Network Meta-analysis of Food and Drug Administration-approved Treatment Options for Adults with Aquaporin-4 Immunoglobulin G-positive Neuromyelitis Optica Spectrum Disorder

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Supplementary Material

Appendices

Appendix A. Literature search strategies

EMBASE 1974 to 2020 September 10; Search executed: 11 September 2020 (via Ovid)

Table S1 Search strategy for EMBASE

No.	Strings
1	exp Neuromyelitis Optica/
2	(neuromyelitis optica or NMO Spectrum Disorder or NMO Spectrum Disorders or Neuromyelitis Optica Spectrum Disorders or Devic Neuromyelitis Optica or Devic Neuromyelitis Opticas or Neuromyelitis Optica, Devic or Neuromyelitis Opticas, Devic or Devic's Disease or Devics Disease or Disease, Devic's or Devic Disease or Disease, Devic or Devic Syndrome or Syndrome, Devic or Devic's Syndrome or Devics Syndrome or Syndrome, Devic's or Devic's Neuromyelitis Optica or Devics Neuromyelitis Optica or Neuromyelitis Optica, Devic's or Neuromyelitis Optica Spectrum Disorder).mp.
3	1 or 2
4	exp eculizumab/
5	(eculizumab or Alexion or Soliris or H5G1-1 or H5G11).mp.
6	exp satralizumab/
7	(satralizumab or sapelizumab or SA237).mp.
8	exp inebilizumab/
9	(inebilizumab or MEDI-551 or MEDI551).mp
10	or/4-9
11	Clinical Trial/
12	Randomized Controlled Trial/
13	controlled clinical trial/
14	multicenter study/
15	Phase 3 clinical trial/
16	Phase 4 clinical trial/
17	exp RANDOMIZATION/
18	Single Blind Procedure/
19	Double Blind Procedure/
20	Crossover Procedure/
21	PLACEBO/
22	randomi?ed controlled trial$.tw.
23	rct.tw.
24	(random$ adj2 allocat$).tw.
25	single blind$.tw.
26	double blind$.tw.
27	((treble or triple) adj blind$).tw.

No.	Strings
28	placebo$.tw.
29	Prospective Study/
30	or/11-29
31	Case Study/
32	case report.tw.
33	abstract report/ or letter/
34	Conference proceeding.pt.
35	Conference abstract.pt.
36	Editorial.pt.
37	Letter.pt.
38	Note.pt.
39	or/31-38
40	30 not 39
41	3 and 10 and 40
42	limit 41 to english language

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to September 10, 2020; Search executed: 11 September 2020 (via Ovid)

Table S2 Search strategy for MEDLINE

No.	Strings
1	exp Neuromyelitis Optica/
2	(neuromyelitis optica or NMO Spectrum Disorder or NMO Spectrum Disorders or Neuromyelitis Optica Spectrum Disorders or Devic Neuromyelitis Optica or Devic Neuromyelitis Opticas or Neuromyelitis Optica, Devic or Neuromyelitis Opticas, Devic or Devic's Disease or Devics Disease or Disease, Devic's or Devic Disease or Disease, Devic or Devic Syndrome or Syndrome, Devic or Devic's Syndrome or Devics Syndrome or Syndrome, Devic's or Devic's Neuromyelitis Optica or Devics Neuromyelitis Optica or Neuromyelitis Optica, Devic's or Neuromyelitis Optica Spectrum Disorder).mp.
3	1 or 2
4	(eculizumab or Alexion or Soliris or H5G1-1 or H5G11).mp.
5	(satralizumab or sapelizumab or SA237).mp.
6	(inebilizumab or MEDI-551 or MEDI551).mp
7	or/4-6
8	Randomized Controlled Trials as Topic/
9	randomized controlled trial/
10	Random Allocation/
11	Double Blind Method/
12	Single Blind Method/
13	clinical trial/
14	clinical trial, phase i.pt.

