SYMPOSIUM

Latest developments in neuromyelitis optica spectrum disorder:

Diagnostics, treatments and patient-centred care

Official symposium in conjunction with the 2023 Annual Meeting of the Consortium of Multiple Sclerosis Centers

Dr Dalia Rotstein

Dr Eoin Flanagan

Dr Jeffrey Bennett

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Introduction and welcome

Dr Dalia Rotstein
University of Toronto,
ON, Canada

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Learning objectives

- Recall strategies that facilitate an early and accurate diagnosis of NMOSD
- Describe how evidence from clinical trials investigating current and emerging treatments for NMOSD informs clinical decision making
- Select individualized management plans for patients with NMOSD to reduce the patient-reported burden of symptoms

NMOSD, neuromyelitis optica spectrum disorder.

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Agenda

Presentation	Speaker(s)
Introduction and welcome	**Dr Dalia Rotstein**
Identifying NMOSD early: Current and emerging approaches (Followed by Q&A with the audience)	**Led by Dr Eoin Flanagan**
Implementing the latest data into clinical decision making for NMOSD (Followed by Q&A with the audience)	**Led by Dr Jeffrey Bennett**
Panel discussion: Managing the broader clinical features of NMOSD (Followed by Q&A with the audience)	**All faculty** **Moderated by Dr Dalia Rotstein**
Meeting summary and close	**Dr Dalia Rotstein**

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Expert panel

Dr Dalia Rotstein (Chair)
University of Toronto,
ON, Canada

Dr Eoin Flanagan
Mayo Clinic,
Rochester, MN, USA

Dr Jeffrey Bennett
University of Colorado
School of Medicine,
Aurora, CO, USA

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Identifying NMOSD early: Current and emerging approaches

Dr Eoin Flanagan
Mayo Clinic,
Rochester, MN, USA

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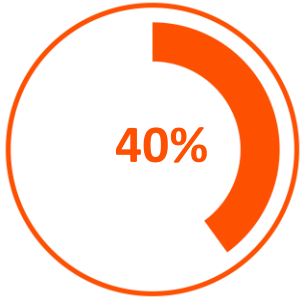
NMOSD

- Unpredictable relapses[1]
- Permanent neurological damage and disability[1,2]

- >90% of patients are AQP4-IgG positive[3]



- Up to 40% of patients misdiagnosed with MS or other diseases[2]

- Some disease-modifying drugs for MS may exacerbate the disease[4–7]

It is critical that NMOSD is differentiated from a diagnosis of MS at presentation

AQP4, aquaporin-4; IgG, immunoglobulin G; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder.

1. Capobianco M, et al. *Neurol Ther*. 2023;12:635–50; 2. Smith AD, et al. *Mult Scler Relat Disord.* 2023;70:104498; 3. Prain K, et al. *Front Neurol*. 2019;10:1028; 4. Kim HJ, et al. *Neurology.* 2015;84:1165–73; 5. Kleiter I, et al. *Arch Neurol.* 2012;69:239–45; 6. Gelfand JM, et al. *Neurol Neuroimmunol Neuroinflamm*. 2014;1:e34; 7. Brod SA. *Mult Scler Relat Disord*. 2020;46:102538.

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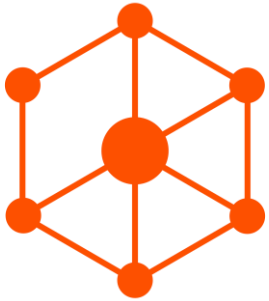
NMOSD diagnostic challenges



Phenotype mimicked by other diseases:[1]

- Autoimmune
- Vascular
- Infectious
- Neoplastic

Overlapping symptoms with other conditions in early disease stages[1]

AQP4-IgG test results affected by:

- Assay methods[1]
- Serologic status[1]
- Disease stages[1]
- Treatment types[1]
- Serum vs CSF[2]

No AQP4-IgG in some patients with NMOSD – additional diagnostics required[1]

AQP4-IgG test results may not be readily available for the acute management of NMOSD[1]

AQP4, aquaporin-4; CSF, cerebrospinal fluid; IgG, immunoglobulin G; NMOSD, neuromyelitis optica spectrum disorder.

1. Kim SM, et al. *Ther Adv Neurol Disord.* 2017;10:265–89; 2. Majed M, et al. *Neurol Neuroimmunol Neuroinflamm.* 2016;3:e231.

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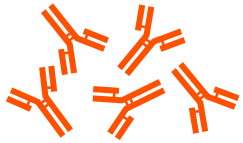
Diagnosing AQP4-IgG positive NMOSD



- **AQP4-IgG positive**
- **No alternative diagnosis**

Plus ≥1 of

Core clinical characteristics

- Optic neuritis
- Acute myelitis
- Area postrema syndrome
- Acute brainstem syndrome
- Narcolepsy or acute diencephalic clinical syndrome*
- Symptomatic cerebral syndrome*

*With NMSOD-typical brain lesions.
AQP4, aquaporin-4; IgG, immunoglobulin G; NMOSD, neuromyelitis optica spectrum disorder.
Wingerchuk DM, et al. *Neurology.* 2015;85:177–89.

