Supplementary Material

Comparative Evaluation of Rituximab Versus Approved Therapies in Aquaporin-4-IgG Positive Neuromyelitis Optica Spectrum Disorder: A Systematic Review and Network Meta-Analysis

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Qualitative Assessment of Heterogeneity and Inconsistency in Network Meta-Analysis

A random-effects model was used for all network meta-analysis estimates, allowing for between-study variability in treatment effects and providing a more conservative approach when clinical heterogeneity is anticipated. Given the small number of included studies (eight trials across two networks), formal statistical assessments of heterogeneity (e.g., τ^2, I^2) and inconsistency (e.g., design-by-treatment interaction models or node-splitting approaches) were considered unlikely to provide reliable or informative results because of limited statistical power and the absence of closed loops within the network. Accordingly, these analyses were not performed.

Instead, a qualitative assessment of heterogeneity and transitivity was undertaken by examining study characteristics that could act as treatment-effect modifiers. Key differences in study populations, eligibility criteria, relapse definitions, outcome adjudication procedures, and concomitant immunosuppressive therapy use are summarized in Tables S3–S6. Important sources of clinical and methodological heterogeneity included:

- Differences in baseline disease activity, with higher pre-enrollment ARR reported in the complement inhibitor trials than in the rituximab trial.
- Variation in relapse eligibility criteria, ranging from no minimum relapse requirement in RIN-I to multiple relapses required in PREVENT and other studies.
- Differences in relapse definitions and adjudication procedures, including investigator-assessed versus independently adjudicated relapses and variable use of MRI confirmation.
- Variation in the use of concomitant immunosuppressive therapy.
- Differences in study populations, including the exclusively Japanese cohort enrolled in RIN-I.

- Differences in study design, including the open-label CHAMPION-NMOSD trial versus the double-blind placebo-controlled designs used in most other studies.

These factors represent potential effect modifiers that may influence indirect treatment comparisons and should be considered when interpreting the results. Nevertheless, the included studies evaluated broadly comparable populations with AQP4-IgG-positive NMOSD and assessed similar clinical outcomes, supporting the plausibility of the transitivity assumption underlying the network meta-analysis.

Table S1: Search Queries and Literature Hits for AQP4-NMOSD Treatments	
Search Term	**Search Query Summary**
NMOSD	(("NMO Spectrum Disorder"[all] OR "NMO Spectrum Disorders"[all] OR "Neuromyelitis Optica Spectrum Disorder"[all] OR "Neuromyelitis Optica Spectrum Disorders"[all] OR "Devic Neuromyelitis Optica"[all] OR "Devic Neuromyelitis Opticas"[all] OR ("Neuromyelitis Optica"[all] AND Devic[all]) OR ("Neuromyelitis Opticas"[all] AND Devic[all]) OR "Devic's Disease"[all] OR "Devics Disease"[all] OR (Disease[all] AND Devic's[all]) OR "Devic Disease"[all] OR (Disease[all] AND Devic[all]) OR "Devic Syndrome"[all] OR (Syndrome[all] AND Devic[all]) OR "Devic's Syndrome"[all] OR "Devics Syndrome"[all] OR (Syndrome[all] AND Devic's[all]) OR "Devic's Neuromyelitis Optica"[all] OR "Devics Neuromyelitis Optica"[all] OR ("Neuromyelitis Optica"[all] AND Devic's[all]) OR "Neuromyelitis Optica Spectrum Disorder"[all] OR "Neuromyelitis Optica Spectrum Disorders"[all] OR NMO[all] OR NMOSD[all] OR "Neuromyelitis Optica"[all] OR (Neuromyelitis[all] AND Optica[all]))
Rituximab	("Rituximab"[all] OR "Rituximabs"[all] OR "Mabthera"[all] OR "Rituxan"[all] OR "Anti-CD20 Antibody"[all] OR "Anti-CD20 Antibodies"[all] OR "Anti CD20 Antibody"[all] OR "Anti CD20 Antibodies"[all] OR "Anti-CD20 Monoclonal Antibody"[all] OR "Anti-CD20 Monoclonal Antibodies"[all] OR "Anti CD20 Monoclonal Antibody"[all] OR "Anti CD20 Monoclonal Antibodies"[all] OR "Monoclonal Antibody Rituximab"[all] OR "Monoclonal Antibody Rituximabs"[all] OR "Rituximab Monoclonal Antibody"[all] OR "Rituximab Monoclonal Antibodies"[all] OR "Chimeric Monoclonal Antibody Rituximab"[all] OR "Chimeric Monoclonal Antibody Rituximabs"[all] OR "Rituximab Chimeric Monoclonal Antibody"[all] OR "Rituximab Chimeric Monoclonal Antibodies"[all])