No.	Strings
15	clinical trial, phase ii.pt.
16	clinical trial, phase iii.pt.
17	clinical trial, phase iv.pt.
18	controlled clinical trial.pt.
19	randomized controlled trial.pt.
20	multicenter study.pt.
21	clinical trial.pt.
22	exp Clinical Trials as topic/
23	or/8-22
24	(clinical adj trial$).tw.
25	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
26	PLACEBOS/
27	placebo$.tw.
28	randomly allocated.tw.
29	(allocated adj2 random$).tw.
30	or/24-29
31	23 or 30
32	case report.tw.
33	letter/
34	historical article/
35	or/32-34
36	31 not 35
37	3 and 7 and 36
38	limit 37 to english language

EBM Reviews - Cochrane Central Register of Controlled Trials to August 2020; Search executed: 11 September 2020 (via Ovid)

Table S3 Search strategy for Cochrane Central Register of Controlled Trials

No.	Strings
1	exp Neuromyelitis Optica/
2	(neuromyelitis optica or NMO Spectrum Disorder or NMO Spectrum Disorders or Neuromyelitis Optica Spectrum Disorders or Devic Neuromyelitis Optica or Devic Neuromyelitis Opticas or Neuromyelitis Optica, Devic or Neuromyelitis Opticas, Devic or Devic's Disease or Devics Disease or Disease, Devic's or Devic Disease or Disease, Devic or Devic Syndrome or Syndrome, Devic or Devic's Syndrome or Devics Syndrome or Syndrome, Devic's or Devic's Neuromyelitis Optica or Devics Neuromyelitis Optica or Neuromyelitis Optica, Devic's or Neuromyelitis Optica Spectrum Disorder).mp.
3	1 or 2
4	(eculizumab or Alexion or Soliris or H5G1-1 or H5G11).mp.
5	(satralizumab or sapelizumab or SA237).mp.
6	(inebilizumab or MEDI-551 or MEDI551).mp

7	or/4-6
8	3 and 7
9	limit 8 to english language

Table S4 Evidence base: included publications by RCT

Trial ID	Trial Number	Principal publication	Associated publications
N-MOmentum	NCT02200770	Cree et al., 2019	Cree et al., 2019; *Multiple Sclerosis Journal*
			Cree et al., 2019; *Multiple Sclerosis Journal*
			Marignier et al., 2019; *Multiple Sclerosis Journal*
			Cree et al., 2020; AAN Enterprises
PREVENT	NCT01892345	Pittock et al., 2019	Berthele et al., 2019; *Multiple Sclerosis Journal*
			Kim et al., 2019; *Multiple Sclerosis Journal*
			Palace et al., 2019; *Multiple Sclerosis Journal*
			Pittock et al., 2019; *Multiple Sclerosis Journal*
			Wingerchuk et al., 2019; *Multiple Sclerosis Journal*
			Pittock et al., 2020; ECTRIMS 2020
			Levy et al., 2020; ECTRIMS 2020
			Fujihara et al., 2020; ECTRIMS 2020
			Wingerchuk et al., 2020; ECTRIMS 2020
			Oreja-Guevara et al., 2020; EUROPEAN JOURNAL OF NEUROLOGY2020
			Wingerchuk et al., 2020; AAN Enterprises
SAkuraSky	NCT02028884	Yamamura et al., 2019	Yamamura et al., 2018; *European journal of neurology*
			Araki et al., 2019; *Clinical neurology*
			Yamamura et al., 2019; *Clinical neurology*
			Yamamura et al., 2019; *Journal of the neurological sciences*
			Yamamura et al., 2019; *Neurology*
			Yamamura et al., 2019; *European journal of neurology*

Trial ID	Trial Number	Principal publication	Associated publications
SAkuraStar	NCT02073279	Traboulsee et al., 2020	Bennett et al., 2019; *Multiple Sclerosis Journal*
			Bennett et al., 2019; *Journal of the neurological sciences*
			Traboulsee et al., 2019; *Multiple Sclerosis Journal*
			Traboulsee et al., 2019; *Journal of the neurological sciences*

RCT, randomized controlled trial.

Appendix B. Prespecified data extraction items

Trial characteristics

The following study characteristics were extracted:

- Trial name or ID
- Trial year
- Trial authors
- Trial design (phase, blinding)
- NCT code
- Number of patients randomized
- Number of patients completed
- Trial duration
- Trial initiation date
- Trial completion date
- Treatment arms
- Follow-up duration
- Study inclusion criteria
- Study exclusion criteria
- Outcome endpoint definitions

Intervention characteristics

The following intervention characteristics were extracted:

- Treatment regimen
- Treatment dose
- Method of administration
- Frequency of administration
- Number of treatments
- Duration of treatment

- Concomitant/background therapies

Patient characteristics

The following patient characteristics were extracted:

