WHAT ARE THE LONG-TERM TREATMENTS FOR NMOSD AND MOGAD?

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TREATMENT: ACUTE VS. PREVENTATIVE

Acute

Preventive

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Acute

Preventive

AGENDA: OVERVIEW OF LONG-TERM TREATMENTS

NMOSD

- FDA- Approved for AQP4 IgG+ Only
  - *Eculizumab *(Soliris)*
  - Satralizumab *(Ensyprng)*
  - Ineblizumab *(Uplinza)*
  - *(Rituximab) → Not FDA approved, but also first-line*

- Off label, Use in AQP4 IgG+ or Seronegative NMOSD
  - *Rituximab *(Rituxan)*
  - Azathioprine *(Imuran)*
  - Mycophenolate Mofetil *(Cellcept)*
  - Tocilizumab *(Actemra)*

MOGAD

- *IVIG or SCIG
- Rituximab *(Rituxan)*
- Azathioprine *(Imuran)*
- Mycophenolate Mofetil *(Cellcept)*
- Tocilizumab *(Actemra)*
- Chronic low-dose steroids

LONG-TERM MANAGEMENT APPROACH

NMOSD (AQP4 IGG POS OR NEG)

- Recovery from attacks can be more limited
- Prevention of ALL attacks is the name of the game!
- All individuals with AQP4 IgG positive NMOSD are recommended to initiate immunotherapy and continue it indefinitely

- In case of long-term stability in seronegative NMOSD, discontinuation of immunotherapy can be discussed on a case-by-case basis

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MOGAD

- 40-50% have a monophasic course, and recovery from relapses is often quite good → Therapy is often deferred unless a second attack occurs to prevent overtreatment
- Exceptions:
  - Significant residual deficits / risk of disability with subsequent attack
  - Very high MOG titers
  - Personal preference
- Patients may trial discontinuation of immunotherapy after several years of stability

LONG-TERM MANAGEMENT: APPROACH

- Many therapeutic options exist → no single 'right answer,' and a lot of factors to consider:
  - Route and frequency of administration: IV, Subcutaneous, Oral
  - Side effect profile: GI side effects, infusion reactions, increased infection risk / decreased vaccine efficacy.
    - Rare significant side effects vs. common minor side effects
  - Onset of action (ranges from days to months)
  - Efficacy
  - Severity of prior attacks / degree of recovery
  - Patient preference

LONG-TERM TREATMENTS FOR NMOSD

NMOSD

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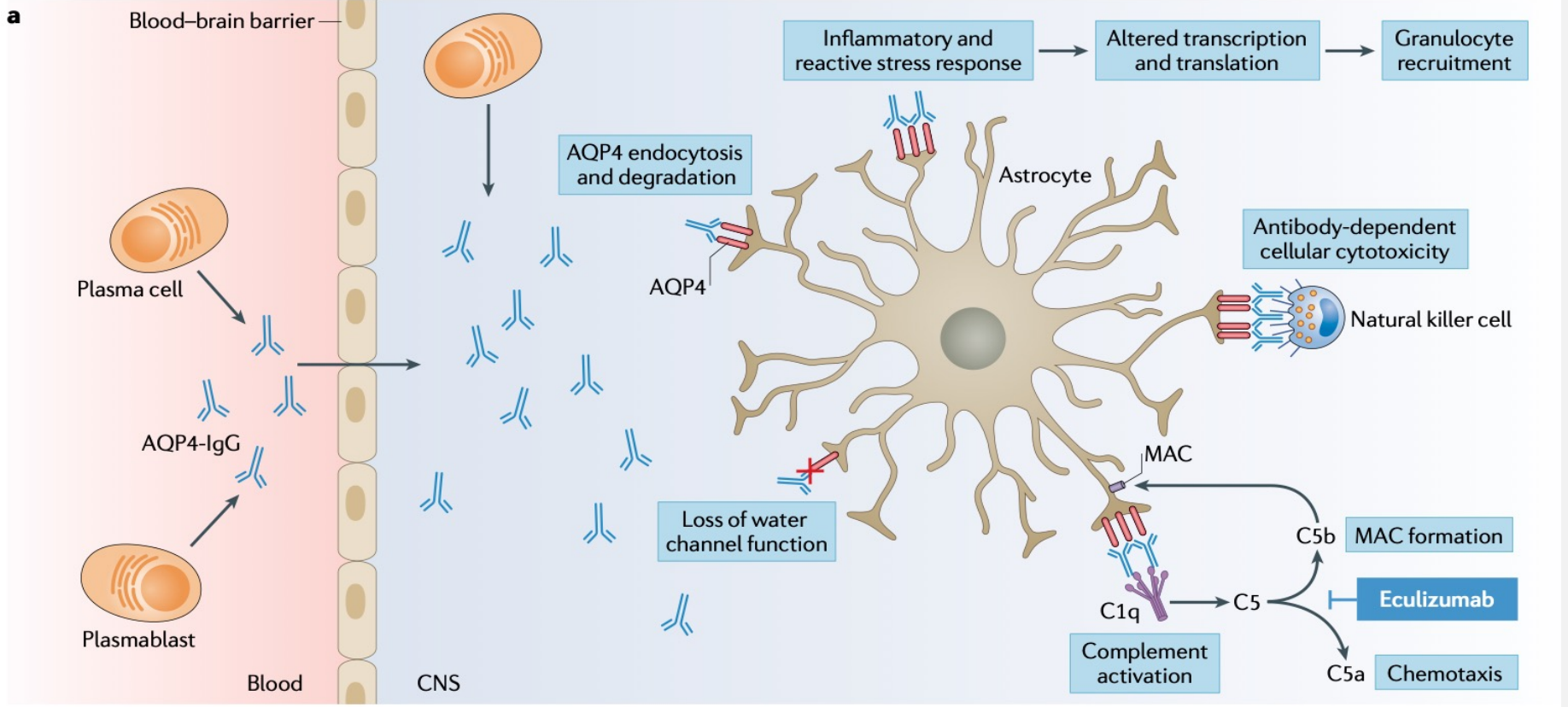
MECHANISMS AND TREATMENTS FOR NMOSD

