Satralizumab in patients with neuromyelitis optica spectrum disorder (NMOSD) and concomitant autoimmune disease (CAID)

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Background: NMOSD and concomitant autoimmune diseases (CAIDs)

NMOSD is a **chronic, debilitating autoimmune disease** of the CNS, characterized by inflammatory lesions that primarily affect the optic nerves and spinal cord[1]

Concomitant autoimmune diseases are the most frequently reported comorbidities associated with NMOSD, most of which are antibody-mediated diseases[2]

Further research is required to understand the **safety and efficacy of NMOSD treatments** in patients with **concomitant autoimmune diseases**

CNS, central nervous system; NMOSD, neuromyelitis optica spectrum disorder.

1. Wingerchuk DM, et al. *Lancet Neurol* 2007;6:805–815; 2. Shahmohammadi S, et al, *Mult Scler Relat Disord* 2019;27:350–363.

Objective: Safety and efficacy of satralizumab in NMOSD patients with CAIDs

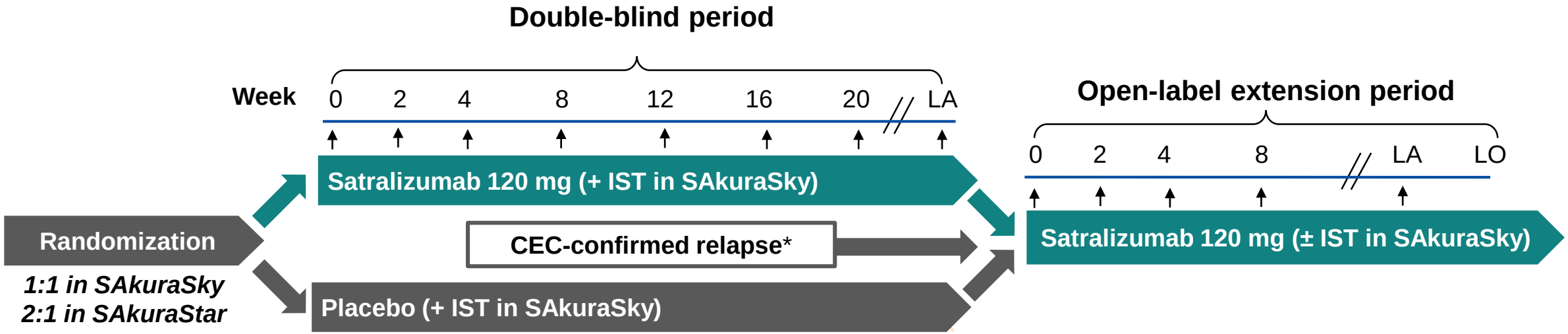
- Satralizumab is a subcutaneously administered, humanized, monoclonal, recycling antibody that targets the IL-6R, inhibiting the IL-6 inflammatory signaling pathways associated with NMOSD[1,2]
- IL-6 signaling may also play a pathological role in various other autoimmune diseases[3]
- Satralizumab significantly reduced patients' risk of NMOSD relapse and demonstrated a favorable safety profile in two randomized, placebo-controlled, phase 3 trials: SAkuraSky and SAkuraStar[4,5]
- The SAkura studies enrolled a diverse patient population reflective of real-world practice, including patients with concomitant autoimmune diseases

The objective of the current analysis was to evaluate the **safety and efficacy of satralizumab** in **NMOSD patients with concomitant autoimmune diseases** from the SAkura studies

CAID, concomitant autoimmune disease; IL-6, interleukin-6; IL-6R, interleukin-6 receptor; NMOSD, neuromyelitis optica spectrum disorder.

1. Kaplon H, Reichert JM. *MAbs* 2018;10:183–203; 2. Tanaka T, et al. *Cold Spring Harb Perspect Biol* 2014;6:a016295; 3. Tanaka T and Kishimoto T. *Int J Biol Sci* 2012;8:1227–1236; 4. Yamamura T, et al. *N Engl J Med* 2019;381:2114–2124; 5. Traboulsee A, et al. *Lancet Neurol* 2020;19:402–412.

