## CADTH REIMBURSEMENT REVIEW

# Patient and Clinician Group Input

**ravulizumab (Ultomiris)**

(Alexion Pharma GmbH)

**Indication:** For the treatment of adult patients with anti-aquaporin 4 (AQP4) antibody-positive neuromyelitis optica spectrum disorder (NMOSD).

**September 1, 2024**

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 Template for CADTH CDR and pCODR Programs

| | |
|---|---|
| **Name of the Drug and Indication** | **Ravulizumab** |
| **Name of the Patient Group** | **MS Canada** |
| **Author of the Submission/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, ravulizumab, 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 now have PTSD [from living with NMOSD]."***

***"I have disabilities from living with NMO & have chronic pain. The fatigue makes it hard to just go about my life."***

***"[NMOSD] It has impacted my life in two ways. 1) don't take your daily life for granted, 2) slows you down dramatically in any aspect of life."***

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) as well as the use of off-label immunosuppressants 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.

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. Eculizumab and satralizumab are the two authorized medications indicated for NMOSD however eculizumab is available only through compassionate use from the manufacturer. Eculizumab is administered by infusion every two weeks which can be onerous and disruptive to the lives of individuals living with NMOSD.

***"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."***

NMOSD attacks cause irreversible damage and disability so it is imperative that individuals have access to all Health Canada-approved therapeutic options for NMOSD. Therapeutic options are essential to provide varied administrations and dosing schedules for individuals newly diagnosed with NMOSD initiating treatment as well as different mechanisms of action for individuals who are unresponsive or intolerant to other medications indicated for NMOSD. Different therapeutic options encourages shared decision-making between healthcare teams and individuals living with NMOSD which in turn will increase medication adherence, improve quality of life and reduces or prevents NMOSD attacks, decreasing the potential burden to health and social systems.

***"The whole point of being on therapy for NMOSD is to prevent relapses, which is how all the damage occurs, resulting in disability and as I've mentioned in some cases, death. In clinical trials, ravulizumab had a ZERO relapse rate and it remained the same after clinical trials. It's an absolutely incredible result. Having access to ravulizumab would not only save lives, help mitigate disability and improve patients' quality of life, but also save the government significant costs by keeping NMOSD patients out of the hospital and rehabilitation centres."***

## 4 Improved Outcomes

Ravulizumab has the ability to reduce attacks and accrued disability and provide individuals with a reduced dosing schedule, and reduced cost savings per treatment year as compared with the other complement inhibitor approved by Health Canada and indicated for NMOSD.

***"Eculizumab has a short half life and has to be infused every 2 weeks. The beauty of ravulizumab is that the frequency has been lessened-a patient only needs to be infused every 8 weeks. That's 6 infusions of ravulizumab vs 26 of eculizumab. This significant difference between the two therapies combined with an improved efficacy allows NMOSD patients to experience less chance of a relapse, spend less time having treatment and have more time to just live their lives. This is what patients and their families want and deserve.***

***As someone whose life has been deeply impacted by this terrible disease and who cares deeply about my community, I implore you to join me in fighting to make ravulizumab accessible to patients who so desperately need it."***

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."***

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

## 5 Experience With Drug Under Review

None of the respondents have experience with ravulizumab however two respondents are treated with eculizumab, also a complement inhibitor, which must be administered via infusion every two weeks. Comparatively, ravulizumab dosing is every 8 weeks, offering a considerable improvement to dose frequency as well as negating the time and effort required by the person living with NMOSD on a treatment day. From a risk-benefit perspective, respondents were provided with a list of the most common side effects reported for ravulizumab and asked if they would consider taking this medication. Five respondents indicated they would consider ravulizumab and four responded that they would not consider treatment with ravulizumab 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. Approval of ravulizumab will provide individuals with additional Health Canada-approved and NMOSD-indicated medication options.
- Ravulizumab is a complement inhibitor with a significantly decreased dosing schedule and reduced cost per treatment year as compared with the other Health Canada-approved complement inhibitor indicated for NMOSD.
- Reduced dosing schedule will result in reduced absenteeism from the workplace and an increased ability to fulfill family and recreational commitments. Reduced loss of productivity will provide cost savings both to the person living with NMOSD as well as to social and health 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 an 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