Trials of 3 dedicated drugs for NMOSD conducted in 2019



Pittock, S.J., Zekeridou, A. & Weinshenker, B.G. Hope for patients with neuromyelitis optica spectrum disorders — from mechanisms to trials. *Nat Rev Neurol* **17,** 759–773 (2021). https://doi.org/10.1038/s41582-021-00568-8

LONG-TERM TREATMENTS FOR NMOSD (AQP4+)

ECULIZUMAB

- **Trial:** *PREVENT*
- **Mechanism:** Complement inhibitor
- **Size**: 96 treated/47 placebo (100% AQP4+)
- 94% risk reduction

SATRALIZUMAB

- **Trial:** *SAkuraSky / SAkuraStar*
- **Mechanism:** IL-6 receptor blocker
- **Size:** 41 treated/42 placebo & 63 treated/32 placebo (65-72% AQP4+)
- 74-79% risk reduction

INEBILIZUMAB

- **Trial:** *N-Momentum*
- **Mechanism:** CD19 B-Cell blocker
- **Size**: 174 treated/56 placebo (92% AQP4+)
- 77% risk reduction

RITUXIMAB

- **Trial:** *RIN-1*
- **Mechanism:** CD20 B-Cell blocker
- **Size**: 19 treated/19 placebo (100% AQP4+)
- 0/19 vs 7/19 with relapses

LONG-TERM TREATMENTS FOR NMOSD (AQP4+)