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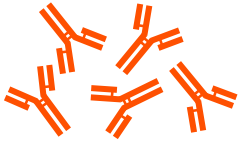
Diagnosing AQP4-IgG negative/unknown NMOSD



- **AQP4-IgG negative/unknown**
- **No alternative diagnosis**
- **MRI findings**

Plus ≥2 of

Core clinical characteristics

- **Optic neuritis***
- **Acute myelitis with LETM***
- **Area postrema syndrome***
- Acute brainstem syndrome
- Symptomatic narcolepsy or acute diencephalic clinical syndrome†
- Symptomatic cerebral syndrome†

*Must include one of these characteristics; †With NMSOD-typical brain lesions.
AQP4, aquaporin-4; IgG, immunoglobulin G; LETM, longitudinally extensive transverse myelitis; MRI, magnetic resonance imaging; NMOSD, neuromyelitis optica spectrum disorder.
Wingerchuk DM, et al. *Neurology*. 2015;85:177–89.

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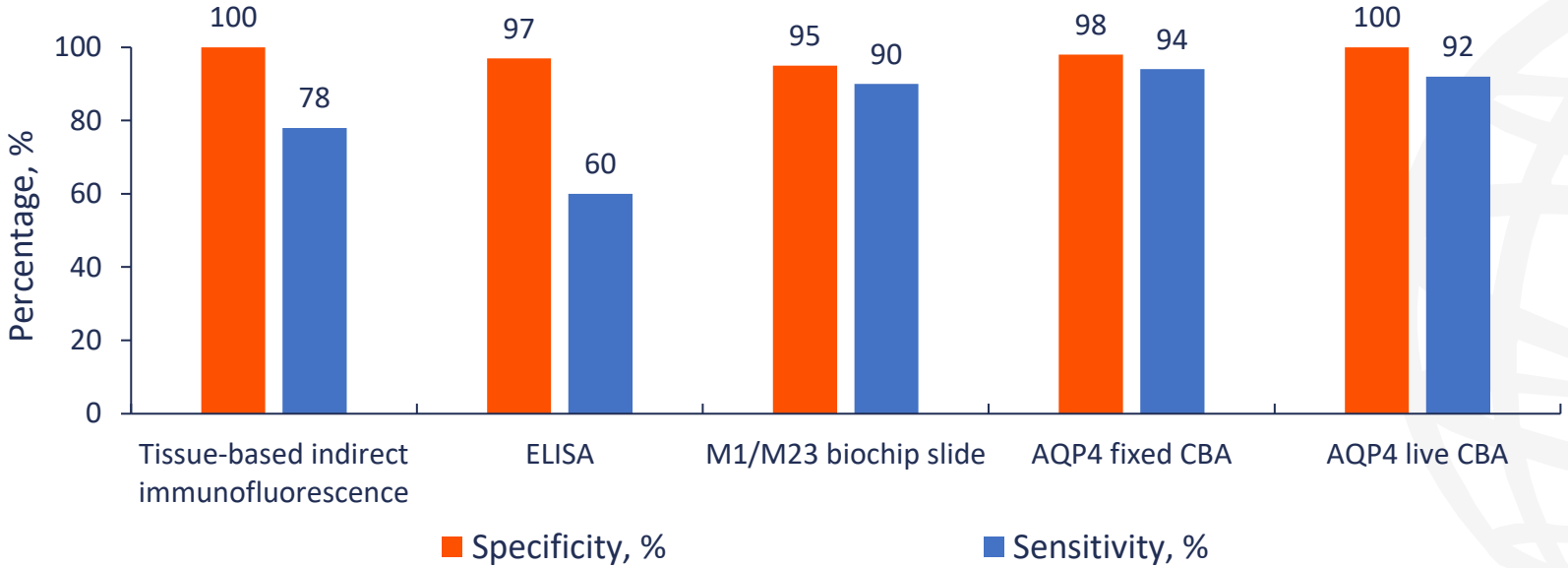
Cell-based assay testing for AQP4-IgG in NMOSD



ELISA assays are associated with **high false positive** rates,[1] however even CBAs can show **initial negative test results**, highlighting the importance of a repeat test if NMOSD is highly suspected[2]

AQP4, aquaporin-4; CBA, cell-based assay; ELISA, enzyme-linked immunosorbent assay; IgG, immunoglobulin G; NMOSD, neuromyelitis optica spectrum disorder.