The current analysis uses pooled data from the double-blind periods of the SAkuraSky and SAkuraStar studies



	SAkuraSky[1] *(Satralizumab + IST)*	SAkuraStar[2] *(Satralizumab monotherapy)*
Key inclusion criteria	• Diagnosis of NMO using 2006 Wingerchuk criteria,[3] or AQP4-IgG-seropositive NMOSD with ≥1 episode of optic neuritis or LETM[4] • EDSS score of ≤6.5	
	• **Aged from 12 to 74 years** (adolescents included) • **≥2 relapses in last 2 years** (≥1 relapse in last year) • **Receiving stable dose of IST** (AZA, MMF, or OCs)†	• **Aged from 18 to 74 years** • **≥1 relapse in last year** (patients could enrol after first NMOSD attack) • **Concomitant ISTs were not permitted**
End of double-blind period	• Total number of PDRs reaches 26 (CCOD June 6, 2018)	• 1.5 years after the date of randomization of the last patient enrolled (CCOD October 12, 2018)

Treatment administered. *PDR or clinical relapse requiring rescue therapy in SAkuraSky or PDR in SAkuraStar; †For patients aged 12–17 years, AZA + OCs or MMF + OCs were also permitted.
AQP4-IgG, aquaporin-4–immunoglobulin G; AZA, azathioprine; CCOD, clinical cut-off date CEC, clinical endpoint committee; EDSS, Expanded Disability Status Scale; IST, immunosuppressive therapy; LA, last administration; LETM, longitudinally extensive transverse myelitis; LO, last observation; MMF, mycophenolate mofetil; NMO, neuromyelitis optica; NMOSD, neuromyelitis optica spectrum disorder; OC, oral corticosteroid; PDR, protocol-defined relapse.
1. Yamamura T, et al. *N Engl J Med* 2019;381:2114–2124; 2. Traboulsee A, et al. *Lancet Neurol* 2020;19:402–412; 3. Wingerchuk DM, et al. *Neurology* 2006;66:1485–1489; 4. Wingerchuk DM, et al. *Lancet Neurol* 2007;6:805–815.

Disease characteristics in patients with CAIDs were generally balanced between treatment groups, and were consistent with the overall SAkura study population

- **31 NMOSD patients with a medical history of CAIDs** were enrolled in the SAkura studies and included in this analysis
  - 15 patients were enrolled in SAkuraSky (satralizumab, n=5; placebo, n=10) and 16 were enrolled in SAkuraStar (satralizumab, n=10; placebo, n=6)
- **The most frequently reported CAIDs** in this cohort were Sjögren's syndrome (n=9), SLE (n=7), Hashimoto's thyroiditis (n=6), myasthenia gravis (n=4), psoriasis (n=3), and Basedow/Grave's disease (n=2)

	Patients with concomitant autoimmune diseases (N=31)		Overall SAkura study population (N=178)	
	Placebo (N=16)	Satralizumab (N=15)	Placebo (N=74)	Satralizumab (N=104)
Mean age (SD), years	47.6 (9.4)	53.3 (11.5)	42.1 (11.4)	43.5 (13.9)
Female, n (%)	16 (100)	14 (93)	71 (96)	83 (80)
AQP4-IgG seropositive, n (%)	12 (75)	13 (87)	51 (69)	68 (65)
Race, n (%)				
American Indian/Alaska Native	0	2 (13)	0	2 (2)
Asian	2 (12)	3 (20)	24 (32)	25 (24)
Black or African American	0	3 (20)	5 (7)	13 (13)
White	14 (88)	5 (33)	43 (58)	61 (59)
Other	0	2 (13)	2 (3)	3 (3)
Baseline treatment*				
AZA	6 (60)	2 (40)	13 (31)	16 (39)
MMF	1 (10)	1 (20)	8 (19)	4 (10)
OCs	3 (30)	2 (40)	20 (48)	17 (41)
AZA + OCs	0	0	0	3 (7)
MMF + OCs	0	0	1 (2)	1 (2)
Prior treatment†				
B-cell depleting therapy	1 (17)	2 (20)	4 (13)	8 (13)
Immunosuppressants/others	5 (83)	8 (80)	28 (88)	55 (87)

*Baseline treatment in SAkuraSky. †Prior treatment in SAkuraStar.
AQP4-IgG, aquaporin-4–immunoglobulin G; AZA, azathioprine; CAID, concomitant autoimmune disease; MMF, mycophenolate mofetil; NMOSD, neuromyelitis optica spectrum disorder; OCs, oral corticosteroids; SD, standard deviation; SLE, systemic lupus erythematosus.