FDA-Approved

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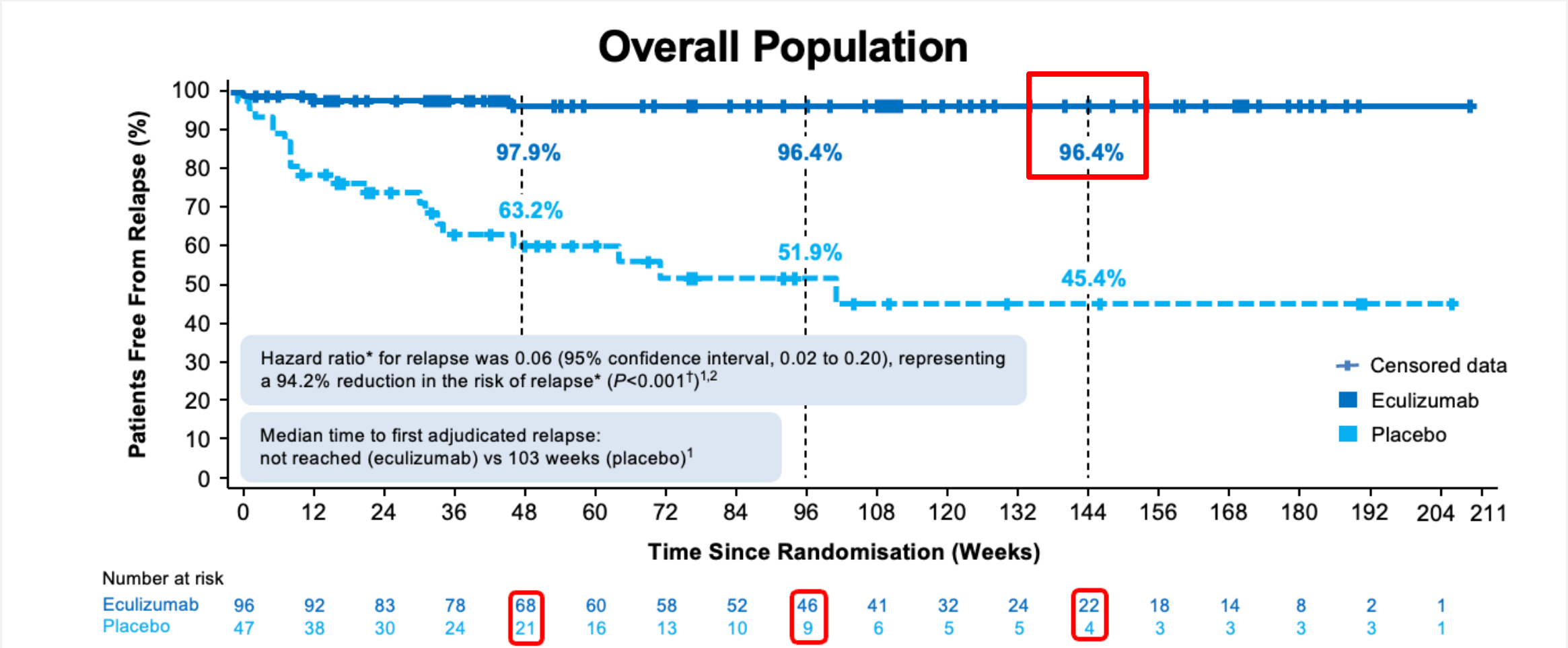
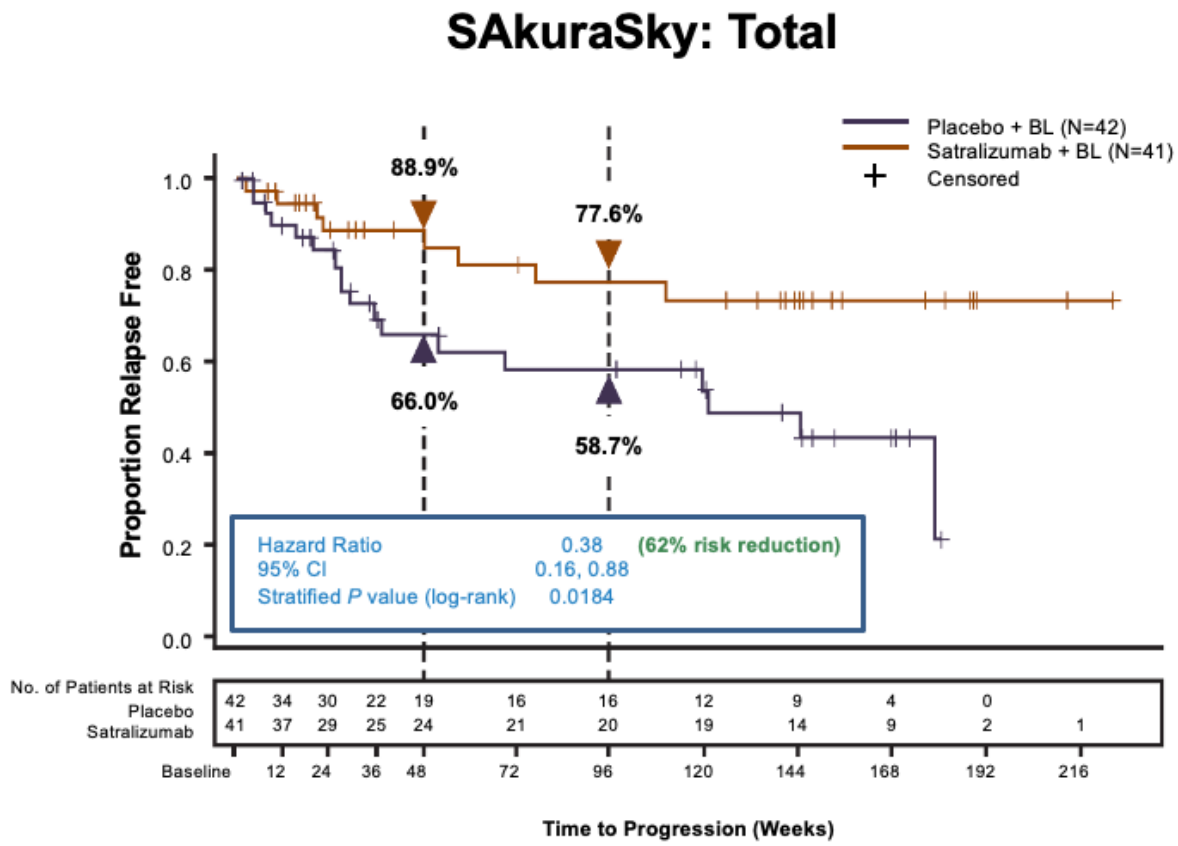
PRIMARY OUTCOME: ECULIZUMAB