1. Prain K, et al. *Front Neurol*. 2019;10:1028; 2. Smith AD, et al. *Mult Scler Relat Disord.* 2023;70:104498.

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Differential diagnosis of NMOSD using MRI

	Lesion length	Location	Appearance	Post-attack imaging
NMOSD	≥3 contiguous vertebral segments, some shorter[1]	Cervical/upper thoracic cord, central grey matter[1]	T2: bright spotty lesions T1: hypointense acute lesions[1]	May transition to short, distinct lesions or replacement by spinal cord atrophy[1]
MS	<3 contiguous vertebral segments, multiple[1]	Cervical cord, peripheral in posterior or lateral white matter[1]	Well demarcated, asymmetric[1]	Complete lesion resolution and spinal cord atrophy rare[1,2]
MOGAD	Frequently <3 contiguous vertebral segments, shorter lesions more common than NMOSD[1]	More caudal, may involve conus medullaris[1]	Axial T2: H-shaped hyperintensity[1]	Lesions may resolve; spinal cord atrophy rare[1]

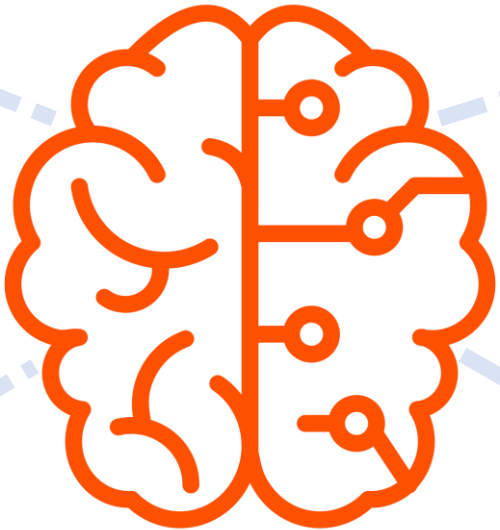
MOGAD, myelin oligodendrocyte glycoprotein antibody disease; MRI, magnetic resonance imaging; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder.

1. Solomon JM, et al. *Ther Adv Neurol Disord.* 2021;14:1–18; 2. Sechi E, et al. *Neurology*. 2021;97:e1097–109.

fMRI and rs-MRI in NMOSD

Data from fMRI studies have shown occurrences of brain functional alterations

fMRI data have shown significantly reduced functional connectivity in primary and secondary visual cortex*



rs-MRI data have shown significant changes in the cerebral network of the brain*

fMRI provides insight into the visual dysfunction occurring during disease cascade

*Vs healthy controls.
fMRI, functional magnetic resonance imaging; NMOSD, neuromyelitis optica spectrum disorder; rs, resting-state.
Wei R, et al. *Mult Scler Relat Disord.* 2022;59:103542.

Utilizing visual outcome measures in NMOSD

Optical coherence tomography

Provides high-resolution 3D images of retinal structures, and is used in the quantification of neuroaxonal retinal damage[1]

Promising method for NMOSD diagnosis and individual monitoring of disease course and severity[1]

Allows tracking of neuroaxonal injury and may aid in differentiating NMOSD from MS and MOGAD[2]

Provides unique insights into the identification of foveal pitting in NMOSD, possibly from damage to Müller cells, which carry an abundance of AQP4 channels[2]

AQP4, aquaporin-4; MOGAD, myelin oligodendrocyte glycoprotein antibody disease; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder.

1. Oertel FC, et al. *EPMA Journal.* 2018;9:21–33; 2. Graves JS, et al. *Neurol Neuroimmunol Neuroinflamm.* 2022;9:e1126.

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Implementing the latest data into clinical decision making for NMOSD

Dr Jeffrey Bennett
University of Colorado School of Medicine,
Aurora, CO, USA

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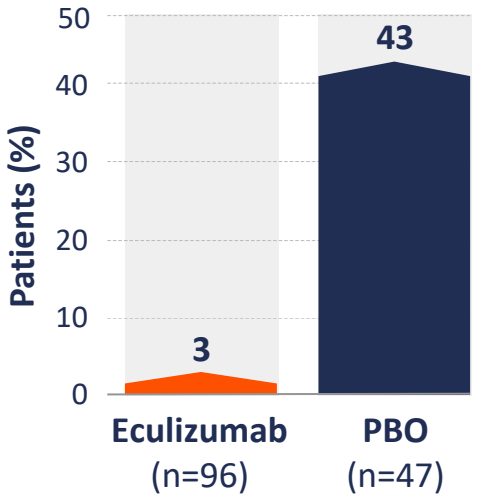
Eculizumab: PREVENT (AQP4-IgG positive)

PREVENT primary analysis[1*]

First adjudicated relapse



94%

reduction in risk of attack

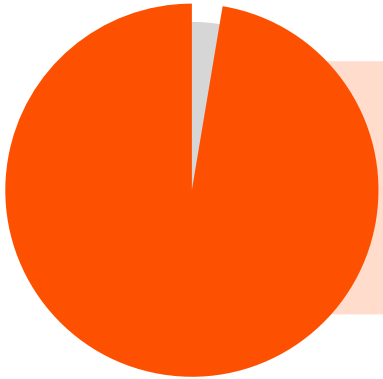
HR 0.06
(95% CI 0.02–0.20; p<0.001)

Concomitant immunotherapy: YES

Open-label extension (interim analysis)[2†]

Eculizumab monotherapy (N=33)

Proportion relapse-free at 3.7 years



96%

Cumulative probability
KM analysis: 0.962
(95% CI 0.757–0.994)

Median monotherapy duration (years)

2.8

NCT01892345 (PREVENT); NCT02003144 (open-label extension). *Double-blind phase III RCT. Patients were randomly assigned 2:1 to receive intravenous eculizumab or matched placebo; †Crossover to eculizumab from placebo was permitted.

