CADTH

CADTH COMMON DRUG REVIEW

Patient Input

Nusinersen (Spinraza)

(Biogen Canada Inc.)

Indication: Treatment of patients with 5q SMA

CADTH received patient input from:

Muscular Dystrophy Canada

Canadian Organization for Rare Disorders and Cure SMA Canada

July 21, 2017

CADTH

Patient Group	Muscular Dystrophy Canada

1. About Your Patient Group

Muscular Dystrophy Canada (MDC) supports people affected by muscular dystrophy and related muscle diseases. Together, these rare conditions are referred to as “neuromuscular disorders.”

Neuromuscular disorders are a group of diseases that weaken the body’s muscles. The causes, symptoms, age of onset, severity and progression vary depending on the exact diagnosis and the individual.

Muscular Dystrophy Canada is a national, non-profit organization of dedicated volunteers and staff who continually work to provide support and resources to clients like you who are impacted by 1 of over 150 neuromuscular disorders. Through well-funded research, we are on a mission striving to find a cure as soon as possible.

Muscular Dystrophy Canada has close to 60 years of experience in helping to improve the lives of those affected by neuromuscular disorders.

Muscular Dystrophy Canada reaches over 10,000 people living with a neuromuscular disorder. Muscular Dystrophy offers a basket of services that include system navigation, education, financial assistance, accessing coping and emotional support and advocacy.

Spinal Muscular Atrophy (SMA) is one of the neuromuscular disorder types that falls under MDC’s umbrella. Spinal Muscular Atrophy (SMA) is a group of inherited genetic muscle-wasting disorders. SMA affects the nerve cells that control voluntary muscles. These nerve cells are called motor neurons, and SMA causes them to die off. Without motor neurons, the brain cannot deliver signals to the muscles. When unable to fully use them, the muscles of a person with SMA will waste away.

People with SMA are generally grouped into one of four types (I, II, III, IV) based on their highest level of motor function or ability.

- Type I (severe) – also known as infantile-onset or Werdnig-Hoffman disease
- Type II (intermediate)
- Type III (mild) – also known as Kugelberg-Welander disease
- Type IV – also known as adult SMA

SMA is caused by a missing or abnormal (mutated) gene known as survival motor neuron gene 1 (SMN1). In a healthy person, this gene produces a protein in the body called survival motor neuron (SMN) protein. In a person with mutated genes, this protein is absent or significantly decreased, and causes severe problems for motor neurons. Motor neurons are nerve cells in the spinal cord, which send out nerve fibers to muscles throughout the body. Since SMN, protein is critical to the survival and health of motor neurons, nerve cells may shrink and eventually die without this protein, resulting in muscle weakness. www.muscle.ca

2. Information Gathering

Muscular Dystrophy Canada has Neuromuscular Service Support Staff in all provinces across Canada. The Neuromuscular Service Support Staff provide front line support to thousands of Canadians affected by neuromuscular disorders. Support includes, navigating systems and accessing resources, providing information and education so that people affected by neuromuscular disorders can make informed decision as well connecting people for peer support.

The Staff conducted interviews over the time from July 7th to July 21st. by telephone and in person. There are over 700 clients registered with MDC affected by Spinal Muscular Atrophy (SMA). Over 350 caregivers and 123 patients were interviewed.

3. Disease Experience

Spinal Muscular Atrophy affects people in different ways. Most types of SMA can affect either males or females. The onset depends on the type of SMA involved. SMA Type 1 is the most common genetic cause of infant mortality. With SMA Type 2 motor milestones are delayed, respiratory issues are present and may have a shortly life expectancy. With SMA Type 3 often experiences muscle weakness that is progressive in nature. With SMA Type 4 is adult onset and muscle weakness will vary. Dealing with a fatal and or progressive disease is devastating. Patients most often need to rely on caregivers (mainly parents) for all daily living activities that include feeding, bathing, transferring, dressing, etc. Caregivers and patients face many barriers that affect a patient's quality of life that include lack of resources both in the medical and community sectors, , dealing with a progressive muscle disease also has such a significant impact on physical and psychological well-being, social isolation and overall quality of life.