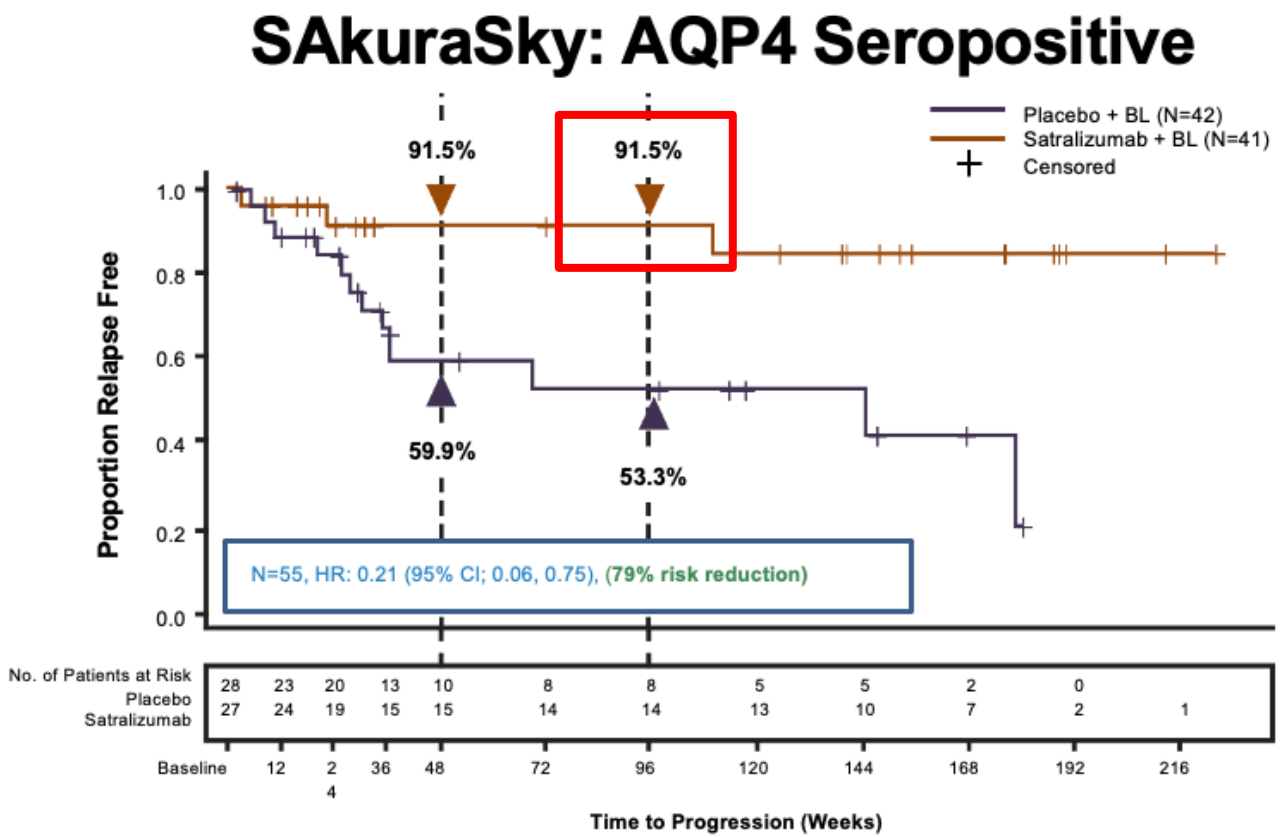


*Based on a stratified Cox proportional hazards model.[2]
†Based on a stratified log-rank test.[2]

1. Pittock SJ, et al. *N Engl J Med*. 2019;381(7):614-625. 2. Pittock SJ, et al. Presented at: American Academy of Neurology Annual Meeting; May 4-10, 2019; Philadelphia, PA.

