MASSACHUSETTS GENERAL HOSPITAL
NEUROLOGY

HARVARD MEDICAL SCHOOL

Long-term Treatments for Preventing Relapses

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Treatment: Acute vs. Preventive

Acute

Preventive

Off-Label Treatment: Preventive

Medication	Date	Lead Author	Location	Population size
Azathioprine	1998	Mandler	United States	7
	2008	McKeon	United States	10
	2010	Bichuetti	Brazil	25
	2010	Sarhaian	Iran	28
	2011	Constanzi	United States	99
	2014	Elsone	United Kingdom	103
	2015	Qiu	China	77
Mycophenolate	2009	Jacob	United States	24
	2014	Mealy	United States	28
	2014	Huh	South Korea	59
Rituximab	2005	Cree	United States	8
	2008	McKeon	United States	8
	2008	Jacob	United States	25
	2011	Bedi	United States	23
	2011	Pellkofer	Germany	10
	2011	Kim	South Korea	30
	2013	Ip	China	7
	2013	Gredler	Austria	6
	2014	Mealy	United States	30
	2014	Dale	Australia	20
	2015	Fernandez-Megia	Spain	6
	2015	Kim	South Korea	100
	2015	Zephir	France	32
	2015	Radaelli	Italy	21
	2015	Collongues	France	11
Methotrexate	2000	Minagar	United States	8
	2013	Kitley	United Kingdom	14
Oral corticosteroids	2007	Watanabe	Japan	11
Mitoxantrone	2006	Weinstock-Guttman	United States	5
	2011	Kim	Korea	20
	2013	Cabre	French West Indies	51
Eculizumab	2013	Pittock	United States	14
Tocilizumab	2014	Araki	Japan	7
	2015	Ringelstein	Germany	8