Name of Drug: ravulizumab-cwvz (Ultomiris)

Indication: For the treatment of adult patients with anti-aquaporin 4 (AQP4) antibody-positive neuromyelitis optica spectrum disorder (NMOSD)

Name of Patient Group: The Sumaira Foundation

Author of Submission: Sumaira Ahmed & Michael Devlin

### 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, funding research, and advocating on behalf of our patient communities globally. TSF has established a local presence in the United States, Canada, Germany, France and Italy. We lead a team of over 60 patient Ambassadors based in 19 countries around the world. TSF's website is available in 16 languages. 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

The Sumaira Foundation was founded in 2014 and has been actively working in Canada since 2019. The information contained in this submission is based on a number of information sources available to us through our own patient advocacy initiatives, including various surveys of patients & caregivers, patient narratives, focus groups, roundtables, discussions with key opinion leaders, our own patient Ambassadors who work with us directly, TSF's global Medical Advisory Board, our strategic advisors, peer-reviewed medical literature, and TSF's own extensive experience working in the NMOSD and rare neuroimmune disorder communities around the world.

### 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 certain cells in the central nervous system (CNS), leading to demyelination, nerve damage, serious disability and sometimes even death. The condition is much more prevalent in women, who make up 85-90% of the NMOSD patient population, as well as in certain ethnic minorities. The initial attack can be quite severe, often leading to partial or total vision loss, paralysis, loss of mobility, and/or other disabilities, frequently with only partial or even no recovery. Subsequent attacks can be equally devastating without effective, long-term therapy. Until recently, even with therapy, patients often suffered additional attacks and continued loss of vision/mobility/function/quality of life. Many patients ended up dependent on a wheelchair and with severe or total vision loss after the first five years post-diagnosis.

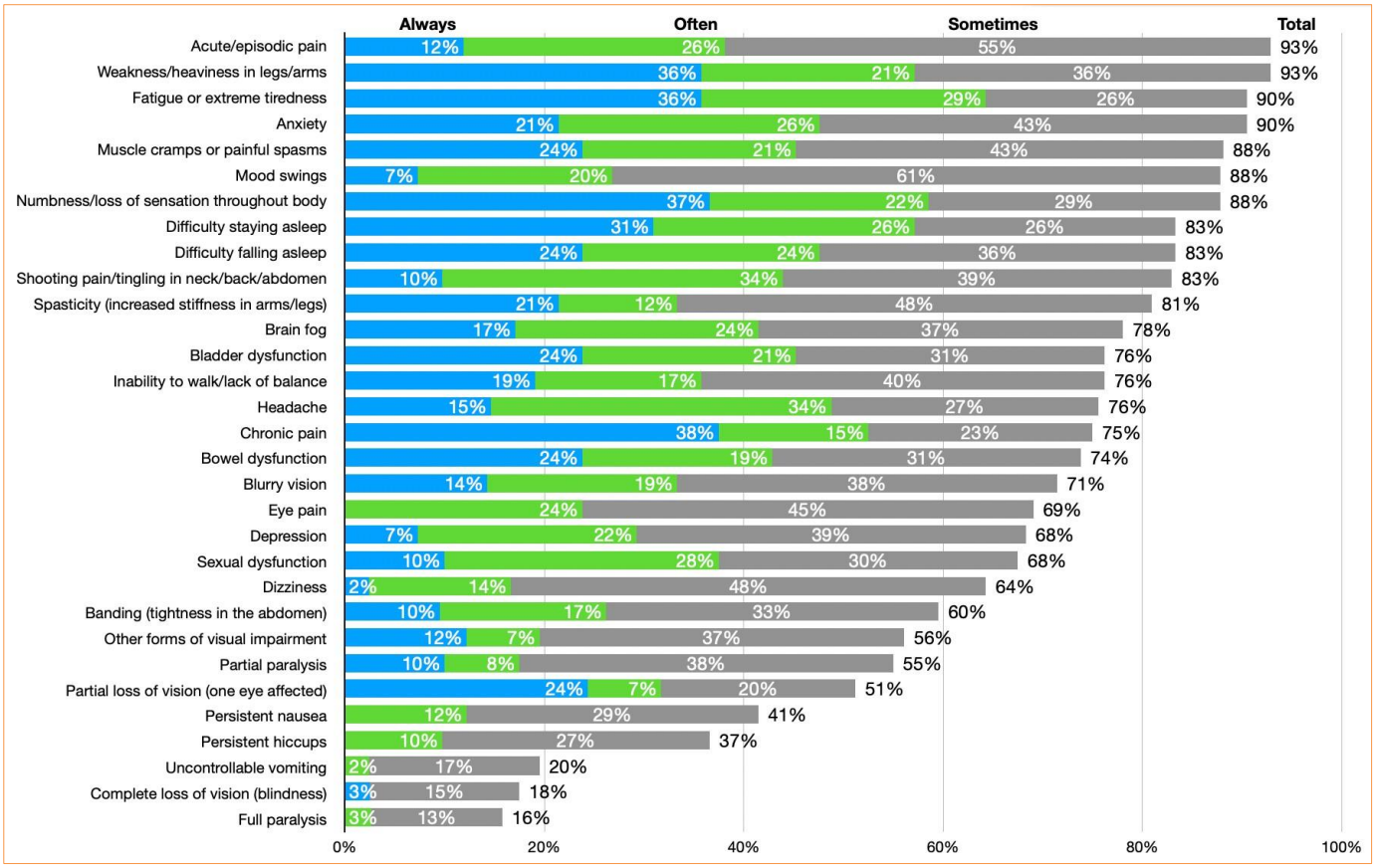
In addition to loss of vision and mobility, patients very often deal with many other co-morbidities, including frequent and extensive pain in the limbs, bladder/bowel incontinence, significant fatigue, muscle cramps/spasms, difficulties sleeping, as well as significant mental health challenges (such as anxiety, mood swings and depression) resulting from having to live with NMOSD. These symptoms and co-morbidities are well-documented in the clinical literature focused on the lived experiences of NMOSD patients.

