients who would most likely develop SMA type I. The exclusion criteria of the study included hypoxemia at presentation, history of a condition that would preclude a patient from receiving lumbar puncture, and previous exposure to experimental SMA treatment.

Baseline characteristics

A total of 121 patients were randomized to the nusinersen treatment arm or control arm in the ENDEAR trial. Overall, 55% of the randomized patients were females, and 86% were Caucasian. The diagnosis of SMA was established at a median age of 13.1 weeks (range 0 to 25.9 weeks), and received the first dose of the treatment/ (or sham) was received at a median age of 175 days (range 30 to 262 days). There were imbalances noted in some baseline characteristics between the treatment and the control group with respect to the mean age of screening, first dose, and diagnosis, which were higher in the control group than in the treatment group. There were also differences between the two groups in

characteristics related to the symptoms of the disease; with a 13% higher proportion of patients in the treatment group experiencing pneumonia or respiratory symptoms (35% versus 22%), and a 22% higher proportion of patients in the treatment group experiencing difficulty swallowing (51% versus 29%). Baseline values of HINE section 2 characteristics were, overall, similar between groups, except in the categories of 'voluntary grasp' and 'no rolling'. The proportion of patients who were able to use the whole hand to grasp was numerically higher in the control group (73% in control group versus 63% in treatment group), while the proportion of patients who were unable to roll was numerically lower in the control group (88% in control group versus 99% in treatment group). It is noted that a numerically higher proportion of patients in the treatment group required ventilator support than in the control group (26% versus 15%).

Table 4: Summary of Baseline Characteristics

	ENDEAR	
	Nusinersen (N=80)	**Control (N=41)**
Demographics		
Age at screening, mean (SD)	147.2 (46.9) days	164.7 (48.5) days
Age at first dose of study treatment, mean (SD)	163.4 (49.6) days	180.5 (50.9) days
Female, n (%)	43 (54)	24 (59)
White, n (%)	68 (85)	36 (88)
Asian, n (%)	5 (6)	1 (2)
[redacted]	[redacted]	[redacted]
SMN2 copy number		
Two copies, n (%)	80 (100)	40 (98)
Three copies, n (%)	0	1 (2)
Four copies, n (%)	0	0
Unknown, n (%)	0	0
Disease history		
Time from disease onset to study screening (weeks), mean (SD)	13.2 (5.5)	13.9 (5.7)
Age at symptom onset (weeks), mean (SD)	7.9 (4.0)	9.6 (4.7)
Age at diagnosis (weeks), mean (SD)	12.6 (6.6)	17.5 (7.5)
Disease symptoms		
Hypotonia, n (%)	80 (100)	41 (100)
Developmental motor delay, n (%)	71(89)	39 (95)
Paradoxical breathing, n (%)	71(89)	27 (66)
Pneumonia or respiratory symptoms, n (%)	28(35)	9 (22)
Limb weakness, n (%)	79 (99)	41 (100)
Swallowing or feeding difficulties, n (%)	41(51)	12 (29)
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

	ENDEAR	
	Nusinersen (N=80)	Control (N=41)
[redacted]	[redacted]	[redacted]
Disease supports		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Source: Clinical study report: ISIS 396443-CS3B.[73]

Abbreviations: CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE = Hammersmith Infant Neurological Exam; NR = not reported; SD = standard deviation.

Interventions

Patients enrolled in the ENDEAR study were randomized to either a scaled equivalent of 12 mg dose nusinersen treatment or sham injection based on the patient's age. The aim of adjusting the dose and volume was to achieve the same dose effect while accounting for the smaller cerebrospinal fluid volume. Nusinersen was administered using a single intrathecal injection through lumbar puncture using a spinal anesthesia needle and a 5 mL syringe, delivered as a slow bolus at the L3/L4 spinal space (plus or minus one lumbar spine level if needed). The treatment was administered according to a loading schedule (on study days 1, 15, 29, and 64) and a subsequent maintenance schedule of once every 4 months (on study days 183 and 302).

The sham procedure matched the dosing and the maintenance schedule of nusinersen treatment. It consisted of a needle prick, breaking the skin, at the site of an L3/L4 lumbar puncture. Patients were kept in the procedure room for the same duration of time as the nusinersen-treated patients, and the needle prick site was covered by the same type of bandage. The administration of both procedures was conducted by unblinded personnel in an enclosed procedure room where study investigators and parents were not allowed.

Concomitant medications were allowed as necessary to address any adverse events or to provide supportive care, as deemed necessary by the treating physician. Only experimental treatments for SMA were prohibited (e.g., salbutamol, valproate, creatine, and hydroxyurea).

[redacted]

ENDEAR		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Source: Clinical study report: ISIS 396443-CS3B.[73]

Outcomes

Details regarding the validity and reliability of outcomes measure are presented in Appendix 5.

a) Proportion of motor milestone responders (Section 2 of the Hammersmith Infant Neurological Examination [HINE])

The proportion of HINE Section 2 responders was the first of two primary outcomes. The Section 2 of the HINE scale is concerned with motor milestones and assesses eight motor milestones: head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing, and walking.[50] Each milestone has three to five possible descriptive ratings, ranging from 'not performing the task at all' to 'fully demonstrating the milestone'.[50]

Although the original HINE developers did not define a quantitative scoring system for section 2, scores for each milestone were obtained by assigning a value of 0 to the absence of the activity and adding 1 point for each incremental rating.[74] Specifically, a one point increase from baseline can be achieved if an improvement took place in any of the categories of head control, rolling, sitting, crawling, standing, or walking, a two point improvement is achieved through exhibiting the ability to kick or touch toes. Voluntary grasp was excluded from the analysis. The manufacturer indicated that it was excluded because voluntary grasp lacks movement against gravity, and many infantile SMA patients would achieve all milestones in this category.[75] Worsening was considered as at least a 2-point decrease or a decrease to the lowest possible level, no kicking in the ability to kick category, and at least a 1-point decrease for the other categories. Although a total score was not described in the original development of the tool, it is assumed by the reviewer that a total HINE score for section 2 was calculated by scoring each milestone on an ordinal scale (with 0 representing no ability) and summing the scores. The manufacturer provided the following definition for motor milestone responders:

> "The definition of a motor milestones responder was based on the motor milestones categories in Section 2 of the HINE (with the exclusion of voluntary grasp) using the assessment at the later of the Day 183, Day 302, or Day 394 Visits as follows:
>
> (i) The patient demonstrated at least a 2-point increase in the motor milestones category of ability to kick or achievement of maximal score on that category (touching toes), or a 1-point increase in the motor milestones of head control, rolling, sitting, crawling, standing, or walking, AND
>
> (ii) among the 7 motor milestone categories (with the exclusion of voluntary grasp), the patient demonstrated improvement (as defined in [i]) in more categories than worsening. Note: for the category of ability to kick, similar to the definition of improvement in (i) above, worsening is defined as at least a 2-point decrease or decrease to the lowest possible score of no kicking. For the other 6 categories, worsening is defined as at least a 1-point decrease."[73]

An MCID score was not specifically identified from the literature for this measure. Although, the manufacturer reported that based on the natural history of SMA type I, a change in score of > 1 point for any given milestone is highly unlikely in untreated SMA type I patients.