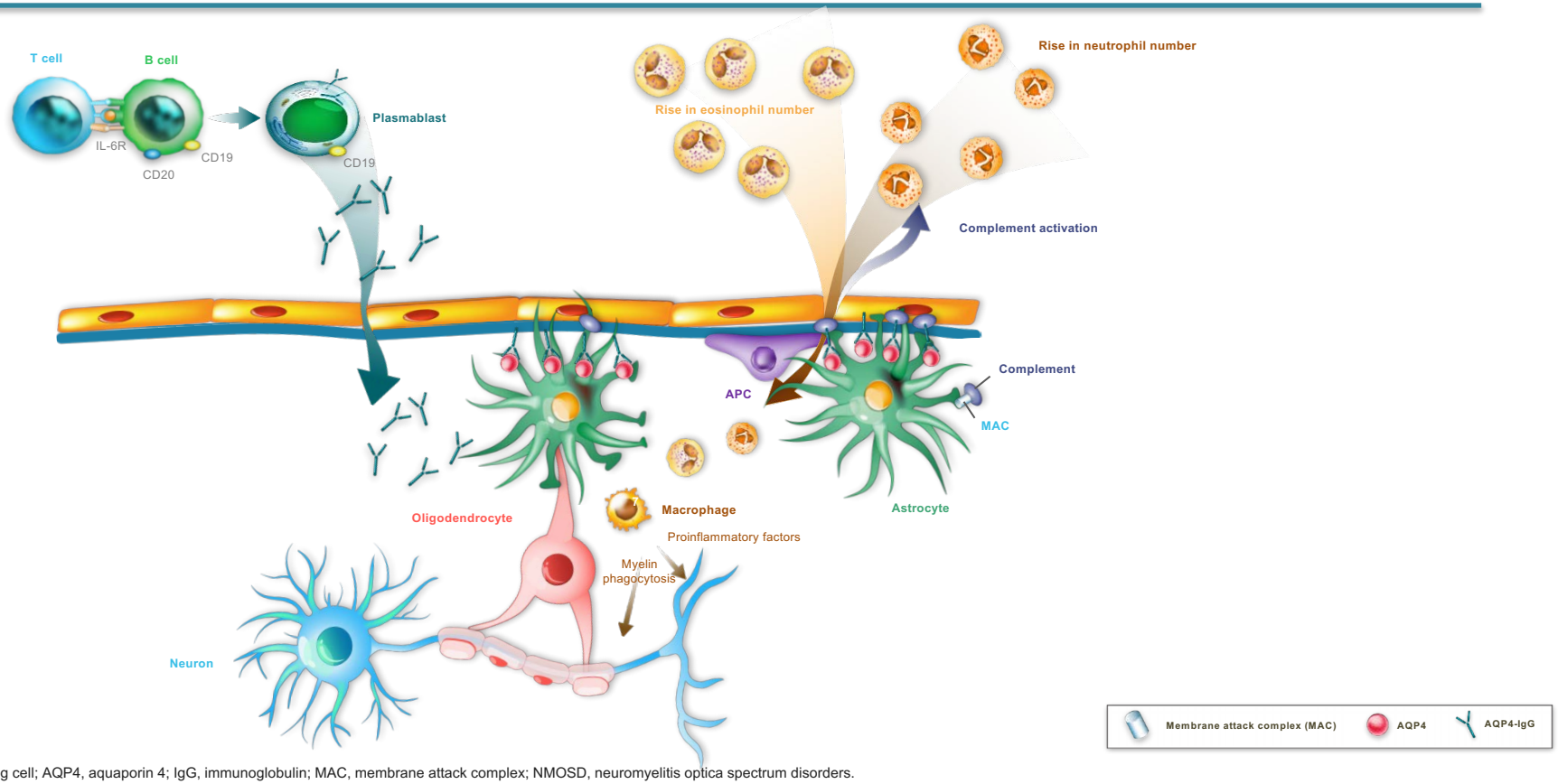
Off-Label Treatment: Comparison

Table 3. Failure Rates With Azathioprine, Mycophenolate Mofetil, and Rituximab

Medication	Failure Rate, %
Azathioprine	53
Mycophenolate mofetil	
Total	36
Optimal dosing	25
Rituximab	
Total	33
Optimal dosing	17
Switched treatments	22

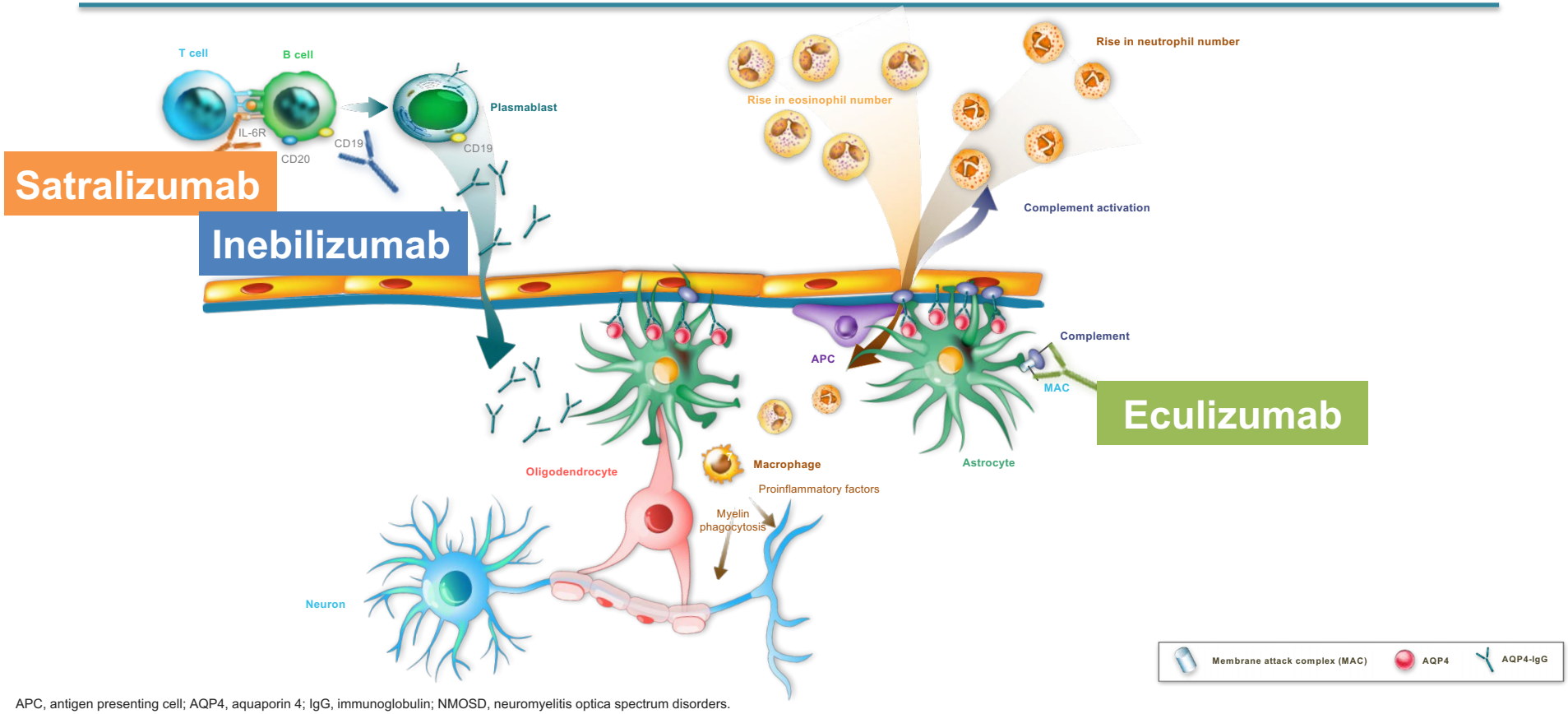
Mealy MA. *JAMA Neurol*. 2014 Mar;71(3):324-30