The impact of NMOSD spills over into all aspects of patients' lives. Many are no longer able to work or continue with schooling, leading to significant loss of income and economic independence. In many cases, the needs of the patient also often have a dramatic impact on their caregivers, taking a real toll on the main caregiver's employment and income as well as their mental and emotional well-being. Intimate relationships also come under pressure due to the severity of NMOSD. Many patients report trouble maintaining

healthy partnerships and marriages, and some see relationships end due to the challenges of living with and caring for a loved one with NMOSD.

Living with NMOSD requires tremendous resourcefulness from patients who may already face significant visual and physical disabilities. Many patients have to contend with a range of wheelchairs, walkers, canes, and specialized equipment for daily living just to get through the day. Only a third of patients can cope without such assistive technologies. Patients who have endured multiple attacks before getting proper diagnosis and therapy typically contend with much more significant disabilities, underscoring the importance of commencing proper and effective long-term therapy with proven medicines as early as possible.

**Symptoms patients experience living with NMOSD & their frequency**




Source: Global NMOSD Patient Survey, The Sumaira Foundation, July 2023

## 4. Experiences With Currently Available Treatments

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, where these these on-label therapies are available, insurance coverage for and access to them are 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.

Prior to the approval of on-label therapies for NMOSD, patients were usually placed on one or more off-label therapies. Many patients had to cycle through such therapies to find one that worked for them, both in terms of efficacy and tolerability. The more common off-label therapies include rituximab, mofetil mycophenolate, oral prednisone/methylprednisolone, azathioprine, and often

one or more other immunosuppressive agents and drugs to help cope with associated symptoms and co-morbidities (e.g., gabapentin, baclofen, tocilizumab, pregabalin).

While some of these agents do seem to work for some patients at least some of the time, the lack of any rigorous data proving their safety and efficacy for NMOSD has forced patients to go through a frustrating and often risky series of trial-and-error cycles with one medicine or another before finally landing on one that they and their doctor feel is at least somewhat effective for them. Many patients suffer significant additional attacks and additional disability while cycling through off-label therapies. In some cases, patients were even put back on one of the same therapies they failed on earlier due to a lack of any other alternative. Throughout this sort of "therapeutic odyssey," many patients suffer additional attacks, often losing significant additional vision, mobility and other important bodily functions as a result. It is important to note that a significant minority of NMOSD patients have "failed" on all commonly used off-label therapies, and another significant fraction have felt only "partially managed" on them, due to worsening symptoms and/or challenging side effects.