Ravulizumab	(Ravulizumab[tiab] AND “C5 inhibitors” [tiab] OR “C5 inhibitor” [tiab] OR Ultomiris[tiab] OR “C5 complement inhibitor” [tiab] OR “C5 complement blocker” [tiab] OR “C5 inhibitor therapy” [tiab] OR ALXN1810[tiab] OR ALXN-1810[tiab] OR ALXN1210[tiab] OR ALXN-1210[tiab])
Eculizumab	(Eculizumab[tiab] OR 5G1.1[tiab] OR H5G1.1VHC+H5G1.1VLC[tiab] OR H5G1.1[tiab] OR H5G1-1[tiab] OR H5G11[tiab] OR Elizaria[tiab] OR Soliris[tiab] OR Alexion[tiab])
Satralizumab	(Satralizumab[tiab] OR enspryng[tiab] OR “Anti-IL-6 receptor antibody” [tiab] OR “IL-6R inhibitor” [tiab] OR “Interleukin-6 receptor antagonist” [tiab] OR “Humanized monoclonal antibody targeting IL-6R” [tiab] OR “IL-6 pathway blockade” [tiab] OR “Interleukin-6 inhibition” [tiab])
Inebilizumab	(Inebilizumab[tiab] OR Uplizna[tiab] OR “Anti-CD19 monoclonal antibody” [tiab] OR “CD19-targeting therapy” [tiab] OR Inebilizumab-cdon[tiab] OR “Anti-CD19 immunotherapy” [tiab] OR “Anti-CD19 biologic” [tiab])
Tocilizumab	(Tocilizumab[tiab] OR RHPM-1[tiab] OR RG-1569[tiab] OR R-1569[tiab] OR MSB11456[tiab] OR MSB-11456[tiab] OR atlizumab[tiab] OR RO-4877533[tiab] OR Actemra[tiab] OR Roactemra[tiab])

QP4, aquaporin-4; NMOSD, neuromyelitis optica spectrum disorder; NMO, neuromyelitis optica; IL-6, interleukin-6; IL-6R, interleukin-6 receptor; CD, cluster of differentiation; tiab, title/abstract

Table S2: Quality Assessment of Included Studies

Author	year of publication	name of study	Type of study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	if not	Q9	Q10	Q11	Q12	Q13	Overall appraisal
Tahara	2020	RIN-1	RCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	Yes	Yes	Include
Nikoo	2017		randomized; open label	Yes	Yes	No	No	No	Unclear	Yes	No	No	Yes	Unclear	Yes	Yes	Yes	Include
Pittock	2019	PREVENT	RCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	Yes	Yes	Include
Cree	2019	N-Momentum	RCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	Yes	Yes	Include
Pittock	2023	CHAMPION	One arm open-label	No	No	No	No	No	No	Yes	Yes		Yes	Yes	Yes	Yes	Yes	Include
Traboulsee	2020	SAkuraStar	RCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	Yes	Yes	Include
Yamamura	2019	SAkuraSky	RCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	Yes	Yes	Include
Zhang	2020	TANGO	randomized; open label	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	Yes	Yes	Include

Quality assessment was independently conducted by two reviewers.

Quality assessment criteria (Q1–Q13) are based on the following questions:

1. Was true randomization used for assignment of participants to treatment groups?
2. Was allocation to treatment groups concealed?
3. Were treatment groups similar at baseline?
4. Were participants blinded to treatment assignment?
5. Were those delivering treatment blinded to treatment assignment?
6. Were outcome assessors blinded to treatment assignment?
7. Were treatment groups treated identically aside from the intervention?

8. Was follow-up complete, or were differences in loss to follow-up described and analyzed?

9. Were participants analyzed in the groups to which they were randomized (intention-to-treat)?

10. Were outcomes measured consistently across treatment groups?

11. Were outcomes measured reliably?

12. Was appropriate statistical analysis used?

13. Was the trial design appropriate, and were deviations accounted for in conduct and analysis?

RCT, randomized controlled trial

Table S3. Demographical and clinical characteristics of included studies								
Trial ID	Traetment arm	Number	Female, n (%)	Baseline age, yr mean (SD)	Baseline AQP4+, n (%)	Baseline ARR, mean (SD)	Baseline EDSS, mean (SD)	Prior rituximab, n (%)
RIN-I	Rituximab	19	17 (90)	51.5 (4.6)	19 (100)	1.4	3.8 (1.0)	-
	Placebo	19	19 (100)	49 (8.1)	19 (100)	0.7	4 (1.2)	-
PREVENT	Eculizumab	96	88 (92)	43.9 (13.3)	96 (100)	1.9 (0.9)	4.2 (1.6)	26 (27)
	Placebo	47	42 (89)	45 (13.3)	47 (100)	2.1 (1)	4.3 (1.5)	20 (43)
CHAMPION-NMOSD	Ravulizumab	58	52 (90)	47.4 (14)	58 (100)	1.9 (1.6)	3.3 (1.6)	21 (36)
SAkuraSky	Satralizumab	41	37 (90)	40.8 (16.1)	27 (66)	1.5 (0.5)	3.8 (1.6)	-
	Placebo	42	40 (95)	43.4 (12)	28 (67)	1.4 (0.4)	3.6 (1.3)	-
SAkuraStar	Satralizumab	63	46 (73)	45.3 (12)	41 (65)	-	3.9 (1.5)	8 (13)
	Placebo	32	31 (97)	40.5 (10.5)	23 (72)	-	3.7 (1.6)	4 (19)
N-MOmentum	Inebilizumab	174	159 (91)	43.2 (11.6)	161 (93)	1.7 (1.5)	3.8 (1.8)	12 (7)
	Placebo	56	50 (89)	42.6 (14.3)	52 (93)	1.6 (1.5)	4.2 (1.7)	4 (8)
Nikoo et al	Rituximab	40	34 (85)	34.3 (8.9)	17 (42)	1.3 (0.6)	3.3 (1.9)	-
	Azathioprine	46	38 (83)	32.1 (9.4)	25 (54)	1.0 (0.4)	2.4 (1.2)	-
TANGO	Tocilizumab	59	55 (93)	48.1 (13.4)	50 (85)	1.7 (0.6)	4.6 (0.5)	-
	Azathioprine	59	53 (90)	45.3 (14.5)	53 (90)	1.7 (0.7)	4.7 (0.6)	-

AQP4+, aquaporin-4 immunoglobulin G seropositive; ARR, annualized relapse rate; EDSS, Expanded Disability Status Scale; SD, standard deviation.

