CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

inebilizumab (Uplizna)

(Horizon Therapeutics Canada)

Indication: As monotherapy for the treatment of adult patients with neuromyelitis optica spectrum disorders (NMOSD) who are anti-aquaporin-4 immunoglobulin G (AQP4-IgG) seropositive.

September 01, 2023

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CADTH in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings.

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Patient Group Input

Patient Input

Patient Input Template for CADTH CDR and pCODR Programs

Name of the Drug and Indication	**Inebilizumab (Uplizna)**
Name of the Patient Group	**MS Canada**
Author of the Submission	**Jennifer McDonell**
Name of the Primary Contact for This Submission	**Jennifer McDonell**
Email	[redacted]
Telephone Number	[redacted]

MS Canada provides programs and services for people with MS and their families, advocates for those living with MS, and funds research to help improve the quality of life for people living with MS and ultimately find a cure. The mission of MS Canada is to connect and empower the MS community to create positive change. In addition to supporting Canadians affected by MS, MS Canada provides support and services to people living with allied diseases, including neuromyelitis optica spectrum disorder (NMOSD). Since 1948 MS Canada has contributed over $210 million towards MS research. This investment has enabled the advancement of critical knowledge of MS and allied diseases and the development of a pipeline of exceptional researchers. The patient input contained in this report is to support the review of a new medication, inebilizumab, indicated as monotherapy for the treatment of adult patients with neuromyelitis optica spectrum disorders (NMOSD) who are anti-aquaporin-4 immunoglobulin G (AQP4-IgG) seropositive.

1 Information Gathering

MS Canada launched an online survey from August 4, 2023, to August 14, 2023, posted to MS Canada's social media channels (Facebook and Instagram accounts) in both English and French. MS Canada also received an open letter to government decision-makers from an individual within the Canadian NMOSD Community who has been an MS Canada ambassador and advocate for those affected by NMOSD for many years. The survey was targeted at Canadians living with NMOSD and their caregivers however respondents were anonymous and their country of residence was not requested. People living with NMOSD and their loved ones were asked to provide feedback related to their quality of life and experience with the drug being reviewed. In total 13 responses to the survey were received. Most respondents were female (83%) and ranged in age from 25 to over 65, with the largest number of respondents within the 45-54 age range, followed by 25-34 and 55-64. Almost all respondents are diagnosed with NMOSD, two caregivers, and one person living with primary progressive MS who did not complete the full survey.

2 Disease Experience

Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune syndrome of the central nervous system (CNS) whereby antibodies damage the spinal cord and/or optic nerves during attacks. NMOSD is a demyelinating condition that is characterized by optic neuritis (affecting eye function), transverse myelitis (affecting limb function), and area postrema syndrome (episodes of otherwise unexplained hiccups or nausea and vomiting). Attacks to the optic nerves produce swelling and inflammation that cause

symptoms of pain and loss of vision while damage to the spinal cord causes weakness or paralysis in the legs or arms, loss of sensation, and problems with bladder and bowel function. Attacks can result in permanent neurological damage and disability.

NMOSD is most commonly seen in women (ratio 4:1) however it has been diagnosed in preschool-aged children and older adults. There are approximately 1,000 to 3,000 Canadians living with NMOSD. Symptoms of NMOSD generally begin rapidly and will vary from person to person in duration and severity, including level of disability. NMOSD follows an unpredictable course of relapsing-remitting with a variable time to remission. The cause of NMOSD in the majority of cases is due to a specific attack on the aquaporin-4 (AQP4) water channel located within the optic nerves and spinal cord. There is currently no cure for NMOSD, however, there are medications that prevent further attacks. With each attack, an individual living with NMOSD will accrue additional disability, which has a significant impact on every aspect of daily life including a negative effect on independence, their family, community, employment, and ultimately society.

Six respondents reported living with NMOSD between less than one year to five years, three reported living with NMOSD for six to ten years, and one respondent had been living with NMOSD for more than twenty years. Regardless of how long an individual has lived with NMOSD, the impact on their quality of life is significantly impacted as reported below.

"I can no longer work and struggle to find purpose. Even walking the dog is sometimes too difficult. I've given up the idea of having a life partner. I'd say it's very much impacted my overall quality of life."

"I have been part of a medical study in the first two years for which I was incredibly grateful, but it required a great deal of time away from regular life. I have suffered several relapses and have residual nerve damage which affects my ability to perform daily tasks and my level of activity in general. My eyesight has also been affected. While I still live my life to the fullest that I can, I have to be aware and careful of my health and the risks associated with overdoing and/or exposing myself to health risks."

"It has restricted my ability to drive. I have constant nerve pain which can be exhausting. I don't always have the energy to do the activities that I like to enjoy. I have always loved the summer heat and sunshine and cannot enjoy it now. I can no longer drive after dark. The activities I had planned for retirement I have not been able to do it. But if I was still working I would not have been able to go to the office full time."

One caregiver reported that providing care for their loved one living with NMOSD impacted their daily routines due to the stress associated with living with NMOSD.

"Dealing with my partner's stress can be challenging in my day-to-day life."

3 Experiences With Currently Available Treatments

Up until 2019, standard treatment for NMOSD involved intravenous steroids, and additional treatments to remove antibodies (intravenous immunoglobulin or plasmapheresis/plasma exchange). In addition, off-label immunosuppressants were, and in some cases continue to be used to help prevent further attacks though with varying levels of therapeutic benefit. Symptoms such as neuropathy, pain, stiffness, muscle spasms, and bladder and bowel control problems can be managed with various medications and therapies.

"Up until four years ago, the only treatment options NMOSD patients had were three off-label use drugs, used for transplant patients to suppress the immune system (mycophenolate, azathioprine, and rituximab). While these drugs are better than having no therapies, they were not designed for NMOSD. Patients on these therapies were faced with relapses while on them. In an effort to bolster immunosuppression, patients were forced to combine these therapies with daily doses of steroids in an effort to stay in remission which had mixed results. Many continued to relapse, resulting in lengthy hospital stays and grueling interventions, like plasma exchange (PLEX), used to treat an attack. Being on steroids long-term comes with serious side effects, which include a higher risk of infection, weight gain, increased risk of ulcers and gastritis, high blood sugar and steroid-induced diabetes, increased blood pressure, cataracts, tendon ruptures, bone loss (osteoporosis), neuropathy, anxiety, depression, and insomnia among others. I can tell you from personal experience that being on all three of these off-label use therapies along with daily steroids for over a decade was fraught. I was constantly relapsing, I became an insulin pump dependent type one diabetic, I had significant weight gain and I developed severe osteoporosis, resulting in 17 fractures, a torn Achilles tendon, and a torn rotator cuff in 3 years. None of these injuries were due to a fall. I live with severe chronic pain and as a result, became a wheelchair user in 2020. I'd run out of options and no one knew

what to do to help me. I can't tell you how terrifying being in this position was. It not only impacted me but also all those who love and care about me."

Currently, there are two Health Canada-approved medications indicated for adults with NMOSD who are AQP4-IgG seropositive however access to these medications is limited. Respondents reported treatment with the following medications; eculizumab (2 respondents), satralizumab (2 respondents), and rituximab (4 respondents). All respondents felt their medication was effective in managing their NMOSD. Of the two authorized medications indicated for NMOSD, one is not available through public drug programs further limiting access to life-altering medications. Given the outcome of irreversible damage and disability associated with attacks, it is imperative that individuals have access to all Health Canada-approved therapeutic options for NMOSD. As described by respondents, medication administration and dosing are essential to their health and well-being. In particular, therapeutic options with less frequent dosing schedules are of great value to people living with NMOSD. As well, it is critical for individuals who are unresponsive or intolerant to other medications indicated for NMOSD to have access to a medication with a different mechanism of action.

"ANY and all treatments that minimize relapses will cost the health system less than the relapses and the progressive deterioration of health that NMOSD patients will continue to experience in the absence of effective treatments."

Providing individuals with choice via shared decision-making with their healthcare team also serves to increase medication adherence. Adherence improves the clinical benefit of the medication and the quality of life of the individual, resulting in a potential decrease of burden to the Canadian health and social systems. The importance of administration and dose was clearly expressed by respondents. The following is a personal account of the experience of an individual living with NMOSD who was treated with off-label medications prior to the introduction of the Health Canada-approved medications indicated for NMOSD.

Some respondents indicated delays in initiating treatment due to a lack of access to healthcare providers, issues with private and/or public insurance, long wait times for blood work and other pre- treatment work-ups, and challenges in organizing infusions.

4 Improved Outcomes

The approval of inebilizumab is significant as it will be the first authorized B cell treatment option indicated for NMOSD. Authorization of inebilizumab will also provide access to the manufacturer's patient support program which specializes in treatment and care for individuals living with NMOSD, unlike the current B cell therapy which is prescribed off-label without a specialized patient support program.

"It does us no good to have targeted therapies (the first ones in over 100 years of NMO history) if we don't have access. Also, I have relapsed all over the place on off-label use drugs and suffered permanent drug injuries that are life-altering. Patients need these new drugs and they need them NOW."

Left untreated, the burden of increasing disability from NMOSD impacts all areas of a person's life including employment stability or loss, family income, increased need for assistance or caregiving, loss of independence, isolation, cognitive decline, and increased mobility challenges. Inebilizumab has the ability to reduce attacks and accrued disability and provide individuals with a reduced dosing schedule, requiring one infusion every six months. Respondents indicated that the administration and dosing schedules of their current medications can have a negative impact on their work, family, and recreational commitments and activities.

"Administration and dosing are very important. I want to have to do it as little amount as possible."

"I like the twice-yearly infusions. I'm able to have a life instead of having my medication dictate my life."

"Time away from regular life must be planned for and worked around, to minimize the impact on school, work, and other obligations."

"My drug treatment is IV infusion every 2 weeks, which is limiting in travel. Also, it is challenging over time is always finding a good vein for infusion."

5 Experience With Drug Under Review

One respondent had experience with inebilizumab through a clinical trial and was on the medication for 18 months. At the end of the clinical trial the patient could no longer access the medication and was switched to another therapy. The side-effects reported

included mild skin rash and a dry cough. From a risk-benefit perspective, respondents were provided with a list of the most common side effects reported for inebilizumab and asked if they would consider taking this medication. Four respondents indicated they would consider inebilizumab and five responded that they would not consider treatment with inebilizumab based on the side effects.

6 Companion Diagnostic Test

Data on companion testing was not requested as part of the survey.

7 Summary points

- Up until 2019, there were no treatments specifically indicated for NMOSD (globally). Current treatments for NMOSD have limited access or are used off-label with varying levels of therapeutic benefit.
- Medication administration and dosing are essential to health and well-being. Therapeutic options with less frequent dosing schedules such as inebilizumab are of great value to people living with NMOSD. It is also critical for individuals who are unresponsive or intolerant to other medications indicated for NMOSD to have access to a medication with a different mechanism of action.
- Inebilizumab is the first authorized B cell therapy indicated specifically for NMOSD and therefore fills a significant therapeutic need that has been unmet in NMOSD treatment and allows patients a reduced dosing schedule and access to a patient support program for NMOSD.
- Treatment with inebilizumab has the potential to allow people living with NMOSD to remain in the workforce, sustain family and social roles and responsibilities longer, improve their quality of life, decrease the need for caregiving (family caregiver or paid caregiver) and reduce the financial burden to health and social systems.