Patients were assessed by a neurologist at the study center, the assessment was performed at screening, and before the lumbar puncture procedure on study days 64, 183, 302, and 394.

b) Time to death or permanent ventilation

Time to death or permanent ventilation was the second primary outcome reported in the ENDEAR study. Permanent ventilation was defined in the study as the need for 16 hours or more of continuous ventilatory support per day for 21 or more consecutive days, in the absence of an acute reversible event, or the of the patient required tracheostomy. A patient's ventilation use was recorded daily by the caregiver and collected during study visits and weekly telephone contacts. The time to death or permanent ventilation was assessed by an adjudication committee blinded to the patient's assignment.

c) Proportion of Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease (CHOP INTEND) responders

A secondary outcome, the CHOP INTEND was developed in SMA type I infants and designed for use to measure motor function in infants and children with neuromuscular disorders.[54] It is made up of 16 items, each rated 0 to 4 (no response, minimal, partial, nearly full, and complete level of response) giving a maximum total score of 64 when summed with higher scores indicate better performance.[54]

The manufacturer defined a CHOP INTEND responder was defined in the study as a patient with a score change from baseline of four or greater points when assessed on study days 183, 302, or 394.

An MCID was not found for the CHOP INTEND score.

d) Survival rate

Overall survival of patients was a secondary outcome in the ENDEAR study.

e) Percent of patients not requiring permanent ventilation

The percentage of patients who did not need permanent ventilation was reported as a secondary outcome in the ENDEAR study.

f) Growth parameters

Growth parameters was a tertiary outcome, where trained staff would assess weight, body length, arm circumference, chest circumference, and head circumference at screening and before the lumbar puncture on study days 29, 64, 183, 302, and 394. A growth failure was captured through using two definitions – the first as a post-baseline weight below the fifth percentile, and the second as a weight drop crossing 2 or more major percentiles in six months.[73]

g) Hospitalization

The number of hospitalizations that occurred during the study period was measured as a tertiary outcome.

h) Drug related adverse events and serious adverse events

An adverse event was recorded as “treatment emergent” if it either; existed before the first procedure and worsened subsequently, or if it was not present before the first procedure and subsequently appeared.

Statistical analysis

ENDEAR was a randomized, double-blind, sham procedure control, clinical trial. [redacted]

At the interim analysis, only the motor milestone primary outcome was to be tested. [redacted] The outcomes hierarchy was according to the following:

1) Second primary efficacy endpoint, time to death or permanent ventilation
2) The proportion of CHOP INTEND responders
3) Time to death
4) Percentage of patients not requiring permanent ventilation
5) Proportion of compound muscle action potential (CMAP) responders
6) Time to death or permanent ventilation in subgroup of patients with disease duration at screening below or at study median
7) Time to death or permanent ventilation in subgroup of patients with disease duration at screening above study median

[redacted]

[redacted] Two subgroup analyses in the first primary outcome of motor milestone responders were conducted based on the cut-off of the median disease duration of 12 weeks.

The analysis of the differences in the two groups for the second primary endpoint, time to death or permanent ventilation, was conducted using the log-rank test stratified by disease duration at screening (≤12 weeks or >12 weeks), [redacted]

[redacted]

Analysis populations

According to the previously described method of assigning study days for the premature end-of-study visit, the following analysis population were defined:

ITT Set: All patients who were randomized and received at least 1 dose of study treatment/sham procedure. Patients were analyzed in the treatment group to which they were randomized. [redacted]

Efficacy Set: All patients with a recorded study visit on day 183, 302, or 394 [redacted]

[redacted]

Safety Set: All patients who were randomized and received at least 1 dose of study treatment/sham procedure.

Patient Disposition

Table 6 summarizes the disposition of enrolled patients. By the time the study was prematurely terminated, 31% of patients had completed the full-length of the study including the follow-up and 40% had completed the double-blind treatment period. The proportion of patients that completed the study in the nusinersen group was higher than in the control group.

Table 6: Patient Disposition

	ENDEAR	
	Nusinersen	**Control**
Screened, N	149	
Randomized, N (%)	81	41
Withdrawal prior to dosing, N	1	0
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		

	ENDEAR	
	Nusinersen	Control
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
ITT, N (%)	80 (99)	41 (100)
Interim Efficacy Set, N (%)	51 (63)	27 (66)
Efficacy Set, N (%)	73 (90)	37 (90)
[redacted]	[redacted]	[redacted]
Safety, N (%)	80 (99)	41 (100)

Source: Clinical study report: ISIS 396443-CS3B.[73]

Abbreviations: ITT = intention to treat; PP = per protocol.

* No SAE was determined to related to study treatment

Exposure to study treatments

Tablee 7 summarizes treatment exposure. As of the data cut-off date, 73 patients out of the 80 that were allocated to the nusinersen treatment arm (91%) received at least 4 doses, 32 (40%) received all 6 doses. In the sham group, 34 (83%) had 4 sham procedures, and 14 (34%) underwent all 6 sham procedures.

Table 7: Exposure to study treatment

	ENDEAR	
	Nusinersen	Control
Number of patients, N	80	41
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviation: SD = standard deviation

Source: Clinical study report: ISIS 396443-CS3B[73]

Critical Appraisal

Internal validity

ENDEAR was a randomized, sham-procedure control, double-blind, clinical trial. The study methods were generally well-reported (as summarized above), including the details of power analysis, randomization, allocation concealment, and statistical analysis. Overall, potential issues pertaining to the internal validity of the study can be identified as relating to the following points:

1) Un-equal randomization ratio:

The manufacturer randomized patients in a 2:1 ratio to nusinersen or sham procedure, respectively. An ethical rationale for this approach was provided. Potential challenges that may be associated with such allocation ratio includes the need for larger sample size to capture differences in treatment effect, and the potential of reducing the effectiveness of blinding as investigators and assessors would be aware that the probability of being allocated to active treatment is twice that of control.[76] Based on the primary endpoints of the study, it appears to be adequately powered given that statistically significant differences were observed. A reduction in statistical power due to the 2:1 randomization ratio could potentially have an effect on the secondary outcomes and subgroups analyses.