AQP4, aquaporin-4; CI, confidence interval; HR, hazard ratio; IgG, immunoglobulin G; KM, Kaplan-Meier; NMOSD, neuromyelitis optica spectrum disorder; PBO, placebo; RCT, randomized controlled trial.

1. Pittock SJ, et al. *N Engl J Med.* 2019;381:614–25; 2. Pittock SJ, et al. *Mult Scler J.* 2022;28:480–6.

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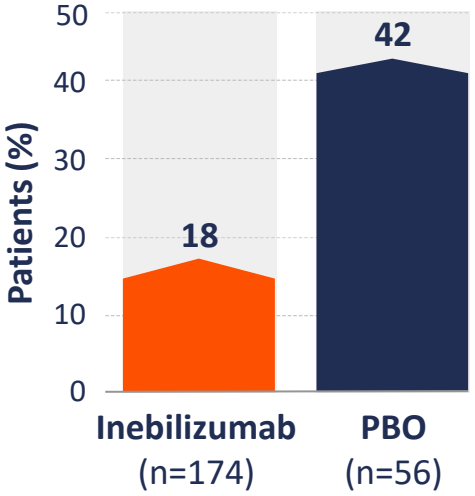
Inebilizumab: N-MOmentum study

N-MOmentum primary analysis[1*]

Proportion of AQP4-IgG positive patients with adjudicated attack



77%

reduction in risk of attack

HR 0.227
(95% CI 0.121–0.423; p<0.0001)

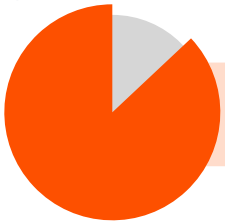
Concomitant immunotherapy: NO

Open-label extension (interim analysis)[2†]

Inebilizumab monotherapy (N=216)

Proportion attack-free at 4 years

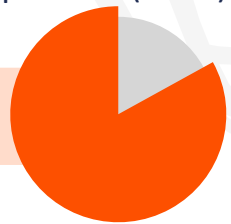
Originally received inebilizumab (n=165)



87.7%

Originally received placebo (n=51)

83.4%



NCT02200770 (N-MOmentum).
*Double-blind phase II/III RCT. Patients were randomized 3:1 to receive either inebilizumab or placebo; †Crossover to eculizumab from placebo was permitted.
AQP4, aquaporin-4; CI, confidence interval; HR, hazard ratio; IgG, immunoglobulin G; PBO, placebo; RCT, randomized controlled trial.
1. Cree BAC, et al. *Lancet.* 2019;394:1352–63; 2. Cree BAC, et al. Presented virtually at: ACTRIMS Forum 2021. 25–27 February 2021. Poster P144.

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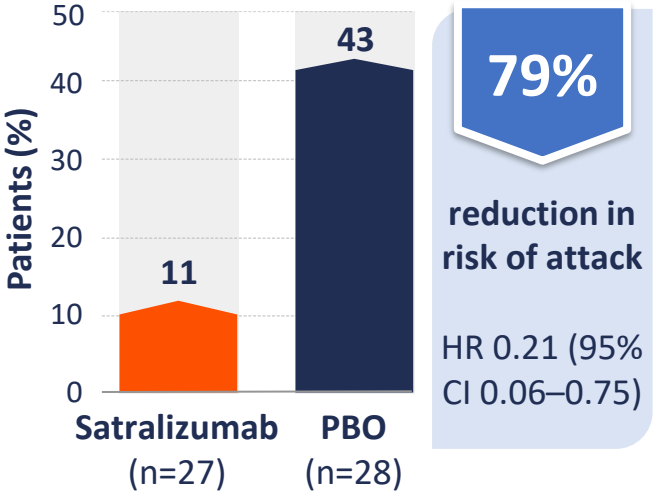
Satralizumab: SAkuraSky and SAkuraStar studies

SAkuraSky primary analysis[1*]

AQP4-IgG positive patients with protocol-defined relapse



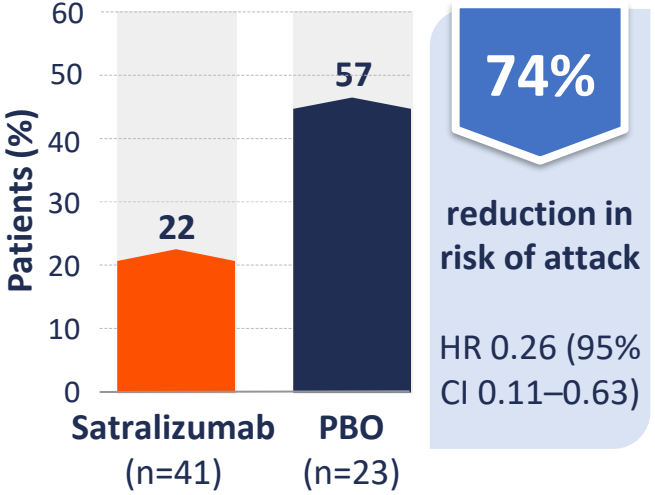
79% reduction in risk of attack

HR 0.21 (95% CI 0.06–0.75)

Concomitant immunotherapy: YES

SAkuraStar primary analysis[2†]

AQP4-IgG positive patients with protocol-defined relapse



74% reduction in risk of attack

HR 0.26 (95% CI 0.11–0.63)

Concomitant immunotherapy: NO

Open-label extension[3‡]

AQP4-IgG positive patients relapse-free at 3.7 years

SAkuraSky (n=49)*

71%

SAkuraStar (n=62)†

73%

NCT02028884 (SAkuraSky); NCT02073279 (SAkuraStar).