8 Appendix: Patient Group Conflict of Interest Declaration

No industry help was received from outside MS Canada to collect, analyze data or complete this submission, or used in this submission. The following companies have provided MS Canada with financial payments over the past two years. No company has interest in the drug 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
EMD Serono				X
Hoffmann La Roche				X
Biogen				X
Novartis				X
Sanofi-Genzyme			X	
Pendopharm (Pharmascience)			X	
Bristol-Myers Squibb			X	
Sandoz	X			
Alexion			X	
JAMP			X	
Abbvie			X	
AstraZeneca			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: Jennifer McDonell

Position: Director, MS Information and Resources Patient Group: MS Canada

Date: August 18, 2023

CADTH Reimbursement Review Patient Input - inebilizumab

Patient Input for CADTH Reimbursement Review

Name of Drug: inebilizumab (Uplizna)

Indication: Monotherapy for the treatment of adult patients with neuromyelitis optica spectrum disorders (NMOSD) who are anti-aquaporin-4 immunoglobulin G (AQP4-IgG) seropositive

Name of Patient Group: The Sumaira Foundation

Author of Submission: Sumaira Ahmed

1. About Your Patient Group

The Sumaira Foundation (TSF) is a charitable non-profit organization dedicated to generating global awareness of neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), building communities of support for patients and their caregivers, supporting research and advocating on behalf of our patient communities around the world. TSF has established a local presence in the United States, Canada, Germany, France and Italy. In Canada, we work with a team of five Ambassadors and one Canadian-based Board Member and have been registered since 2021 as a not-for-profit organization (corporation number 1356179- 8). For more information, please visit our website at www.sumairafoundation.org.

2. Information Gathering

Some of the information contained in this submission was gathered by The Sumaira Foundation through two online surveys – one designed for people living with NMOSD, and the other for caregivers/loved ones of people living with NMOSD. TSF has also been active in NMOSD patient advocacy since its founding in 2014, and we have a wide range of experience working with all stakeholders, including patients, caregivers, researchers, top clinicians and other advocacy organizations around the world. Our long-standing experience is also reflected in the content of this submission. Survey respondents were recruited by TSF through email, social media, and other online platforms. The following populations were invited to take part: people living with NMOSD ("patients") and those who are or were caregivers and/or loved ones of people living with NMOSD ("caregivers").

The survey responses were supplemented with information gathered through videoconference interviews with four patients and one caregiver. Four interviews were conducted in English and one in French. All but one interview subject had direct experience with inebilizumab.

Responses to the online surveys were collected between July 13 and July 31, 2023, and videoconference interviews were also conducted during that timeframe, with the final interviews taking place on August 8, 2023. The data was anonymized when aggregated for analysis to protect patient confidentiality.

A total of 60 patients and caregivers responded to the online surveys. Most (n=51) were patients, and the remainder (n=9) were caregivers. The majority of respondents were from USA (approx. 40%), with others from Canada, South Africa, Italy, Germany, France, Denmark, Sweden, Australia, Bulgaria, Mexico, Bolivia, UK, Nigeria, Indonesia, Pakistan and India. Respondents from Canada were from Ontario, Alberta, Manitoba and Quebec.

Around 54% of the respondents were between 35 and 54 years of age, approximately 32% were between the ages of 55 and 74, and 25% of the patients were between the ages of 25 and 34. Less than two percent of survey respondents were below 18 years of age.

Among the respondents affected by NMOSD, approximately 62% reported they or their loved one received a diagnosis as a young adult (between 18 to 39 years of age) and 30% received a diagnosis in middle-adulthood (between 40 to 64 years of age). Others reported receiving their diagnosis as a toddler or infant, or as an adolescent. The largest number of respondents – around 36% – indicated that they or their loved ones had received a diagnosis between five to 10 years ago, followed by 28% of the respondents who indicated receiving a diagnosis less than two years ago.

3. Disease Experience

NMOSD is a rare neuroimmune condition with an estimated prevalence ranging from 0.7 to 10 per 100,000 population where the immune system attacks cells in the central nervous system (CNS), mistaking them as non-self. It occurs predominantly among women at a ratio of up to 9:1 women vs. men.

In NMOSD, new inflammation in the nervous system produces attacks (flare-ups, relapses or exacerbations). With an attack, patients may experience optic neuritis (inflammation of the optic nerves that causes eye pain and reduced vision in one or both eyes), and/or transverse myelitis – inflammation of a segment of the spinal cord causing sensory changes, potential loss of bladder and bowel control, numbness, tingling and possible paralysis. While less common, attacks of the brainstem can also occur, leading to intractable hiccupping, nausea and/or vomiting.

After treatment for acute attacks, the disease exists in a remission state where there is no active disease progression, but patients continue to suffer from symptoms due to previous damage to the nervous system.

The mortality associated with NMOSD is high and variable, especially when the disease remains untreated or mismanaged. About 30% of patients die within the first five years and 50% of patients become blind and/or wheelchair bound. Death in patients due to NMOSD, when it occurs, typically is attributed to respiratory failure following an acute attack.

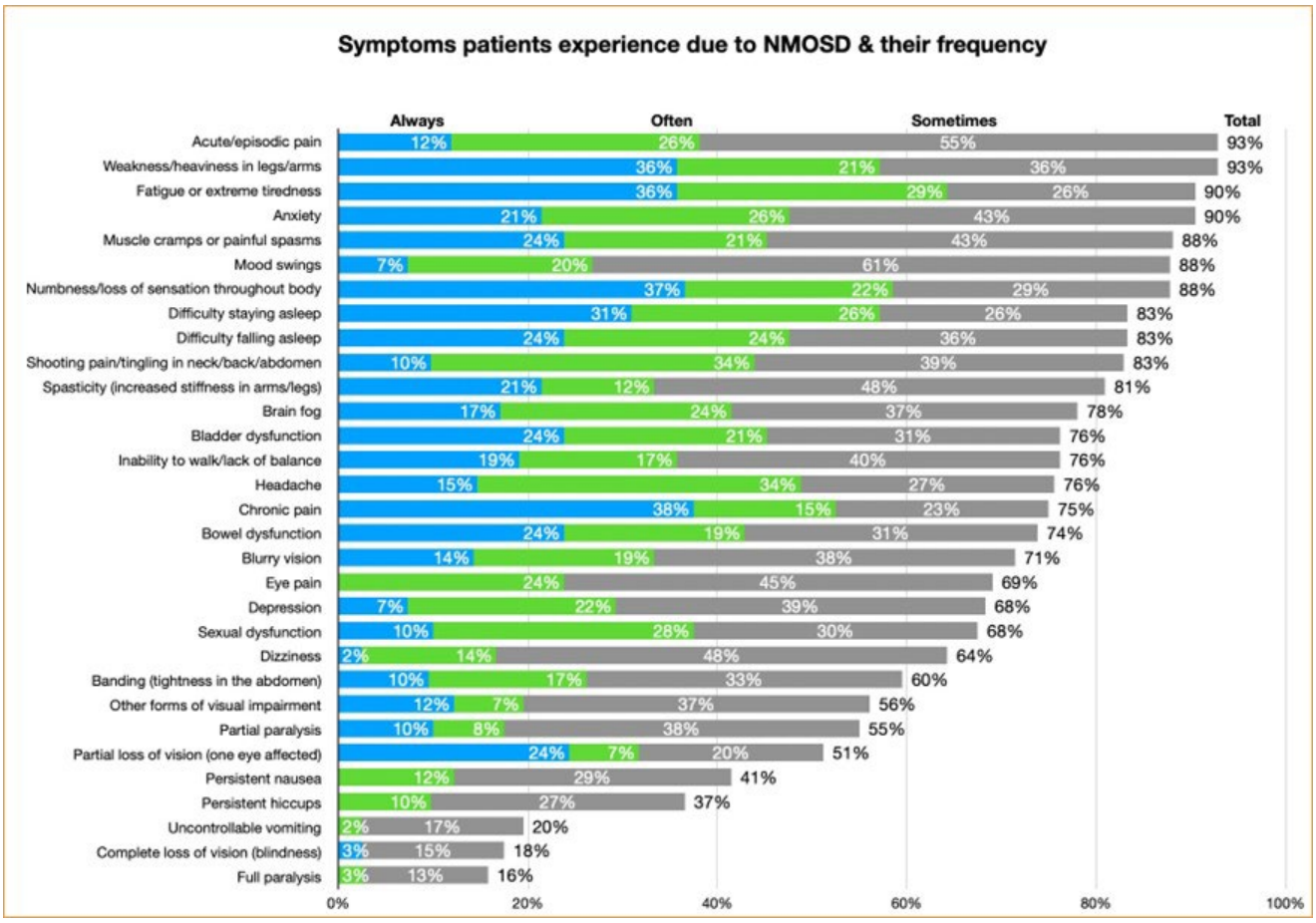
Until a few years ago, there were no proven, on-label therapies for treating NMOSD. Since then, three new, highly effective therapies have received regulatory approval in some countries, while in other countries approval has not yet been granted by the relevant regulatory bodies. In other cases, insurance coverage and access to these on-label therapies is quite limited, forcing patients to rely on unproven, off-label therapies, many of which are of variable effectiveness and often come with significant and sometimes debilitating side effects. TSF believes all NMOSD patients around the world should have access to proven, safe and effective on-label therapies for their condition and that is one of our primary objectives as a patient advocacy organization.

Symptoms:

In responding to our survey, **patients** with NMOSD indicated they experience a wide range of symptoms. Among the most commonly mentioned were partial loss of vision (usually with one eye more affected), numbness or loss of sensation throughout the body, weakness or heaviness in the legs and/or arms, chronic pain, muscle cramps or painful spasms, fatigue or extreme tiredness, bowel and bladder dysfunction, and difficulty falling and staying asleep. These symptoms were also among the most important to manage for people living with NMOSD, in addition to vision loss, inability to walk/lack of balance.

Several **patients** also highlighted brain fog, spasticity (increased muscle tone or stiffness in the arms and legs), sexual dysfunction, inability to walk/lack of balance, anxiety, acute pain and eye pain as symptoms often experienced, as seen in the table below.