2) Imbalances in the baseline patient characteristics after randomization between treatment groups:

Patients that were randomized to the sham procedure were older than patients randomized to the nusinersen group in terms of age at screening and age at first dose. Patients allocated to the treatment group had disease onset at a younger age, had 13% higher proportion of experiencing pneumonia or respiratory symptoms, 22% higher proportion experiencing difficulty swallowing, and a higher percentage of patients in the treatment group required ventilator support than in the control group (26% versus 15%). While this could bias the result in favour of the sham procedure, as patients in the nusinersen group were at higher risk of pulmonary complications, it is also possible that these patients may have a greater potential to improve. As such, a definitive direction of this potential bias remains unclear.

3) Potential for investigators to unmask patients assignment:

While allocation concealment was maintained by including a sham procedure, there was a potential for treatment status to be unmasked post-randomization. It is possible that investigators who had previous experience caring for or researching SMA could ascertain treatment assignment in patients who exhibited considerable improvements in motor milestone development that are otherwise unlikely to be observed in untreated patients.[75] It is unclear if potential unblinding would introduce operational bias into the subsequent conduct of the study.

4) Premature termination of the study:

Since the study was prematurely concluded, only one-third of the population completed the full study length with the follow-up period. The missing data can be viewed as largely due to late enrollment relative to the interim analysis date. In light of the positive interim analysis results and the severity of the disease, a decision to prematurely terminate the study and allow all patients to receive the active drug was made for ethical reasons. However, the

data loss due to this premature cut-off may affect our ability to draw insight from secondary and subgroup analysis due to the smaller sample size than originally planned. Further, the premature cut-off reduced the available data for the second primary outcome in that the median time to death or permanent ventilation in the treatment group was not reached, despite the study being originally powered to double the median time to death or permanent ventilation. As well, premature termination of the study reduces the amount of longer-term safety data relative to a control group.

5) First primary outcome not using an ITT population:

The analysis of the first primary outcome (HINE Section 2 motor milestone responders), as well as the secondary outcome (CHOP INTEND), was based on an "efficacy population". One aspect of this population is a complex process of handling missing data and varying study visit dates as end dates. However, the manufacturer provided several sensitivity analyses testing different approached in handling missing data. This seemed also the conclusion reached in the FDA statistical review report.[77]

6) Lack of valid statistical inference for outcomes in the hierarchy after a nonsignificant result:

To control for multiple outcome testing, the manufacturer established a hierarchy for all secondary outcomes assessed. Statistical testing should have been stopped after the first non-statistically significant outcome was established. All outcomes that are lower on the hierarchy than the first non-significant outcome should be treated as nominal in nature.

7) Variation in use than original design of the HINE Section 2 tool:

The manufacturer used a summary score of the HINE Section 2 tool while excluding the section of voluntary grasp. The psychometric properties of the HINE Section 2 summary score in this form have not been characterized extensively. The summary score with all the milestones demonstrated acceptable test-retest reliability and moderate correlations with measure of motor function in a sample of 19 patients with SMA type 1.[78] A natural history study in 33 SMA type I patients observed only one occurrence of milestone improvement, which was a 1-point improvement in the ability to kick.[74] While the available evidence supports a 1-point (2-point for ability to kick) increase as the threshold for improvement in this population, motor milestone responder as defined in the ENDEAR study has not been thoroughly evaluated as an outcome measure.

External validity

The ENDEAR study included two Canadian sites, and according to the clinical expert consulted for this review, the inclusion and exclusion criteria of the study were reasonable, and the patients enrolled in the ENDEAR trial are representative of patients typically seen in clinical practice who are likely to develop infantile-onset SMA type I. [redacted] This may indicate that there are likely several patients with SMA that do not meet the inclusion and exclusion criteria of the study, and the efficacy of nusinersen in such population is unknown. In addition, it is possible that the the requirement of patients to have two copies of SMN 2 gene may have excluded a small proportion of patients that exhibit the phenotype of SMA type I but carry three copies of the SMN 2 gene. According to the clinical expert, the control group was also considered appropriate as standard and supportive care were allowed in the sham procedure group and there is lack of any effective therapy beyond supportive care.

Based on input from the clinical expert consulted for this review, the outcomes described in the ENDEAR study are relevant in addressing the major symptoms observed in patients most likely to develop SMA type I. One limitation of the motor functional outcomes using the HINE section 2 and the CHOP INTEND scoring is their infrequent use in practice, as described by the clinical expert. Another limitation of the ENDEAR study is the inability of infants to self-report adverse events, such as headache, back pain, and dizziness. As such, these potentially common adverse events that are expected due to the lumbar puncture may not be given attention. In addition, no assessment of caregivers' quality of life or the burden of the disease was conducted in the study.

SMA is a lifelong disease that potentially may require nusinersen treatment for many years. The ENDEAR study provides evidence regarding the efficacy of nusinersen for up to 10 months of treatment and an additional 3 months of follow-up. Moreover, the trial was concluded early, [redacted] As such it is difficult to generalize the results of the ENDEAR study on to patients that have been diagnosed with infantile onset SMA for a duration longer than 26 weeks.

Efficacy

Only those efficacy outcomes and subgroups identified in the review protocol are reported below (Section 2.2, Table 3). See Table8 for summary of efficacy data.

HINE section 2 motor milestone responders

The first primary outcome, the proportion of motor milestone responders was analyzed based on the efficacy analysis set. In this set, 37 patients out of 73 in the nusinersen group (51%) compared with 0 patients out of 37 in the sham procedure control group were classified as responders. There was a statistically significant difference between groups in the percentage of patients who were classified as motor milestone responders (50.7, 95%CI 31.8 to 66.5, $P < 0.0001$). All conducted sensitivity analyses showed similar results to the base case. At the data cut-off date, 16 patients (22%) achieved full head control, 6 (8%) achieved independent sitting, and 1 (1%) achieved standing in the nusinersen group, whereas no patients in the sham procedure group achieved any of these milestones.