Satralizumab was well tolerated in patients with CAIDs, with a consistent safety profile to that observed in the overall SAkura study populations

Patients with concomitant autoimmune diseases (ITT population)

	Placebo (N=16; PY=21.1)			Satralizumab (N=15; PY=29.7)		
	No. of AEs	Patients, n (%)	AEs/100PY (95% CI)	No. of AEs	Patients, n (%)	AEs/100PY (95% CI)
All AEs	168	16 (100)	795.9 (680.1, 925.7)	210	15 (100)	708.0 (615.5, 810.5)
Serious AE	7	5 (31)	33.2 (13.3, 68.3)	13	7 (47)	43.8 (23.3, 75.0)
Serious AE related to study treatment	5	3 (19)	23.7 (7.7, 55.3)	2	2 (13)	6.7 (0.8, 24.4)
AE leading to treatment discontinuation	4	4 (25)	19 (5.16, 48.5)	1	1 (7)	3.4 (0.1, 18.8)
Severe AE	5	3 (19)	23.7 (7.7, 55.3)	12	6 (40)	40.5 (20.9, 70.7)
Infection AE*	49	10 (63)	232.1 (171.7, 306.9)	52	12 (80)	175.3 (130.9, 229.9)
Serious infection AE*	1	1 (6)	4.7 (0.1, 26.4)	3	3 (20)	10.1 (2.1, 29.6)
Injection-related reaction	3	3 (19)	14.2 (2.9, 41.5)	7	2 (13)	23.6 (9.5, 48.6)

- The safety profile of satralizumab in patients with CAIDs was comparable to the overall SAkura study populations[1,2]
- The overall rates of AEs were comparable between the placebo and satralizumab groups
- In patients with CAIDs, no AEs related to exacerbation of CAIDs were reported in those treated with satralizumab
- The rates of infections and serious infections were comparable between the satralizumab and placebo groups
- The safety profile of satralizumab in AQP4-IgG-seropositive patients with CAIDs was consistent with the ITT population with CAIDs:
  - Satralizumab group (n=13): rate of AEs, 699.1 AEs/100PY (95% CI 605.3, 803.3); rate of serious AEs, 42.2 AEs/100PY (95% CI 21.8, 73.6)
  - Placebo group (n=12): rate of AEs, 984.0 AEs/100PY (95% CI 818.4, 1173.2); rate of serious AEs, 47.6 AEs/100PY (95% CI 17.5, 103.6)

*MedDRA system organ class: Infections and Infestations.

AE, adverse event; AQP4-IgG, aquaporin-4–immunoglobulin G; CAID, concomitant autoimmune disease; CI, confidence interval; ITT, intention-to-treat; MedDRA, Medical Dictionary for Regulatory Activities; PY, patient-years; SLE, systemic lupus erythematosus.

1. Yamamura T, et al. *N Engl J Med* 2019;381:2114–2124; 2. Traboulsee A, et al. *Lancet Neurol* 2020;19:402–412.

The most frequently reported AEs in patients with CAIDs were infections and infestations

	Patients with concomitant autoimmune diseases (ITT population)					
	Placebo (N=16; PY=21.11)			Satralizumab (N=15; PY=29.66)		
	No. of AEs	Patients, n (%)	AEs/100PY (95% CI)	No. of AEs	Patients, n (%)	AEs/100PY (95% CI)
Infections and infestations	49	10 (63)	232.1 (171.7, 306.9)	52	12 (80)	175.3 (130.9, 229.9)
Urinary tract infection	5	3 (19)	23.7 (7.7, 55.3)	13	4 (27)	43.8 (23.3, 75.0)
Upper respiratory tract infection	10	3 (19)	47.4 (22.7, 87.1)	5	3 (20)	16.9 (5.5, 39.3)
Influenza	4	3 (19)	19.0 (5.2, 48.5)	0	0 (0)	0 (NE, 12.4)
Cellulitis	0	0 (0)	0 (NE, 17.5)	3	3 (20)	10.1 (2.1, 29.6)