Here are the most prevalent responses:

- ✓ Ongoing loss of independence
- ✓ Fear of the unknown
- ✓ Ongoing deterioration and progressive loss
- ✓ Watching my child decline
- ✓ Caregiver burnout

Here is responses form the interviews that were conducted by MDC:

"*We had no clue what spinal muscular atrophy was. We never heard of it and no one in our family has ever had it. It was as we were stopped head on, right in our tracks. We were told, however, that he has the mild form of the disease. It is still hard to categorize the word "mild" when the phrase "He will lose the ability to walk" accompanies that word.* ***We are now so devastated to see him not walking just under 3 months****"*

"The hardest part is watching yourself get weaker and weaker and needed more and more help with things you use to be able to do"

"Life of parent is consumed with appointments and therapies and constantly monitoring child. Not able to work and need to have additional family support to help in these situations"

".As my child ages it gets difficult for bathing, toileting, Physio, exercise, a lot of pressure on me as a caregiver"

"Nothing in life is easy, everything has to be thought out meticulously and planned. I love to do activities like any other families but with that comes a lot of planning and additional expense, often it is easier to turn down invitations to go places or travel in fear of what is going to be a struggle."

"I *have got progressively weaker, I have lost my independence and unable to breath or swallow independently"*

"*Affects everything, physical health, emotional, mental, along with parents because of transfers, lifting, live with worry every day and extra time takes to navigate normal things. Affects ability to make friends and siblings emotionally. Literally all-encompassing and drives every decision in family."*

"From a caregiver perspective, takes time, very expensive, physically hard on body (from moving), tough job. Disheartening to watch decline, have a certain level of independence and gradually losing it over time. Knowing there is treatments coming give hope".

"Went from walking to standing to power chair in 5 years, progresses very quickly and change life. Make it difficult to move away from home and go to school/ find work. Financially and emotionally."

"Physical, mental and emotional part. From a caregiver perspective difficult watching progression of disease, loosing strength that have. The hardest part the lack of control. The unknown of the diagnosis"

Every part of my life is affected by this disease, raising my children, marriage, physical and emotional well-being."

"Muscle weakness has constantly been progressing since infancy. As a child and teenager, I was able to brush my teeth, wash my hair, shave, etc., independently. I used a manual wheelchair indoors and a motorized wheelchair outdoors until late teens, where I eventually transitioned uniquely to the motorized wheelchair because I was no longer able to propel myself in the manual wheelchair. As an adult, I can no longer perform my own daily hygienic activities, such as brush my teeth, wash my hair, or shave without the assistance of personal care attendants. It is more difficult to swallow as well as move my arms, hands and fingers. I now rely more on personal care attendants to help with positioning in my wheelchair during the days and in bed during the night, which means I need more hours of personal care attendants each day compared to the past. It is difficult for family members because I require constant assistance and some of my personal care can be complex and physically difficult"

"My son is 12 years old and has SMA type 3. He is currently walking for short distances, and is gradually losing his mobility. He will soon spend most of his time in a motorized wheelchair. For us the aspect that is most important to control is the loss of mobility, which includes walking, and being able to write during class as his hands are quickly tired."

4. Experiences With Currently Available Treatments

The United States (US) Food and Drug Administration (FDA) have approved Spinraza for use in all patients with SMA. Spinraza has demonstrated clear efficacy in SMA type I, II and III. Data from the infantile SMA has been published. Moreover, larger clinical trials involving infants ('ENDEAR' study) and older children with type II and III ('CHERISH' study) have been closed when interim analysis demonstrated Spinraza to be effective. These children (including some Canadian children) are continuing to receive open-label treatment of Spinraza through "SHINE" open-label extension study.