Table S4: Overview of Outcome Definitions in Included Trials			
Author	**Name of Study**	**Outcomes - Randomization**	**Definition of Relapse**
Tahara et.al.	RIN-1	**Primary Outcome:** Time to first relapse during the 72-week study period **Secondary Outcomes:** Change from baseline in: • EDSS score (0 to 10; higher = more disability) • QOSI score (0 to 69; higher = more optic nerve and spinal cord impairment) Rate of oral steroid reduction **Post-Hoc Analyses** Changes in: • AQP4 antibody titres • HACA and JCV antibodies (in context of progressive multifocal leukoencephalopathy) • CD19 and CD20 lymphocyte subsets • Annualized Relapse Rate (ARR): Number of relapses per person-year **Safety Monitoring** **Stratification Factors for Randomisation** • Number of relapses in prior 2 years (≥1 vs none) • Steroid dose at baseline (5–10, 11–20, 21–30 mg/day)	**Relapse was defined as any symptoms reported by the patient or any new signs that were consistent with CNS lesions and were associated with objective abnormalities (new lesions on T2 or Gd-enhanced images on MRI).** A diagnosis of optic neuritis relapse was made by the principal investigator at each study site according to three criteria: • New findings of alterations in visual acuity or visual field, or a reduction in critical flicker frequency; • New T2 lesions or Gd-enhancing lesions on MRI of optic nerves, or a delay in visual evoked potential; The cause is attributable to optic neuritis as judged by the principal investigator at each study site.
Nikoo et. al.		**Primary Outcome:** ARR after 12 months of intervention. **Secondary Outcome:** EDSS after 12 months. **Other Measurements:** • Δ-ARR (change in ARR from baseline to 12 months). • Δ-EDSS (change in EDSS from baseline to 12 months). • Proportion decline in ARR (Δ-ARR / baseline ARR).	**Relapse was defined clinically as occurrence of new neurological symptoms or acute increased EDSS.**

		• Side effects were recorded and compared between groups. Patients were evaluated at 6 and 12 months for all outcomes and adverse events.	
Pittock et. al.	PREVENT	**Primary Outcome:** Time to first adjudicated relapse. (Originally physician-determined relapse—changed mid-study). **Secondary Outcomes (hierarchical):** • Adjudicated ARR. • Change in EDSS. • Modified Rankin Scale. • Hauser Ambulation Index. • EQ-5D-3L VAS. • EQ-5D-3L summary index. **Adverse events also assessed with seriousness and relatedness.** **Stratification Factors for Randomisation** • EDSS score on day 1 (≤2.0 or 2.5–7.0). • Use of immunosuppressive therapy (none, stable, or recently changed): - No prior therapy (except glucocorticoids). - Continuing same therapy after last relapse. - New therapy or discontinuation after last relapse. Study continued until 24 relapses were reached (terminated at 23).	**Physician-defined criteria: Relapse was defined as a new onset of neurologic symptoms or worsening of existing neurologic symptoms with an objective change on neurologic examination that persisted for more than 24 hours, signs and symptoms attributable to NMOSD rather than other causes, and onset preceded by at least 30 days of clinical stability.** **Changes in imaging were not considered to be an indication of relapse without related clinical findings.** **Adjudication (after protocol amendment): Independent committee of 2 neurologists and 1 neuro-ophthalmologist-Reviewed all suspected relapses using same criteria as treating physicians**
Cree et. al.	N-MOmentum	**Primary Outcome:** Time (in days) from Day 1 to the onset of an NMOSD attack (as determined by a blinded adjudication committee), on or before Day 197. **Secondary Outcomes (controlled for type I error):** • Worsening of EDSS score from baseline: - Increase of ≥2 from baseline of 0 - Increase of ≥1 from baseline of 1–5	**An attack was defined as the presence of new or worsening neurological symptoms related to NMOSD that met at least one of the protocol-defined criteria upon neurological evaluation. These criteria were assessed by a blinded adjudication committee.** Key Components: • Symptom Evaluation: New or worsening neurological symptoms attributable to NMOSD.