- Consistent with the overall safety population, the most commonly reported AEs were under the SOC* “Infections and Infestations” in patients with CAIDs from both treatment groups
- The most commonly reported infection AEs (reported in >2 patients in either group) were similar between treatment groups
  - When grouping AEs with a similar medical concept* the rates of urinary tract infection (satralizumab: 47.2 AE/100PY [95% CI 25.8, 79.2] vs placebo: 37.9 AE/100PY [95% CI 16.4, 74.7]) and upper respiratory tract infection (satralizumab: 57.3 AE/100PY [95% CI 33.4, 91.8) vs placebo: 80.5 AE/100PY [95% CI 46.9, 128.9]) were comparable between treatment groups
- No opportunistic infections were observed in the SAkuraStar study (monotherapy); one patient treated with satralizumab in the SAkuraSky study (with baseline IST) reported a mild herpes zoster infection and recovered in 16 days
- No cases of progressive multifocal leukoencephalopathy were reported
- Consistent with the ITT population with CAIDs, the most commonly reported AEs in AQP4-IgG-seropositive patients with CAIDs were under the SOC “Infections and Infestations” in both treatment groups

*System organ class as per MedDRA v16.1. †AEs were grouped by similar medical concept (e.g., urinary tract infection, cystitis, etc.) into baskets; baskets of MedDRA Preferred Terms for safety analysis of infection events included upper respiratory tract infection, lower respiratory tract infection, skin infection, urinary tract infection, gastrointestinal tract infection, sepsis, and an opportunistic infection screening basket.
AE, adverse event; AQP4-IgG, aquaporin-4–immunoglobulin G; CAID, concomitant autoimmune disease; CI, confidence interval; ITT, intention-to-treat; IST, immunosuppressive therapy; MedDRA, Medical Dictionary for Regulatory Activities; NE, not estimable; PY, patient-years; SOC; system, organ class.