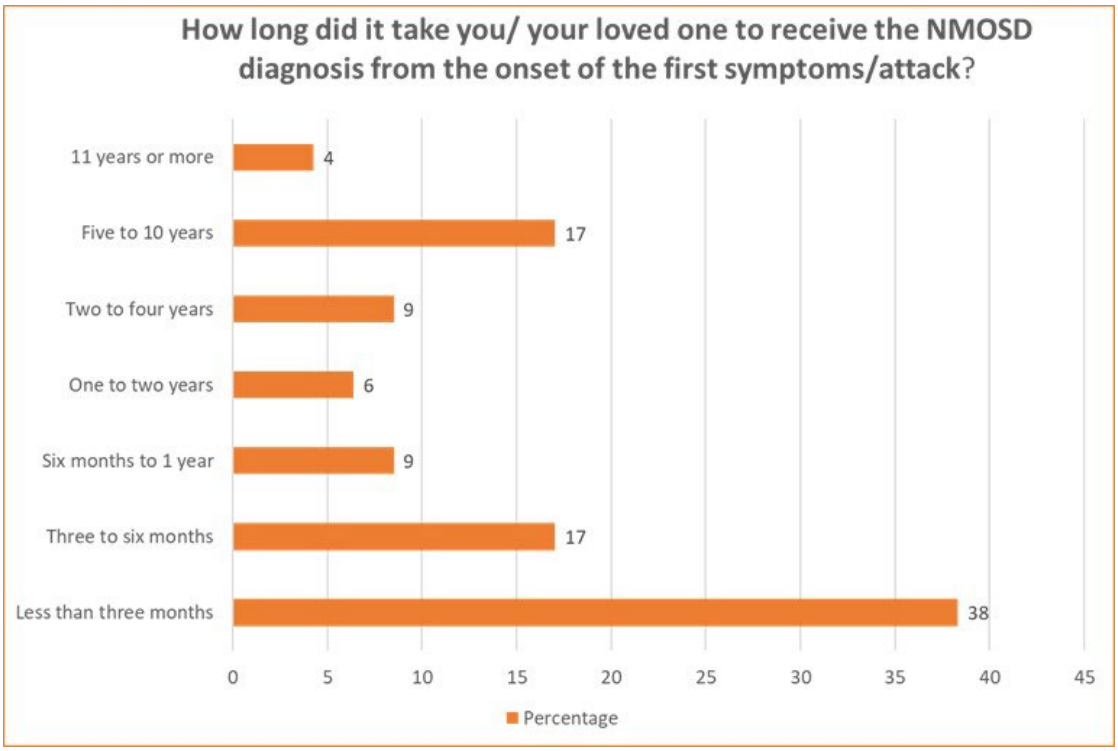
Other symptoms reported by **patients** included vertigo and of significant concern, breathing issues.



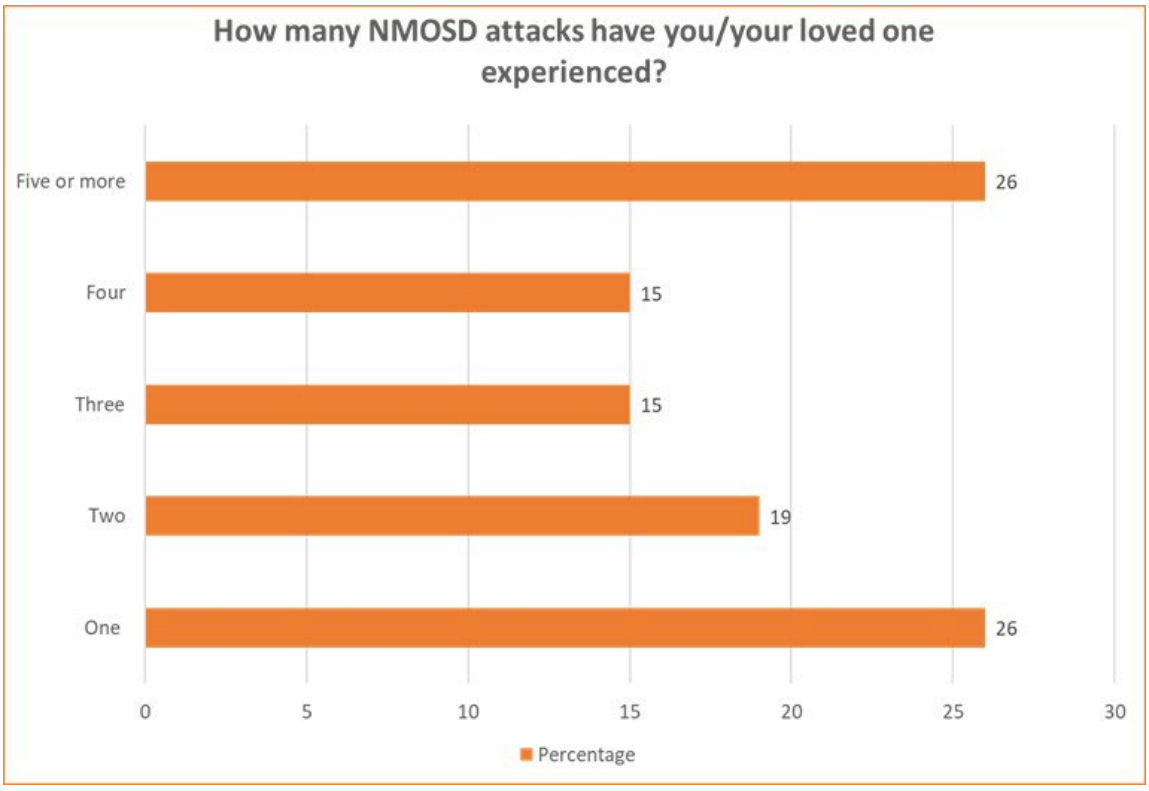
With respect to their loved ones with NMOSD, **caregivers** reported acute and episodic pain, mood swings, brain fog, sexual dysfunction, spasticity (increased muscle tone or stiffness in the arms and legs), anxiety and dizziness as the most important symptoms to manage in the NMOSD patients they care for.

NMOSD Attacks:

Around 38% of the **survey responders** reported receiving a diagnosis less than three months after their first attack or onset of symptoms, and more than 20% of the **survey respondents** waited for more than five years to receive a diagnosis following first visible symptoms or attack



Attacks are the hallmark of NMOSD and the frequency of those attacks, as reported by **patients and caregivers** ranged from one attack (26%) to five or more (26%).

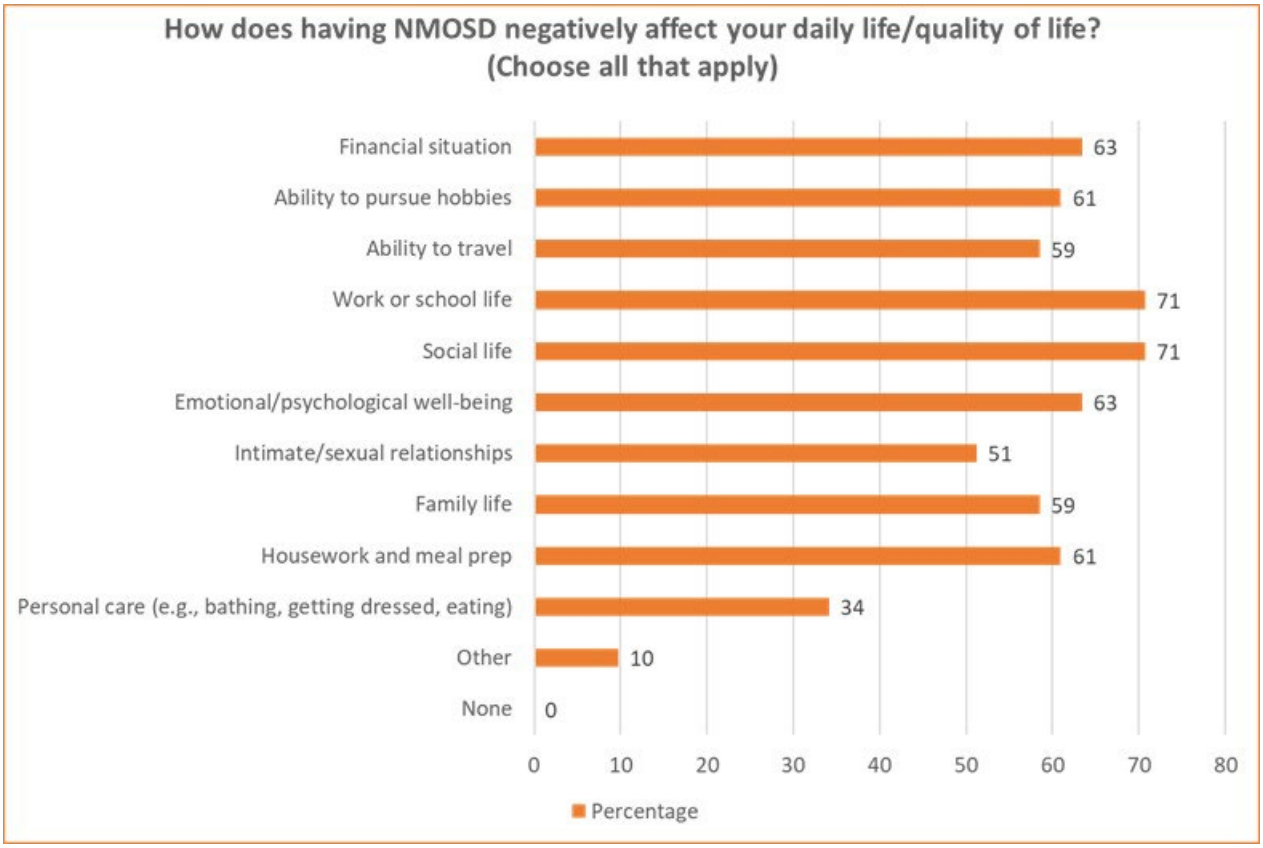


When asked to describe in their own words, the experience of living through/surviving an NMOSD attack, **patients** said:

- "*The initial uncertainty of an NMOSD attack is the most terrifying because you are at the mercy of the doctors in the emergency rooms (most of whom have absolutely no clue what your disease is or what attacks present as or can lead to). So, you are never sure if you will be completely paralyzed or blind from the attack, or if you will be lucky and be minimally affected. It is often disheartening to be misunderstood when trying to explain the pain and numbness I experience all at the same time*."
- "*The initial attack was frightening, as I lost my sight in one eye, and I did not know what was causing it. I had another nerve pain that happened at the same time and doctors did not know they were related. I also found I had symptoms for a year I didn't know…There was so much to learn it was a bit overwhelming. Some of the nerve pain was excruciating and exhausting*."
- "*Two weeks after giving birth to my daughter, I collapsed in my home and lost my vision. I was paralyzed for a few weeks and eventually got double vision… I also got a blood clot in my brain which was treated with a heparin drip and blood thinners for six months*."
- "*Attacks are life changing. Each attack left me with new challenges, some I still face today. My most severe attack left me unable to walk unassisted, but after intensive therapy, I can now walk short distances unassisted. I have permanent vision loss on my right and cannot drive, which is tough for a young mother…"*
- "*Living through an NMOSD attack or flare-up is the single most nerve-wracking, scary, demoralizing, dark, unsettling thing I have ever experienced in my life. It was very lonely and led me to a deep depression for about a year after my diagnosis. Then having continual attacks and having to relearn how to use my hands and walk properly was very frustrating and painful. I wouldn't say I am on the other side of it because I never know when an attack will come, even while being on medication to prevent such attacks*."

Disease Impact:

When asked how living with NMOSD has negatively affected their quality of life, **patients** indicated their social life, work or school has significantly suffered.



The disease impact was said to be extensive, especially the loss of independence which touched all aspects of patients' lives. Over half (61%) of **patient** respondents reported receiving up to 10 hours of assistance each week from family, friends, or other informal caregivers to perform activities of daily living and almost 20% reported receiving between 31-50 hours of assistance each week.