Recently diagnosed patients living in countries where the newer on-label medicines are available are more likely to initiate therapy on one of these therapies: eculizumab, satralizumab, and inebilizumab. Other patients often are switched to the newer agents after failing on their most recent therapy (e.g., due to a relapse/attack, or due to side effect/tolerability issues). We know many patients who were recently diagnosed, sometimes quite quickly, made a full or near-full recovery from their initial attack, and have been living largely symptom- and attack-free after being prescribed one of these on-label therapies. The clinical data show that, while each drug works through a different mechanism, all three therapies are highly effective in reducing subsequent attacks, by as much as 80-90% or more.

In light of the proven efficacy and safety of these newer therapies, new guidelines for treating NMOSD have been developed or are currently under development/revision around the world. The Sumaira Foundation has been involved in guideline revision discussions in the United States, at the European Union level, and in Germany; in Latin America, TSF is co-sponsoring the development of the very first NMOSD guidelines for the region in partnership with LACTRiMS (The Latin American Committee for Treatment and Research in Multiple Sclerosis). Many of the more recently developed/revised guidelines make provisions for access to these proven on-label therapies, often allowing initiation after the patient's first attack.

## 5. Improved Outcomes

While a patient with NMOSD is often initially mis-diagnosed as having multiple sclerosis (MS), the key difference is that NMOSD, if managed properly, is not a progressive disease (unlike MS). Of course, without any effective therapy, additional attacks will cause patients to worsen, losing sight and mobility, and can even trigger respiratory arrest. But if attacks are eliminated, patients will retain their existing abilities indefinitely, without any progression of the disease. Therefore, the most important outcome for nearly all NMOSD patients is simple: to prevent any further attacks.

Beyond attack prevention, many patients value having more proven alternatives to choose from, given that each drug works via a different mechanism, with different administration routes and dosage frequencies. Since different patients can respond differently to the same medicine, having more than one option is also important in the case of variations in efficacy, unwanted side effects or strong preferences regarding route & frequency of administration. Many prefer the convenience of less frequent infusion dosing, so improvements on that front are always welcome. Other patients would like to see better side-effect profiles, particularly when it comes to immunosuppression and the elevated risks of opportunistic infections. Most patients do realize however that this is a trade-off that often comes with any immunosuppressant therapy and are realistic about the prospects of such improvements. Nonetheless, many patients who have lived with NMOSD for ten or more years have had to cycle through many different therapies before finding on suitable for them, and therefore having more on-label options in case they begin to have difficulty with their current therapy is always a comforting thought.

Eculizumab was the first therapy to become available to patients with proven efficacy in managing NMOSD attacks. We know many patients around the world who are currently on eculizumab and consider it to be highly effective in preventing relapses and generally helping them return to a more normal life free of attacks and disease progression. Ravulizumab, in our understanding, is simply a more stable analog of eculizumab, with a longer serum half-life, which therefore requires much less frequent dosing after initiation (every 8 weeks vs. every 2 weeks). So in this particular instance, the real improvement is in much less frequent infusion sessions. It turns out that for many patients, infusion therapy every 2 weeks becomes very difficult to adhere to long-term and can really interfere with work, travel, holidays, and life in general. We personally know patients who, while fully acknowledging the efficacy of the therapy

while on it, have switched therapy away from eculizumab because for various reasons they simply could not manage adhering to an infusion therapy every 2 weeks over the longer term.

## 6. Experience With Drug Under Review

NMOSD is considered to be a rare disease. As a result, clinical trials typically only involve 100-200 patients, often with novel trial designs (e.g., synthetic placebo arms from prior trials) to reduce the recruitment burden and generate insights/results in a more timely way. To our knowledge, ravulizumab is not yet available to NMOSD patients outside the clinical trial setting anywhere in the world; therefore, we do not have any direct experience with patients on ravulizumab therapy. We do know that the mechanism of action is very similar to eculizumab, however, and we have many patients in our communities who are currently on, or have been on eculizumab, and overall, their experience has been very positive, with two-thirds of patients on eculizumab viewing the therapy as highly effective for managing NMOSD. Many patients on eculizumab also indicated they would prefer a less frequent infusion dosing schedule.