In July 2017, Health Canada approved SPINRAZA for the treatment of 5q SMA. Because of the robust efficacy and safety profile demonstrated in the clinical trials it is believed that SPINRAZA will have a meaningful impact on individuals living with this devastating disease.

The Health Canada approval of SPINRAZA was based on positive results from multiple clinical studies in more than 170 patients.

Here are some responses from MDC's interviews:

"*Travel costs is a barrier and so is taking time off work for parents to take children to therapies or clinic visits"*

"*Our friends have access in BC, but we don't have access in Manitoba"*

"*My daughter's joints have stopped contracting . her tendons have relaxed, and her joints are moveable"*

*"Stren*gth *seems to be improving during the trial"*

"The cost is stressful"

"There was no other treatments been given to him before, because there is none for him. (type one). With the new medication, all of his caregivers, and both me and my husband all feel he had improving"

"He is getting stronger. We have hope"

"I know that the costs are extremely expensive but quality of life should not be measured in dollars. Giving people potential to improve quality of life would makes a huge impact, cost should not be the issue quality of life can not be measured by financial numbers."

"Today at age 4, after having been very lucky to take part in the phase 3 trials for Nusinersen, our son has not regressed at all. He is continuing to gain strength after every injection. He can now bare weight on his legs again with his braces, he can maintain a 4-point position and is slowly starting to shift his own weight to crawl, we never worry about him falling when sitting, he has gain much core strength (can bend over to pick up his toys and pick himself back up from his wheelchair), he has not had the need for a power chair at this point and only uses a manual wheelchair. He has great dexterity and head control and recovers for colds and illnesses much quicker. He has had no hospitalizations due to pulmonary infections since starting the medication. We are hopeful that by continuing his treatments, he will one day be able to do his own transfers and maybe even walk with a walker or crutches like so many of the other kids that have the same type as our son have been doing since starting the drug."

Here are the most prevalent responses from clients when asked about difficulties in accessing Spinraza

- ✓ Affordability – this was the greatest concern.
- ✓ Access due to not having SMA type 1
- ✓ Difficult to travel due to complex care needs
- ✓ Difficulty navigating the process
- ✓ Access due to living in rural areas

Here are most prevalent responses from clients when asked about side effects:

- Constipation
- Headache

5. Improved Outcomes

There is evidence that this medication offers definite benefit to children with all forms of SMA. In particular, children, who are showing rapid disease progression may benefit the most from treatment. Clients expressed without Spinraza, patients are at an extremely high risk of completely losing the ability to walk independently and even bear weight on their legs. Furthermore, are at a of high risk of developing progressive weakness in upper extremities. It was felt that Spinraza could prevent the permanent and irreversible loss of motor neurons that is resulting in muscle atrophy and weakness. Without Spinraza, individuals are at a high risk of losing the ability to perform basic self-care tasks such as feeding themselves, bathing or changing his clothes. Without treatment individuals will be placed at heightened risk for needing permanent, invasive, respiratory supports that could include night-time BiPAP or even tracheostomy and mechanical ventilation.

Here are the most prevalent responses from our interview process:

- Regain some range of motion
- Slow the process of degeneration & maintain muscle strength

- Be less dependent on others
- More freedom & better quality of life
- Decrease in respiratory health issues

6. Experience With Drug Under Review

Spinraza was accessible via clinical trials. No other treatment has been available. Clients have shared they are on other medications that include Salbutamol, VPA, creatine, celecoxib.

It is believed that Spinraza will have positive outcomes for all forms of SMA.