Overview of serious AEs

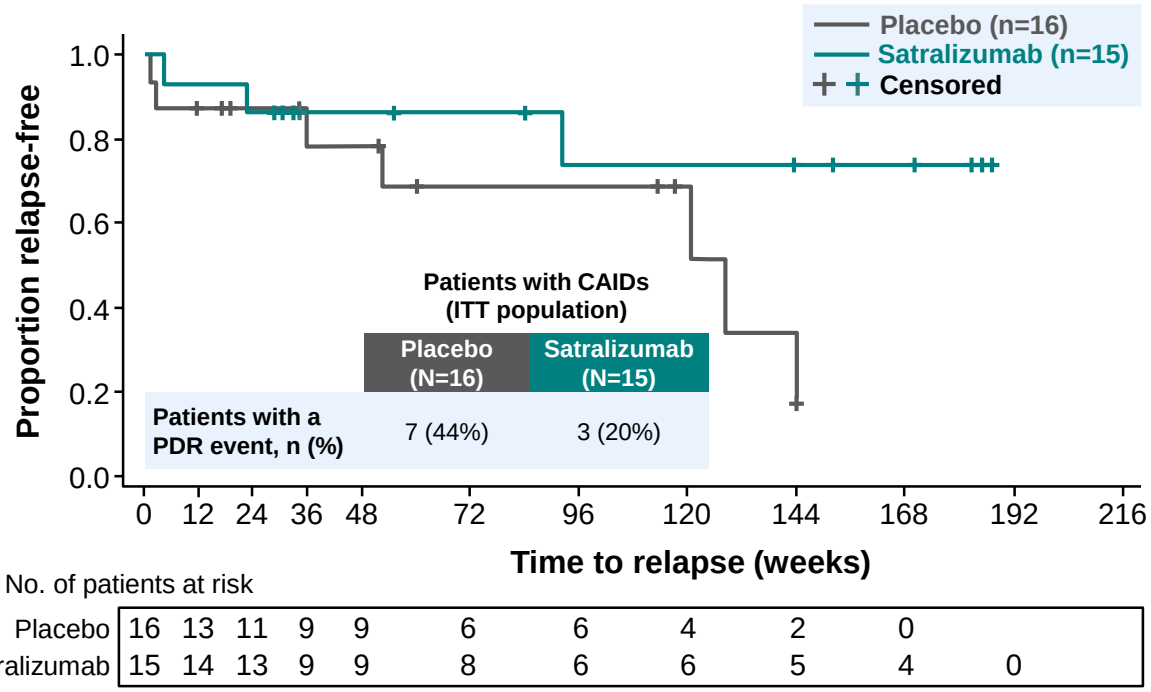
SOC/PT (number of events)†	Serious AE (patients with CAIDS, ITT population) Placebo (N=16; PY=21.1)	Satralizumab (N=15; PY=29.7)
Respiratory, thoracic, and mediastinal disorders	-	Apnea* (1) Pulmonary edema (1)
Cardiac disorders	-	Bradycardia* (1)
General disorders and administration-site conditions	-	Hypothermia* (1)
Psychiatric disorders	-	Mental status changes* (2)
Infections and infestations	Escherichia sepsis (1)	Pyelonephritis* (1) Pulmonary sepsis (1) Pneumonia (1)
Neoplasms benign, malignant, and unspecified	Hepatic cancer (1)	-
Blood and lymphatic system disorders	Leukopenia (1) Lymphopenia (1) Autoimmune thrombocytopenia (1)	Anemia macrocytic (1)
Reproductive system and breast disorders	Uterine polyp (1)	Cervical dysplasia (1)
Eye disorders	Retinal vein thrombosis (1)	-
Injury, poisoning, and procedural complications	-	Femur fracture (2)

- Numerically higher rates of serious AEs in the satralizumab group than in the placebo group were mainly **driven by multiple events (n=6*) reported in one patient** in the SAkuraStar study
  - All 6 AEs were classified by the investigator as **not related to satralizumab treatment**
- No serious AEs related to exacerbation of CAIDs were reported with satralizumab

†SOC and PT as per MedDRA v16.1.
AE, adverse event; CAID, concomitant autoimmune disease; ITT, intention-to-treat; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; PY, patient-years; SOC, system organ class.

Fewer patients in the satralizumab group experienced a protocol-defined relapse than in the placebo group

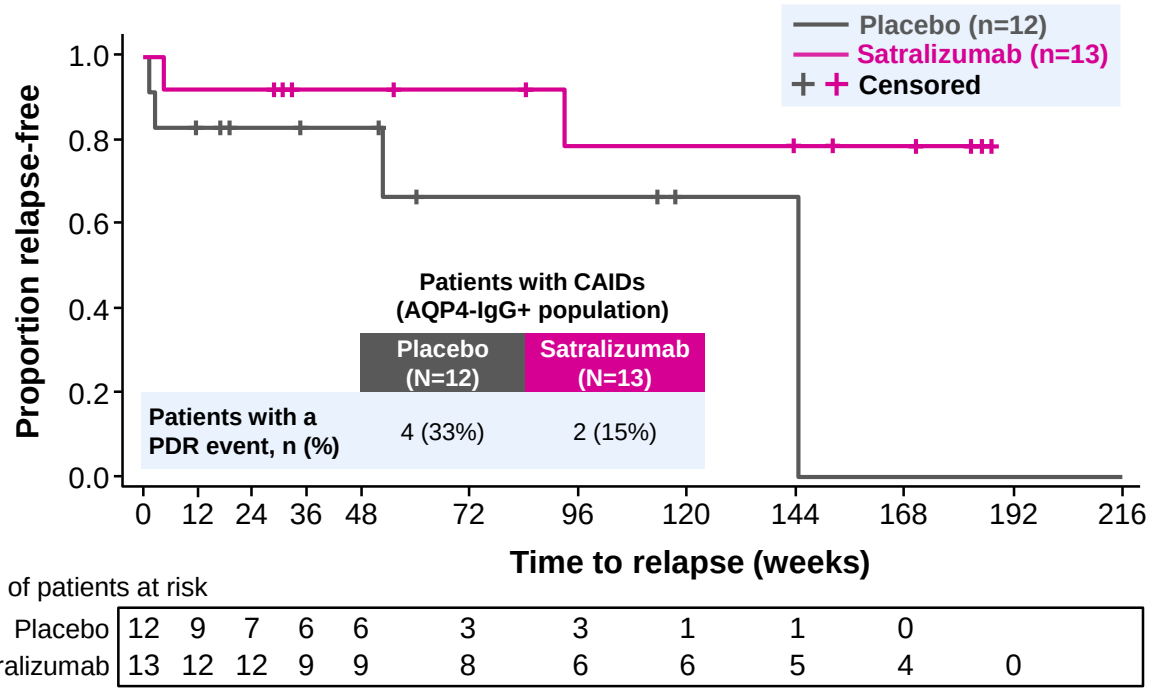
Time to first PDR (ITT CAIDs population)