		- Increase of ≥0.5 from baseline of ≥5.5 • Change from baseline in binocular low-contrast visual acuity (Landolt C broken ring chart) • Cumulative total number of active MRI lesions (new Gd-enhancing or new/enlarging T2) • Number of NMOSD-related hospitalisations (overnight stays) **Other secondary endpoints:** Reported descriptively; not controlled for type I error.	• Objective Findings: The symptoms had to be accompanied by objective changes in neurological examination. • Duration: Symptoms must have persisted for more than 24 hours. • Clinical Stability: Onset of symptoms had to be preceded by at least 30 days of clinical stability. • Exclusion of Other Causes: Symptoms should not be better explained by other causes such as infections, fever, or adverse reactions to medications. • MRI Confirmation: While MRI findings were not required for attack confirmation, relevant MRI scans were reviewed when available to support the clinical assessment. **Adjudication Process:** Potential attacks were evaluated by the treating physician and then reviewed by a blinded adjudication committee comprising neurologists. The committee assessed whether the event met the predefined criteria for an attack. Only attacks confirmed by the adjudication committee were considered in the primary efficacy analysis.
Pittock et. al.	CHAMPION-NMOSD	**Primary Outcomes**: Time to first adjudicated on-trial relapse in the ravulizumab group compared with the PREVENT placebo group. **Secondary Outcomes (tested in a prespecified hierarchical order, type I error):** • Adjudicated on-trial ARR. • Clinically important change from baseline in Hauser Ambulation Index (HAI). • Change from baseline in EQ-5D index and EQ-5D visual analog scale (VAS). • Clinically important worsening in EDSS score. **Adverse events also assessed with seriousness and relatedness.** **Randomization** Not applicable in the conventional sense: CHAMPION-NMOSD was an open-label, non-randomized trial. The comparator was an external placebo group from the PREVENT trial, due to ethical concerns around assigning a concurrent placebo in NMOSD.	**Same as PREVENT**

Traboulsee et. al.	SAkuraStar	**Primary Outcomes**: First protocol-defined relapse in the double-blind period in a time-to-event analysis **Secondary Outcomes**: • Change from baseline to week 24 in VAS pain score (0–100; higher = more pain) • Change from baseline to week 24 in FACIT-F score (0–52; lower = more fatigue) **Additional secondary Outcomes**: • SF-36 (eight domains, 0–100) • EQ-5D (−0.109 to 1) • Modified Rankin Scale (0–6) • Zarit Burden Interview (0–88) • EDSS score • Visual acuity (Snellen chart, decimal format) • Percentage of patients free from relapse **Safety outcomes**: Incidence and severity of adverse events and serious adverse events (relapses were not categorized as AEs) **Stratification Factors for Randomisation** • Baseline annualized relapse rate (1 vs. >1) • Geographic region (Asia vs. Europe or other)	**An attack was defined as new or worsening objective neurologic symptoms, with one of the following:** • **An increase of at least 1.0 on the EDSS from a baseline score of more than 0,** **or an increase of ≥2.0 from a baseline score of 0** • **An increase of at least 2.0 on one appropriate symptom-specific functional-system (FS) score for:** ○ **the pyramidal system,** ○ **cerebellar system,** ○ **brain stem,** ○ **sensory system,** ○ **bowel or bladder,** ○ **or a single eye** • **An increase of at least 1.0 on more than one FS score with a baseline score of at least 1.0** • **An increase of at least 1.0 on an FS score in a single eye with a baseline score of at least 1.0** **Symptoms were required to be:** • **Attributable to neuromyelitis optica or NMOSD** • **Persist for more than 24 hours** • **Not attributable to confounding clinical factors such as fever, infection, injury, mood changes, or adverse drug reactions** Relapses were adjudicated by a clinical end-point committee whose members were blinded to trial-group assignments A sensitivity analysis was conducted for the first clinical relapse, including both protocol-defined and investigator-assessed relapses that did not meet protocol criteria
Yamamura et. al.	SAkuraSky	**Primary Outcome**: Time to first protocol-defined relapse in the double-blind period **Secondary Outcomes**: • **Change from baseline to week 24** in: - Visual Analogue Scale (VAS) pain score (0–100) - FACIT-Fatigue score (0–52; higher = less fatigue) **Additional Secondary Outcomes**: • Proportion of relapse-free patients • Annualized relapse rate (ARR)	**Protocol-defined relapses were new or worsening objective neurological symptoms with at least one of the following:** • **Increase of 1·0 or more EDSS points from a baseline EDSS score of more than 0,** • **or increase of ≥2·0 EDSS points from a baseline EDSS score of 0;** • **Increase of 2·0 or more points on at least one appropriate symptom-specific functional system score for either the pyramidal, cerebellar, brainstem, sensory, bowel or bladder, or a single eye;**