- Age at initial clinical presentation
- Age at study start
- Annualized relapse rate (ARR; preferably reported in previous 2 years)
    - Type of relapse (optic neuritis, myelitis, brain, and so on)
- Diagnosis (NMO or NMOSD)
- Disease duration
- Expanded Disability Status Scale (EDSS) score
- Gender
- Geographical region of study
- Immunosuppressive therapy at baseline
- Presence of AQP4 antibodies
- Prior treatment experience
- Race and ethnicity
- Sample size at baseline

Outcomes

The following outcomes were extracted:

- Efficacy
    - Time to first trial relapse
    - Annualized relapse rate (ARR)
- Health-related quality of life
    - Expanded Disability Status Scale (EDSS) score
    - Modified Rankin Scale (mRS) score
    - Hauser Ambulation Index (HAI) score

    - EuroQol 5-Dimension Questionnaire (EuroQoL EQ-5D) score
    - 36-Item Short Form Survey (SF-36) score
- Safety
    - Adverse events proportion by reactions (overall, grade 3 or above, treatment-related, serious, discontinuations, and mortality)

Study quality

Included trials were evaluated using the Cochrane Risk of Bias tool, which assessed the following criteria:

- Details regarding randomization process
- Details regarding deviations from intended interventions
- Details regarding missing outcome data
- Details regarding measurement of the outcome
- Details regarding selection of the reported result
- Details regarding other possible sources of bias

Table S5 Assessment of risk of bias of included trials

	N-MOmentum	PREVENT	SAkuraSky	SAkuraStar
Overall assessment[a]	Low risk	Low risk	Low risk	Low risk

[a]Assessment results covered randomization process, deviations of the intended interventions, missing outcome data, and selection of the reported result, and all were deemed low risk.

Appendix C. Trial characteristics of included studies

Table S6 Trial characteristics of included studies

Characteristic		N-MOmentum	PREVENT	SAkuraSky	SAkuraStar
Study design	**Allocation**	Randomized	Randomized	Randomized	Randomized
	Intervention model	Parallel assignment	Parallel assignment	Parallel assignment	Parallel assignment
	Masking	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	Double (Participant, Investigator)	Double (Participant, Investigator)
	Phase	2/3	3	3	3
Actual study start date		January 2015	April 2014	February 2014	August 2014
Primary or estimated completion date		October 2022	July 2018	June 2018	August 2018
Recruitment status		Active, not recruiting	Not active[a]	Active, not recruiting	Active, not recruiting
RCP length		197 days (~6 months)	Occurrence of 23 on-trial relapses	Occurrence of 26 on-trial relapses	Occurrence of 35 on-trial relapses
Study site regions		25 countries across the Americas, Europe, Asia-Pacific, Africa	18 countries across the Americas, Europe, Asia-Pacific	11 countries across North America, Europe, Asia-Pacific	15 countries across the Americas, Europe, Asia-Pacific
Sample size		230	143	83	95
Intervention		Inebilizumab	Eculizumab ± IST	Satralizumab + IST	Satralizumab
Comparator		Placebo	Placebo ± IST	Placebo + IST	Placebo
Inclusion	**Age**	≥ 18	≥ 18	12–74	18–74
	EDSS	≤ 7.5	≤ 7	≤ 6.5	≤ 6.5
	Relapse history	≥ 1 in previous 12 months; ≥ 2 in previous 24 months	≥ 2 in previous 12 months; ≥ 3 in previous 24 months	≥ 2 in previous 2 years	≥ 1 in previous 12 months
	Background therapy	No IST permitted during RCP	If patient entered trial receiving IST, patient must	Continued baseline treatment of azathioprine, mycophenolate	No concomitant treatment for NMOSD was allowed

Characteristic		N-MOmentum	PREVENT	SAkuraSky	SAkuraStar
			continue stable maintenance doses for the duration of the trial	mofetil, or oral glucocorticoids allowed during RCP	
Exclusion	**Comorbidity**	Other immune diseases	Other immune diseases	Other immune diseases	Other immune diseases
	Prior treatment	**Prior**: alemtuzumab, total lymphoid irradiation, bone marrow transplant, T-cell vaccine **Within 6 months**: rituximab or experimental B-cell depleting agent **Within 3 months**: natalizumab, cyclosporine, methotrexate, mitoxantrone, cyclophosphamide, tocilizumab **Within 1 month**: receipt of IVIG	**Within 3 months**: rituximab, mitoxantrone, IVIG	**Prior**: IL-6 inhibitor, alemtuzumab, total body irradiation, bone marrow transplantation **Within 2 years**: anti-CD4, cladribine, cyclophosphamide, mitoxantrone) **Within 6 months**: anti-CD20, eculizumab, anti-BLyS antibody, MS relapse prevention treatments	**Prior**: IL-6 inhibitor, alemtuzumab, total body irradiation, bone marrow transplantation **Within 2 years**: anti-CD-4, cladribine, cyclophosphamide, mitoxantrone) **Within 6 months**: anti-CD20, eculizumab, anti-BLyS antibody, MS relapse prevention treatments