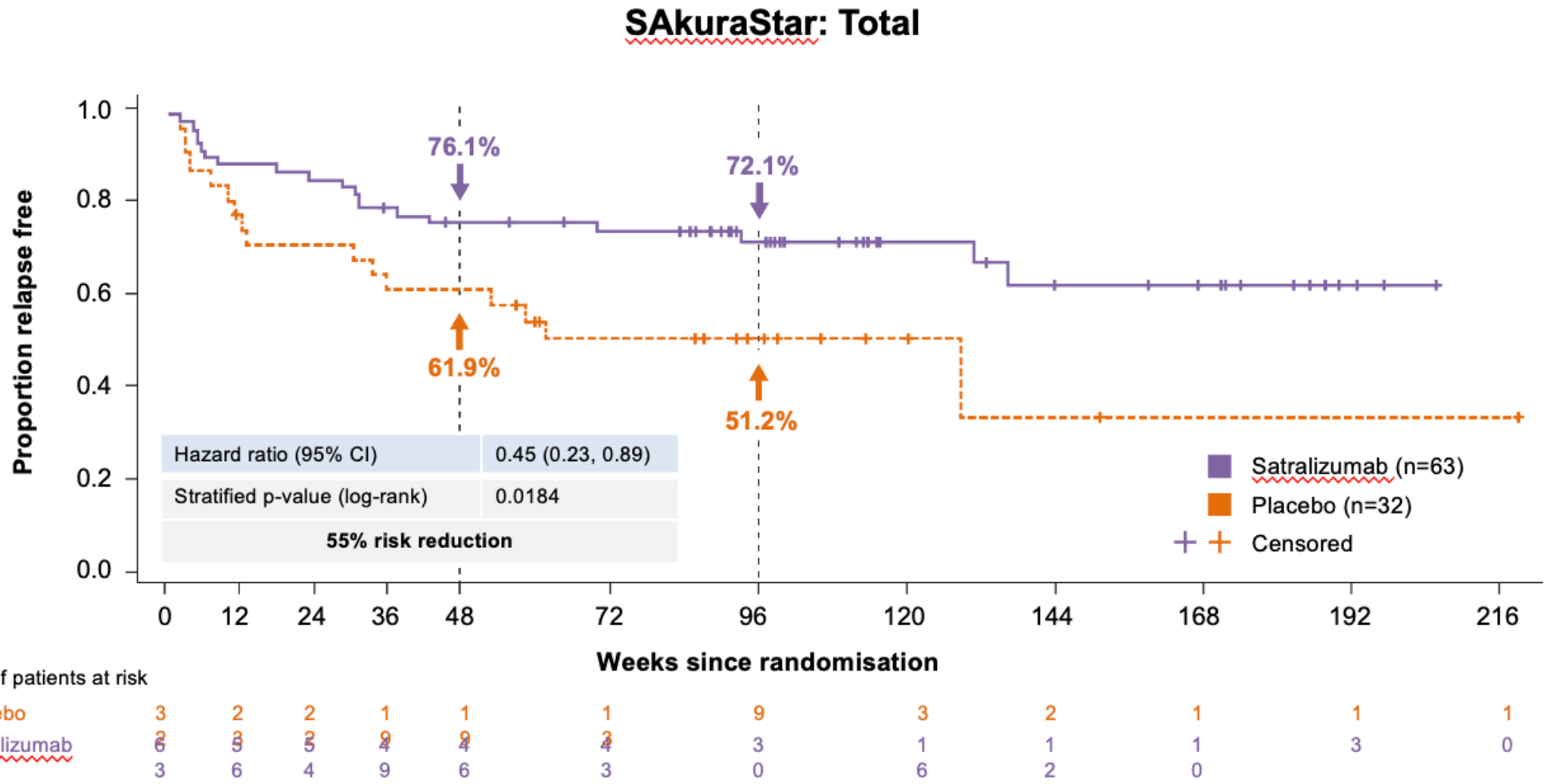
PRIMARY OUTCOME: SATRALIZUMAB





Analysis based on ITT population; *P* values based on log-rank test stratified by geographic region and baseline relapse rate.
Protocol-defined relapse as adjudicated by the independent clinical endpoint committee. EDSS/FSS was assessed within 7 days of relapse reporting.
AQP4, aquaporin 4; BL, baseline treatment; CI, confidence interval; EDSS, Expanded Disability Status Scale; FSS, functional system scores; HR, hazard ratio; ITT, intent to treat.
1. Yamamura T et al. Presented at: ECTRIMS 2018; October 10-12, 2018; Berlin, Germany.

PRIMARY OUTCOME: SATRALIZUMAB

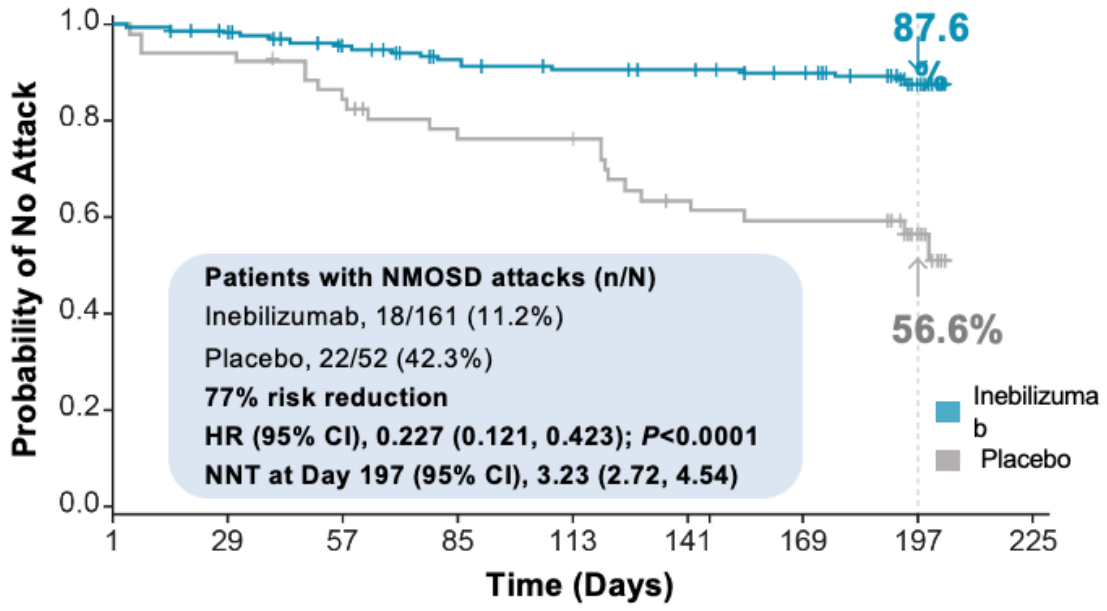


CI, confidence interval; PDR, protocol-defined relapse.

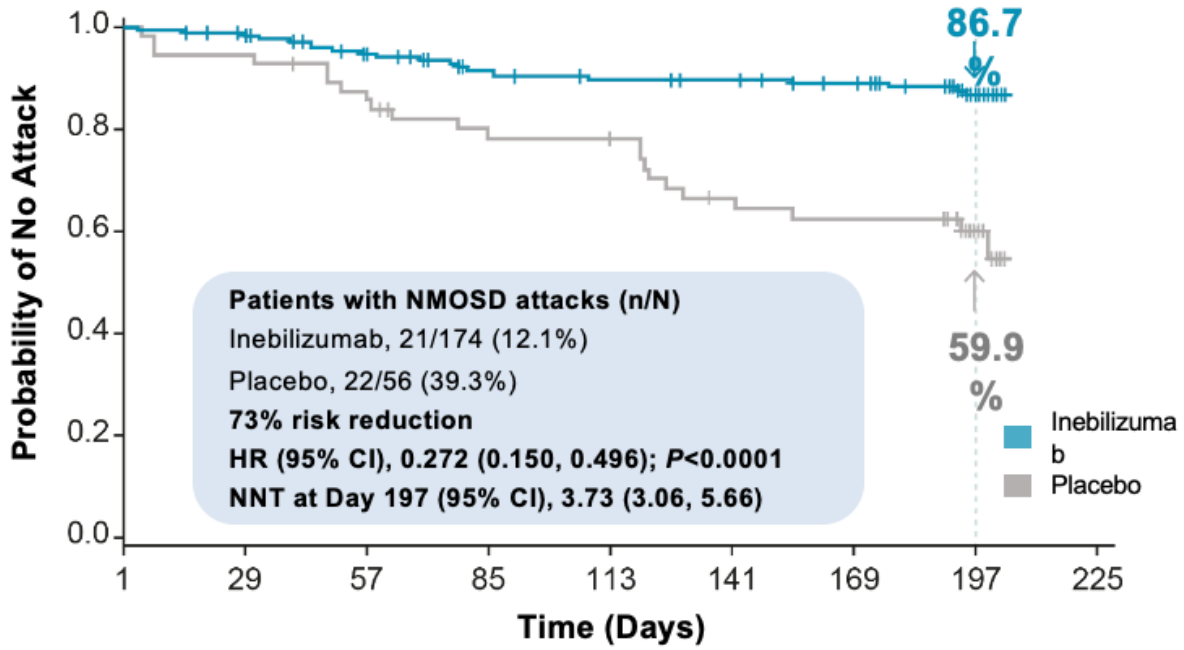
Traboulsee A. Sep 11, 2019; 278963; P603 Presented at ECTRIMS September 11-13, 2019 Stockholm, Sweden