		• Change in: SF-36, EQ-5D, timed 25-foot walk, modified Rankin Scale, Zarit Burden Interview, EDSS, visual acuity (Snellen), low-contrast VA (Sloan chart) **Safety Outcomes** **Stratification Factors for Randomisation** • Previous therapy for relapse prevention (B-cell depletion vs other) • Nature of most recent attack (first attack vs relapse)	• **Increase of 1·0 or more points on more than one symptom-specific functional system score with a baseline of at least 1·0;** • **or increase of 1·0 or more points on a single-eye symptom-specific functional system score with a baseline score of at least 1·0.** **Symptoms were required to be attributable to NMOSD, persisting for more than 24 h, and not attributable to confounding clinical factors such as fever, infection, injury, change in mood, or adverse reactions to medications.** **EDSS and functional system scores were assessed within 7 days of a patient reporting their symptoms to the clinical trial coordinating centre.** Relapses were adjudicated by a Clinical Endpoint Committee (CEC) masked to treatment assignment. The CEC adjudicated relapses as they occurred, following investigator assessment of relapse.
Zhang et. al.	TANGO	**Primary Outcome:** Time to first relapse **Prespecified Subgroup Analyses**: • With/without comorbid autoimmune disease • Stratified by AQP4-IgG status, baseline EDSS, number of previous relapses, disease duration, age, and relapse history (1–2 years pre-randomisation) **Secondary Outcomes** • Confirmed disability progression (≥12 weeks): - EDSS ↑≥1.0 (baseline ≤5.5) - EDSS ↑≥0.5 (baseline >5.5) • Change in serum AQP4-IgG titres from baseline to week 60 • Early discontinuers with unconfirmed EDSS progression were still counted as having disability progression **Exploratory Outcomes** • Confirmed disability progression (24 weeks) using same EDSS criteria • Changes from baseline to 60 weeks in: - High-/low-contrast visual acuity	**Relapse was defined as new onset of neurological symptoms or worsening of existing neurological symptoms with an objective change on neurological examination that persisted for more than 24 h, with signs and symptoms attributable solely to NMOSD, and preceded by at least 30 days of clinical stability.** **MRI was used to confirm cases of relapse for which clinical changes on examination did not meet relapse criteria. A relapse required a change in the EDSS score regardless of MRI.**

		- Mean pRNFL thickness - Ganglion cell complex volume - P100 latency/amplitude (VEPs) - New/enlarging T2 MRI lesions (brain/spine) - Peripheral B-cell subset counts **Safety Outcomes**	

AQP4, aquaporin-4; AQP4-IgG, aquaporin-4 immunoglobulin G; ARR, annualized relapse rate; CNS, central nervous system; EDSS, Expanded Disability Status Scale; EQ-5D, EuroQol 5-Dimension questionnaire; EQ-5D-3L, EuroQol 5-Dimension 3-Level questionnaire; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; FS, functional system; Gd, gadolinium; HACA, human anti-chimeric antibodies; HAI, Hauser Ambulation Index; JCV, John Cunningham virus; MRI, magnetic resonance imaging; NMOSD, neuromyelitis optica spectrum disorder; pRNFL, peripapillary retinal nerve fiber layer; QOSI, Quantification of Optic Nerve and Spinal Cord Impairment score; SF-36, 36-Item Short Form Health Survey; VAS, visual analogue scale; VEP, visual evoked potential

Table S5: Overview of Treatment Protocols (Intervention Design)						
Author	**Name of Study**	**Intervention**	**Control**	**Steroid Background Therapy**	**Eligibility Based on Prior Treatment and Treatment History**	**Follow-up & Monitoring**
Tahara er.al.	RIN-1 study	Rituximab 375 mg/m² weekly for 4 weeks (induction), followed by 1000 mg infusions at weeks 24 and 48 (maintenance). NSAIDs and antihistamines were given 30 minutes before each infusion to reduce infusion-related reactions.	Matching placebo used in control arm with same schedule.	All patients were on oral prednisolone (≥5 mg/day). Dose remained stable for 8 weeks, then tapered by 10% every 4 weeks to 2 mg/day. Prednisolone was used as adjunctive therapy in both arms.	Treatment-Free Interval Before Trial not specified. Not restricted to treatment-naïve. Eligibility required neurological stability and a stable corticosteroid dose (≤30 mg/day) for at least 3 months prior to enrolment. Use of high-dose corticosteroids (>30 mg/day) or concurrent oral immunosuppressants other than steroids led to exclusion. Prior treatment with rituximab or other immunosuppressive therapies was not explicitly excluded, provided they had been discontinued. No additional immunosuppressive agents were permitted during the trial period.	Study duration: 72 weeks (minimum 60 weeks in case of early relapse events). Patients could enter the open-label extension (RIN-2) after study completion or relapse.
Nikoo et. al.		Rituximab 1 g IV (two vials of RediTux® 500 mg/50 ml, produced by CinnaGen, Iran), given in two doses 2 weeks apart;	Oral azathioprine (produced by Mehrdaru®, Iran) starting at 50 mg twice daily, increased	All patients received oral prednisolone (1 mg/kg/day), continued for 3–5 months, then tapered to	The treatment-free interval before trial was at least 2 months for immunosuppressive medications.	Study duration: 48 weeks (12 months).