One **patient** shared, "*My husband or mother now needs to drive me where we have to go. I cannot just drive myself and the kids to activities they want to do in the summer. My children have picked up extra chores and help with food prep. Grocery shopping is done by my husband. Before my diagnosis, I was doing all these things independently*." **Another** said, "*Personally I try as much as I can to ensure that my disease does not negatively impact others, especially not my family, even if this means me struggling to do things on my own*."

Patients indicated that they commonly rely on a range of assistive devices including walkers, canes, wheelchairs, specialized bathroom equipment and phone apps or memory aids to help them manage the activities of daily life. Other supports commonly used included bed rails, lift chair, service animals, stair lift, elbow crutches, leg straps, wooden wheelchair ramps and lymphedema pumps.

Approximately 36% of **patients** reported they did not use any assistive devices, equipment, or aids to manage symptoms and/or support their daily activities.

When asked to describe in their own words how their daily lives and quality of life have been impacted by NMOSD, **patients** said:

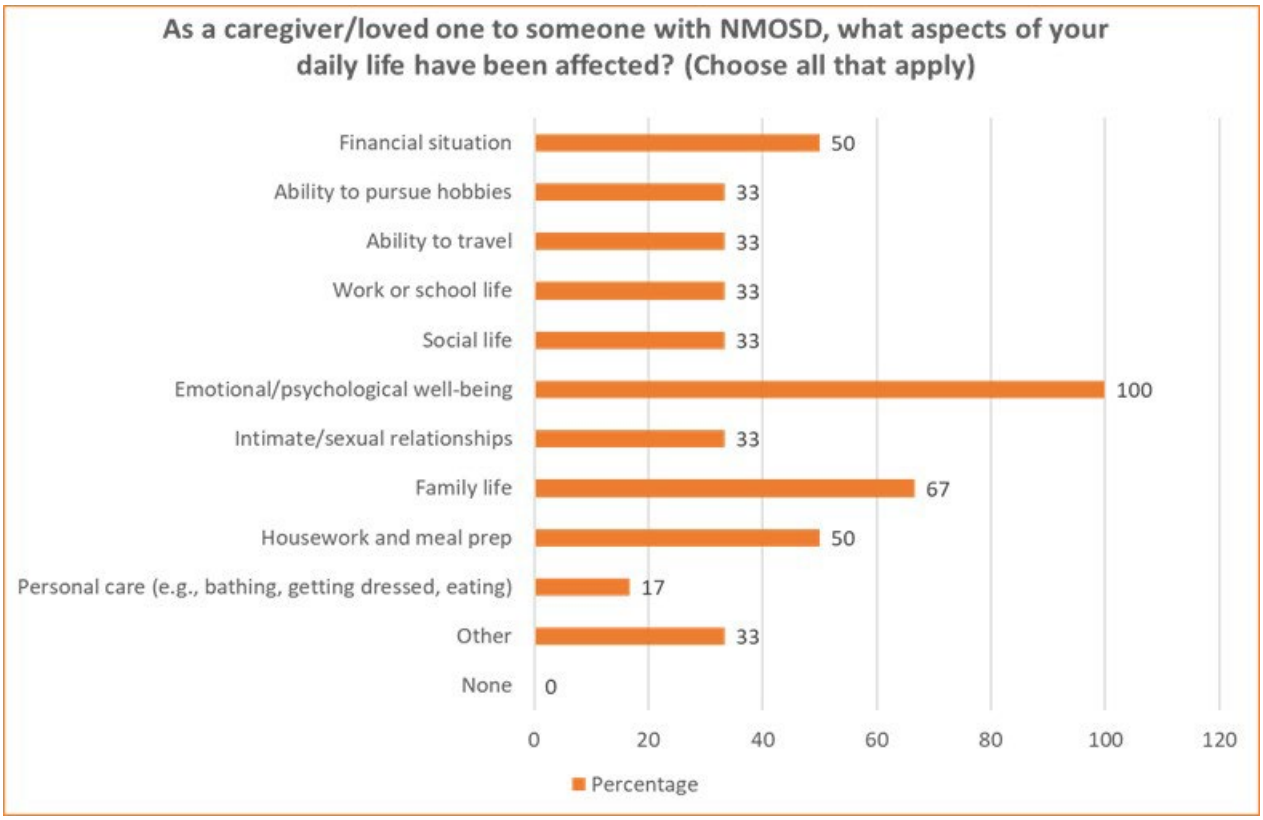
- "*An NMO diagnosis becomes the center of everything. It becomes part of every decision, alters the algorithms of life, and forces you to live strategically and tactically. Can I sleep in another 10 minutes to try and store some extra rest, or will I be too slow-moving and be late? Should I shave today, or do I have to save that energy for a work lunch? I still have to feed and take the dog out. So, no extra sleep and I will have to forgo shaving. I am presenting to a group today and am working against a deadline. Do I need to skip my pain meds to improve my cognitive function so I can focus, or will the unchecked pain be too distracting? What is the weather? Do I need to bring extra shirts because I may sweat through what I am wearing? How bad is the neuropathic pain? Can I wear regular socks and appropriate shoes, or do I need to wear the old, sloppy, broken-in shoes because they are the only thing I can remotely tolerate? I can't really differentiate between colors*

and hues, so does this tie even match? How long is my commute or meeting schedule like for the day? This dictates if I can drink water because I may not be able to get to the restroom in time. Welcome to my world; you survived until breakfast. That is assuming you think you can keep it in."

- "*It has forced me to become disabled back when I was in my mid 20's. Now that I am in my later 30's, life has not been any easier. I can still have problems with trying to walk around and being independent. It is nearly impossible to work with the fatigue and physical limitations that the disease has left me with. It is depressing to have lost my independence and forced to rely on others to help me through daily life*."
- "*I lost my job as a result of NMO and only have been able to find part-time contracting work resulting in an approximate loss of 91% of my income and 75% of my household income. Being immunosuppressed during the pandemic has created a situation where the world has moved on while I still have to calculate the risks of seeing my parent or children, let alone non-immediate family or friends. The anxiety of being of little value or a drag on the well-being and happiness of others gets overwhelming*."

From a **caregiver** perspective, NMOSD has negatively affected many areas of their lives, with **all (100%)** of respondents noting a significant impact of their emotional and psychological well-being as a result of their loved ones' diagnosis.

Several **caregivers** reported experiencing 'anxiety' for their loved one. As **one caregiver** said, "*I'm constantly worried about my son. If he catches a cold, I freak out. We usually have to plan family trips with nearby hotels so that he can go to the hotel to rest during the day... I just have to travel with a plan*." Another shared, "*I feel as if her siblings don't get as much attention as needed because I am constantly worried about my 15-year-old daughter*."

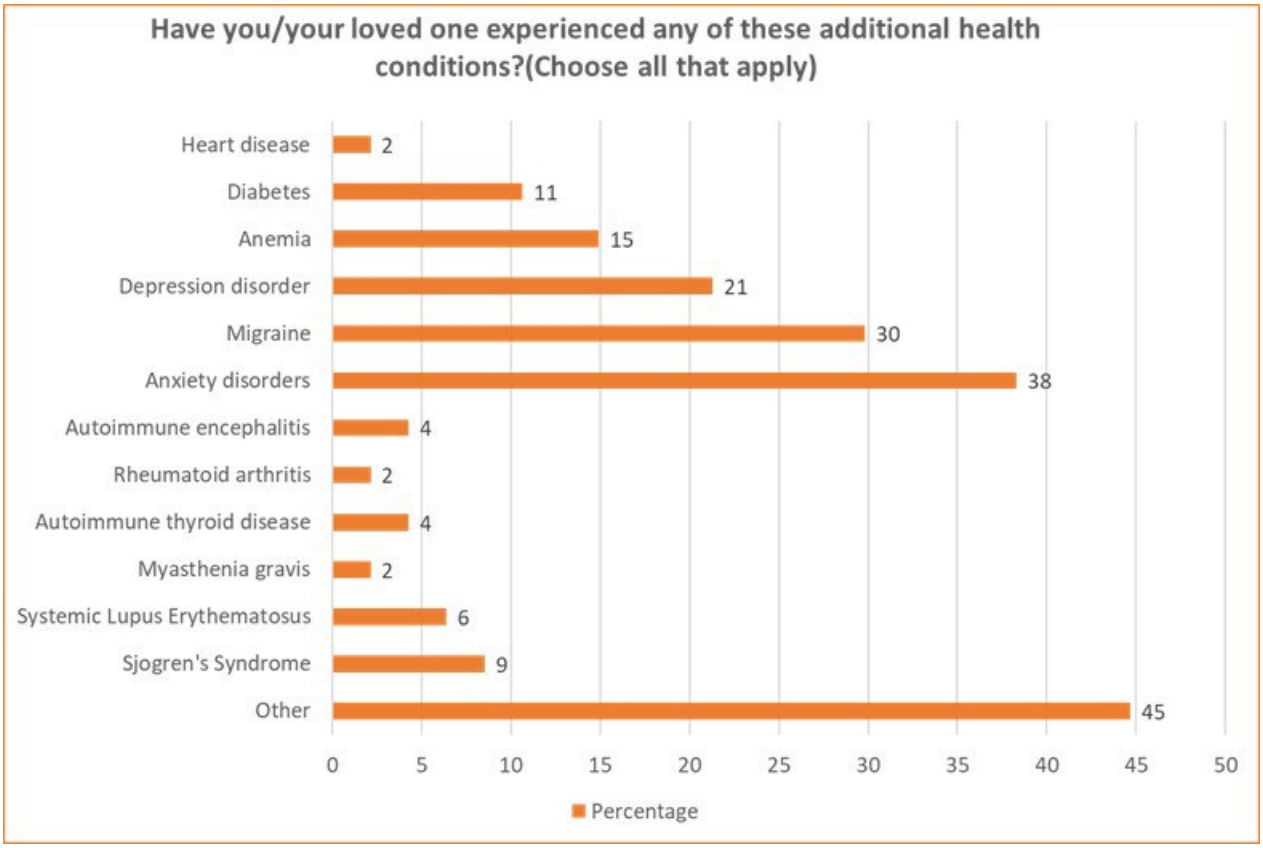


When asked to describe in their own words how their daily lives and quality of life have been affected by providing care for someone living with NMOSD, **caregivers** said:

- "*It is a constant strain. The economic burden of increased medical costs and having to provide for me weighs on my caregiver. The physical demands inhibit their ability to focus on wellness, hobbies, social activities etc. Emotionally, they are always waiting for the next attack or symptom to happen*."