PRIMARY OUTCOME: INEBILIZUMAB

AQP4-IgG Seropositive Population



Overall Population



AQP4, aquaporin 4; CI, confidence interval; HR, hazard ratio; IgG, immunoglobulin; NNT, number needed to treat; NMOSD, neuromyelitis optica spectrum disorders.

1. Cree B, et al. *Lancet* .2019. dx.doi.org/10.1016/S0140-6736(19)31817-3. 2. Cree B, et al. Presented at: American Academy of Neurology Annual Meeting; May 4-10, 2019; Philadelphia, PA..

COMPARISON OF CONVENIENCE AND ADVERSE EFFECTS

ECULIZUMAB

- **Side Effects**: Risk of severe meningococcal infection, or other infections with encapsulated organisms
- **Onset:** Fastest onset
- **Cost:** Extremely expensive, PAs always required
- **Convenience:** ↓↓ IV infusion weekly for 4 weeks, then every 2 weeks

SATRALIZUMAB

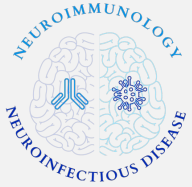
- **Side Effects:** Skin reactions/rashes, high cholesterol, liver function abnormalities, low blood counts, infections (gastrointestinal perforation)
- **Onset:** Slow efficacy onset
- **Cost:** Expensive, PAs always required
- **Convenience:** ↑↑ Self-administered, subcutaneous every 2 weeks in month 1, then every 4 weeks

INEBILIZUMAB

- **Side Effects:** Infusion reactions, infections, decreased vaccine response, low blood counts, hypogammaglobulinemia, (PML)
- **Onset:** Medium onset
- **Cost:** Expensive, PAs always required
- **Convenience:** ↑ IV infusion 2x in 1st month for loading dose, then every 6 months

RITUXIMAB

- **Side Effects:** Infusion reactions, infections, decreased vaccine response, low blood counts, hypogammaglobulinemia, (PML)
- **Onset:** Medium onset
- **Cost:** Available as generic, less expensive.
- **Convenience:** ↑ IV infusion 2x in 1st month for loading dose, then every ~6 months (alternative regimens possible)



LONGTERM TREATMENTS FOR MOGAD AND NMOSD (OFF-LABEL)

OVERVIEW OF LONGTERM TREATMENTS

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NEUROIMMUNOLOGY NEUROINFECTIOUS DISEASE

RITUXIMAB

MOGAD

- Less effective than for MS or NMOSD
- Could be an option in MS / MOGAD overlap cases
- Systematic review with 30% of patients relapsing while having full B cell depletion
- Chen et al: 61% (22 of 36) relapses on rituximab

NMOSD

- Often used as first-line therapy for seronegative NMOSD
- Also widely used and highly effective for AQP4 IgG positive therapy

Zhang, Chao, et al. "Safety and efficacy of tocilizumab versus azathioprine in highly relapsing neuromyelitis optica spectrum disorder (TANGO): an open-label, multicentre, randomised, phase 2 trial." *The Lancet Neurology* 19.5 (2020): 391-401.

AZATHIOPRINE

- Antagonist of purine metabolism → Blockage of DNA, RNA, and protein synthesis
- Takes several months to take effect → requiring concomitant steroid therapy
- Oral dosing, low cost, widely available → amongst the most commonly prescribed worldwide
- Side effects: Infections, low blood counts, abnormal liver counts, long-term use can be associated with skin or hematologic malignancies

MOGAD

- Chen et al: 59% (13 of 22) relapses on AZA
- Other studies have found more significant relapse reductions

NMOSD

- Many case series suggesting efficacy
- TANGO RCT: 91.5% RF in Toci group vs. 67.8% RF in azathioprine group (48 weeks)

Zhang, Chao, et al. "Safety and efficacy of tocilizumab versus azathioprine in highly relapsing neuromyelitis optica spectrum disorder (TANGO): an open-label, multicentre, randomised, phase 2 trial." *The Lancet Neurology* 19.5 (2020): 391-401.