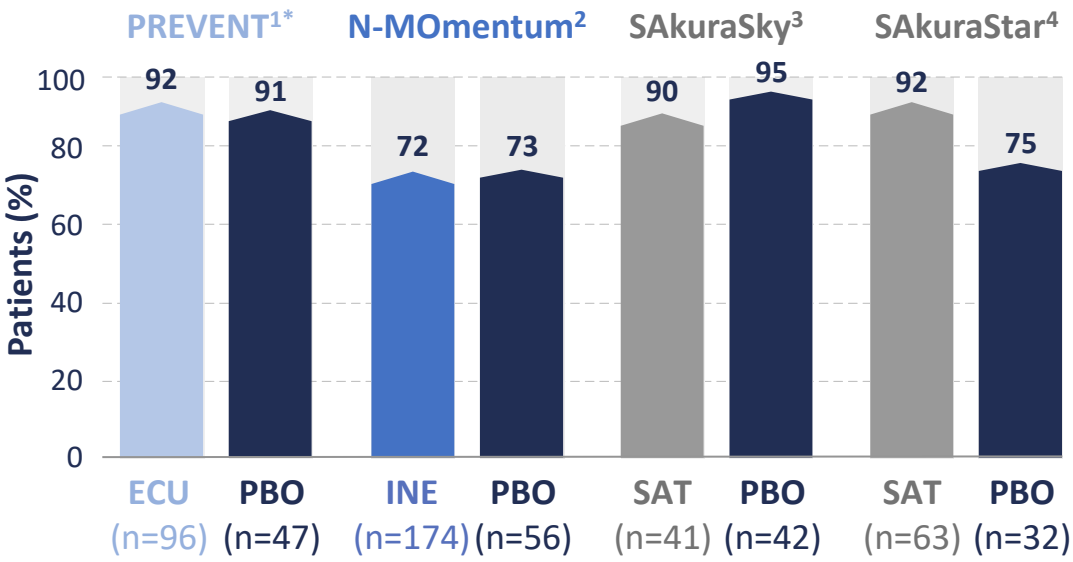
*Double-blind phase III RCT. Patients were randomized 1:1 to receive either satralizumab or placebo; †Double-blind phase III RCT. Patients were randomized 2:1 to receive either satralizumab or placebo; ‡Of the original study populations, 80% entered the SAkuraSky open-label extension and 89% entered the SAkuraStar open-label extension.

AQP4, aquaporin-4; CI, confidence interval; HR, hazard ratio; IgG, immunoglobulin G; PBO, placebo; RCT, randomized controlled trial.

1. Yamamura T, et al. *New Engl J Med*. 2019;381:2114–24; 2. Traboulsee A, et al. *Lancet Neurol*. 2020;19:402–12; 3. Kleiter I, et al. *Neurol Neuroimmunol Neuroinflamm.* 2023;10:e200071.

AE profiles of immunotherapies for NMOSD

TEAE rates in primary clinical trials



Generally similar TEAE rates vs placebo in primary trials

AEs occurring in >10% of patients per FDA-approved prescribing information[5]

Eculizumab	URI, nasopharyngitis, back pain, dizziness, diarrhoea, influenza
Inebilizumab	Urinary tract infection, arthralgia
Satralizumab	Rash, arthralgia, pain in extremity, fatigue, nausea, nasopharyngitis

Direct comparisons of clinical trial results cannot be made due to differences in study designs and patient characteristics. *AQP4-IgG positive patients only.
AE, adverse event; AQP4, aquaporin-4; ECU, eculizumab; IgG, immunoglobulin G; INE, inebilizumab; NMOSD, neuromyelitis optica spectrum disorder; PBO, placebo; SAT, satralizumab; TEAE, treatment-emergent AE; URI, upper respiratory infection.

1. Pittock SJ, et al. *N Engl J Med.* 2019;381:614–25; 2. Cree BAC, et al. *Lancet.* 2019;394:1352–63; 3. Yamamura T, et al. *New Engl J Med.* 2019;381:2114–24;
4. Traboulsee A, et al. *Lancet Neurol.* 2020;19:402–12; 5. FDA. Individual drug PIs. Available at: www.accessdata.fda.gov/scripts/cder/daf/ (accessed 15 May 2023).