		cycle repeated every 6 months. Premedication with IV methylprednisolone, chlorpheniramine, and acetaminophen was given before each infusion.	gradually with the aim of lymphocyte count below 1500 per µl until a maximum dose of 2–3 mg/kg/day.	10–20 mg/day over 6 months. Prednisolone was used as adjunctive therapy in both arms.	Not restricted to treatment-naïve. Patients with prior azathioprine or rituximab exposure, or use of other immunosuppressants (mycophenolate mofetil, cyclophosphamide, methotrexate) within 2 months before enrollment, were excluded. Use of other immunosuppressants during the study was not permitted.	
Pittock et. al.	PREVENT	Eculizumab: 900 mg IV weekly (first 4 weeks), then 1200 mg every 2 weeks	Matching placebo IV on same schedule.	Allowed; patients could continue immunosuppressive therapy for relapse prevention if they were receiving stable-dose regimens Prednisone >20 mg/day or the equivalent for other glucocorticoids at screening was excluded	Not restricted to treatment-naïve. Prior rituximab or mitoxantrone use within 3 months excluded; IVIG within 3 weeks excluded; High-dose prednisone (>20 mg/day) not allowed at screening; only stable immunotherapy regimens allowed	Study duration: Variable follow-up, with a minimum of 12 months, terminated after 23 adjudicated relapses, followed by entry into an open-label extension (PREVENT) with eculizumab.
Cree et. al.	N-MOmentum	Inebilizumab 300 mg IV on Day 1 and Day 15 (total 600 mg in RCT period)	Placebo (matched appearance); administered on Day 1 and Day 15 during randomized period.	All patients received oral corticosteroids (prednisone 20 mg/day or equivalent) on Days 1–14, tapered until Day 21 to reduce risk of relapse post-therapy initiation. No other immunosuppressants permitted during this period.	Not restricted to treatment-naïve. Interval not explicitly quantified. Patients with prior AQP4-IgG positive or negative status were eligible. Recent use of off-label immunosuppressants was allowed, but patients had to discontinue them before baseline.	Study duration: Up to 197 days (~28 weeks) per participant, or until the first adjudicated attack occurred.

					Seronegative patients had to meet 2015 NMOSD criteria.	
Pittock et. al.	CHAMPION-NMOSD	Ravulizumab Dosing Regimen: Weight-based loading dose (2,400–3,000 mg IV) on Day 1, Maintenance dose (3,000–3,600 mg IV) on Day 15, then Every 8 weeks thereafter.	Control group was the placebo arm of the PREVENT trial (eculizumab study)	Allowed if stable before enrollment. Consistent with PREVENT criteria. Treating physicians could administer IV methylprednisolone or adjust ISTs at their discretion for relapse Treatment: Patients were not withdrawn from study drug post-relapse, unlike PREVENT.	Not restricted to treatment-naïve. Stable-dose IST permitted (e.g., azathioprine, mycophenolate mofetil). Use of mitoxantrone or rituximab within 3 months, or IVIG within 3 weeks before screening and prior complement inhibitor use were not allowed.	Study Periods: Screening → Primary treatment → Long-term extension → Safety follow-up.
Traboulsee et. al.	SAkuraStar	Satralizumab 120 mg subcutaneously at weeks 0, 2, and 4, then every 4 weeks thereafter Same dosing continued during the open-label extension period	Placebo, administered at same intervals as satralizumab during the double-blind period	Allowed during double-blind phase if stable-dose: Azathioprine (≤3 mg/kg/day) Mycophenolate mofetil (≤3000 mg/day) Oral glucocorticoids (≤15 mg/day prednisolone equivalent) Adolescents could receive stable doses of these therapies Dose increases not allowed during double-blind phase (decreases allowed for safety) Extension phase: background therapies could be changed or discontinued	Not restricted to treatment-naïve. Stable baseline IST for ≥8 weeks before baseline was permitted. Excluded if prior use of: -Received anti-CD20 agents (e.g., rituximab) during the trial or within 6 months before baseline -Used eculizumab, belimumab, or multiple sclerosis disease–modifying treatment within 6 months before baseline -Used anti-CD4 agents, cladribine, or mitoxantrone within 2 years before baseline	**Double-Blind Period:** This period was planned to end after the occurrence of 26 protocol-defined relapses, based on sample-size and power calculations. **Open-Label Extension Period:** After completing the double-blind phase (due to relapse or study endpoint), all patients received open-label satralizumab at the same dosing intervals. **Patients were eligible to enter the extension period if:** They had a protocol-defined relapse,

						They received rescue therapy, Or they remained in the study when the 26-event threshold was reached. During this phase, background ISTs could be continued, modified, or discontinued.
Yamamura et. al.	SAkuraSky	Satralizumab 120 mg administered subcutaneously at: Weeks 0, 2, 4, then every 4 weeks thereafter. Same schedule during open-label extension	Placebo, identical in appearance and dosing schedule to satralizumab Administered subcutaneously at weeks 0, 2, 4, then every 4 weeks	Prohibited during the study (corticosteroids, IVIG, and immunosuppressants such as azathioprine, mycophenolate mofetil) Allowed only as rescue therapy in the case of: Protocol-defined or non-protocol-defined relapse (e.g., pulse IV corticosteroids) Analgesics were permitted for pain management	Not restricted to treatment-naïve. Patients were excluded if they had received: -IL-6 inhibitors, alemtuzumab, total body irradiation, bone marrow transplant (ever) -Anti-CD20 agents, eculizumab, belimumab, or MS DMTs (within 6 months) -Anti-CD4 agents, cladribine, cyclophosphamide, or mitoxantrone (within 2 years) -Any investigational drug within 3 months prior to baseline	Double-blind period ended after: 44 protocol-defined relapses OR Maximum of 1.5 years after the last patient was randomized
Zhang et. al.	TANGO	Intravenous tocilizumab 8 mg/kg every 4 weeks Up to 60 weeks after randomisation Permitted Adjustments: Infusion rate adjustments Symptomatic treatment (e.g., prednisone or diphenhydramine) for infusion-related reactions	Oral azathioprine Began at 25 mg/day, increased in 25 mg/day increments Titrated to 2–3 mg/kg/day Target Dose Maintenance: Once reached, continued until relapse, discontinuation, or end of trial	Systemic corticosteroids were not used as baseline therapy Permitted only as rescue therapy for relapses (either protocol-defined or not) Includes IV glucocorticoids, IVIG, or plasma exchange	Not restricted to treatment-naïve. Patients were excluded if: -Prior relapse on azathioprine therapy -Rituximab or any B-cell–depleting agent within 6 months before screening -CD19+ B cells >1% in peripheral blood mononuclear cells	Planned treatment duration: → 60 weeks after randomisation for both groups (tocilizumab and azathioprine) Post-treatment follow-up: → 24-week follow-up for patients who withdrew or