Proposed Pathogenesis of NMOSD & Mechanisms of Emerging Agents



APC, antigen presenting cell; AQP4, aquaporin 4; IgG, immunoglobulin; MAC, membrane attack complex; NMOSD, neuromyelitis optica spectrum disorders.
Adapted from Jasiak-Zatonska M, et al. *Int J Mol Sci.* 2016;17(3):273.

Proposed Pathogenesis of NMOSD & Mechanisms of Emerging Agents



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Overview of Emerging Therapies

	Eculizumab	Satralizumab	Inebilizumab
Target	Complement C5	IL-6R	CD19
Route of administration	IV	SC	IV
Dosing schedule	Induction: q1w for 4 weeks Maintenance: q2w	q4w	Induction: d1, d15 Maintenance: q6m
Associated clinical trial(s)	PREVENT	SAkuraSky, SAkuraStar	N-MOmentum

d, day; IL-6R, interleukin 6 receptor; IV, intravenous; q1w, weekly; q2w, biweekly; q4w, every 4 weeks; q6m; every 6 months; SC, subcutaneous.

1. Pittock SJ, et al. *N Engl J Med.* 2019;381(7):614-625. 2. Yamamura T, et al. Presented at: American Academy of Neurology Annual Meeting; May 4-10, 2019; Philadelphia, PA. 3. Traboulsee A, et al. Presented at: ECTRIMS 2018; Oct 12, 2018; Berlin, Germany. 4. Cree B, et al. *Lancet.* 2019. dx.doi.org/10.1016/S0140-6736(19)31817-3.

Trial Design Overview

PREVENT eculizumab

- AQP4-IgG$^+$ pts only
- 2 relapses in the last 12 mos or 3 relapses in the last 24 mos + ≥1 relapse in last 12 mos