Here are some responses from our interview process:

"Through SAP (special access program) doctor worked to get it for him. Experiences movement of fingers and legs more, louder (lung function has improved) oxygen levels more stable. No direct disadvantages, did get sick on first treatment (head ache, dizzy")

"2 years ago, called centres for trials and put on waitlist, clinical trial. Increase in strength, increase in cough strength, and confidence. Disadvantages, anxiety form lumbar puncture, anxiety from sedation and pinched nerve, spinal headache (all manageable). Gives hope for the future"

"Respiratory has improved and she is sitting up better than before the trial"

"I don't have access to Spinraza because I don't have SMA type 1. Please can I have access?"

Throughout the interview process, no disadvantages were expressed about the medication. Challenges expressed involved access, traveling with a person who has complex care needs, navigating complex process and costs associated with travel.

7. Anything Else?

SMA is a devastating disease. Through our interview process, it was apparent that affordability and access to Spinraza was the greatest concern. Spinraza has demonstrated remarkable positive outcomes that will make a significant impact on the lives of people affected by SMA. The ability to hold a utensil to eat independently to eliminating the need for invasive procedures like relying on a ventilator to breathe is life changing. Spinraza can allow the opportunity for patients to live fuller and better quality of lives. Spinraza will assist in decreasing caregiver burnout and alleviate some of the pressures families deal with every minute of the day. Often clients affected by SMA require total care for all daily living activities. It was expressed that medical and community resources are lacking in all provinces, leaving the burden to families to be the main caregivers while managing other responsibilities.

The affordability of Spinraza is also a great concern. Families affected by SMA expressed overwhelmingly there concern about their current financial situation. Living with SMA is expensive. Travel visits to clinics, the need for assistive devices that are often not covered by government funding and or insurance, modifications to homes and vehicles, the need for ongoing expenses due to the progressive nature of this disease. Often, one family member needs to leave employment to provide care to their child.

The other concern was related to the challenges of accessing Spinraza in their respective provinces. Many were concerned with the process of accessing the medication. Many expressed a concern with navigating a very complicated health care system and provinces often have very different processes in approving a medication and access, which cause barriers and delays. Another, concern with regards to access, relates to patients having access to Spinraza who are affected with other forms of SMA. Clients expressed that there is medical opinion that Spinraza can have good outcomes for other forms of SMA and the desire to have this medication accessible to other SMA patients.

Appendix 1: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   No

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Biogen		x		

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Stacey Lintern
Position: VP, Mission
Patient Group: Muscular Dystrophy Canada
Date: July 21, 2017

CADTH

Patient Groups	Canadian Organization for Rare Disorders and Cure SMA Canada

1. About Your Patient Group

The Canadian Organization for Rare Disorders is registered charity that provides a strong common voice to advocate for health policy and a healthcare system that works for those with rare disorders. CORD provides education and resources to patient groups to enable them to better meet their members' needs.

Cure SMA Canada is the national registered charity; supporting families and individuals affected by Spinal Muscular Atrophy from the point of diagnoses, through the life course and even after loss of life. Cure SMA Canada also funds critical Canadian research projects with the aim of affecting accessible treatments for SMA. Cure SMA Canada provides advocacy, information and resources to families, communities and health professionals.

2. Information Gathering

This submission summarizes the perspectives of individuals, family members, and other caregivers affected by spinal muscular atrophy (SMA) collected through a focus group, semi-structured interviews, and a survey created by the Canadian Organization for Rare Disorders (CORD) in collaboration Cure SMA Canada (CSC). The focus group and interview data provided rich in-depth understanding of the impact of all types of spinal muscular atrophy on the patient, the family, and extended family. The elicited patient experiences and perspectives were also used to develop the survey and, as importantly, provide a context for interpreting and validating the survey results and especially the quantitative analyses. The survey consisted of open-ended questions, rating scales, and forced-choice options. The individual participants were recruited through CSC as well as several localized patient networks. The links to the survey was distributed through the CSC database posted on the CSC website, CSC Facebook and Twitter, with request for secondary distribution to other patients and relatives. The survey was available only in English but responses in French to the open-ended questions were also submitted versions of the survey. They were active on Survey Monkey from 12 June to 7 July 2017.