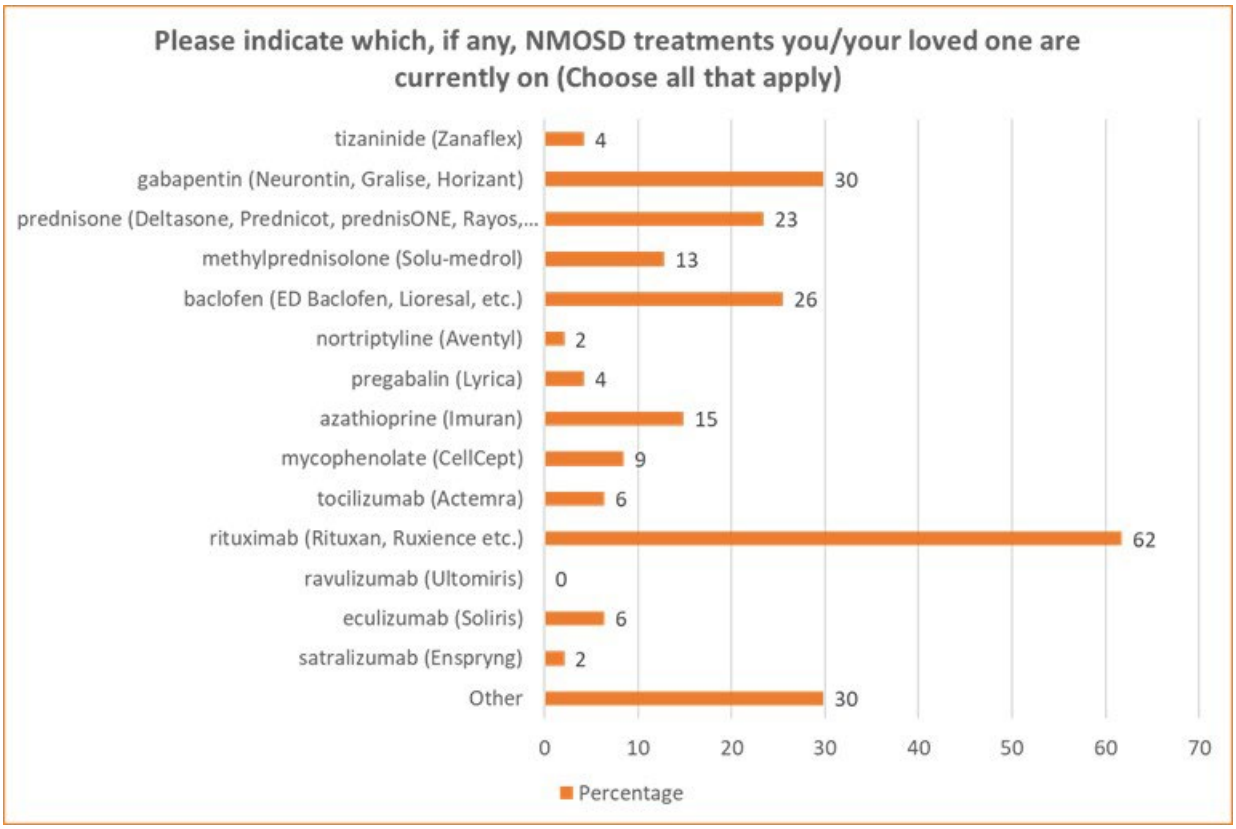
- *"My world was turned on its head. I went from full time work, having a social life, paying a mortgage and owning my own home to none of these."*

When questioned about experiencing **additional health conditions**, most of the **survey respondents** reported anxiety disorders followed by migraine, depression, and anemia. Of the respondents 45% shared experiencing additional conditions including Avascular Necrosis, Asthma, liver damage, enlarged spleen, high cholesterol, Hypertension, weight gain, Pulmonary Sarcoidosis, Transverse Myelitis, Spondyloarthritis and PTSD.

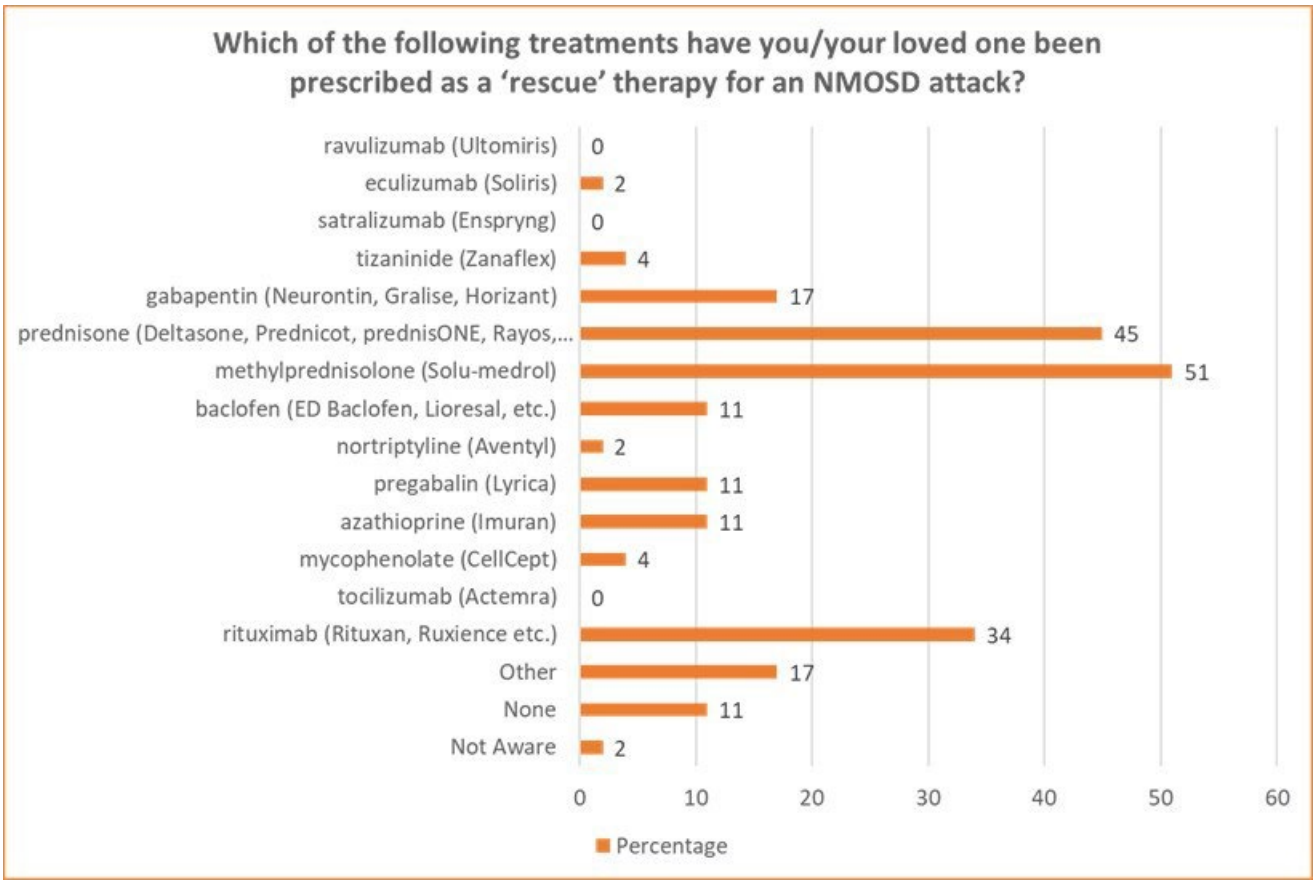


4. Experiences With Currently Available Treatments

Patients and caregivers were asked directly about their experience with a number of current standards of care **accessible in Canada** for the treatment of NMOSD**,** including satralizumab (Enspryng), eculizumab (Soliris), ravulizumab (Ultomiris), rituximab (Rituxan, Ruxience etc.), tocilizumab (Actemra), mycophenolate (CellCept), azathioprine (Imuran) and prednisone (Deltasone, Prednicot, prednisONE, Rayos, Sterapred, Winpred, etc.). *Other* treatments used by respondents to manage NMOSD and its symptoms include but are not limited to tizanidine (Zanaflex), gabapentin (Neurontin, Gralise, Horizant), methylprednisolone (Solu-medrol), baclofen (ED Baclofen, Lioresal), nortriptyline (Aventyl) and pregabalin (Lyrica).



When asked about treatments prescribed specifically as a ‘rescue therapy’ for an NMOSD attack, most **survey respondents** indicated that methylprednisolone, followed by prednisone, rituximab and gabapentin were the most commonly used. Other treatments noted by **survey respondents** included plasma exchange (PLEX), IVIG, intravenous steroids, solumedrol and plasmapheresis.



Rituximab (Rituxan, Ruxience, etc.):

Around 54% of **patients** on rituximab indicated the treatment was 'very effective' for NMOSD, and approximately 18% reported that they experienced 'no perceived effect.' Around seven percent of the **patient respondents** were 'not sure' about its effectiveness.

When asked **how rituximab helped** them or their loved ones, **patient and caregiver respondents** said:

- "*I have not had any new attacks that have left me with significant physical damage. It's important for me not to have more after-effects than what I have now*."
- "*It has continued to keep my vision stable*."
- "*I think I have had some improvement of my fatigue*."
- "*Once she (*the patient*) started rituximab she has remained attacked free. It lifts her mood and lessens her fatigue for approx. 4 months and then she starts to know her body needs the next infusion."*

Regarding **side effects** related to rituximab, most **patients** indicated back pain, fever, weakness, drowsiness, dizziness /light-headedness, inflammation of the stomach lining (gastritis) and stomach pain.

- "*It was not beneficial for me. Rituxan put me in a coma after my second infusion. I felt sick after my first dose as if I had food poisoning*."
- "*I received rituximab infusions every 6 months for over 1.5 years and suffered constant attacks. Every time I cycled off of steroids, symptoms returned*."
- "*I had an allergic reaction and had to stop the treatment on the third infusion; I noticed no effects during this period*."

- "*First session of treatment Benadryl given for skin rash. Second treatment fever and upper respiratory with coughing and significant phlegm*."
- "*Reoccurring issues with low blood pressure during infusions which make them even longer, between 16 hours and 21 hours.*"
- "*My greatest concern is the effects on my heart, liver, and gallbladder. I want to swap to rituximab infusions, but NHS rules say I'm ineligible until I have a severe attacks (which I really don't want!) so I'm stuck*."

On **difficulty taking or receiving rituximab**, about 32% of **patients** pointed out the inability to self- administer the drug, travel time to clinic and having to take time off work. Most c**aregivers** (75%) indicated travel time to clinic as a difficulty in taking or receiving the drug.

Regarding **difficulty in accessing rituximab**, 18% of **patients** and 25% of **caregivers** reported out- of-pocket costs as a key barrier, followed by coverage not being available through private insurance (11% of patients, 25% of caregivers). Most **survey respondents** reported accessing rituximab through private insurance (36% of patients, 25% of caregivers), or through public (government) insurance (29% of patients, 75% of caregivers).

Mycophenolate (CellCept):

Around 33% of the **patients** on mycophenolate indicated the treatment was 'very effective' for NMOSD, and approximately 22% reported that they experienced 'no perceived effect' from mycophenolate, and a little over 22% of the respondents were 'not sure' about its effectiveness.

Regarding **problems and complications** related to mycophenolate, respondents shared that symptom including drowsiness and loss of appetite, infections, inflammation of the stomach lining (gastritis), headache and drowsiness were the **least manageable**. Some of the '**more manageable**' symptoms indicated were stomach pain, fever, weakness, diarrhea, numbness, or tingly feeling in or around your mouth, confusion, burning while urinating or urinating more often than usual, among others.