SAkuraSky satralizumab

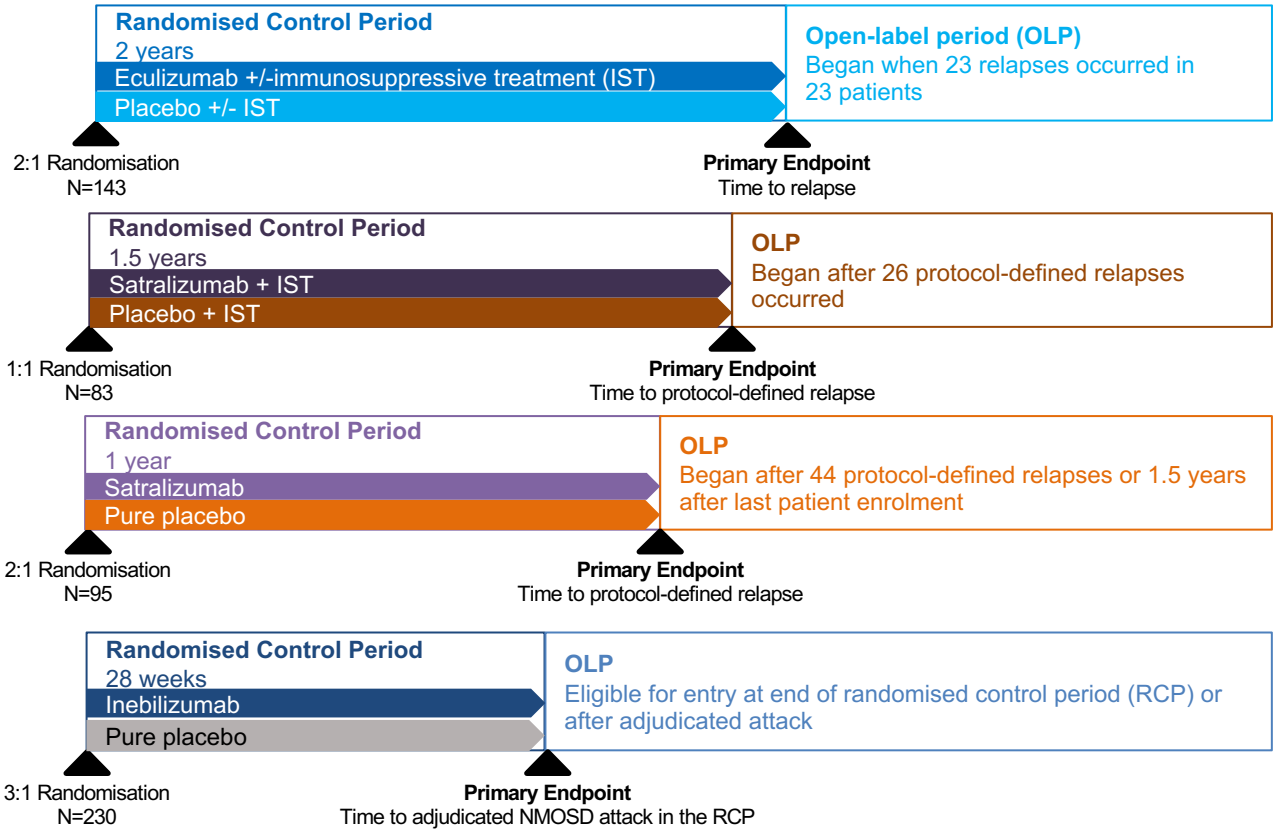
- AQP4-IgG$^+$ and $^-$pts
- Pts aged 12-17 years (n=8), a minimum of 4 pts seropositive
- ≥2 relapse/attack in last 2 yrs with ≥1 relapse in last 12 mos

SAkuraStar satralizumab

- AQP4-IgG$^+$ and $^-$pts
- 1 relapse in the last yr

N-MOmentum inebilizumab

- AQP4-IgG$^+$ and $^-$pts
- 1 relapse in the last yr or 2 relapses in the last 2 yrs



AQP4, aquaporin 4; IgG, immunoglobulin; IV, intravenous; NMOSD, neuromyelitis optica spectrum disorders; pts, patients; SC, subcutaneous; q2w, biweekly; q4w, every 4 weeks.

1. Pittock SJ, et al. *N Engl J Med.* 2019;381(7):614-625. 2. Yamamura T, et al. Presented at: American Academy of Neurology Annual Meeting; May 4-10, 2019; Philadelphia, PA. 3. Traboulsee A. Sep 11, 2019; 278963; P603 Presented at ECTRIMS September 11-13, 2019 Stockholm, Sweden 4. Cree B, et al. *Lancet.* 2019. dx.doi.org/10.1016/S0140-6736(19)31817-3.

Not for direct comparison; no head-to-head trials have been conducted.

Baseline Characteristics Summary

	Eculizumab PREVENT		Satralizumab				Inebilizumab N-MOmentum	
			SAkuraSky (SA307)		SAkuraStar (SA309)			
	PBO (+/-) IST	Ecu (+/-) IST	PBO (+) IST	Satra (+) IST	Placebo	Satralizumab	PBO	Inebilizumab
Proportion of AQP4-IgG (+), %	100%		67%	66%	72%	65%	91%	91%
Female, n (%)	42 (89%)	88 (92%)	40 (95%)	37 (90%)	31 (97%)	46 (73%)	50 (89%)	159 (91%)
Age, mean (SD)	45 (13)	44 (13)	43 (12)	41 (16)	41 (11)	45 (12)	43	43
Age at initial clinical presentation, mean (SD)	39 (15)	36 (14)	39 (12)	35 (17)	39 (13)	36 (11)	NR	NR
Baseline EDSS	4.0*	4.0*	3.6 (1.3)†	3.8 (1.6)†	3.6 (1.6)†	3.9 (1.2)†	4.0*	3.5*
Baseline ARR, prior 2 years, mean (SD)	2.1 (1.0)	1.9 (0.9)	1.4 (0.5)	1.5 (0.5)	1.4 (0.6)	1.5 (0.7)	1.6 (1.5)	1.7 (1.5)