The survey was also announced through Cure SMA in the United States.

This submission is based on responses obtained through one focus, four interviews, and 247 survey responses. The focus group included young adult patients and parents. The interviews were conducted with one patient and three parents of children with SMA Type I or II. Of the 247 survey responses, 178 were from patients or immediate family caregivers. (Other respondents were more distant relatives such as grandparents or friends and neighbors.) The

While we recognize that SMA is increasingly regarded as a "spectrum" of severity and impact, most patients will have received a diagnosis that includes a "type" of SMA, sometimes with a qualifier as to severity. For the sake of consistency, the survey provided a very brief description of each "type" of SMA and they were asked to indicate which of the four types best described the person they were reporting about. Among the 247 respondents, 15% identified SMA Type I, 60% SMA Type II, 20% SMA Type III, and 1% SMA Type IV, with about 4% responding unsure or other. In terms of relation to SMA, only 12% self-identified as a patient. Most, 44%, were parents or guardians with another 24% identifying as another family member and 2% identified as a nonprofessional caregiver, 2% a professional care provider, 3% a patient advocate. The remaining 10% identified as "friends." The gender of the person with SMA was almost evenly balanced, with 50% males and

48% females and the remainder choosing not to specify. In terms of age, the largest cohort (37%) were in the range of 5 to 10 years; the second and third cohorts were age range 1 to 5 years (26%) and 18 to 35 years (24%), with only 3% between 35 and 50 years, and 2% over the age of 50.

In terms of residence, 90% of respondents live in Canada, 8% in the USA, and the remaining 2% in European countries. There was good representation across the provinces, with 23% from Ontario, 21% from BC, 17% each from Quebec and Alberta, 14% from Saskatchewan, another 6% from Manitoba, and 1% each from New Brunswick, Nova Scotia, and PEI.

The subsequent analyses were conducted on the responses from the 178 respondents who self-identified as patients or immediate family caregivers. These included those with Type I, Type II, and Type III. In this group, about 12% had been diagnosed for under 1 year, while 23% had been diagnosed for more than 20 years. The largest cohort (37%) had been diagnosed between 2 and 10 years, while 19% said they were diagnosed between 10 and 20 years ago, and 6% between 1 and 2 years ago. About 3% of the responses were for patients who were no longer living.

3. Disease Experience

Respondents were asked to describe "how the disease impacts" their daily lives or those of their caregivers. Regardless of the type of SMA or the age of diagnosis, a diagnosis of SMA was experienced as "overwhelming", "devastating", "cataclysmic, or "just awful." For parents with a child with SMA Type I, it was apparent almost from birth that there was "something very wrong" based on the limited physical capabilities. *"She was never able to lift her head or sit up."* One parent talked about the challenges of getting an accurate diagnosis. *"At two months, she was turning blue and had breathing issues. We were sent home from hospital with antibiotics."* Luckily, she was referred to a major hospital where they did a tracheotomy and got a diagnosis at five months. *"By that time she had lost a lot of muscle function. She could only slightly wiggle or move her hands; she even lost the ability to smile or frown."* With Type I, swallowing is often difficult. *"Due to her lack of strength she required a feeding tube and as she grew…required the use of a ventilator/bipap with oxygen to help her breathe."* Children with Type I may often die as infants or young children by the age of five.