Subgroup analyses based on the median disease duration (≤12 weeks, >12weeks) were performed, however, results are considered exploratory as these analyses were outside of the stage-wise hierarchical strategy and, therefore, not adjusted for multiplicity.

[redacted]

Source: Clinical study report: ISIS 396443-CS3B [73]

Time to death or permanent ventilation

The second primary outcome was analyzed using the ITT analysis set. Thirty-one patients (39%) in the nusinersen group died or required permanent ventilation versus 28 patients (68%) in the sham procedure group resulting in a statistically significant difference between groups (HR 0.53 [95%CI 0.32 to 0.89], *P* = 0.0164). Seven sensitivity analyses were conducted in relation to event definition, statistical model, and analysis population (described in the statistics section). The results of the sensitivity analyses were similar to the primary analysis.

The results of the subgroup analysis based on median disease duration (≤12 weeks, >12weeks), showed statistically significant differences compared to the sham procedure group in the subpopulation below the median disease duration (HR = 0.24, 95%CI 0.10 to 0.58) but failed to show statistically significant differences in the subpopulation over the disease median duration (HR = 0.84, 95%CI 0.43 to 1.67). However, due to the nonsignificance of a prior outcome in the stage-wise hierarchical strategy, (percentage of patients not requiring permanent ventilation) these analyses can only be considered exploratory and inconclusive.

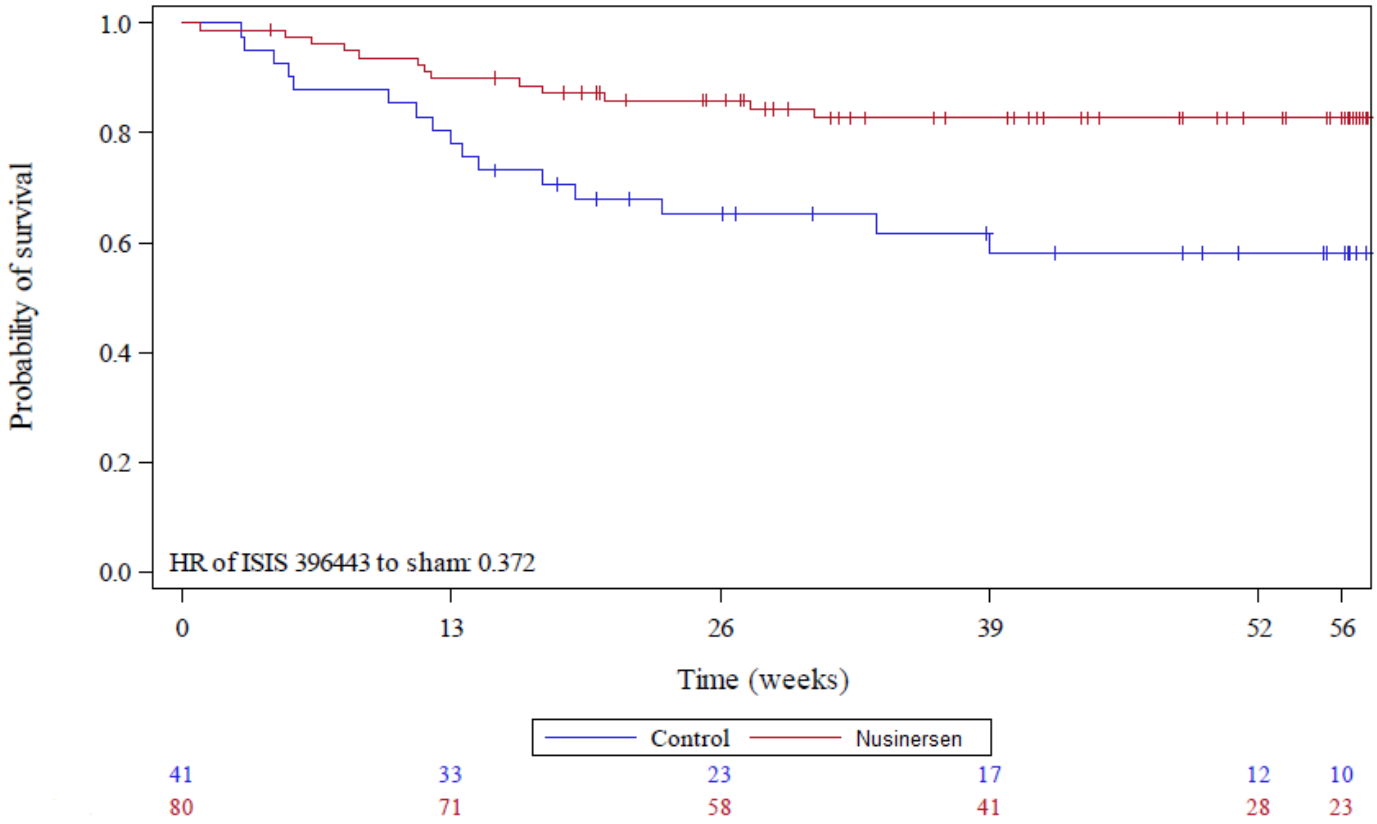
[redacted]

Source: Clinical study report: ISIS 396443-CS3B.[73]

Overall survival

When considering time to death in both groups, analysis using the ITT set indicated a statistically significant difference between nusinersen group and the sham procedure (HR = 0.37, 95%CI 0.18 to 0.77). A Kaplan-Meier curve is presented in Figure.

Figure 4: Kaplan-Meier Curves for Time to Death – ITT Set



Source: Clinical study report: ISIS 396443-CS3B.[73]

Proportion of patients requiring permanent ventilation

When considering the proportion of patients requiring permanent ventilation in both groups, analysis using the ITT set did not show a statistically significant difference (HR = 0.66, 95% CI 0.32 to 1.37). Because of the nonsignificance of this result, all subsequent tests in the statistical hierarchy were then considered exploratory.

CHOP INTEND improvement

Analysed using the efficacy set, patients in the nusinersen experienced greater proportion of patients that were able to achieve an improvement of four or more points (71%) compared to patients allocated to the sham procedure group (3%).(percentage difference = 68.53, 95%CI 51.27 to 81.99, *P* < 0.0001).