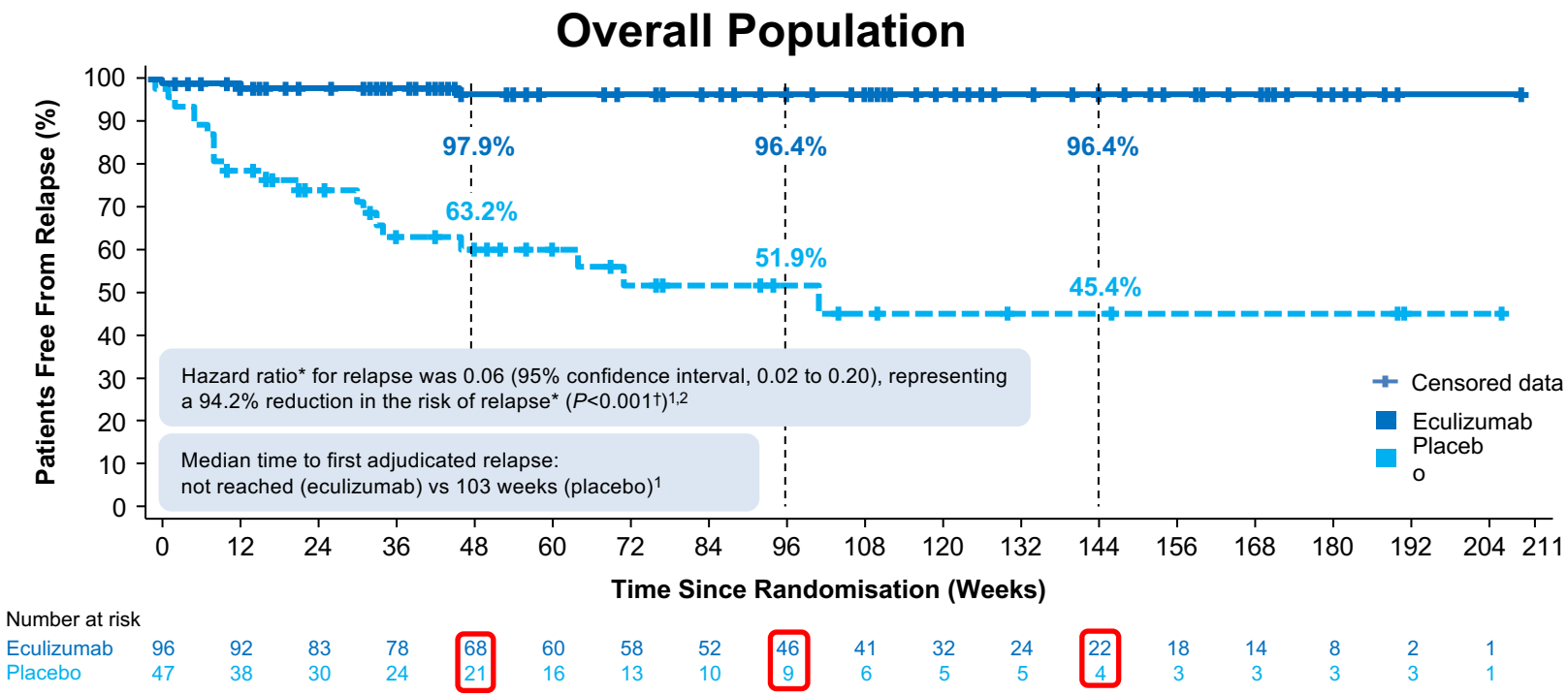
*Median. †Mean.

Not for direct comparison; no head-to-head trials have been conducted.

AQP4, aquaporin 4; ARR, annualised relapse rate; Ecu, eculizumab; EDSS, Expanded Disability Status Scale; IgG, immunoglobulin; IST, immunosuppressive treatment; NR, not reported; PBO, placebo; Satra, satralizumab; SD, standard deviation.

1. Pittock SJ, et al. *N Engl J Med.* 2019;381(7):614-625. 2. Yamamura T, et al. Presented at: American Academy of Neurology Annual Meeting; May 4-10, 2019; Philadelphia, PA. 3. Traboulsee A, et al. Presented at: ECTRIMS 2018; Oct 10-12 2018; Berlin, Germany. 4. Data on file. 5. Cree B, et al. *Lancet.* 2019. dx.doi.org/10.1016/S0140-6736(19)31817-3.