For those with Type II SMA, there is an equally tremendous physical impact. *"[She] cannot do anything independently. If she has an itch in the middle of the night, she can't even scratch it." "She had been losing function and was finally diagnosed at 18 months. She had lost the ability to sit up; she had never been able to crawl using her arms but was also not eating or napping; nothing could soothe her."*

For those with Type III, the loss of physical function will be later but is no less impactful. *"Our daughter has SMA type 3. She is unable to get up by herself, go up or down the stairs or to the bathroom by herself. She can only walk with assistance and is unable to enjoy the playground like all other children.*

She has difficulty breathing at night and suffers from severe sleep apnea. Her tonsils and adenoids were removed to buy some more time but she will soon need a machine to help her breathe at night." A parent of an 11-year-old boy with SMA type 3 said, *"SMA is a devastating disease no matter the type or age of onset…. He lost the ability to walk and requires a manual wheelchair full time. It's frustrating and heartbreaking to witness such a wonderful boy suffering from progressing paralysis and muscle atrophy."* The progressive loss of function, in some respects, can be even more challenging psychologically than not having these capabilities in early life. *"Although my daughter is somewhat walking, she falls a lot and can t get up and it s so painful to see your child so frustrated. The other day she fell and cried and with tears in her eye she said 'mommy I'm broken'.....what do you say to that?"*

"The pain/disease have caused my sister to be very depressed. She gets very sad, or angry, and will go days eating barely anything."

The responses from young adults painted an equally devastating impact as physical capabilities declined. *"I am confined to a wheelchair and have limited use of my arms…it is only bound to get worse. As a recent graduate of Mechanical engineering, I am losing my independence at the moment I should be flying from the nest. I will most likely never own a house, have children of my own, etc."*

Obviously, SMA is experienced as a tremendous toll on the whole (extended) family, in terms of time and physical support required, psychological and emotional impact, financial burden, and severe limitations on family and social functions. *"The impact socially has been awful, it's hard to get out of the house, hard to enjoy life." "It's has been incredibly hard for our family of 5… When the other kids are home or we are out and hear someone cough Owen is pretty much guaranteed to catch something."*

"We live and breathe SMA daily. I have had to go down in work to 2 days a week. We have a heightened level of anxiety because we fear going out in public in winter months, getting ill, what will happen if we get sick, school unknowns, if we will get the equipment she needs..."

"[O]ur family was in constant crisis mode awaiting the next time Hannah would need medical intervention. We had a wonderful family and support system yet we were isolated in so many ways. Financially we struggled to acquire deserved insurance coverage monthly, and to acquire the provincial help."

"Our type 3 child has a manual wheelchair, a dynamic trainer, a scoliosis back brace, daytime orthotics and night time orthotics. He is also in need of a dynamic stander and a manual rigid wheelchair with power assist, an accessible bathroom, a shower wheelchair, a converted accessible van and a hoyer lift. He follows up with an Orthopedic Surgeon, Neurologist, Pulmonologist, Gastroenterologist, Occupational Therapy, Speech Therapist and Physical Therapist. It's almost impossible to express how frustrating it is that all this intervention is NOT making him better and that we have been unable to treat the root cause of his SMA."

"The cost financially has been tremendous, each year we have spent $18,000-$20000 out of pocket for expenses which are not covered."

Respondents were also asked to "rate" on a five-point the degree of difficulty experienced with each of five "common" symptoms of SMA (regardless of type). Overall, the action that posed the most difficulty was "walking", rated by over 90% as "not at all able" to do. The second area of difficulty was "muscle strength" defined as "lack of weakness, pain or fatigue"; about 12% said they considered they were "not at all" able and another 68% said this was a major problem. About equally difficult were "fine motor skills" and "(deep) breathing, experienced as a "major problem" or "not at all able" by 42% and 41% of respondents, respectively. Finally, only 35% reported "swallowing or feeding" as a major problem or not do-able with 18% indicating it was "not at all" a problem. This last finding is compatible with the types of SMA represented in the survey; most SMA Type I will experience feeding (swallowing) issues but not most Types II or III.

Clearly, most (if not all) of the patients represented experienced multiple physical challenges that severely limited mobility, required use of mechanical aides, and also required assistance from others to complete daily life activities.

4. Experiences With Currently Available Treatments

There are, of course, no previous treatments specific to SMA, with most supportive therapies consisting of mechanical aides, rehabilitation services, or supportive medications. When asked whether they had received treatment for SMA, only 34% responded affirmatively while 50% said "no" and 15% responded they were "not

sure." Consequently, only those who indicated they had received treatment went on to complete the questions as to the types of treatment and their effectiveness.