## 7. Companion Diagnostic Test

Not applicable in this instance.

## 8. Anything Else?

Neuroimmune conditions prove challenging in that they involve the subtle interplay of the two most complex systems in the human body: the nervous system and the immune system. This complexity is further compounded by rare diseases such as NMOSD, where the sheer rarity of the condition makes it difficult to study in depth, recruit patients, and generate statistically significant clinical findings. Yet because these conditions affect the nervous system, including our bodies, our movement, our sight, our minds, their repercussions can be severe and debilitating. Society as a whole has prioritized finding therapies for other neuroimmune conditions such as MS, with 20 or more newly discovered biopharmaceuticals now available to patients after decades of research. Society is also prioritizing rare cancers, with many more biologics and immune-modulating therapies available for rare lymphomas and other cancers, even when the benefits are measured in mere months of additional lifespan.

The Sumaira Foundation believes that **all** rare diseases require the same level of attention, effort and support. The good news is that with NMOSD, scientists have already found three separate mechanisms of action amenable to direct intervention via therapeutics proven highly effective to stop attacks. These therapies clearly work well. And TSF believes continued innovation is needed to make these therapies even better and available to a wider number of patients, because if administered soon after diagnosis, they can allow NMOSD patients to live often entirely normal and healthy lives. In TSF's experience, ravulizumab represents an improvement and innovation in therapy and therefore we hope to see it become the fourth proven, on-label therapy available to NMOSD patients around world, including in Canada.

## 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 received no external help or support in completing this 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.

The Sumaira Foundation received no external help or support in completing this submission.

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.

Please see the table below.

**Table 1: Financial Disclosures**

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

| 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**: August31st, 2023

# Clinician Group Input

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|---|---|
| CADTH Project Number: | **SR0785-000** |
| Generic Drug Name (Brand Name): | Ravulizumab (ULTOMIRIS) |
| Indication: | Neuromyelitis optica spectrum disorder (NMOSD) |
| Name of Clinician Group: | Canadian Network of Multiple Sclerosis (MS) Clinics (CNMSC) |
| Author of Submission: | Jodie Burton MD, MSc, FRCPC<br>Clinical Associate Professor<br>Departments of Clinical Neurosciences and Community Health Sciences<br>Member, Hotchkiss Brain Institute<br>University of Calgary<br>[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. The signatories to this specific submission are a group of neurologists who specialize in demyelinating diseases including neuromyelitis optica spectrum disorder (NMOSD) and multiple sclerosis (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 knowledge of the medical literature. Additionally, the group gathered input from other colleagues 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 result in rapid and permanent neurological damage and disability. Without treatment, it is typically a devastating disease often leading to permanent blindness or

paralysis within five years from onset. Natural history studies have shown that survival is impacted in patients with NMOSD: 5-year survival rate is 68%, while median survival after diagnosis 17.5 years.[1]

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.[2] 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 therapy is to prevent these attacks, given the permanent nature of the sequelae. 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 therapies not specifically indicated for NMOSD, 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 (ECU), satralizumab, and inebilizumab. Eculizumab and satralizumab have been approved in Canada, but access to these therapies is extremely limited due to their stringent funding coverage criteria. In particular, Canadians living with NMOSD very rarely qualify for coverage of ECU and, when they do, only through private insurers (i.e., there is no public drug program funding for ECU in NMOSD at this time).

All of the therapies in use for NMOSD work by suppressing the immune system through various mechanisms, with some being more targeted than others.

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 that have a significant impact on preventing and/or reducing attacks. Many patients continue to have attacks despite treatment with drugs such as azathioprine and mycophenolate, and to a lesser extent, rituximab. For instance, a meta-analysis in NMOSD treatment by Gao *et al* showed 63% of patients (330 of 528) were relapse-free on rituximab,[3] while Poupart *et al* showed that of 62 drug naïve patients started on rituximab, at year 3, approximately 80% were relapse-free.[4]

It is important to understand the implications of treatment failure in the context of NMOSD. Failure of treatment, with even just one relapse, can lead to profound, permanent disability including blindness and paralysis . Relapses in NMO are often severe, and recovery is typically incomplete. The following summarizes the effects of relapses in patients with NMOSD: the chance of recurrence within 5 years is > 90%; 40% will be blind in one eye and 10% blind in both eyes; 22% require a walker by year 5 and

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[1] Wingerchuk DM, Hogancamp WF, O'Brien PC, et al. The clinical course of neuromyelitis optica (Devic's syndrome). Neurology 1999;53(5):1107–14.