Primary Outcome: Eculizumab

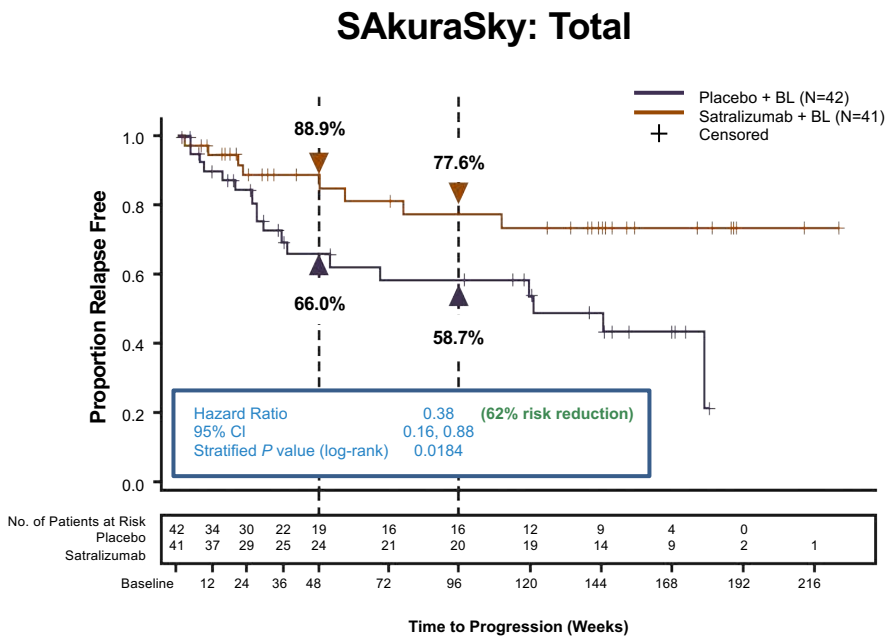


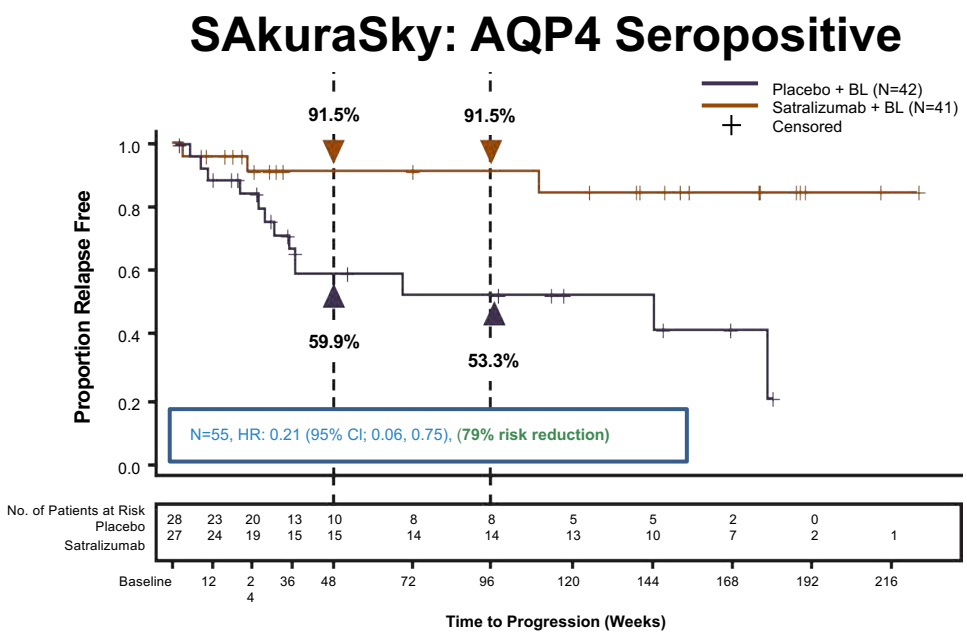
Number at risk

Eculizumab	96	92	83	78	68	60	58	52	46	41	32	24	22	18	14	8	2	1
Placebo	47	38	30	24	21	16	13	10	9	6	5	5	4	3	3	3	3	1

*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.