		Concomitant Immunosuppressants: Allowed during first 12 weeks Thereafter, tocilizumab was used as monotherapy	Concomitant Immunosuppressants: Allowed during first 24 weeks, depending on prior azathioprine exposure: - Naïve: 24 weeks of add-on IST - <24 weeks prior exposure: supplemental IST to complete 24 weeks - ≥24 weeks prior exposure: no concomitant IST After 24 weeks, continued as monotherapy	No other new immunosuppressants were permitted during the trial		discontinued study drug early, during which disability was assessed Total possible individual follow-up: → Up to 84 weeks (60 weeks treatment + 24 weeks follow-up)

AQP4-IgG, aquaporin-4 immunoglobulin G; DMT, disease-modifying therapy; IL-6, interleukin-6; IST, immunosuppressive therapy; IV, intravenous; IVIG, intravenous immunoglobulin; MS, multiple sclerosis; NSAIDs, nonsteroidal anti-inflammatory drugs

Table S6: Inclusion and Exclusion Criteria Overview		
Author	**Name of Study**	**Inclusion and Exclusion Criteria**
Tahara er.al.	RIN-1	Multicentre, randomised, double-blind, placebo-controlled trial. Conducted at eight hospitals in Japan - February 2016 to March 2019. **Inclusion Criteria:** • Age: 16–80 years • Seropositive for AQP4 antibody (including individuals who were previously seropositive but are now seronegative) • History of either optic neuritis or myelitis • Currently receiving oral steroids: Minimum dose ≥5 mg/day-Steroid dose had not changed by >10% in the 3 months before registration • EDSS score of 7.0 or less • Neurologically stable at the time of enrollment **Exclusion Criteria:** • Receiving oral corticosteroids at a dose >30 mg/day (converted to equivalent prednisolone) • Receiving oral immunosuppressive agents other than steroids
Nikoo et. al.		Open-label randomized clinical trial (Double-blind). Conducted in the Department of Neurology of the Kashani hospital, affiliated to Isfahan University of Medical Sciences, Isfahan, Iran. - September 2015 and December 2016. **Inclusion Criteria:** • A diagnosis of NMOSD based on the international consensus diagnostic criteria in 2015, • age between 18 and 50 years • EDSS between 0 and 7 **Exclusion Criteria:** • Pregnancy or lactation during the study • Decision to leave the study • Lack of cooperation for follow-up • Severe side effects of the administered medication, • Treatment with other immunosuppressant medications (including but not limited to mycophenolate mofetil, cyclophosphamide, methotrexate) within 2 months before intervention • Taking any other immunosuppressant or other type of medication (including herbal drugs) without permission of the physician during the study • Presence of other autoimmune diseases (including but not limited to Behcet disease, systemic lupus erythematosus, rheumatoid arthritis), Presence of liver disorders, Presence of hematologic disorders, presence of heart failure, • Receipt of a live vaccine within 4 weeks prior to intervention, • Previous treatment with AZA or RIT, • History of human immunodeficiency virus (HIV), hepatitis B or hepatitis C,

		• History of severe allergic or anaphylactic reaction to monoclonal antibodies.
Pittock et. al.	PREVENT	Phase 3, randomized, double-blind, placebo-controlled, time-to-event Study. Conducted at 70 sites in 18 countries. - From April 2014 to October 2017. **Inclusion Criteria:** • Age ≥18 years. • Diagnosis per 2006/2007 NMOSD criteria. • AQP4-IgG seropositive via Euroimmun assay, centrally confirmed. • ≥2 relapses in past 12 months or ≥3 in 24 months (≥1 in past 12 months). • EDSS score ≤7. • Stable immunosuppressive therapy allowed. **Exclusion Criteria:** • Mitoxantrone or rituximab in past 3 months. • IVIG in past 3 weeks. • Prednisone >20 mg/day at screening. • Active meningococcal disease or significant untreated infections.
Cree et. al.	N-MOmentum	Multicentre, double-blind, randomised placebo-controlled phase 2/3 trial with an open-label extension period Conducted at 99 outpatient specialty clinics or hospitals in 25 countries. **Inclusion Criteria:** • Adults (≥18 years old) with a diagnosis of NMOSD. • EDSS score of ≤8.0. • History of: - At least one attack requiring rescue therapy (IV corticosteroids, IVIG, plasma exchange, or a combination) in the year before screening, or - At least two attacks requiring rescue therapy in the two years before screening. • AQP4-IgG status: - Determined centrally. - Both seropositive and seronegative patients were eligible. • Seronegative patients had to meet the 2015 Wingerchuk et al. criteria. • No pre-planned recruitment target for AQP4-IgG serostatus (expected distribution: ~80% seropositive, 20% seronegative). • All participants provided written informed consent. **Exclusion Criteria:** • Prior use of certain immunotherapies or biologics (e.g., recent B-cell depleting agents). • Significant uncontrolled comorbidities or safety risks that could interfere with study participation or outcomes.
Pittock et. al.	CHAMPION-NMOSD	Phase 3, externally placebo-controlled, open-label, multicenter study (The PREVENT placebo group was used as an external comparator.)