- "*It worked for a short period of time before I started breaking through the medication and having attacks*."
- "*It was my first preventative medication and I relapsed and needed plasmapheresis*."
- "*I didn't like self-administering this medication.*"

On **difficulty taking or receiving mycophenolate**, more that 22% of **patients** pointed out the inability to self-administer the drug.

Regarding **difficulty in accessing mycophenolate**, more that 22% of **patients** reported out-of- pocket costs as a key barrier and one patient shared that by the time a diagnosis was confirmed, progression has reached a point where the therapy was no longer considered effective. Most **survey respondents** reported accessing mycophenolate through private insurance, and public (government) insurance (around 22% respectively).

Azathioprine (Imuran):

Of the **patient respondents** who have used azathioprine to treat NMOSD, 58% indicated the treatment was 'somewhat effective', 25% reported it as 'very effective' and approximately 17% reported that they experienced 'no perceived effect' from azathioprine.

When asked **how azathioprine helped** them or their loved ones, **survey respondents** said:

- "*I used it for approx. four years on a daily basis. Major benefit was I could stop steroids, and I did not get a relapse.*"
- "*Was episode free for 8 years while on azathioprine, relapsed when azathioprine was discontinued*."

Regarding **problems and complications** related to azathioprine, most **patients** noted fever, chest pain, back pain, stomach pain and infections as the **least manageable** symptoms while fast heartbeat, nausea and/or vomiting, headache, muscle stiffness and swelling of legs or feet were reported as the **most manageable** symptoms.

- "*It was the very first medication we tried back in 2004, but after a short period of time I was breaking through and having relapses.*"

- "*Bad memories with this treatment because of the side effects*."
- "*I had two relapses on Imuran… after starting the Imuran, I lasted about six months and had a relapse and in that relapse was I had uncontrollable hiccups and some vomiting with that as well.*"

On **difficulty taking or receiving azathioprine**, more that 25% of **patients** referred to difficulty swallowing the pills.

Regarding **difficulty in accessing azathioprine**, almost half of the **patient respondents** (42%) reported out-of-pocket costs as a key barrier.

Of the **patient respondents**, 33% reported accessing azathioprine through public (government) insurance, followed by 25% through private insurance and out-of-pocket payments respectively.

Prednisone (Deltasone, Prednicot, prednisONE, Rayos, Sterapred, Winpred, etc.):

Around 42% of the **survey respondents** who had used prednisone indicated the treatment was 'somewhat effective' for NMOSD, and approximately 39% reported this as 'very effective,' whereas 9% of the **survey respondents** shared that they experienced 'no perceived effect' from prednisone. Another 9% indicated that they were 'not sure' about the impact of this treatment in managing their NMOSD.

When asked **how prednisone helped** them or their loved ones, **survey respondents** said:

- "*It has helped reduce inflammation in the past, and the intravenous version is given to me as a rescue medication when I have relapses*."
- "*The prednisone helped to bring my eyesight back after my attack as well as improve my balance*."

Regarding **side effects** related to prednisone, patients indicated restlessness, joint pain (arthralgia), fast heartbeat and drowsiness as the **least manageable** symptoms while restlessness, swelling of the legs or feet, sweating, headache and fast heartbeat were indicated as the **most manageable** symptoms.

- "*Prednisone does not help my symptoms; it makes me feel awful and I end up with gastritis/colitis for weeks afterwards*."
- "*My daughter continued to relapse on prednisone and had to be admitted for IV prednisone about every 18 months (prior to diagnosis with NMOSD)*."
- "*Negative impact on bone density - osteoporosis*."
- "*The weight gain was a tough one and made it even more difficult to function normally in school since all my old friends didn't know what to think or say when I gained a lot of weight in such a short period of time. It was mentally challenging to be a young teenager who couldn't recognize herself in the mirror*."

When asked about **difficulty taking or receiving prednisone**, about 21% of **patients** pointed out swallowing pills as a problem, followed by travel time to clinic and having to take time off work or school (around 17% of patients respectively), inability to IV started (14% of patients), frequent infusions and inability to self-administer (10% of patients respectively).

Regarding **difficulty in accessing prednisone**, most 24% of **patients** reported out-of- pocket cost as a key barrier followed by coverage not being available through private insurance (7%) and one patient reported that by the time a diagnosis was confirmed, progression has reached a point where the therapy is no longer considered effective.

Most **survey respondents** reported accessing prednisone through private insurance (41% of patients, 50% of caregivers), followed by public (government) insurance (31% of patients, 25% of caregivers). Several **survey** respondents reported accessing this treatment through out-of-pocket payment.

Tocilizumab (Actemra):

Of the **patients** on tocilizumab, 75% indicated the treatment was 'very effective' for NMOSD, and 25% reported it as 'somewhat effective.'

Regarding **problems and complications** related to tocilizumab, **patients** indicated headache, blood pressure problems, slow or fast heartbeat, infections, and sudden sweating among others as some of the **most manageable** symptoms. Some of the **more manageable** symptoms reported include swelling in legs or feet, tenderness, bleeding or bruising, mood changes, and body ache among others.

On **difficulty taking or receiving tocilizumab**, about 25% of **patients** pointed out the inability to get the IV started. No other issues were reported.

Regarding **difficulty in accessing rituximab**, 25% of **patients** reported coverage not being available through private insurance. No other issues were shared.

All respondents reported accessing rituximab through public (government) insurance.

Eculizumab (Soliris):

Of the NMOSD **patients** surveyed who were taking Soliris, 67% indicated the treatment was 'very effective' and 33% reported it as 'somewhat effective.'

When asked **how Soliris helped** them or their loved ones, **survey respondents** shared:

- "*Since being on Soliris, I have experienced no true relapses. I was also part of the clinical trial, where it was successful as well*."
- "*The worst of my nerve pain is gone. I can live a fairly normal almost pain free life*."
- "*I have been better this summer when taking Soliris; the sunlight and heat do not bother me near as much and I feel better*."

Regarding **problems and complications** related to Soliris, **patients** indicated muscle pain or spasms, stiffness in muscles, skin redness or rash, joint pain and numbness, and a tingly feeling around the mouth as some of the **most manageable** symptoms. Some of the **more manageable** symptoms reported include increased sensitivity to light, burning while urinating or urinating more often than usual, loss of appetite, inflammation of the stomach lining (gastritis), and constipation.

On **difficulty taking or receiving Soliris**, about 68% of **patients** pointed out the inability to get IV started and 33% of patients pointed out having to schedule activities of daily living around infusion schedule (too often).

Regarding **difficulty in accessing Soliris**, 33% of **patients** reported out-of-pocket costs as a barrier. No other issues were shared.

An equal number of **survey respondents** (33%) reported accessing Soliris through public (government) insurance, compassionate use through the manufacturer, and through private insurance.

Satralizumab (Enspryng):

Half (50%) of the p**atients** on Enspryng indicated the treatment was 'very effective' for NMOSD, and 50% reported they were 'not sure' about its impact.

When asked **how Enspryng helped** them or their loved ones, **survey respondents** shared:

- "*I was switched to Enspryng due to low IgG (Immunoglobulin G) number and constant infections... I have had no NMO attacks, and I feel a little better. It is easy to administer at home myself and it takes less of my time.*
- "*The injections were easy to self-administer*."

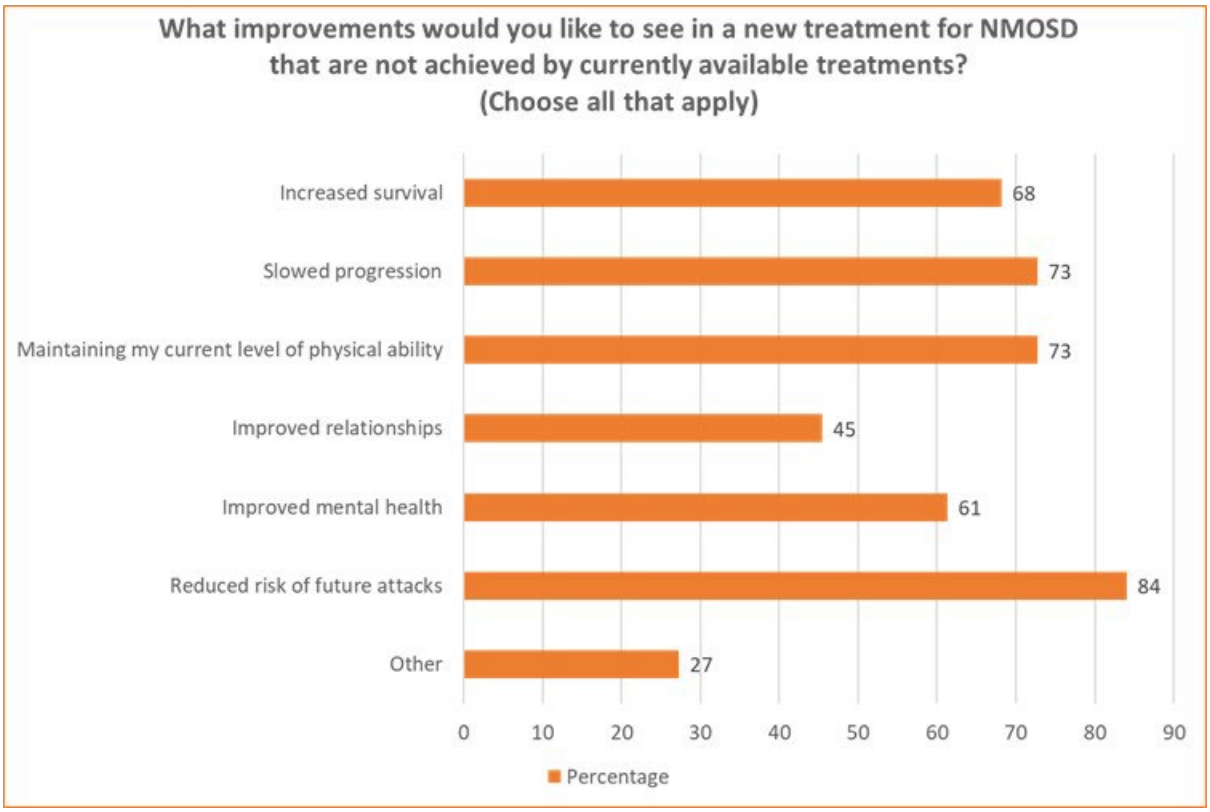
Regarding **problems and complications** related to Enspryng, **survey respondents** shared weakness, drowsiness, dizziness or light headedness, extremity pain and increased sensitivity to light as some of the **most manageable** symptoms. Some of the **least manageable** symptoms reported include pain or sores on body, kidney problems, inflammation of the stomach lining, stomach pain and flu symptoms (chills, tiredness, aches, cough, sore throat) among others.

No **difficulty taking or receiving** Enspryng was reported by **survey respondents**. Regarding **difficulty in accessing** Enspryng, none were shared by **survey respondents**.

An equal number of **survey respondents** (50%) reported accessing Enspryng through public (government) and private insurance.