Growth parameters

[redacted]

[redacted]

Table 8: Key Efficacy Outcomes

	ENDEAR	
HINE section 2 Motor Milestone Responders	**Nusinersen**	**Control**
Number of patients, N*	73	37
Motor milestone responders (Improvement of any HINE categories in which there are more categories with improvement than with worsening), N (%)	37 (51)	0
Difference in percentages between treatment groups (95%CI)	50.7 (31.8, 66.5)	
p-value	<0.0001	
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
CHOP INTEND		
Number of patients, N*	73	37
Baseline CHOP INTEND score, mean (SD)	26.5 (8.2)	28.0 (7.6)
Change from baseline in total score improved >=4 points, n (%)	52 (71)	1 (3)
[redacted]		
p-value	<0.0001	
Time to death or permanent ventilation		
Number of patients, N	80	41
Number of patients who died or required permanent ventilation, n (%)	31 (39)	28 (68)
Estimated proportion of patients who died or required permanent ventilation by:		
Day 91 (13 weeks/3 months)	0.24	0.27
Day 182 (26 weeks/6 months)	0.29	0.61
Day 273 (39 weeks/9 months)	0.40	0.70
Day 364 (52 weeks/12 months)	0.45	0.74
Day 394 (13 months)	0.45	0.74
Median survival time (weeks), median (95%CI)	NA (36.3 to NA)	22.6 (13.6 to 31.3)
Hazard ratio (95%CI)	0.53 (0.32 to 0.89)	
p-value	0.0164	

	ENDEAR	
Overall survival		
Number of patients, N	80	41
Number of patients who died	13 (16)	16 (39)
Estimated proportion of patients who died by:		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Hazard ratio (95%CI)	0.37 (0.18 to 0.77)	
p-value	0.0082	
Permanent ventilation		
Number of patients, N	80	41
Number of patients who required permanent ventilation	18 (23)	13 (32)
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
Growth parameters		
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
Hospitalization		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

	ENDEAR
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Source: Clinical study report: ISIS 396443-CS3B.[73]

Abbreviations: CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CI = confidence interval; HFMSE = Hammersmith Functional Motor Scale – Expanded; HINE = Hammersmith Infant Neurological Examination; NA = not applicable; RULM = Revised Upper Limb Module; WHO = World Health Organization.

* **Efficacy Set**: All patients with a recorded study visit on day 183, 302, or 394 and all patients with a time difference of at least 190 days between date of first dose and the cut-off date for the final analysis.

** adjusted for age at symptom onset and disease duration at screening.

Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol). Summary of harms is presented in
Table 9.

Adverse events

At least one adverse event was reported in 96% of all enrolled patients. None of the adverse events were considered related to the study treatment by the study investigators. The only lumbar puncture related adverse event reported was vomiting, which was observed in 5% in the nusinersen group but not in the control group. Withdrawals due to adverse events were due to fatal adverse events only, an outcome captured by the second primary outcome of the study.

Serious adverse events

A lower percentage of patients in the nusinersen group had an SAE compared to the sham control group (nusinersen vs. control: 76% vs. 95%).

Withdrawals due to adverse events

All withdrawals due to adverse events were due to the death of the patient. There were numerically higher WDAE in the control group (39%) versus the nusinersen group (16%).

Mortality

There were 16 deaths (39%) reported in the control group versus 13 deaths reported in the nusinersen group (16%). Deaths were attributed to respiratory, thoracic and mediastinal disorders were the highest proportion in both groups (9% in the nusinersen group and 29% in the control group).

Notable harms

Vomiting was noted in the nusinersen group as related to the lumbar puncture procedure (5% in nusinersen group, 0% in the control group). Two patients (3%) in the nusinersen treatment arm were reported as having an adverse effect related to renal and urinary disorders, compared with one patient (2%) in the control group.

Table 9: Harms

	ENDEAR	
AEs	**Nusinersen N = 80**	**Control N = 41**
Patients with > 0 AEs, N (%)	77 (96)	40 (98)
Infections and infestations	65 (81)	31 (76)
Respiratory, thoracic and mediastinal disorders	61(76)	36 (88)
Gastrointestinal disorders	53 (66)	26 (63)
General disorders and administration site conditions	51 (64)	28 (68)
Skin and subcutaneous tissue disorders	23 (29)	15 (37)
Investigations	21 (26)	14 (34)
Cardiac disorders	19 (23)	13 (32)
Injury, poisoning, and procedural complications	19 (24)	10 (24)
Metabolism and nutrition disorders	14 (18)	13 (32)
Musculoskeletal and connective tissue disorders	11(14)	5 (12)
Psychiatric disorders	9 (11)	5 (12)
Nervous system disorders	9 (11)	2 (5)
Congenital, familial and genetic disorders	4 (5)	4 (10)
Blood and lymphatic disorders	1 (1)	3 (7)
SAEs		
Patients with > 0 SAEs, N (%)	61 (76)	39 (95)
Respiratory distress	21 (26)	8 (20)
Respiratory failure	20 (25)	16 (39)
Pneumonia	19 (24)	5 (12)
Atelectasis	14 (18)	4 (10)
Acute respiratory failure	11 (14)	9 (22)
Pneumonia aspiration	8 (10)	5 (12)
Rhinovirus infection	7 (9)	2 (5)
Respiratory tract infection	6 (8)	1 (2)
Cardiorespiratory arrest	5 (6)	5 (12)
Respiratory arrest	5 (6)	4 (10)
Viral infection	5 (6)	1 (2)
WDAEs		
WDAEs, N (%)*	13 (16)	16 (39)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

	ENDEAR	
Deaths		
Number of deaths, N (%)	13 (16)	16 (39)

Source: Clinical study report: ISIS 396443-CS3B. A phase 3, randomized, double-blind, sham-procedure controlled study to assess the clinical efficacy and safety of ISIS 396443 administered intrathecally in patients with infantile-onset spinal muscular atrophy [**CONFIDENTIAL** internal manufacturer's report].[73]

* All WDAE were caused by the death of the patient.

Discussion

Summary of Available Evidence

One randomized, double-blind, sham procedure controlled, phase III clinical trial was included in this review, the ENDEAR study. The study recruited patients up to 7 months of age with infantile onset SMA with documented 5q SMA homozygous gene deletion, homozygous mutation, or compound heterozygote, and only two copies of the SMN2 gene. These characteristics make this group of patients likely to develop SMA type I. In addition, the resulting baseline characters of enrolled patients indicate that all of them were relatively recently diagnosed with SMA (between 0 and 25.86 weeks of disease duration).