[2] 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.

[3] Gao F, Chai B, Gu C, et al., 2019. Effectiveness of rituximab in neuromyelitis optica: a meta-analysis. BMC Neurol. 19, 36. https://doi.org/ 10.1186/s12883-019-1261-2.

[4] Poupart J, Giovannelli J, Deschamps R, et al., 2020. (NOMADMUS study group). Evaluation of efficacy and tolerability of first-line therapies in NMOSD. Neurology 94 (15), e1645–e1656. https://doi.org/10.1212/ WNL.0000000000009245. Epub 2020 Mar 13. PMID: 32170036.

almost 10% require a wheelchair. It is because of these profound impacts that the goal of treatment is the complete avoidance of all relapses.

There is no treatment that is supported by high-quality RCT evidence of efficacy in NMOSD that is easy to access. Use of some of the off-label therapies are limited by side effects, including: cytopenias and liver dysfunction with azathioprine and mycophenolate; infections with all agents; an increased risk of meningococcal disease with ECU, 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 soon as possible after the first 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?

Complement activation is a key step in activating NMOSD-inflammation. Ravulizumab (RAV) has.a similar mechanism of action to one other approved drug, ECU, but has a much less onerous dosing/administration schedule. It is given by infusion every 8 weeks instead of every 2 weeks.

Ravulizumab is a terminal complement inhibitor that specifically binds to the complement protein C5, inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex membrane attack complex (MAC) or C5b9. In the context of NMOSD, the complement cascade plays a central role in driving the autoimmune response and, thus, C5 inhibition lessens the underlying inflammatory response associated with this disease. The C5 mechanism of action is distinct from other products used in the treatment of NMOSD (aside from ECU).

Ravulizumab was created by introducing a small change to the chemical structure of ECU, making the former more stable and long-acting and, thus, allowing for less frequent dosing than the latter. Maintenance doses of RAV are given every eight weeks, compared with the every-other-week regimen of ECU. Eculizumab and RAV are regarded by clinicians to be the most efficacious therapies for NMOSD based on extrapolation of RCT evidence and clinical experience.

Ravulizumab will be used as a monotherapy in the treatment of NMOSD in adult patients who are anti-AQP4 antibody positive. It is not intended for acute treatment of an NMOSD relapse.

It is worthwhile to summarize the clinical data for RAV, to put it into context. The CHAMPION-NMOSD[5] trial assessed the time to first on-trial relapse and associated relapse risk reduction in Ultomiris-treated patients compared with the external placebo group (i.e., from the ECU PREVENT trial).[6] As noted by the study authors, there was a very strong rationale for the study design, based on important issues such as ethical considerations (i.e., the devastating impact of the suboptimal disease control), feasibility of alternative designs for rare diseases, and the proven efficacy of complement pathway mediation in NMOSD.

In terms of results, there were no confirmed relapses among RAV-treated patients, while 20 patients in the external group experienced relapses. This represented a significant drop, by 98.6%, in the risk of relapse with RAV relative to a placebo. This is comparable to the results seen for ECU in the placebo-controlled PREVENT TRIAL. A 97.9% reduction in relapse risk was also observed among patients receiving RAV without additional immunosuppressants, when compared with those given a placebo in PREVENT in the absence of such medications. All patients treated with RAV were free from relapses at 48 weeks (nearly one year) versus 63% of those in the external placebo group. The study also showed that RAV-treated patients had significantly fewer relapses per year than would be expected in an NMOSD population. Ravulizumab was associated with a significantly lower chance

[5] Pittock SJ, Barnett M, Bennett JL, et al. Ravulizumab in Aquaporin-4-Positive Neuromyelitis Optica Spectrum Disorder. Ann Neurol. 2023 Jun;93(6):1053-1068. doi: 10.1002/ana.26626. Epub 2023 Apr 5. PMID: 36866852.