MYCOPHENOLATE MOFETIL

- Inhibits DNA synthesis (IMP blocker)
- Takes several months to take effect → requiring concomitant steroid therapy
- Oral dosing, low cost, widely available → amongst the most commonly prescribed worldwide
- Side effects: Infections, low blood counts, abnormal liver counts, possible skin malignancies

MOGAD

- Observational cohort study had a relapse rate of 7.4% (4/54) on MMF, and 44% (11/25) on placebo.
- Chen et al: 74% (14 of 19) relapses on MMF
- Australian cohort: high relapse rates

NMOSD

- Systematic reviews (often including MOGAD, seronegative, and AQP4 positive cases) have demonstrated reduced ARR.

Long-term efficacy of mycophenolate mofetil in myelin oligodendrocyte glycoprotein antibody-associated disorders A prospective study. Shengde Li, Haitao Ren, Yan Xu, Tao Xu, Yao Zhang Xiaotun Ren, Fang Fang, Wenhan Li, Yicheng Zhu, Bin Peng, Jing Wang, Yong Zhong, Liying Cui Neurol Neuroimmunol Neuroinflamm May 2020, 7 (3) e705; DOI: 10.1212/NXI.0000000000000705

TOCILIZUMAB

- IL-6 Receptor Blocker (like Satralizumab)
- Given IV, once monthly (subcutaneous formulation also exists)
- Side effects: Low blood counts, infections, high cholesterol, liver function test abnormalities, Diverticular perforation (rare)

MOGAD

- Case series of 10 patients showed no relapses over average duration of 28.6mo
- Look out for RCT for Satralizumab (related mechanism)

NMOSD

- May be used off-label for seronegative cases
- TANGO RCT: 91.5% RF in Toci group vs. 67.8% RF in azathioprine group (48 weeks)

Elsbernd, Paul M., et al. "Interleukin-6 inhibition with tocilizumab for relapsing MOG-IgG associated disorder (MOGAD): a case-series and review." *Multiple Sclerosis and Related Disorders* 48 (2021): 102696.
Zhang, Chao, et al. "Safety and efficacy of tocilizumab versus azathioprine in highly relapsing neuromyelitis optica spectrum disorder (TANGO): an open-label, multicentre, randomised, phase 2 trial." *The Lancet Neurology* 19.5 (2020): 391-401.

INTRAVENOUS IMMUNOGLOBULIN (IVIG) & SUBCUTANEOUS IMMUNOGLOBULIN (SCIG)

- Likely the most efficacious MOGAD therapy:
  - In 70 patients with MOGAD, those receiving IVIG had lower relapse rates (20%) compared to azathioprine (59%), rituximab (61%), and mycophenolate mofetil (74%)
  - Reduction in relapse rate seen after IVIG in both first-line and second-line cases
- More effective with higher doses, more frequent administration
- Cost, availability, and convenience are a significant limitation
  - 0.4g/kg/day x5 days, followed by re-treatment monthly
  - IVIG can be given via home infusions when available/covered
- SCIG may be self-administered at home, but high liquid volumes may limit tolerability
  - Newer, less widely available and less widely studied

Chen JJ, Huda S, Hacohen Y, Levy M, Lotan I, Wilf-Yarkoni A, et al. Association of maintenance intravenous immunoglobulin with prevention of relapse in adult myelin oligodendrocyte glycoprotein antibody-associated disease. JAMA Neurol. (2022). doi: 10.1001/jamaneurol.2022.0489

Chen JJ, Flanagan EP, Bhatti MT, Jitprapaikulsan J, Dubey D, Lopez Chiriboga ASS, et al. Steroid-sparing maintenance immunotherapy for MOG-IgG associated disorder. Neurology. (2020) 95:e111–e20. doi: 10.1212/WNL.0000000000009758

OTHER TREATMENTS

- Mitoxantrone
- Methotrexate
- Cyclophosphamide
- Experimental *(Get excited for the next session on clinical trials!)*
  - Stem Cell therapies
  - Ravulizumab for NMOSD
  - Satralizumab for MOGAD
  - Rozanolixizumab for MOGAD
  - BTK inhibitors
  - Others!

EXTRA REFERENCE SLIDES

Table 1 | **Design of randomized controlled trials in neuromyelitis optica spectrum disorders**

Trial (drug)	Patients	Inclusion criteria	RCP	Treatment arm	Control arm	Open-label period
PREVENT[23] (eculizumab)[a]	143 total 143 AQP4-IgG$^+$	≥2 attacks in previous 12 months or ≥3 attacks in previous 24 months with ≥1 in previous 12 months; EDSS score ≤7; IST allowed	2 years 2:1 randomization	Eculizumab ± IST 900 mg IV weekly for 4 weeks, then 1,200 mg IV every 2 weeks	Placebo ± IST	Eligible for entry at end of RCP or after physician-determined or adjudicated attack
SAkuraSky[24] (satralizumab)	83 total 55 AQP4-IgG$^+$	≥2 attacks in previous 24 months with ≥1 in previous 12 months; EDSS score ≤6.5; IST allowed	1.5 years 1:1 randomization	Satralizumab + IST 120 mg SC at weeks 0, 2 and 4, then every 4 weeks	Placebo + IST	Eligible for entry at end of RCP or after an attack requiring rescue treatment or an adjudicated attack
SAkuraStar[25] (satralizumab)	95 total 64 AQP4-IgG$^+$	≥1 attack in previous 12 months; EDSS score ≤6.5; no IST allowed	1 year 2:1 randomization	Satralizumab 120 mg SC at weeks 0, 2 and 4, then every 4 weeks	Pure placebo	Eligible for entry at end of RCP or after an attack requiring rescue treatment or an adjudicated attack
N-MOmentum[22] (inebilizumab)	230 total 213 AQP4-IgG$^+$	≥1 attack in previous 12 months or ≥2 attacks in previous 24 months; EDSS score ≤8; no IST allowed	28 weeks 3:1 randomization	Inebilizumab 300 mg IV every 2 weeks	Pure placebo	Eligible for entry at end of RCP or after an adjudicated attack
RIN-1 (REF.[26]) (rituximab)	38 total 38 AQP4-IgG$^+$	≥1 attack of optic neuritis or myelitis ever; EDSS score ≤7; low-dose steroid treatment allowed	72 weeks 1:1 randomization	Rituximab 375 mg/m^2 IV weekly for 4 weeks, then 6-month interval dosing (1,000 mg every 2 weeks)	Placebo + prednisolone	Eligible for entry at end of RCP or after an attack