Additional studies assessing the safety and efficacy of nusinersen that did not meet the inclusion criteria due to study design and/or intervention include two single phase II single arm trials (non-matching dosing, as well as CS3A not matching the dosing regimen of the nusinersen) and one phase III randomized controlled trial (not matching the dosing regimen of nusinersen), and were summarized in Appendix 4.These studies assessed the efficacy and safety of nusinersen in pre-symptomatic patients (NURTURE study), infantile onset SMA (CS3A), and childhood onset SMA (CHERISH). In addition, extension and long-term safety studies assessing the safety of nusinersen were also summarized in Appendix 6.

Interpretation of Results

Efficacy

The ENDEAR study randomized 121 patients with SMA (likely to develop SMA type I) in a 2:1 ratio to nusinersen treatment and sham-procedure control group, respectively. There were two primary outcomes: motor milestone responders according to the HINE Section 2 tool, and time to death or permanent ventilation. After the interim analysis of the first primary outcome, HINE Section 2 motor milestone responders, the positive results led to the premature termination of the study to allow patients in the sham-procedure group the opportunity to receive the nusinersen treatment. The final analysis demonstrated a statistically significant difference in the proportion of HINE 2 motor milestone responders between the nusinersen treatment group and the sham procedure control group (difference in percentage = 50.7, 95%CI 31.8 to 66.5). Several sensitivity analyses using different definitions of responders and different analysis sets supported the primary analysis. When analyzing this outcome in subgroups of patients that had disease duration of 12 weeks or of less and patients with disease duration of more than 12 weeks, a statistically significant difference was maintained; however, it should be noted that this was an exploratory analysis, not adjusted for multiplicity. The captured improvements in motor milestones of patients was also supported by a second motor milestone measure, the CHOP INTEND, where 71% of the patients allocated to nusinersen treatment achieved an improvement of 4 or more points on the CHOP INTEND scale as compared to 3% in the sham procedure

control group (percentage difference = 68.53, 95%CI 51.27 to 81.99). Regarding the validity of the motor milestone tools used in the ENDEAR study, the Hammersmith Infant Neuromuscular Examination (HINE) Section 2: Motor Milestones has adequate test-retest reliability.[78] Change in the score moderately correlates with change in other measures of motor function in type I SMA patients receiving nusinersen.[78] The definition of treatment responders have been noted in Health Canada Reviewer Report to be broad in that it captures many patients with minimal improvement, and treats those patients in a similar way to those that gained more significant improvements.[75] Natural history in type I SMA patients suggests that an improvement greater than one point in any milestone is highly unlikely.[74] The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) is a set of activities assessing motor function in infants and children with neuromuscular disorders.[54] It has adequate intra-rater and inter-rater reliability,[62] and its construct validity has been demonstrated in patients with type I SMA.[55,57]

The second primary outcome in the ENDEAR study, time to death or permanent ventilation, is more difficult to interpret. The main analysis indicated that 31 patients (39%) in the nusinersen group died or required permanent ventilation versus 28 patients (68%) in the sham procedure group during a period of roughly approximately 13 months (Hazard ratio = 0.53, 95%CI 0.32 to 0.89). However, when the manufacturer conducted a subgroup analysis based on the median disease duration (≤12 weeks, >12weeks), the results showed statistically significant differences compared to the sham procedure group in the subgroup below the median disease duration (HR = 0.24, 95%CI 0.10 to 0.58) but failed to show statistically significant differences in the subpopulation over the disease median duration (HR = 0.84, 95%CI 0.43 to 1.67). Moreover, when broken down to each event type separately, the results indicated a statistically significant difference between nusinersen group and the sham procedure in overall survival (HR = 0.37, 95% CI 0.18 to 0.77), but not in time until permanent ventilation (HR = 0.66, 95% CI 0.32 to 1.37). It is possible, however, that due to the loss of data from the premature termination of the study, as well as the shortened duration of follow-up, statistical power was reduced. [redacted]

The early termination of the ENDEAR study caused data loss as well as reduction in the time of assessing the efficacy and safety of nusinersen. These two factors may have also contributed to a lack of statistical power necessary to capture differences in the secondary and subgroup outcomes that showed no statistically significant differences. However, it is unlikely that this limitation has affected the two primary outcomes. Health Canada, the European Medicine Agency, and the Food and Drug Administration have all reviewed ENDEAR trial and did not report any major concerns regarding the internal validity of the study.[75,77,79]

The limitation to the external validity of the study mainly revolved around the inability to generalize the results to patients with infantile SMA who had a disease duration of more than 30 weeks, or who have three copies of the SMN 2 gene, as those population are not represented in the study. This becomes important when considering that the natural

disease progression of patients who are likely to be in the SMA type I subtype is characterized by a rapid onset of irreversible motor neuron degeneration,[18] and that the mechanism of action of nusinersen requires viable motor neuron to work on, it can be seen that generalizing the results to patients with a disease duration longer than the patients enrolled in ENDEAR can be extremely uncertain. Although the CS3A phase II single arm trial have attempted to include patients with the phenotype of SMA type I regardless of the SMN2 gene copy number, the design of the study, as a phase II single arm descriptive trial, and the different regimen of the intervention makes the results ungeneralizable.

Efficacy results from other supportive evidence is also limited in generalizability due to either study design (NURTURE was a single arm, non-comparative, descriptive, phase II), or different treatment regimen (CHERISH did not provide the Health Canada indicated treatment regimen). However, in NURTURE, pre-symptomatic infantile SMA patients who undertook nusinersen treatment showed no fatalities after six months of assessment, while in the CHERISH trial, nusinersen-treated patients with childhood onset SMA exhibited a statistically significant gain in motor function over patients in the sham control group.

Harms

Throughout all the manufacturer-provided trials, the most common adverse events are related to infections and/or respiratory problems, two common complications of SMA. A number of patients (5%) in the nusinersen treatment arm experienced vomiting which was related to the lumbar puncture procedure. A lower percentage of percentage reported SAEs in the nusinersen arm (76%) than in the sham-procedure arm (95%). Extension and long-term safety studies reported a similar safety profile. The Health Canada product monograph suggests that the majority of the reported adverse events are related to the disease process or the lumbar puncture procedure.[68]

Limitations of the safety results in the ENDEAR study included the inability of patients to report adverse events that do not show clinical signs. These include adverse events that may be related to the lumbar puncture procedure (e.g., headache, backache). In addition, there is lack of long-term safety data, which is important to note considering the life-long nature of the disease.