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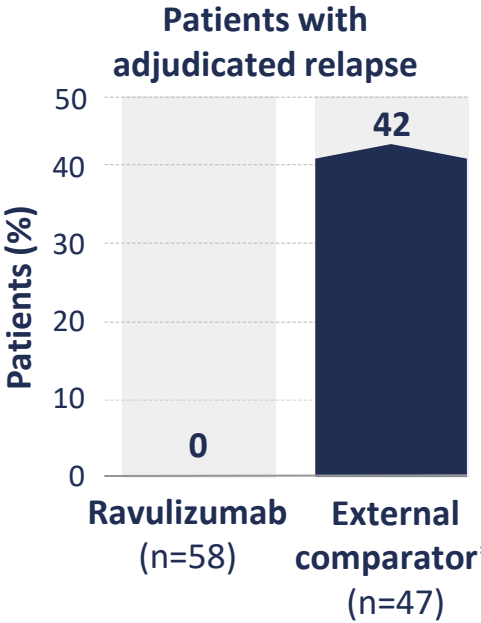
Ravulizumab: CHAMPION-NMOSD (AQP4-IgG positive)

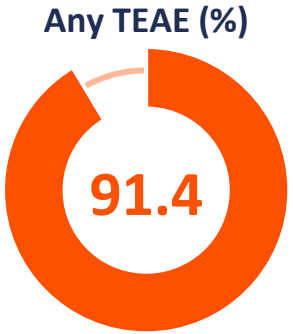


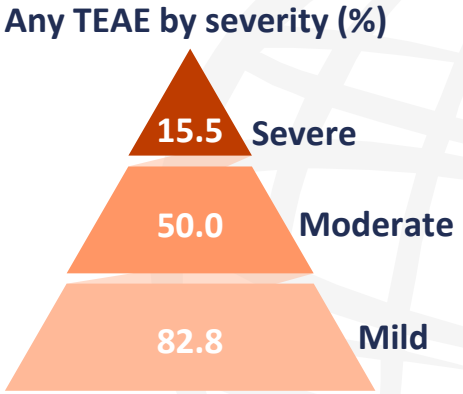
98.6%

reduction in risk of relapse

HR 0.014 (95% CI 0.000–0.103; p<0.0001)

Concomitant immunotherapy: YES





TEAEs reported in >10% of patients: COVID-19, headache, back pain, arthralgia, urinary tract infection

Meningococcal infection on ravulizumab, despite vaccination against *Neisseria meningitidis* (n=2)

NCT04201262 (CHAMPION-NMOSD).

*Open-label, phase III externally controlled study. Availability of eculizumab precluded the use of concurrent placebo control; the placebo group of the PREVENT trial was used as the external comparator.

AQP4, aquaporin-4; CI, confidence interval; HR, hazard ratio; IgG, immunoglobulin G; NMOSD, neuromyelitis optica spectrum disorder; TEAE, treatment-emergent adverse event.

Pittock SJ, et al. *Ann Neurol*. 2023. doi: 10.1002/ana.26626. Online ahead of print.

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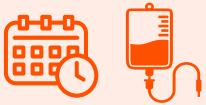
Informing clinical decision making in NMOSD

Previous treatment history

- Patient willingness to switch if stable or relapse-free[1]
- MoA of previous therapies[1]



Administration route and frequency

- Eculizumab: i.v., q2w[2]
- Inebilizumab: i.v., every 6 months[2]
- Satralizumab: self-administered s.c. injection, q4w[2]

Current patient status

- Disease stability and severity[1,3,4]
- Perceived QoL[4]
- Comorbidities[3]
- AQP4-IgG-positive/negative[1]

Accessibility and affordability

- Cost[1]
- Insurance coverage[3]
- Travel for medication and monitoring[1,3]

Safety and infection risk

- Tolerability, associated AEs[1,4]
- Concomitant immuno-suppressives[1,3]
- Meningitis vaccination[1]
- Hepatitis B and C and TB screening[1]

AE, adverse event; AQP4, aquaporin-4; IgG, immunoglobulin G; i.v., intravenous; MoA, mechanism of action; NMOSD, neuromyelitis optica spectrum disorder; q2w, every 2 weeks; q4w, every 4 weeks; QoL, quality of life; s.c., subcutaneous; TB, tuberculosis.

1. Pittock SJ, et al. *Nat Rev Neurol*. 2021;17:759–73; 2. FDA. Individual drug PIs. Available at: www.accessdata.fda.gov/scripts/cder/daf/ (accessed 15 May 2023);
3. Wingerchuk DM, et al. *J Manag Care Spec Pharm*. 2022;28:S2–S27; 4. Min J-H, et al. *Neurol Ther*. 2023;12:619–33.