[a]After a review of blinded data, the sponsor terminated the trial after 23 patients had an adjudicated relapse; based on sample-size calculations, study had at least 80% power to detect between-group difference for primary end point.

BLyS, B-lymphocyte stimulator; CD, cluster of differentiation; EDSS, Expanded Disability Status Scale; IL-6, interleukin-6; IST, immunosuppressive therapy; IVIG, intravenous immunoglobulin; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; RCP, randomized controlled period.

Table S7 Reported time-to-first relapse

Trial	Population	Treatment	N	Time to first relapse, HR (95% CI)
N-MOmentum	ITT	Inebilizumab	174	0.27 (0.15, 0.49)
		Placebo	56	
	AQP4+	Inebilizumab	161	0.23 (0.12, 0.42)
		Placebo	52	
PREVENT	ITT	Eculizumab ± IST	96	0.06 (0.02, 0.20)
		Placebo ± IST	47	
	No baseline IST	Eculizumab	21	0.00 (0.00, NE)
		Placebo	13	
	Baseline IST	Eculizumab + IST	75	0.09 (0.03, 0.28)
		Placebo + IST	34	
SAkuraSky	ITT	Satralizumab + IST	41	0.38 (0.16, 0.88)
		Placebo + IST	42	
	AQP4+	Satralizumab + IST	27	0.21 (0.06, 0.75)
		Placebo + IST	28	
SAkuraStar	ITT	Satralizumab	63	0.45 (0.23, 0.89)
		Placebo	32	
	AQP4+	Satralizumab	41	0.26 (0.11, 0.63)
		Placebo	23	

AQP4+, aquaporin-4 immunoglobulin G-positive; CI, confidence interval; HR, hazard ratio; IST, immunosuppressive therapy; ITT, intent-to-treat; NE, not evaluable.

Appendix D. Treatment characteristics of included studies

Table S8 Treatment characteristics of included studies

Trial	Treatment	Dose	Background treatment
N-MOmentum	Inebilizumab	Inebilizumab, IV (300 mg; D1, D15)	• Tapering of oral corticosteroid at study start • No other use of IST permitted during randomized controlled period
	Placebo	Placebo, IV (300 mg; D1, D15)	
PREVENT	Eculizumab ± IST	Eculizumab, IV (900 mg; W0, W1, W2, W3 then 1200 mg maintenance Q2W)	Various background treatment options, such as: • None or other • Azathioprine: remain on stable dose for duration of the study • Mycophenolate mofetil: remain on stable dose for duration of the study • Steroid: daily steroid cannot be more than prednisone 20 mg or equivalent
	Placebo ± IST	Placebo, IV (900 mg; W0, W1, W2, W3 then 1200 mg maintenance Q2W)	
SAkuraSky	Satralizumab + IST	Satralizumab, SC (120 mg; W0, W2, W4 then Q4W)	• Azathioprine: maximum 3 mg/kg/day • Mycophenolate mofetil: maximum 3000 mg/day • Glucocorticoid: maximum 15 mg/day
	Placebo + IST	Placebo, SC (120 mg; W0, W2, W4 then Q4W)	
SAkuraStar	Satralizumab	Satralizumab, SC (120 mg; W0, W2, W4 then Q4W)	• Other IST prohibited during the study • Corticosteroids and intravenous immunoglobulin also prohibited except as rescue therapy
	Placebo	Placebo, SC (120 mg; W0, W2, W4 then Q4W)	

D, day; IST, immunosuppressive therapy; IV, intravenous; QD, every day; Q2W, every 2 weeks; Q4W, every 4 weeks; SC, subcutaneous; W, week.