Potential Place in Therapy[2]

Spinal muscular atrophy (SMA) results in the irreversible loss of motor neurons and motor nerves. The loss of these nerves causes skeletal muscles to become progressively weaker giving rise to swallowing problems and breathing difficulties and/or weakness of the limbs and trunk. A natural history study using a specialized neurophysiological technique called motor unit number estimation (MUNE) has found that there is a relatively rapid loss of motor neurons early in the course of the disease followed by a more gradual decline.[18] As such, the optimal time for intervention is early in the course of the disease before this rapid andirreversible loss of motor neurons has occurred.

Spinal muscular atrophy is diagnosed in Canada via genetic testing. Initial testing evaluates for the homozygous 5q deletion within the survival motor neuron 1 gene (SMN1) which identifies 95% of cases. If negative, SMN1 gene sequencing will be performed as a second step. Nerve conduction studies and electromyography (EMG) is performed in a subset of patients, however even when evidence of a motor neuronopathy is identified on this study it is followed up with confirmatory genetic testing.

[2] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Current standard of care practice for patients with confirmed SMA include surveillance and anticipatory management ensuring that patients receive monitoring of: 1) growth, gastrointestinal function and nutrition; 2) respiratory complications and; 3) orthopedic complications (i.e. scoliosis and/or contractures).[27] Anticipatory management of respiratory complications are particularly important for children with SMA type I and II since these patients are at high risk of having a weak cough with impaired clearance of airway secretions; nocturnal hypoventilation and; recurrent pulmonary infections. This standard of care is not expected to change with emerging therapies, however it is hoped that the progression and complications of this disease may be lessened.

Nusinersen is the only Health Canada-approved treatment that is available for children with SMA. Treatment is administered via intrathecal injection and has been shown to be safe in several clinical trials.[67,68] There is convincing evidence that nusinersen is effective for children with SMA type I. This includes both early, asymptomatic infants with SMA type I (NURTURE study) and young (< 7 months old) symptomatic infants with SMA type I (ENDEAR study).[67,68] Treated infants show improved survival (compared to natural history data) as well as improvement in their gross motor development as measured by the Hammersmith Infant Neurological Exam (HINE). Clinical improvement was even more pronounced when infants were treated earlier, particularly when pre-symptomatic.[67] According to the clinical expert consulted for this review, given these results, nusinersen should be available for all Canadian infants with SMA type I. Knowing that pre-symptomatic treatment with nusinersen offers the greatest potential for preventing irreversible loss of motor neurons, physicians and public health agencies must consider what can be done to ensure early diagnosis including the potential for including SMA into provincial newborn screening programs.

Nusinersen has also demonstrated efficacy for children (aged 2 to 12 years old) with SMA type II (CHERISH study). The interim results of a placebo-controlled trial identified children to show an improvement in motor strength and function as measured by the Hammersmith Functional Motor Scale Expanded (HFMSE). Since children's muscle fibres undergo an increase in size over the first few years of life, a process known as physiological hypertrophy, any intervention to prevent the irreversible loss of motor neurons and consequently, allow muscle fibres the potential to more normal development is advantageous. Early recognition and treatment is also important in this group. Although nusinersen has not been well studied in children with SMA type III, it would be predicted that children in this group would have a greater potential for increasing SMN protein, if treated early in the course of their disease. Patients with SMA type III comprise about 10-20% all patients with SMA2. These children have had the ability to walk at some point although this can be lost as the disease progresses. Early treatment of patients with SMA type III, particularly young patients with apparent rapid disease progression would have the theoretical potential of preventing loss of ambulation with the significant gain of independence and avoidance of numerous medical complications that can result in non-ambulatory patients.

Conclusions

One randomized, double-blind, sham controlled, trial (ENDEAR, N = 121) met the inclusion criteria of the CDR systematic review. Patients included in the ENDEAR trial had a confirmed diagnosis of SMA, were less than seven months or age, had only two copies of the SMN2 gene, had a disease duration of no more than 25.86 weeks, and were most likely to develop SMA type I. Patients were randomized in a 2:1 ratio to nusinersen treatment or a sham control group. Patients were to receive ten months of treatment and have an additional three months of follow-up, however, the ENDEAR trial was concluded early based on positive results from a pre-planned interim analysis. There were statistically significant differences between the two groups, in favour of the nusinersen group, for both co-primary endpoints in the ENDEAR trial: the proportion of motor milestone responders as assessed by the HINE Section 2 tool and the time to death or permanent ventilation. No adverse events in the ENDEAR trial were considered by the study investigators to be related to the study treatment. The percentage of patients experiencing a SAEs and WDAEs were lower in the nusinersen treatment group versus the sham procedure arm. The main limitations of the ENDEAR trial was the early termination of the study which caused loss of data and a shorter time period to assess the efficacy and safety of nusinersen, and the inability to generalize the results to patients with infantile-onset SMA who had disease durations of more than 26 weeks.

Supportive evidence from two phase II trials (NURTURE, CS3A), one phase III trial (CHERISH), and two extension and long-term safety studies provided additional safety and efficacy data for patients who are likely to develop SMA type I and II. Pre-symptomatic patients who received nusinersen treatment in the NURTURE trial showed no fatalities after six months of assessment, while in the CHERISH trial, nusinersen-treated patients with childhood onset SMA experienced a statistically significant gain in motor function compared to patients in the sham control group. No new safety signals were identified in any of the supporting studies. These studies, however, were limited due to study design (single arm, non-comparative, descriptive, or phase II), and/or the use of a treatment regimen or dose that was not approved by Health Canada.

Appendix 7: Summary of Clinical Expert Input and Corresponding Clinical Evidence

Aim

This section summarizes the input obtained from clinical experts regarding relevant clinical outcomes and spinal muscular atrophy (SMA) patient characteristics, together with the corresponding clinical evidence that is reviewed in the Clinical Report, for each type of patient with SMA (SMA type II, type III, type IV, and pre-symptomatic).

