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

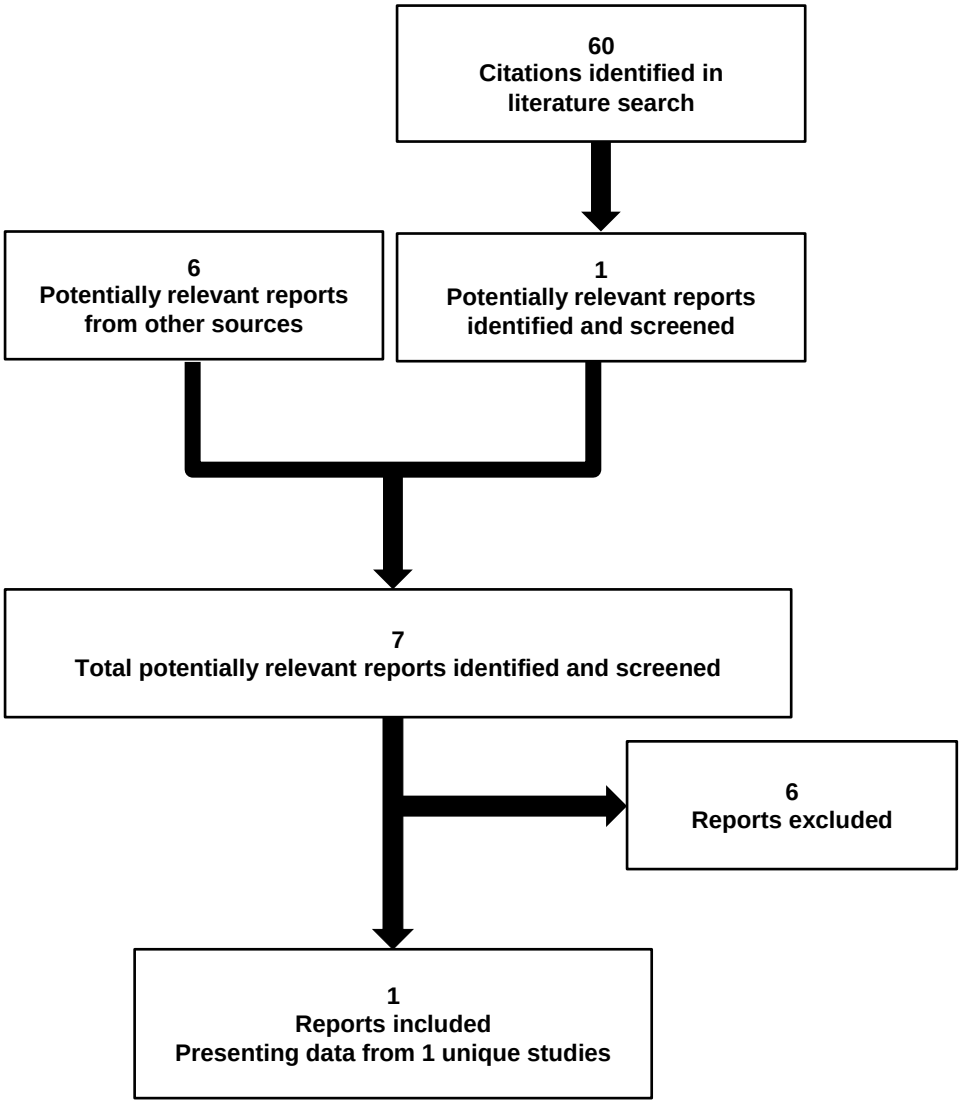


Table 3: Details of Included Study

		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.

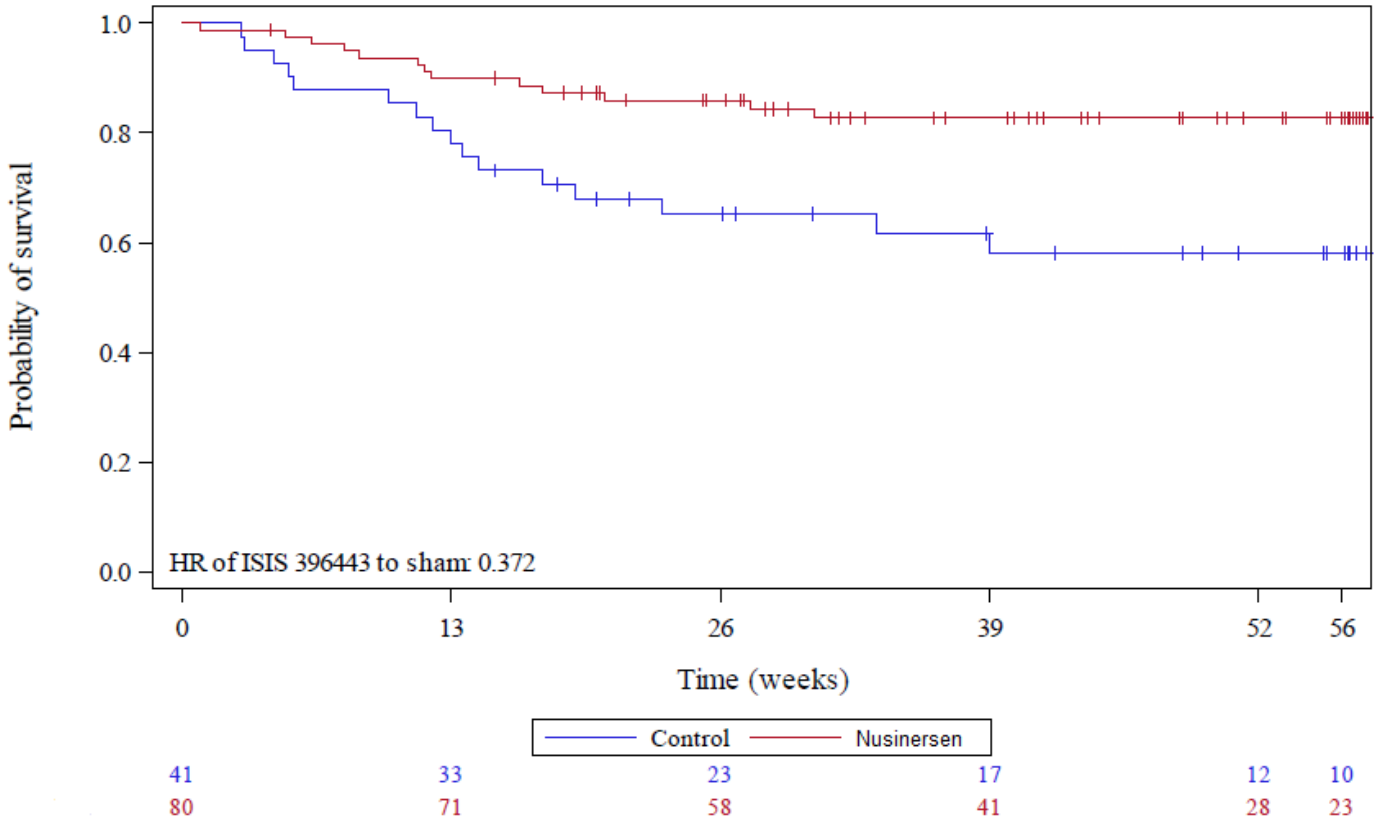
[redacted]

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]
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[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.