Appendix E. Additional baseline patient characteristics of included studies

Table S9 Patient characteristics of included AQP4+ studies (age, race, disease status)

Trial ID	Treatment arm	N	Baseline age, yr mean (SD; range)	Female, n (%)	Race, White n (%)	Race, Asian n (%)	Baseline AQP4+, n (%)
N-MOmentum	Placebo	56	43 (14; 18-74)	50 (89)	28 (50)	8 (14)	52 (93)
	Inebilizumab	174	43 (12; 18-73)	159 (91)	92 (53)	39 (22)	161 (93)
PREVENT	Placebo ± IST	47	45 (13; 21-75)	42 (89)	24 (51)	15 (32)	47 (100)
	Eculizumab ± IST	96	44 (13; 19-70)	88 (92)	46 (48)	37 (39)	96 (100)
SAkuraSky	Placebo + IST	42	43 (12; 14-65)	40 (95)	--	18 (43)	28 (67)
	Satralizumab + IST	41	41 (16; 13-73)	37 (90)	--	16 (39)	27 (66)
SAkuraStar	Placebo	32	41 (11; 20-56)	31 (97)	22 (69)	6 (19)	23 (72)
	Satralizumab	63	46 (12; 21-70)	46 (73)	37 (59)	8 (13)	41 (65)

AQP4+, aquaporin-4 immunoglobulin G-positive; IST, immunosuppressive therapy; SD, standard deviation; yr, year.

Table S10 Patient characteristics of included studies (disease and relapse history)

Trial ID	Treatment arm	N	Disease duration yr, mean (SD)	Baseline ARR mean (SD)	Baseline EDSS mean (SD)	Type of most recent attack			Prior rituximab n (%)
						Optic neuritis n (%)	Myelitis n (%)	Brain n (%)	
N-MOmentum	Placebo	56	2.8 (3.5)	1.6 (1.5)	4.2 (1.7)	21 (35)	34 (61)	10 (18)	4 (8)
	Inebilizumab	174	2.4 (3.3)	1.7 (1.5)	3.8 (1.8)	85 (49)	99 (57)	8 (5)	12 (7)
PREVENT	Placebo ± IST	47	3.93 (4.5)	2.1 (1)	4.3 (1.5)	22 (47)	42 (89)	15 (0)	20 (43)
	Eculizumab ± IST	96	3.33 (3.6)	1.9 (0.9)	4.2 (1.6)	58 (60)	74 (77)	18 (0)	26 (27)
SAkuraSky	Placebo + IST	42	--	1.4 (0.5)	3.6 (1.3)	--	--	--	--
	Satralizumab + IST	41	--	1.5 (0.5)	3.8 (1.6)	--	--	--	--
SAkuraStar	Placebo	32	4.1 (3.9)	1.5 (0.7)[a]	3.7 (1.6)	--	--	--	B-cell depleting therapy: 9 (14)
	Satralizumab	63	6.1 (6.5)	1.4 (0.6)[a]	3.9 (1.5)	--	--	--	

[a]Undefined in source.

ARR, annualized relapse rate; EDSS, Expanded Disability Status Score; IST, immunosuppressive therapy; SD, standard deviation; yr, year.

Appendix F. Reported outcomes from selected trials and full results of the network meta-analysis (NMA)

Table S11 Results of fixed-effects NMA for time-to-first relapse in AQP4+ monotherapy population

Placebo	**4.41 (2.37, 8.28)**	**3.83 (1.59, 9.22)**	**39.72 (7.36, 215.14)**
0.23 (0.12, 0.42)	**Inebilizumab**	0.87 (0.29, 2.53)	**8.96 (1.47, 55.61)**
0.26 (0.11, 0.63)	1.15 (0.39, 3.39)	**Satralizumab**	**10.37 (1.54, 70.36)**
0.03 (0.00, 0.14)	**0.11 (0.02, 0.68)**	**0.10 (0.01, 0.65)**	**Eculizumab**

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment. All **bolded** values are statistically significant at the 0.05 significance level. DIC: 5.36; Deviance: 2.36.
AQP4+, aquaporin-4 immunoglobulin G-positive; *CrI,* credible interval; *NMA,* network meta-analysis.

Table S12 Results of fixed-effects NMA for time-to-first relapse in AQP4+ combination therapy population

Placebo + IST	**4.76 (1.36, 16.77)**	**11.62 (3.52, 37.86)**
0.21 (0.06, 0.74)	**Satralizumab + IST**	2.43 (0.43, 13.82)
0.09 (0.03, 0.28)	0.41 (0.07, 2.34)	**Eculizumab + IST**

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment. All **bolded** values are statistically significant at the 0.05 significance level. DIC: 3.39; Deviance: 1.39.
AQP4+, aquaporin-4 immunoglobulin G-positive; *CrI,* credible interval; *IST,* immunosuppressive therapy; *NMA,* network meta-analysis.