5. Improved Outcomes

When asked what improvements they would like to see in a new treatment for NMOSD that are not achieved in currently available treatments, the vast majority of **patient** respondents prioritised a reduced risk of future attacks, followed by maintaining the current level of physical ability and slowed disease progression. The majority of **caregivers** prioritised improved mental health and slowed progression above others.



In terms of other improvements not achieved with currently available treatments, **survey respondents** shared a desire to see the following:

- "*Fewer side effects - especially liver, heart, kidneys, spleen, gallstones, bone density, and positive impact on joint pain, spasticity, and nerve damage."*
- "*I would love to have INCREASED physical ability, but I guess I'll accept maintaining current physical ability*."
- "*Reduced MRI activity to include brain atrophy data, potential nerve repair/protection, less dependence on polypharmacy*."
- "*Pain management.*"

When asked about how they would like to see a new treatment impact the quality of life of their loved one, it is not surprising that **caregivers** noted freedom from anxiety, along with a desire to see their loved ones retain their functions as long as possible to have a better quality of life.

If the desired improvements they hoped for in a new treatment were achieved, **patients** and **caregivers** said the result would be:

- "*I have gone through a grieving process for the life that my daughter could have lived if there had been a treatment that would have halted the disease when first presented at 17 years old. She then would have enjoyed a life equal to her peers*."

- "*Improved mental health will have a positive effect on my relationships. IF I can do all the things I could normally do before I fell ill, it will improve the overall quality of family/daily life as I would be able to cope with commuting to work and working in a normal environment without being distracted or confused by noise*."
- "*Not worrying about a future attack leaving me paralyzed again and totally dependent on others would improve my daily living... Increased survival would help me to live more freely and to help stop mourning my friends that are passing from this disease often. That would improve the fears that my family face daily with this disease also*."
- "*Independence is the major benefit that I can see. Just being able to contemplate having an intimate relationship would be a big deal. Going out with friends and family without getting tired and having to think about where the closest bathroom is. I might have the ability to volunteer at something I'm passionate about*."
- "*Improve nerve damage from attack (bladder/bowel function, vision), ability to seek employment, reduced dependence on narcotics, improved psychosocial outcomes*."
- "*My mental health would be better. I wouldn't worry so much*."
- "*I would have continued to work, maintain friendships/relationships, worked towards a better pension, owned my own home, travelled, been financially secure*."
- "*Quality of life; know my loved ones are happy and healthy and capable of thriving*."

6. Experience With Drug Under Review

Of the **5 patients and 2 caregivers** who shared their experience using inebilizumab, most accessed the treatment through private insurance followed by clinical trial.

Regarding the sequencing of therapies for NMOSD, **patients interviewed** indicated that they were often first put on other treatments (like rituximab and azathioprine) and had to fail on these treatments (experienced attacks) to gain access to inebilizumab based on the requirement of the insurance used.

All respondents indicated that using inebilizumab has effectively reduced attacks, which has helped them continue to be present and involved with their family, friends and workplace.

Several respondents pointed out the easy-to-manage dosing schedule and favourably referred to the data available on inebilizumab. One **patient** shared their opinion that, "*It's the best medication out on the market for NMOSD. It has the highest probability to prevent future attacks and the infusion schedule is manageable*." A **caregiver** said that their loved one's experience with the drug was "*positive, reduced frequency and severity of attacks and ultimately helped lead to remission*."

A **patient** who is the mother of two children: "*After looking at the dosing schedule for Uplizna, since it's just half an hour, twice a year, my family and I decided that was probably the best way to go…the best option for us because since August 2021 I have been relapse free, compared to having relapses every three months or so*."

Regarding **expectations** from inebilizumab, **one patient** said, "*I am hoping that it'll just prevent me having the severe flare ups that impact my mobility… I'm just really hoping that it either limits my flare ups altogether or at least just minimizes them to maybe some of the less severe symptoms."*

Some of the **side-effects** noted for this drug were joint pain, headaches, back pain, sore throat and painful/frequent urination, all of which were categorized as fairly manageable. Some of the **more manageable** symptoms indicated by respondents included tingling and fever.

- "*In the first infusion, I did have some pretty intense leg pain after infusion so my nurse decided that she would increase the Tylenol dose for the pre-med, and that took care of it the next time*."
- "*I feel like overall I've had a lot more good days than bad days. After getting the infusions, I've been pretty fatigued for a few weeks afterwards and just kind of achy and feel some kind of tingling and numbness, but once that subsides, I feel really good… I didn't have any fever or chills or anything like that*."

- "*I have not had any* (side-effects) *on Uplizna other than just a more even energy level. I don't get sick on infusion days. I did not have any infusion site reactions*."

Patients using inebilizumab and **caregivers** of people on the treatment resoundingly want to see it made accessible to those living with NMOSD. They shared that the treatment has allowed them to retain their quality of life and continue to support themselves and their families without the interruption of traumatic episodes of NMOSD attacks that have the potential to irreversibly disrupt their lives. As one **patient** shared: *It's really given me back that quality of life, that NMOSD completely took away*."

When asked why inebilizumab should be publicly funded, **patients** and **caregivers** shared:

- *"I feel like living in the US with the health care system that we have just makes it so hard for someone that has a rare autoimmune disorder... I had to go automatically on another medication and fail for them to even approve the Uplizna and I ended up getting another lesion on my spinal cord just because they wouldn't put me on it... I feel like if they had just approved the Uplizna in the first place, that would have potentially saved me from dealing with other health issues in future since every attack could leave me blind or quadriplegic or in a situation where I may need breathing treatment or a home health nurse, or even live in a nursing home. That would be so much more expensive...Uplizna is supposed to reduce attacks by about 90%, so I don't understand why if we have that medication available on the market, it wouldn't be made available to people who have the disorder…especially in a country that has a nationalized health system."*

- *"I would tell them (government decision makers) that without Uplizna, I'm not sure where my health would be today…With every relapse, you get worse, and so, by preventing those relapses, I am maintaining a stable health. Uplizna needs to be funded because of those things, because by not providing it to patients, you could be preventing them from living their best lives and living healthy lives. And we could be contributing to early deaths even by not providing these medications to patients…**most of the people I know on Uplizna that I've met… probably 12 people, not one of them has had a relapse while on the drug**. So, why keep this medicine away from people?*

- *"I absolutely recommend that this drug be made available to Canada and the rest of the world. Everywhere. Because even though I may not be able to get out and run a marathon, just to be able to get out of bed, to go outside, to go shopping or to dinner with my family is a blessing, and anybody who has NMO will understand just that any little piece of freedom or independence or feeling good for one or two days in a row is worth it. So yes, this drug needs to be made available and 'yesterday'."*

7. Companion Diagnostic Test

N/A

8. Anything Else?

For about 90% of **patients**, NMOSD is a relapsing-remitting illness. That means patients have "attacks" (relapses) that usually last days. Attacks are followed by periods of recovery (remissions) that can last weeks, months or years. Each attack that an NMOSD patient experiences causes new damage and can lead to incremental loss of function of the optic nerves and spinal cord, and over time, attacks can lead to serious disability and even death.

People with experience using inebilizumab repeatedly reiterated the sentiment that this is an important and effective treatment that can make a major difference to people's lives if they are dealing with NMOSD, by preventing attacks or substantially reducing their severity.

A loved one, who is also a scientist, shared, "*If he (the patient) wasn't given access immediately to one of the high efficacy treatments for NMO… I don't know, I wouldn't wanna know what would happen. The fact that he was able to be on a highly effective treatment* (inebilizumab) *relatively early on in his disease course, I think spared him even more grief and suffering*." She continued, "*I say this, as a PhD immunologist that this (inebilizumab) is an FDA approved therapy that has clinical trial data specifically in NMOSD patients that showed tremendous efficacy at reducing the frequency of attacks, the severity of attacks and what that does to humans' quality of life is priceless. I would only be supportive. I'm not saying this is a cure. I'm not even saying it's "the best", but it should definitely be offered to NMOSD patients based on the best available data*."

9. Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, 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.

The Sumaira Foundation (TSF) completed the submission independently with external support from a public affairs service provider.

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.

As noted above, TSF completed the submission independently with external support from a public affairs service provider.

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range with an X. Add additional rows if necessary.

The companies and organizations listed below have supported The Sumaira Foundation's events, conferences, resource development efforts, and provided general donations to support our other activities.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Ad Scientiam	X			
Alexion Pharmaceuticals				X
Boston Vision	X			
The Brain Health Center of the Rockies	X			
The Dorchester Foundation			X	
The Elliot Lewis MS Center	X			
Everylife Foundation	X			
Genentech (Roche Group Member)				X
Hoag Health System	X			
Horizon Therapeutics				X
The Joi Life Foundation	X			
Marsh McLennan			X	
Mass General Brigham Health System	X			
Massachusetts Eye & Ear Infirmary	X			
MedLearning Group				X
Neurology Center of New England	X			
PAN Foundation	X			
Portal Instruments	X			
Spaulding Rehabilitation Hospital	X			
Siegel Rare Neuroimmune Association			X	
UCB				X
Viela Bio, Inc.				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: Sumaira Ahmed

Position: Founder, Executive Director

Patient Group: The Sumaira Foundation

Date: Aug 31, 2023

Clinician Group Input

Clinician Input

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: **SR0793-000**

Generic Drug Name (Brand Name): inebilizumab (UPLIZNA®)

Indication: Neuromyelitis optica spectrum disorder (NMOSD)

Name of Clinician Group: Neurologists specialized in demyelinating diseases

Author of Submission: Dr. Dalia Rotstein

Neurologist, St. Michael's Hospital

Assistant Professor, Department of Medicine, Division of Neurology University of Toronto

Email: [redacted]

1. About Your Clinician Group

This submission is made on behalf of the Canadian Network of Multiple Sclerosis (MS) Clinics (CNMSC; https://cnmsc.ca/), a national network of academic and community-based clinics established for the advancement of patient services, education, and research in multiple sclerosis (MS). The signatories to this specific submission are a group of neurologists who specialize in demyelinating diseases including neuromyelitis optica spectrum disorder (NMOSD) and MS.

2. Information Gathering

As specialist neurologists, we are clinical experts in these disorders. The information for this submission has been gathered through our clinical experience and from knowledge of the medical literature. Additionally, the group spoke informally with other colleagues from across the country who specialize in this therapeutic area.

3. Current Treatments and Treatment Goals

NMOSD is an inflammatory disease of the central nervous system (CNS) marked by distinct attacks that most commonly include transverse myelitis (spinal cord inflammation with possible symptoms including weakness, sensory impairment, gait impairment and bladder/bowel dysfunction) and optic neuritis (vision loss). Active NMOSD causes severe, immune-medicated demyelination and axonal damage, which presents as repeated attacks of inflammation and progressive damage in the brain, optic nerves and spinal cord. Relapses are unpredictable and severe, often associated with incomplete recovery, and resulting in rapid, and permanent neurological damage and disability.