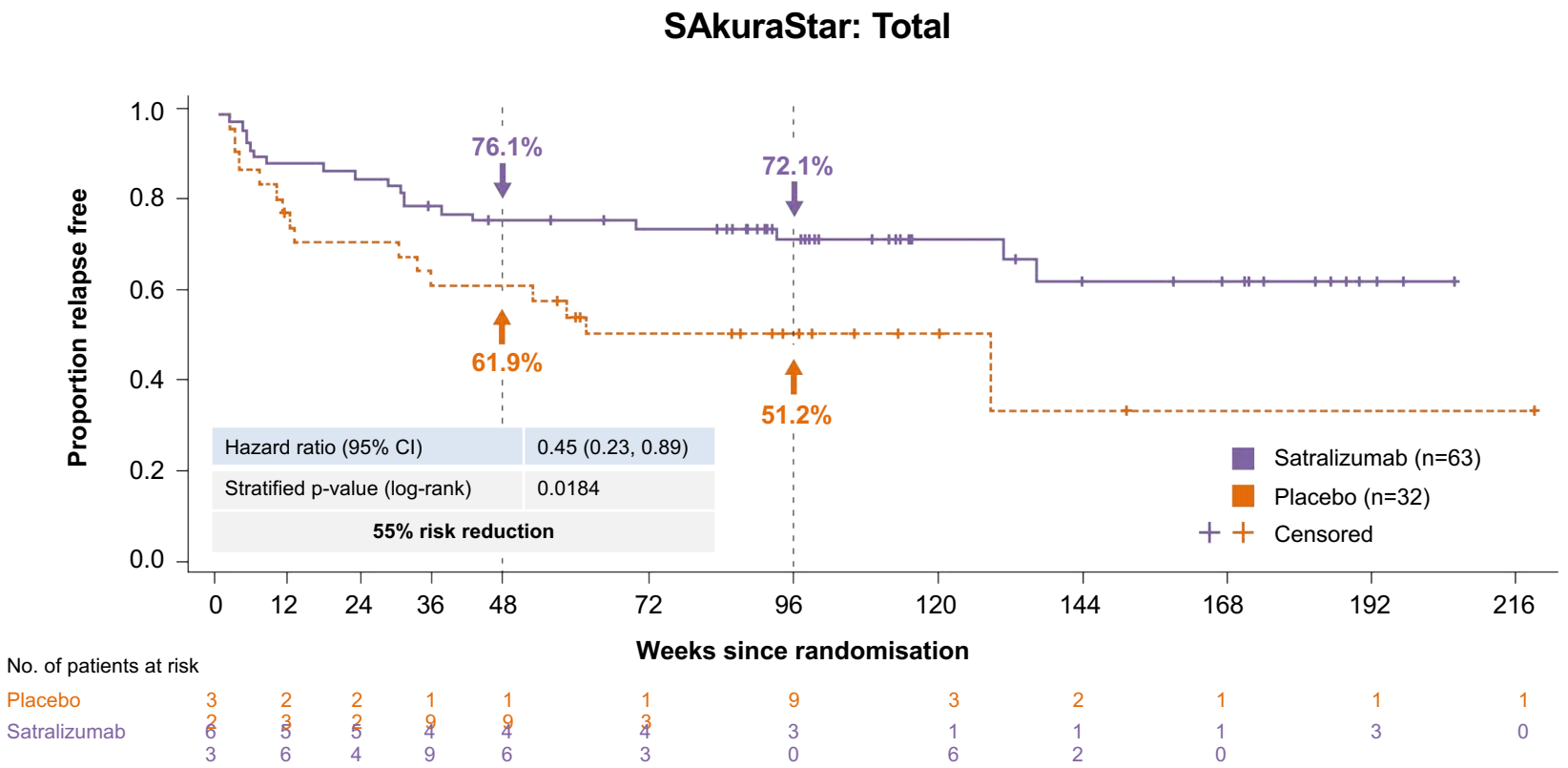
Primary Outcome: Satralizumab





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.