Managing the broader clinical features of NMOSD

Dr Dalia Rotstein
University of Toronto,
ON, Canada

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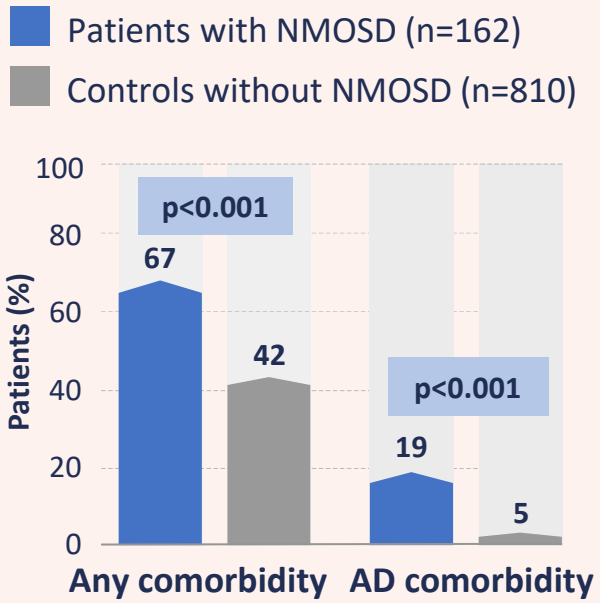
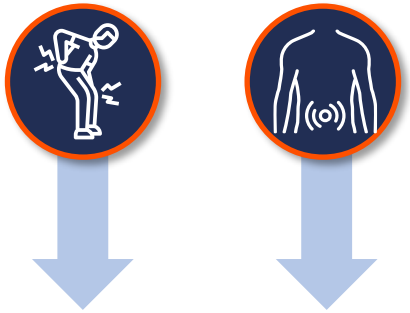
Burden of disease

Comorbidities[1]



QoL and daily activities



Pain and bowel/bladder dysfunction negatively impact QoL, sleep, recreational activities and ability to work[2–4]

Finances

Lost income and **financial hardship** due to hospital visits and hospitalizations[5]

Mean annualized all-cause healthcare expenditure (both groups: N=1,363):[6]

Patients with NMOSD **$60,599** Vs Matched patients **$8912**

Difference attributable to NMOSD: $51,687

AD, autoimmune disease; NMOSD, neuromyelitis optica spectrum disorder; QoL, quality of life.

1. Exuzides A, et al. *J Neurol Sci*. 2021;427:117530; 2. Fujihara K, et al. *J Neurol Sci*. 2021;428:117546; 3. Beekman J, et al. *Neurol Neuroimmunol Neuroinflamm*. 2019;6:e580; 4. Meca-Lallana J, et al. *Neurol Ther*. 2022;11:1101–16; 5. Rice D, et al. *Mult Scler Relat Disord*. 2023;71:104580; 6. Royston M, et al. *Neurol Ther.* 2021;10:767–783.

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Wider clinical symptoms

Wider clinical symptoms of NMOSD

Pain[1]

Fatigue[1]

Visual impairment[1–3]

Bladder and bowel control[1,3]

Neurologic disability*[2]

Cognitive and mood disorders[1,3]

Most common symptoms that patients with NMOSD felt their physician should be more concerned about (n=43)[4]

Pain

Fatigue

Disability

Management of wider clinical symptoms and residual effects of relapses may reduce disease burden and improve patient QoL[3–5]

*Neurological disability was evaluated using the modified Rankin Scale.
NMOSD, neuromyelitis optica spectrum disorder; QoL, quality of life.

1. Meca-Lallana J, et al. *Neurol Ther*. 2022;11:1101–16; 2. Kadish R, et al. *J Neuroimmunol*. 2022;362:577761; 3. Wingerchuk DM and Lucchinetti CF. *N Engl J Med.* 2022;387:631–9; 4. Fujihara K, et al. *J Neurol Sci*. 2021;428:117546; 5. Beekman J, et al. *Neurol Neuroimmunol Neuroinflamm*. 2019;6:e580.

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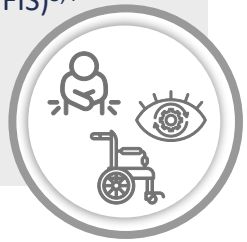
Patient-reported outcome measures

Quality of life

- EuroQol 5-dimensions (EQ-5D)[1]
- Short Form-36 survey (SF-36)[1]
- 29-item Multiple Sclerosis Impact Scale (MSIS-29)[2]

Pain, disability and fatigue

- SymptoMScreen (SyMS)[2]
- MOS Pain Effects Scale (PES)[2]
- PainDETECT questionnaire (PDQ)[3]
- Brief Pain Inventory - Short Form (BPI-SF)[3]
- Short-Form McGill Pain Questionnaire (SF-MPQ)[3]
- Multiple Sclerosis Work Difficulties Questionnaire (MSWDQ-23)[2]
- Modified Fatigue Impact Scale (MFIS)[3,4]
- Fatigue Severity Scale (FSS)[3,4]
- Fatigue Impact Scale for Daily Use (DFIS)[2]



Mental health

- 8-item Stigma Scale for Chronic Illness (SSCI-8)[2]
- Beck Depression Inventory-Fast Screen (BDI-FS)[2]

MOS, Medical Outcomes Study Pain Measures; NMOSD, neuromyelitis optica spectrum disorder.

1. Levy M, et al. *Mult Scler Relat Disord*. 2022;57:103332; 2. Meca-Lallana J, et al. *Neurol Ther*. 2022;11:1101–16;
3. Ayzenberg I, et al. *Neurol Neuroimmunol Neuroinflamm.* 2021;8:e985; 4. Beckerman H, et al. *Sci Rep*. 2020;10:4167.