Among respondents, more than 88% used some mobility aides (braces, splints, walker, and/or wheelchair). More than 68% used some breathing support (mask, mouthpiece, ventilation, or tracheotomy), while 55% had spinal treatment (braces, rods, and/or surgery). About one-third had some form of feeding tube or other aide. More than 90% were currently or in the past had received some form of physiotherapy and 45% had received speech or language therapy. More than 45% had received medications such as valproic acid, phenylbutyrate, hydroxyurea, or albuterol.

When asked to rate the effectiveness of the mechanical aides or "treatments", between 50 and 65% rated them as performing "well" or "very well" in managing the symptoms of SMA, while about 25% said they were not effective. About half said physiotherapy had been effective, while the other half, not so.

When asked to provide "open" comments about treatment effectiveness, most said there were really "no treatments" or they were only managing the symptoms and not really treating the cause of SMA. *"There are no effective treatments for SMA. Treatments are limited to dealing with the results of SMA including respiratory support, physio, medication for pain, etc. I would love to see an effective treatment for SMA to help improve the strength and quality of life for people with SMA."*

"Although they have helped improve life it is like putting a bandaid and treating symptoms rather than being proactive and helping to eliminate the progression. Life has so much more to offer and I notice that her fatigue has impacted her quality of life and we are noticing more serious and severe problems arising as she is getting older."

However some patients (parents) did credit the assistive devices in improving quality of life. "The motorized wheelchair and the kidwalk are pretty new to him but he's is really enjoying it. We have fought a lot with him the first year to get him used to his Bipap, but now he knows that it is really helping him and his chest isn't in a bell shape anymore. He is sleeping better. The feeding tube has helped him gain weight. Speech therapy is helping but he still has a lot of work to do with the pronunciation. Physiotherapy has helped him a lot with strength and posture."

5. Improved Outcomes

Given that there have been no treatments for SMA, patients and parents express feelings of despair and near desperation. Parents of an infant with SMA Type I talk about the desire for any treatment that would improve their child's breathing (fundamental to life), ability to feed, and ability to perform even small movements like rolling over. Parents, especially with Types II and III are looking for an intervention that would improve muscle functioning and slow the progression of the disease, so the child can perform activities independently as much and as long as possible, including self-care (such as feeding, operating a wheelchair, writing or typing). They also want to reduce the pain associated with SMA.

Those patients with SMA who responded to the survey said that slowing progression and maintaining independence are primary goals, including continuing to attend school or to work.

6. Experience With Drug Under Review

There is a lot of awareness about Spinraza (nusinersin), given that it is the only treatment available for SMA. Among respondents, about 24% responded that they knew about Spinraza and how it is used, with another 34% indicating they knew a lot about the drug. Only 25% said they knew little or nothing about the drug.

In an open-ended question, respondents said they expected (hoped) the therapy would improve overall quality of life, maintain or restore respiratory functions (breathing), retain or restore muscle strength/movement, slow or stop disease progression. For those newly diagnosed, the hope is that it will prevent symptoms from manifesting.

Among respondents, 26 said they had received Spinraza through clinical trials, expanded access, compassionate access or other means. All represented patients with SMA Type I or Type II. For infants the responses are primarily parental observations; most speak with enthusiasm and optimism about the experience thus far. While all express conservative expectations, most indicate they are able to see improvements, based on previous capacities. *"It has made her stronger. Her breathing is also stronger. We think she is less frustrated to be able to reach and do things if she chooses. Difficult to ask a 9 month old."*