AQP4, aquaporin 4; EDSS, Expanded Disability Status Scale; IST, immunosuppressive treatment; IV, intravenously; RCP, randomized control phase; SC, subcutaneously. [a]Patients enroled in PREVENT were vaccinated against *Neisseria meningitidis* (MenACWY and MenB) and enrolled in the Risk Evaluation and Mitigation Strategy before receiving a trial agent.

EXTRA REFERENCE SLIDES

Table 2 | **Baseline characteristics of participants in randomized trials in NMOSD**

Study	Study arm	*n*	Percentage AQP4-IgG$^+$	Percentage women participants	Mean age at enrolment (years)	Mean age at onset (years)	Mean disease duration (years)	ARR in prior 2 years	Average EDSS score at entry
PREVENT[23]	Placebo	47	100	89	45	38	4.3	2.1	4.0
	Treatment	96	100	92	44	36	3.3	1.9	4.0
SAkuraSky[24]	Placebo	42	67	95	43	39	4.6	1.4	3.6
	Treatment	41	66	90	41	35	5.4	1.5	3.8
SAkuraStar[25]	Placebo	32	72	97	40	39	4.1	1.5	3.7
	Treatment	63	65	73	45	36	6.1	1.4	3.9
N-MOmentum[22]	Placebo	56	92	89	43	NA	2.8	1.5	4.2
	Treatment	174	93	91	43	NA	2.4	1.7	3.8
RIN-1 (REF.[26])	Placebo	19	100	100	NA	45	6.7	0.7	4.0
	Treatment	19	100	90	NA	46	9.9	1.4	3.5

Not for direct comparison; no head-to-head trials have been conducted. AQP4, aquaporin 4; ARR, annualized relapse rate; EDSS, Expanded Disability Status Scale; NA, not available; NMOSD, neuromyelitis optica spectrum disorder.

EXTRA SLIDES

Table 4 | **Outcomes of randomized trials in NMOSD**

Study	Population	Study arm	Percentage relapse free		Risk reduction (%)	Hazard ratio (95%CI, *P*)	Summary of secondary outcomes in total population
			48 weeks	96 weeks			
PREVENT[23]	Total	Placebo	63.2	51.9	94	0.06 (0.02–0.2, <0.001)	ARR 0.02 with drug, 0.35 with placebo; change in EDSS score 0.18 with drug, –0.12 with placebo; change in mRS –0.24 with drug, –0.09 with placebo
		Treatment	97.9	96.4			
SAkuraSky[24]	Total	Placebo	66.0	58.7	62	0.38 (0.16–0.75, 0.018)	ARR 0.11 with drug, 0.32 with placebo; change in EDSS score –0.1 with drug, –0.21 with placebo
		Treatment	88.9	77.6			
	AQP4-IgG$^+$	Placebo	59.9	53.3	79	0.21 (0.06–0.75, NA)	
		Treatment	91.5	91.5			
SAkuraStar[25]	Total	Placebo	61.9	51.2	55	0.45 (0.23–0.89, 0.018)	No significant changes from baseline to week 24 in pain scores or fatigue scores
		Treatment	76.1	72.1			
	AQP4-IgG$^+$	Placebo	55.4	41.1	74	0.26 (0.11–0.63, 0.001)	
		Treatment	82.9	76.5			
N-MOmentum[22]	Total	Placebo	60.7[a]	NA	73	0.27 (0.15–0.49, <0.0001)	EDSS score worsening 16% with drug, 34% with placebo; 43% fewer new MRI lesions with drug than with placebo; 71% fewer disease-related hospitalizations with drug than with placebo
		Treatment	87.9[a]	NA			
	AQP4-IgG$^+$	Placebo	56.6[a]	NA	77	0.23 (0.12–0.42, <0.0001)	
		Treatment	87.6[a]	NA			
RIN-1 (REF.[26])	Total	Placebo	Numbers too small for accurate quantification				ARR 0.0 with drug, 0.32 with placebo
		Treatment	Group difference 36.8% (95% CI 12.3–65.5, log-rank $P = 0.0058$)				

AQP4, aquaporin 4; ARR, annualized relapse rate; EDSS, Expanded Disability Status Scale; mRS, modified Rankin score; NA, not available; NMOSD, neuromyelitis optica spectrum disorder. [a]Results from randomized controlled phase reported at 28 weeks.