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Managing clinical symptoms of NMOSD

Mood and cognitive impairments

- Antidepressants
- CBT
- Cognitive rehabilitation
- Aerobic exercise

Neuropathic pain

- Anticonvulsants
- Muscle relaxants
- Antidepressants
- TENS

Fatigue and narcolepsy

- Address sleep disorders and/or depression
- Elimination/dose reduction of sedating drugs
- Exercise/aquatic therapy
- Cognitive behavioural interventions
- Stimulants

Muscle weakness and motor dysfunction

- Neurorehabilitation
- Functional electrical stimulation-based therapy
- Dalfampridine (walking impairment)

Tonic spasms and spasticity

- Anticonvulsants
- Muscle relaxants
- Daily stretching and exercise
- Physical therapy

Bladder and bowel dysfunction

Bladder

- Bladder retraining
- Fluid intake timing
- Pelvic floor exercises
- Bladder dysfunction medications
- Neuromodulation
- Catheterization

Bowel

- Dietary fibres, laxatives, stimulants, stool softeners
- Colostomy

CBT, cognitive behavioural therapy; NMOSD, neuromyelitis optica spectrum disorder; TENS, transcutaneous electrical nerve stimulation.

Abboud H, et al. *J Neurol*. 2022;269:1786–1801.

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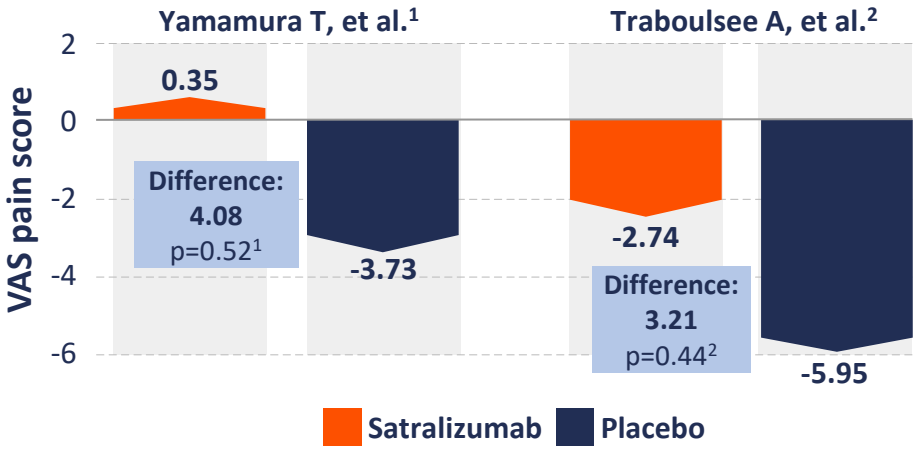
Effect of immunomodulatory treatment on pain

Satralizumab[1,2]

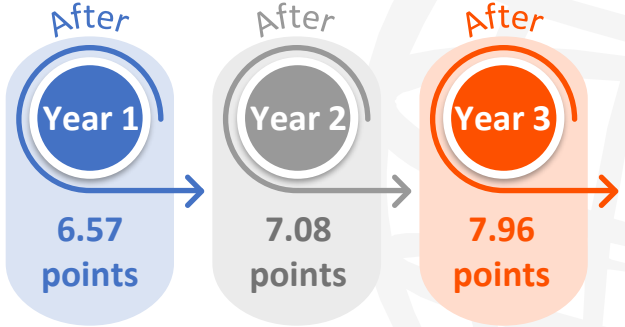
Change in VAS pain score from baseline to 24 weeks[1,2*]



No significant change in VAS pain score with satralizumab vs placebo[1,2]

Inebilizumab[3]

Change in SF36-BPS from baseline reported by patients on inebilizumab with baseline SF36-BPS <40[3†]



Year-on-year improvement in pain scores with inebilizumab[3]

*Data from two double-blind phase III RCTs. Direct comparisons of clinical trial results cannot be made due to differences in study designs and patient characteristics; †Data from the N-MOmentum study, a double-blind phase II/III RCT.
RCT, randomized controlled trial; SF36-BPS, 36-Item Short-Form Survey Body Pain Subscores; VAS, visual analogue scale.
1. Yamamura T, et al. *N Engl J Med.* 2019;381:2114–24; 2. Traboulsee A, et al. *Lancet Neurol.* 2020;19:402–412; 3. Kim HJ, et al. *Neurology*. 2022;98(Suppl. 18):1569.

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MDT care for patients with NMOSD

- Clinical fellow[1]
- Clinical psychologist[1]; psychiatrist[1]
- Physiotherapist[1]; physiatrist[2]
- Social worker[2]
- Occupational therapist[1]
- Ophthalmologist/ orthoptist[1]
- Dietician[1]
- Nurse specialist[1]
- Pain specialist[1]
- Adult/paediatric neurologist[1]

MDT, multidisciplinary team; NMOSD, neuromyelitis optica spectrum disorder.

1. Huda S, et al. *Clin Med.* 2019;19:169–76; 2. Nachemia Y, et al. *J Spinal Cord Med.* 2016;39:311–6.