		CHAMPION-NMOSD was designed to mirror PREVENT in terms of inclusion/exclusion, endpoints, and adjudication procedures. (https://www.neurology.org/doi/10.1212/WNL.0000000000203035) **Inclusion Criteria:** • Adults ≥18 years with AQP4+ NMOSD as per 2015 criteria, confirmed by a validated cell-based assay. • At least one relapse in the past 12 months and EDSS ≤7. • Stable-dose IST allowed for inclusion. **Exclusion Criteria:** Prior complement inhibitor use, active systemic infection, meningococcal infection history, prior participation in PREVENT, rituximab/mitoxantrone within 3 months, IVIG within 3 weeks before screening.
Traboulsee et. al.	SAkuraStar	Phase 3, international, randomized, double-blind, placebo-controlled, parallel-assignment trial. **Inclusion Criteria:** **Adolescents or adults (12 to 74 years of age)** • AQP4-IgG–seropositive or AQP4-IgG–seronegative neuromyelitis optica as defined by published criteria • AQP4-IgG–seropositive NMOSD at screening with: • Idiopathic single or recurrent events of longitudinally extensive myelitis (≥3 vertebral-segment spinal cord lesions on MRI), or • Recurrent or simultaneous optic neuritis in both eyes • The percentage of AQP4-IgG–seronegative patients was limited to approximately 30% of the total population of adults (18 to 74 years of age) in the trial • At least two relapses in the 2 years before screening • At least one relapse in the previous 12 months • EDSS score of 0 to 6.5 at screening • Stable dose of permitted baseline treatments for 8 weeks before baseline **Exclusion Criteria:** • Previous treatment with any agent targeting the interleukin-6 pathway • Previous treatment with alemtuzumab • Previous total-body irradiation • Previous bone marrow transplantation • Use of eculizumab, belimumab, or multiple sclerosis disease–modifying treatment within 6 months before baseline • Use of anti-CD4 agents, cladribine, or mitoxantrone within 2 years before baseline
Yamamura et. al.	SAkuraSky	Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group study of satralizumab monotherapy, followed by an open-label extension period Conducted at 44 sites in 13 countries: Bulgaria, Canada, Croatia, Georgia, Italy, Malaysia, Poland, Romania, South Korea, Taiwan, Turkey, USA, and Ukraine **Inclusion Criteria:** • Adults aged 18–74 years

		• AQP4-IgG seropositive or seronegative neuromyelitis optica based on 2006 Wingerchuk criteria • OR AQP4-IgG seropositive NMOSD with: - Single or recurrent events of longitudinally extensive myelitis (≥3 vertebral-segment spinal cord MRI lesions), or - Optic neuritis • Clinical evidence of at least one documented attack in the 12 months before screening • Expanded Disability Status Scale (EDSS) score ≤6.5 • AQP4-IgG seronegative patients limited to ~30% of the total study population (enrollment of seronegative patients stopped after Dec 2, 2016, except those already in screening) **Exclusion Criteria:** • Clinical relapse ≤30 days before baseline • Previous treatment with: (Any IL-6 pathway inhibitors, Alemtuzumab, Total body irradiation, Bone marrow transplantation) • Within 6 months before baseline: (Anti-CD20 agents (e.g., rituximab), Eculizumab, Anti-B-lymphocyte stimulator, Any multiple sclerosis DMT • Within 2 years before baseline: (Anti-CD4 agents, Cladribine, Cyclophosphamide, Mitoxantrone) • Use of any other investigational drug within 3 months prior to baseline
Zhang et. al.	TANGO	Open-label, multicentre, randomised phase 2 trial Conducted at six hospitals in China **Inclusion Criteria:** • Adults ≥18 years • Diagnosed with highly relapsing NMOSD according to 2015 IPND criteria • EDSS ≤7.5 • History of ≥2 relapses in the previous 12 months or ≥3 relapses in the previous 24 months, with ≥1 relapse in the previous 12 months **Exclusion Criteria:** • Clinically significant infection • Pregnant or planning to conceive • Prior relapse while on azathioprine • TPMT mutation (heterozygous or homozygous) • Rituximab or other B-cell-depleting drug in the 6 months before screening • >1% CD19+ B cells in peripheral blood

AQP4, aquaporin-4; AQP4-IgG, aquaporin-4 immunoglobulin G; CD, cluster of differentiation; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; HIV, human immunodeficiency virus; IL-6, interleukin-6; IPND, International Panel for NMO Diagnosis; IVIG, intravenous immunoglobulin; MRI, magnetic resonance imaging; NMOSD, neuromyelitis optica spectrum disorder; TPMT, thiopurine S-methyltransferase