Table S13 Results of fixed-effects NMA for time-to-first relapse in AQP4+ combined mono- and combination therapy population

Placebo ± IST	**4.11 (1.98, 8.49)**	**17.22 (5.03, 59.24)**
0.24 (0.12, 0.50)	**Satralizumab ± IST**	**4.17 (1.02, 17.58)**
0.06 (0.02, 0.20)	**0.24 (0.06, 0.98)**	**Eculizumab ± IST**

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment. All **bolded** values are statistically significant at the 0.05 significance level. DIC: 3.47; Deviance: 1.47.
AQP4+, aquaporin-4 immunoglobulin G-positive; *CrI,* credible interval; *IST,* immunosuppressive therapy; *NMA,* network meta-analysis.

Table S14 Reported annualized relapse rate, disability, and health-related quality of life measures

Trial	Population	Treatment	ARR	EDSS	EQ-5D	HAI	mRS	SF-36 MCS	SF-36 PCS
				Change from baseline (mean, SD)					
PREVENT	ITT	Placebo ± IST	0.35	0.12 (1.0)	-0.04 (0.2)	0.51 (1.6)	0.09 (0.8)	-0.06 (11.8)	0.7 (8.3)
		Eculizumab ± IST	0.016	-0.18 (0.8)	0.05 (0.2)	-0.39 (1.1)	-0.24 (0.7)	0.45 (10.6)	3.36 (7.7)
	No baseline IST	Placebo	0.625	0.42 (1.0)	-0.002 (0.2)	0.6 (1.5)	-0.20 (0.9)	4.75 (7.5)	-1.47 (8.5)
		Eculizumab	0	-0.36 (0.8)	0.07 (0.2)	-0.4 (1.2)	-0.40 (0.9)	0.58 (11.5)	6.44 (9.5)
	Baseline IST	Placebo + IST	0.33	0 (0.9)	-0.06 (0.2)	0.5 (1.7)	0.2 (0.7)	-1.89 (12.7)	1.52 (8.2)
		Eculizumab + IST	0.02	-0.13 (0.8)	0.04 (0.2)	-0.4 (1.1)	-0.2 (0.7)	0.42 (10.4)	2.5 (7)
SAkuraSky	ITT	Placebo + IST	0.32	-0.21	0.04	--	-0.05	2.3	2.46
		Satralizumab + IST	0.11	-0.1	-0.002	--	-0.03	-0.03	1.1
SAkuraStar	ITT	Placebo	0.41	-0.17	0.04	--	-0.19	1.39	3.59
		Satralizumab	0.17	-0.34	0.03	--	-0.03	4.8	2.54

ARR, annualized relapse rate; EDSS, Expanded Disability Status Scale; EQ-5D, European Quality of Life questionnaire; HAI, Hauser Ambulation Index; IST, immunosuppressive therapy; ITT, intent-to-treat; mRS, modified Rankin Scale; SD, standard deviation; SF-36, 36-Item Short Form Survey (MCS, mental component score; PCS, physical component score).

Table S15 Reported safety characteristics and overall adverse events

Trial	Treatment	N	General AE n (%)	Serious AE n (%)	Treatment-related AE n (%)	Treatment-related SAE n (%)	Discontinued due to AE n (%)	Death due to AE n (%)
N-MOmentum (AQP4+)	Placebo	52	37 (71)	5 (10)	--	--	0	0
	Inebilizumab	161	117 (73)	6 (4)	--	--	2 (1)	0
PREVENT	Placebo ± IST	47	45 (96)	26 (55)	27 (57)	9 (19)	2 (4)	0
	Eculizumab ± IST	96	88 (92)	30 (31)	49 (59)	9 (9)	0	1 (1)
SAkuraSky	Placebo + IST	42	40 (95)	9 (21)	--	--	--	0
	Satralizumab + IST	41	37 (90)	7 (17)	--	--	--	0
SAkuraStar	Placebo	32	24 (75)	5 (16)	--	--	--	0
	Satralizumab	63	58 (92)	12 (19)	--	--	--	0

AE, adverse event; *AQP4+,* aquaporin-4 immunoglobulin G-positive; *IST,* immunosuppressive therapy; *SAE,* serious adverse event.