NMOSD is estimated to affect about 1 in 100,000 people, of whom the vast majority (~90%) are women. In Canada, a much higher risk is seen amongst minority communities, including Black and East Asian individuals and immigrants (Rotstein DL, et al. A national

case–control study investigating demographic and environmental factors associated with NMOSD. *Mult Scler J*. 2023;29(4-5):521-529). While the mean age of onset is approximately 40 years, the range varies widely from childhood to over 80 years of age.

The main goal of treatment is to prevent these attacks, given the permanent, life-altering disability that often arises from a single attack. Secondary goals include reducing the severity of attacks, reducing cumulative disability associated with attacks, and minimizing adverse events related to therapies. An ideal therapy for NMOSD would completely prevent attacks after a patient is diagnosed following the first attack and would also have a good safety and tolerability profile.

For many years, NMOSD has been treated in Canada with off-label therapies including corticosteroids, azathioprine, mycophenolate mofetil, and rituximab. Government drug-program funding of these therapies varies by province and territory in Canada. Generally, azathioprine is perceived by specialists as the least efficacious of the currently available off-label options, while rituximab is perceived as the most efficacious. However, we only have retrospective observational studies comparing these drugs in NMOSD. Breakthrough NMOSD attacks are reported on all of these agents.

More recently, there have been randomized controlled trials (RCTs) showing efficacy of three monoclonal antibodies: eculizumab, satralizumab, and inebilizumab. Eculizumab and satralizumab have been approved in Canada, but access to these therapies is extremely limited due to their cost and stringent funding criteria. In particular, Canadians living with NMOSD very rarely qualify for coverage of eculizumab and, when they do, only through private insurers (i.e., there is no public drug program funding for eculizumab in NMOSD at this time).

All of the therapies in use for NMOSD work by suppressing the immune system. Some are more targeted than others. In general, they do not directly treat symptoms of the disease, but they work by preventing inflammatory attacks. However, there has been hope that some of the newer therapies such as inebilizumab may treat intercurrent symptoms such as pain, based on evidence from the clinical trials.

Non-pharmacologic therapy is not effective at preventing and/or reducing NMOSD attacks.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

There is a large unmet need for high-efficacy, well-tolerated therapies for NMOSD in Canada. Many patients continue to have attacks despite treatment with drugs such as azathioprine and mycophenolate, and to a lesser extent, rituximab (Stellmann JP, et al for NEMOS (Neuromyelitis Optica Study Group). Immunotherapies in neuromyelitis optica spectrum disorder: efficacy and predictors of response. *J Neurol Neurosurg Psychiatry*. 2017;88:639-647). There is no therapy with high-quality RCT evidence of efficacy in NMOSD that is easy to access. Use of some of the off-label therapies is limited by side effects, including: cytopenias and liver dysfunction with azathioprine and mycophenolate; infections with all agents; an increased risk of meningococcal disease with eculizumab, and, thrombocytopenia and neutropenia with satralizumab. Eculizumab is given by an intravenous infusion every 2 weeks, which is too onerous for some patients to tolerate.

In particular, there is a major unmet need for patients who have a breakthrough attack on their first therapy, as it can be challenging to identify a subsequent therapy that will be effective at preventing attacks and will be tolerated by the patient. The best approach for patients is to use as highly efficacious a product as possible after an attack, so as to avoid potentially catastrophic subsequent attacks and, thus, optimize patient outcomes.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Inebilizumab is anti-CD19 molecule that works by suppressing B-cells. The mechanism of action is similar to rituximab, which is an anti-CD20 molecule that is currently used off label for treatment of NMOSD in some Canadian provinces. However, anti-CD19 therapy differs from anti-CD20 therapy in that it directly suppresses plasmablasts and plasma cells. Plasma cells are responsible for producing antibodies, and since NMOSD is an antibody-mediated disease (due to the aquaporin-4 antibody), this mechanism of action could have therapeutic advantages, but inebilizumab and rituximab have not been studied head-to-head, so this remains an area for additional research. However, in the N- MOmentum clinical trials, there were seven patients who were previously treated with rituximab and had breakthrough attacks on this therapy. None of the seven had an attack while receiving inebilizumab (Flanagan

EP, et al. Inebilizumab for treatment of neuromyelitis optica spectrum disorder in patients with prior rituximab use from the N-MOmentum Study. *Mult Scler Relat Disord*. 2022;57:103352). There is also some evidence that patients with polymorphisms of a certain gene, FCGR3A, have an incomplete response to rituximab, but respond better to inebilizumab.

Inebilizumab could be used as a first-line treatment or as a treatment for patients who have a breakthrough attack after starting another therapy. In either scenario, we would expect this drug to be used as monotherapy based on clinical trial evidence and to avoid cumulative immunosuppressive effects. Based on evidence from the clinical trial and from past experience with approved B-cell therapies, safety and tolerability of this agent are both quite high and, from that perspective, it could be considered as a first-line therapy if cost is not prohibitive. We suspect that most clinicians would use it for patients who have disease activity (i.e., a new attack) on another first-line therapy.

There is no clear preferred agent amongst the novel monoclonal antibodies for treatment of NMOSD (e.g., eculizumab, inebilizumab, ravulizumab and satralizumab). Besides eculizumab and ravulizumab, both C5 complement inhibitors, all others have unique mechanisms of action. Our experience and clinical trial evidence suggest that some patients respond to one mechanism and not to the others and that the best mechanism of action varies by patients. In general, we find that C5 complement inhibitors have the highest success rate, but also are very difficult to access right now in Canada and are not funded outside of private insurers.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Potential candidates for this therapy should be assessed and managed by neurologists specialized in demyelinating diseases through a Multiple Sclerosis or Demyelinating Disease Centre. They should have a confirmed diagnosis of NMOSD, with a positive serum test for the aquaporin-4 antibody.

Patients who have had an attack on another first-line therapy would be most in need of this drug. It could also be used as a later therapy in patients who have treatment failure or adverse events on eculizumab (or ravulizumab) or satralizumab, as inebilizumab has a different mechanism of action. It has a similar mechanism of action as rituximab, but there is some evidence from the clinical trial that certain patients with refractory disease despite treatment with rituximab may respond to inebilizumab. (Flanagan EP, et al. Inebilizumab for treatment of neuromyelitis optica spectrum disorder in patients with prior rituximab use from the N-MOmentum Study. *Mult Scler Relat Disord*. 2022;57:103352).

There is no existing test to determine which patients would be most likely to benefit from this drug. However, we know from the pivotal clinical trial that many patients who were refractory to previous therapies did respond to inebilizumab.

5.3. What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

The key outcome measure is a new attack, which is marked by new neurologic symptoms, such as vision loss, weakness, sensory impairment, or bladder/bowel dysfunction. This is usually marked by a new, enhancing lesion on an MRI, but the MRI is not necessary to diagnose an attack.

We would recommend considering the following in the drug renewal process: 1) whether any relapse occurred on drug in the previous year and the number of relapses; 2) Expanded Disability Status Score (EDSS) or other disability measure (Note: the EDSS has not been validated in NMOSD) and any change from baseline.

5.4. What factors should be considered when deciding to discontinue treatment with the drug under review?

We would recommend drug discontinuation if the patient has a new attack on this therapy or if the patient has a serious adverse event related to the therapy or has an EDSS of 8 or higher (again with the caveat that EDSS has not been validated in NMOSD).

5.5. What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Potential candidates for this therapy should be assessed and managed by neurologists specialized in demyelinating diseases through a Multiple Sclerosis or Demyelinating Disease Centre. The drug can be administered in a hospital or private clinic.

6. Additional Information

Many patients with NMOSD live in extreme fear of attacks, which can cause severe, permanent disability including blindness and paralysis. When patients have a breakthrough attack on their first- line therapy, it is particularly challenging right now in Canada to identify a next drug that will offer additional efficacy to prevent subsequent attacks, be well tolerated and be accessible to the patient. Given its favourable efficacy and safety profile, inebilizumab would be an important addition to our armamentarium. It may have some benefits for quality of life in NMOSD. For example, in the clinical trial N-Momentum, inebilizumab treatment was associated with year-on-year improvement in pain scores. (Kim HJ, et al. *Neurology*. 2022;98(18 Supplement):1569).

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict-of-interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

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

A medical writer (Cynthia N. Lank from Halifax, Nova Scotia) reviewed the first draft of this submission and revisions from the reviewing physicians. All revisions were reviewed and approved by the lead author of the submission.

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

N/A

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. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Dalia L. Rotstein
Position: Assistant professor, University of Toronto; Staff neurologist, St. Michael's Hospital
Date: August 14, 2023

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

Table 1: Conflict of Interest Declaration for Clinician 1

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Alexion		x		
Hoffman La-Roche		x		
Horizon Therapeutics	x			

Declaration for Clinician 2

Name: Mark S. Freedman

Position: Professor of Neurology, University of Ottawa

Date: August 14, 2023

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

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Horizon		X		
Alexion			X	
Hoffman La-Roche			X	

Declaration for Clinician 3

Name: Dr. Jiwon Oh

Position: Associate Professor of Medicine, University of Toronto; Staff Neurologist, Scientist, and Medical Director, Barlo Multiple Sclerosis (MS) Program at St. Michael's Hospital

Date: 23-08-2023

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

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Horizon Therapeutics	X			

Declaration for Clinician 4

Name: Dr. Jodie Burton

Position: Associate Professor, Department of Clinical Neurosciences, University of Calgary

Date: 27-08-2023

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

Table 4: Conflict of Interest Declaration for Clinician 4

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Alexion	X			
Roche	X			
Horizon	X			

Declaration for Clinician 5

Name: Dr. Natalie Parks

Position: Assistant Professor of Medicine (Neurology), Dalhousie University

Date: 27-08-2023

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

Table 5: Conflict of Interest Declaration for Clinician 5

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			
EMD Serono	X			
Novartis	X			
Roche	X			

Declaration for Clinician 6

Name: Dr. Penelope Smyth

Position: Professor (Neurology) University of Alberta

Date: 28-08-2023

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

Table 6: Conflict of Interest Declaration for Clinician 6

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
N.A.				

Declaration for Clinician 7

Name: Dr. Fraser Clift

Position: Assistant Professor of Medicine, Memorial University of Newfoundland

Date: 28-08-2023

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

Table 7: Conflict of Interest Declaration for Clinician 7

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
N.A.				

Declaration for Clinician 8

Name: Dr. Moogeh Baharnoori

Position: Assistant Professor of Neurology, Queen's University

Date: 28-08-2023

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

Table 8: Conflict of Interest Declaration for Clinician 8

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Horizon Therapeutics	X			

Declaration for Clinician 9

Name: Dr. Giulia Fadda

Position: Assistant Professor, Neurology, Department of Medicine, University of Ottawa; Associate Scientist, Neuroscience Program, Ottawa Hospital Research Institute, Neurologist, Division of Neurology, Department of Medicine, The Ottawa Hospital

Date: 29-08-2023

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

Table 9: Conflict of Interest Declaration for Clinician 9

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Horizon Therapeutics	X			

Declaration for Clinician 10

Name: Dr. Francis Brunet

Position: Neurologist, CHU de Québec, Université Laval

Date: 29-08-2023

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

Table 9: Conflict of Interest Declaration for Clinician 9

	Check appropriate dollar range*

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
N.A.				