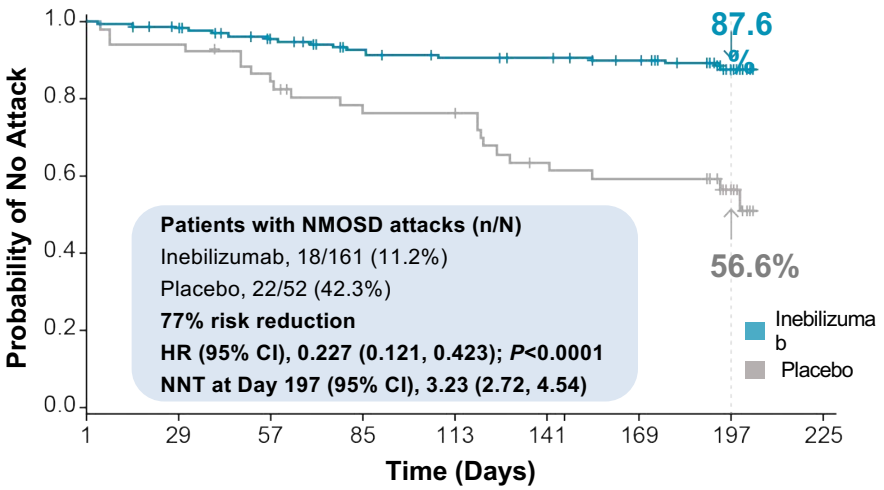
Primary Outcome: Satralizumab



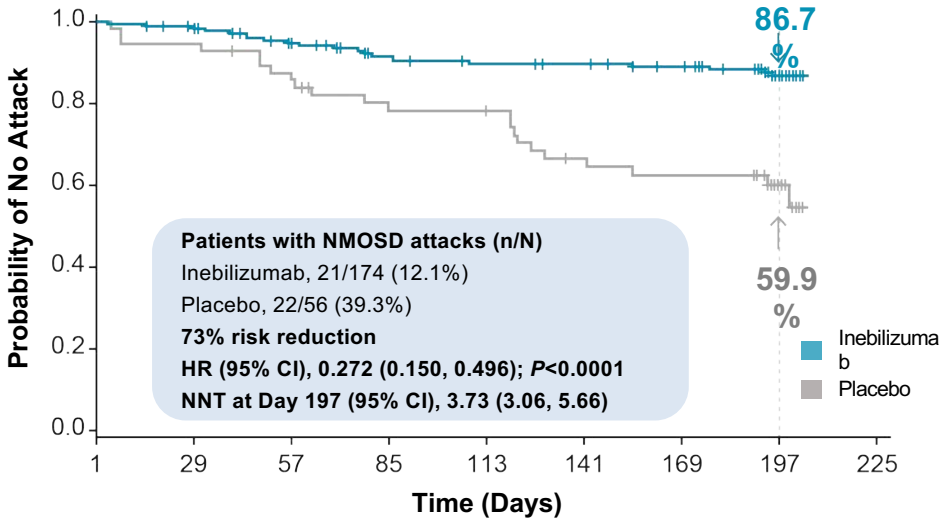
CI, confidence interval; PDR, protocol-defined relapse.
Traboulsee A. Sep 11, 2019; 278963; P603 Presented at ECTRIMS September 11-13, 2019 Stockholm, Sweden

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..

Safety and Tolerability:
Summary—Proportion of Patients (%)

	Eculizumab PREVENT		Satralizumab				Inebilizumab N-MOmentum	
			SAkuraSky (SA307)		SAkuraStar (SA309)			
	PBO (+/-) IST	Ecu	PBO + IST	Satra + IST	PBO	Satra	PBO	Inebilizumab
Total adverse events	91%	92%	95%	90%	75%	92%	73%	72%
Severe adverse events	15%	16%	12%	12%	6%	27%	NR	
Serious adverse events	28%	26%	21%	17%	16%	19%	9%	5%
Deaths	0%	1%*	0%	0%	0%	0%	0%	0%
	NR for OLP		NR for OLP		--		2 deaths in OLP	
Infections	NR		62%	68%	44%	54%	41%	38%
Serious infections	NR		7%	5%	9%†	10%†	NR	
Injection- or infusion-related reactions	NR		5%	12%	16%	13%	11%	9%
Anaphylactic reactions	NR		0%	0%	0%	0%	0%	0%
Neoplasm	NR		7%	7%	NR	NR	NR	

Not for direct comparison; no head-to-head trials have been conducted.

*The patient died from infectious pleural effusion (reported as pulmonary empyema), which the investigator categorised as probably related to the trial agent. †MEDdra system organ calss; infections and infestations
Ecu, eculizumab; IST, immunosuppressive treatment; NR, not reported; OLP, open-label period; PBO, placebo; Satra, satralizumab.
1. Pittock SJ, et al. *N Engl J Med.* 2019;381(7):614-625. 2. Yamamura T, et al. Presented at: American Academy of Neurology Annual Meeting; May 4-10, 2019; Philadelphia, PA. 3. Traboulsee A. Sep 11, 2019; 278963; P603 Presented at ECTRIMS September 11-13, 2019 Stockholm, Sweden 4. Cree B, et al. *Lancet.* 2019. dx.doi.org/10.1016/S0140-6736(19)31817-3.

Logistics

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2020 RNDS

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