Findings Summary of Clinical Expert Input and Corresponding Clinical Evidence

	Domain	Clinical Expert Panel Input	Supporting Data From Included Studies
Pre-symptomatic Patients	**Clinically meaningful outcomes with the largest impact on patients' quality of life**	• Motor milestones • Respiratory function • Onset of the disease • Survival	• No comparative data versus control available. • Nurture study (N = 25) assessed pre-symptomatic patients with two or three SMN2 gene copy number. • Single arm uncontrolled study. • Time to death or respiratory intervention was the primary outcome. • Other outcomes included motor function assessment using the HINE and CHOP INTEND scores, and proportion of patients manifesting SMA.
	Goal of treatment	• Delaying onset of the disease • Gaining and maintaining motor milestones • Protecting respiratory function • Prolonging survival in patients likely to develop SMA type I	• At interim analysis, where patients spent a mean of 467.8 days in study, no deaths were reported and 2 patients required respiratory support. • Assessment at study day 183 shows all patients achieved the HINE responder definition, with a mean change from baseline of 11.3 points (SD = 4.1). • CHOP INTEND total scores exhibited mean improvement from baseline of 10.1 points (SD = 6.4). • At 183 days, 17% of 24 assessed patients showed SMA-related symptoms. • At 365 days, 53% of 17 assessed patients showed SMA-related symptoms.
	Assessment of response to treatment	• Patients should gain and maintain new motor milestones • Assessment to be conducted at 18 months after the injection of the first loading dose	• HINE responders was defined as 2-point increase in the motor milestones category of ability to kick, or a 1-point increase in the motor milestones of head control, rolling, sitting, crawling, standing, or walking, AND among the 7 motor milestone categories (with the exclusion of voluntary grasp), the patient demonstrated improvement in more categories than worsening. • NURTURE study is ongoing with a 5-year planned duration.
	Characteristics of patients	• The earlier the treatment initiation the	• Patients were dosed within 6 weeks of birth.

	Domain	Clinical Expert Panel Input	Supporting Data From Included Studies
	that are most likely to benefit from the drug	more likely to maximize treatment benefit	
	Characteristics of patients that are least likely to benefit from the drug	• The later the treatment is initiated the less likely to achieve maximum benefit of treatment	• No supporting data from included studies.
Patients With SMA Type II	**Clinically meaningful outcomes with the largest impact on patients' quality of life**	• Motor milestones • Respiratory function (e.g., time on ventilation) • Hospitalization • Delay scoliosis surgery	• Most informative trial in this population is the CHERISH study (RCT, N = 126) along with its extension part in the SHINE study. • Change in HFMSE score at 15 months was the primary outcome. • Other outcomes included HFMSE responders, proportion of patients achieving a new motor milestone, RULM score change from baseline, attainment of WHO motor milestones, HRQoL measures, and hospitalization.
	Goal of treatment	• Gaining and maintaining motor milestones • Improving and preventing further deterioration of respiratory function	• A statistically significant finding in favour of the nusinersen group over the placebo group was observed in the change from baseline in HFMSE score (5.9 points [95%CI, 3.7 to 8.1]). • OR of HFMSE responders 5.59 (95%CI, 2.09 to 14.91). • No statistically significant difference in the number of new motor milestones achieved. • One patient in each group was able to achieve the motor milestone of standing alone. • Rate ratio of annualized rate of hospitalization 0.385 (95%CI, 0.153 to 0.968), unadjusted for multiple testing.
	Assessment of response to treatment	• Patients should gain and maintain new motor milestones • Assessment to be conducted at 18 months after the injection of the first loading dose	• HFMSE responder was defined as a patient who gained more than 3 points. • Primary outcome was assessed at 15 months.
	Characteristics of patients that are most likely to benefit from the drug	• Shorter time since symptom onset • Younger age at treatment onset	[redacted]
	Characteristics of patients that are least likely to benefit from the drug	• Longer time since symptom onset • Older age at treatment onset	[redacted]
P ati	**Clinically meaningful**	• Mobility	• No comparative data available.

	Domain	Clinical Expert Panel Input	Supporting Data From Included Studies
	outcomes with the largest impact on patients' quality of life	• Ambulation • In case of loss of ambulation — upper extremities function • The extent of use of ventilatory support	• Data from phase I and II single arm trials, along with the corresponding extension parts in the SHINE study, may provide some insight as a proportion of these patients were diagnosed as having SMA type III (n = 16). • Outcomes reported for this patient group were the HFMSE score, ULM score, and the six-minute walk test. • The extension phase of these studies (i.e., SHINE) is ongoing.
	Goal of treatment	• Maintaining and possibly improving motor function	[redacted]
	Assessment of response to treatment	• Ideally, improving motor function and maintaining existing motor function • Ideally, improving and preventing further deterioration in respiratory function	• HFMSE responder was defined as a patient who gained more than 3 points. • Ongoing study with a planned period of 1,820 days.
	Characteristics of patients that are most likely to benefit from the drug	• Shorter time since symptom onset • Younger age at treatment onset	No data is available.
	Characteristics of patients that are least likely to benefit from the drug	• Longer time since symptom onset • Older age at treatment onset	No data is available.
Adult Patients With SMA	**Clinically meaningful outcomes with the largest impact on patients' quality of life**	• In ambulatory patients, the extent of the distance they are able to walk • In ambulatory patients, the use of stairs • In non-ambulatory patients, upper limbs function to allow independent use of wheel chair	No data is available. Data in the form of poster abstracts do not provide sufficiently reliable information.
	Goal of treatment	• Maintaining motor function • Reduce the risk of falls in ambulatory patients • Increase distance travelled in ambulatory patients	No data is available. Data in the form of poster abstracts do not provide sufficiently reliable information.
	Assessment of response to treatment	• Extent of distance travelled within a specified time period (e.g. the six-minute walk test) • Ability to move themselves from and into a wheelchair • Extent of reported fatigue • Assessment is every 5 years	No data is available. Data in the form of poster abstracts do not provide sufficiently reliable information.

	Domain	Clinical Expert Panel Input	Supporting Data From Included Studies
	Characteristics of patients that are most likely to benefit from the drug	No evidence that nusinersen would be beneficial in adult population; as such it is unclear which patients would benefit the most	No data is available. Data in the form of poster abstracts do not provide sufficiently reliable information.
	Characteristics of patients that are least likely to benefit from the drug	No evidence that nusinersen would be beneficial in adult population; as such it is unclear which patients would benefit the least	No data is available. Data in the form of poster abstracts do not provide sufficiently reliable information.

CI = confidence interval; CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HFMSE = Hammersmith Functional Motor Scale – Expanded; HRQoL = health-related quality of life; OR = odds ratio; RCT = randomized controlled trial; RULM = Revised Upper Limb Module; SD = standard deviation; SMA = spinal muscular atrophy; ULM = upper limb module; WHO = World Health Organization.

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