One parent provided a concise but detailed review of the impact since starting Spinraza. *"Spinraza has helped my daughter to become stronger physically both externally and internally. She is able to do things she was unable to do before. She can reach, move her legs more, hold her head while sitting, push her head from side to side on her tummy, and sit with support. She is working on rolling over with assistance as well. Her breathing has gotten stronger and the shape of her chest has become less bell shaped. Her voice is louder and her coughs and sneezes are more effective. She is a much happier baby and is able to explore and play. We have not had increased medical needs for her since we began. It has given her so much more independence. It has also given our family hope for her and a chance at a life. We are so appreciative to have her receiving it."*

"Spinraza has been a miracle for him. He is now holding his head up, rolling from supine to prone, sitting by himself with back support and a couple of minutes without support, lifting his arms and legs up to his head and above, breathing deeply, coughing louder, walking with the kidwalk and using a little manual wheelchair."

For those with a somewhat older child who have lived through crises prior to Spinraza, the recognition of positive impact is even stronger. *"He has more movement while swimming. His voice has gotten stronger. He is eating more. We have recently been through a bad respiratory infection and stomach virus. Both times he got quite a bit weaker and afterwards his strength came back as well as a little bit more. This would be unheard of [when] he wasn't on Spinraza! We feel better about the future and feel like he will continue to gain little bits of strength. We aren't as worried when he gets sick."*

Similar observations of the observed positive outcomes were offered by other parents.

"He is now able to stand assisted (and briefly unassisted) with AFO's and we are working on getting him comfortable and strong enough to be able to use crutched or a walker. He is less sick and often heals quickly when ill. His overall stamina is better…"

"She is able to clap louder now. She is able to play on a grand piano compared to a keyboard before. She is able to turn a doorknob and open a door. She is gaining confidence. She has more energy in the day."

When asked to comment on adverse (side) effects, most parents indicated there were very few, especially in response to the drug itself and some related to the administration (though surprisingly few given the invasive nature of the procedure). *"Our son has had no side effects from Spinraza." "We have not experienced any!" "After the first dose, she had a headache for 5 days, and vomiting for 1 day. This was because the nurse sat her up too soon and she had been fasting for too long as the dose was given in the late afternoon. For her last 5 injections, there have been no complications in terms of side effects."*

"We have experienced side effects associated with the lumbar puncture. We have not experienced side effects from the drug itself." "Now she is receiving the drug at BC Children's and they don't give the anaesthetic gas [that she was getting at the London Clinic] so she has the poke when she is awake. She screamed her head off and didn't want to do it. Now, with the sedation, it is okay."

7. Companion Diagnostic Test

We are not aware of any specific companion diagnostic tests to determine response to the therapy.

8. Anything Else?

Most parents (and patients) are aware that Spinraza is approved for all types of SMA but has been clinically tested primarily in those with Types I and II. However, given that the disease is progressive and (eventually) has a severe debilitating impact on individuals with all types, there is a strong opinion that the drug should be available for all patients with SMA regardless of type. When asked, 100% of respondents said the drug was "very important" and should be available to all. *"Spinraza is our only proven treatment that can not only save our kids' lives, but *improve* them."*

Given the progressive nature of the disease, there is also a strong sense of urgency. *"We need to get it to SMA patients ASAP before they get any weaker." "We lost 2 babies in our city this last year. Every death hits our community so hard, especially knowing that there is a treatment that works so close to us, but not available to us.*

Appendix 2: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   No outside help was provided. CORD and Cure SMA Canada collaborated to perform the background research, conduct the interviews, prepare the survey, analyze the data, and prepare the submission.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Biogen		x		

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Durhane Wong-Rieger
Position: President & CEO
Patient Group: Canadian Organization for Rare Disorders
Date: 19 July 2017

Appendix 3: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   No outside help was provided. CORD and Cure SMA Canada collaborated to perform the background research, conduct the interviews, prepare the survey, analyze the data, and prepare the submission.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   See above.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Susi Vander Wyk
Position: Executive Director
Patient Group: Cure SMA Canada
Date: July 19, 2017