[6] Pittock SJ, Berthele A, Fujihara K, et al. Eculizumab in Aquaporin-4-Positive Neuromyelitis Optica Spectrum Disorder. N Engl J Med. 2019 Aug 15;381(7):614-625. doi: 10.1056/NEJMoa1900866. Epub 2019 May 3. PMID: 31050279.

of clinically important worsening in walking skills, with 3.4% of patients experiencing such motor worsening versus 23.4% of those given placebo in PREVENT.

It is worth noting that not a single relapse was observed in the treatment arm of the CHAMPION-NMOSD trial. In our clinical experience, most NMOSD patients with aggressive disease who fail rituximab or other therapies do come under control on C5 inhibitor therapy. It is therefore essential for NMOSD patients in Canada to be able to access RAV when needed. Based on the clinical trial data and experience of clinicians, there is an argument to be made for the use of RAV as a first line agent (after first relapse), given the inadequacies of available oral immunosuppressive therapy. There are also ethical concerns with forcing patients to try predictably ineffective therapies with high adverse event rates, thus denying them access to highly effective and tolerable medications as early as possible in their disease process.

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?

An important learning from both the PREVENT AND CHAMPION trials is that complement is a key driver for NMOSD, as the degree of clinical impact demonstrated in these trials is not observed in studies involving non-complement-based therapies. Based on the study population in CHAMPION-NMOSD, RAV should be offered to patients after one or more relapses/attacks. For some patients, this means that RAV would be the first drug treatment offered once the patient is diagnosed with AQP4+ NMOSD after their first relapse/attack. One could argue that is unethical for drug plans to require patients to fail on substandard 1L drugs in order to get to RAV, because the implications of failure are so profound.

In addition, patients who have severe AEs on 1L therapy (e.g., severe colitis on rituximab) should be able to move to RAV without having to wait for their second attack to occur, given the potentially catastrophic implications of a relapse/attack. When a patient has had a breakthrough attack on another therapy, and we know that each attack can be devastating and life-altering, there is a clearly defined need to move to the most efficacious therapy available which would be ECU or RAV.

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.

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 avoidance of a new attack, which is marked by new neurologic symptoms such as vision loss, weakness, sensory impairment, or bladder/bowel dysfunction. A relapse is usually marked by a new, enhancing lesion on an MRI, but the MRI is not necessary to diagnose an attack.

On-going treatment with RAV should be provided for those who continue to benefit from preventative treatment.

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. In the event of therapy-related adverse events, there may be cases when the drug should be continued despite a serious adverse event such as meningitis because the risk of recurrence is deemed low or because the benefits of continuation are thought to outweigh the risks.

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

No additional information.

## 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 pharmaceutical policy consultant (Dr. Judith Glennie, Aurora, Ontario) generated 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.

   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. **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:** Jodie Burton MD, MSc, FRCPC

**Position:** Clinical Associate Professor, Departments of Clinical Neurosciences and Community Health Sciences, Member, Hotchkiss Brain Institute, University of Calgary

**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 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 | | | |
| Roche | | X | | |
| Horizon | X | | | |

* Place an X in the appropriate dollar range cells for each company.

**Declaration for Clinician 2**

Name:  Mark S. Freedman HBSc MSc MD CSPQ FANA FAAN FRCPC

Position:  Professor of Medicine (Neurology), University of Ottawa

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 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** |
| Alexion | | | X | |
| Horizon | | X | | |
| Roche | | | X | |

* Place an X in the appropriate dollar range cells for each company.

**Declaration for Clinician 3**

Name: Penny Smyth, MD, FRCPC

Position: Associate Professor, Division of Neurology, Department of Medicine, University of Alberta

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 3: Conflict of Interest Declaration for Clinician 3**

| **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 Idec Canada | x | | | |
| Novartis Pharmaceuticals | x | | | |
| Roche Canada | x | | | |
| EMD Serono Canada | x | | | |
| Sanofi Genzyme Canada | x | | | |

* Place an X in the appropriate dollar range cells for each company.

**Declaration for Clinician 4**

Name: Dalia L. Rotstein

Position: Assistant professor, University of Toronto; Staff neurology, St. Michael's 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 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 Therapeutics | X | | | |

* Place an X in the appropriate dollar range cells for each company.

**Declaration for Clinician 5**

Name:

Position:

Date:

☐ 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 |
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* Place an X in the appropriate dollar range cells for each company.