No. of patients at risk

Placebo	16	13	11	9	9	6	6	4	2	0	
Satralizumab	15	14	13	9	9	8	6	6	5	4	0

Time to first PDR (AQP4-IgG+ CAIDs population)



No. of patients at risk

Placebo	12	9	7	6	6	3	3	1	1	0	
Satralizumab	13	12	12	9	9	8	6	6	5	4	0

- In an exploratory efficacy analysis of patients with CAIDs from the SAkura studies, fewer patients in the satralizumab group experienced a PDR (20%) than in the placebo group (44%), in line with the results from the primary SAkuraSky and SAkuraStar efficacy analyses[1,2]
- Consistent with the ITT population with CAIDs, fewer AQP4-IgG-seropositive patients with CAIDs in the satralizumab group experienced a PDR (15%) than in the placebo group (33%)

Note: Due to the small number of patients and events, results should be interpreted with caution

AQP4-IgG, aquaporin-4–immunoglobulin G; CAID, concomitant autoimmune disease; ITT, intention-to-treat; PDR, protocol-defined relapse.

1. Yamamura T, et al. *N Engl J Med* 2019;381:2114–2124; 2. Traboulsee A, et al. *Lancet Neurol* 2020;19:402–412.

Conclusions

- Overall, satralizumab was **well tolerated** in NMOSD patients with CAIDs, with comparable safety and efficacy to the overall SAkura study populations
- In NMOSD patients with CAIDs, **no AEs related to exacerbation of CAIDs** were reported in those treated with satralizumab
- The **rates of infections and serious infections were comparable** between the satralizumab and placebo groups, and the most common infection AEs in both treatment groups were upper respiratory tract infection and urinary tract infection
- In exploratory efficacy analyses, **fewer patients with NMOSD and CAIDs experienced a PDR in the satralizumab group** than in the placebo group
- The safety and efficacy of satralizumab in AQP4-IgG-seropositive patients with CAIDs was consistent with the ITT population with CAIDs
- Due to the small number of patients and events in this cohort, results should be interpreted with caution

AE, adverse event; AQP4-IgG, aquaporin-4–immunoglobulin G; CAID, concomitant autoimmune disease; ITT, intention-to-treat; NMOSD, neuromyelitis optica spectrum disorder; PDR, protocol-defined relapse.

Disclosures

The authors hereby declare that since 1 Nov 2020 they have or have had business, personal or material relationships with the following companies, consulting firms or medical institutions and sponsors thereof:

A. Traboulsee has received consulting fees from Genzyme, Roche, and Novartis and is part of a speaker's bureau for Genzyme and Roche.

M. R. Yeaman received grants from the NIH and the DoD, and consulting fees from Roche and Alexion. He is a founder and shareholder in NovaDigm Therapeutics, Inc. and Metacin, Inc. He serves on the Genentech-Roche Strategic Scientific Committee for NMOSD and is Chair Medical Advisor to the Guthy-Jackson Charitable Foundation for NMOSD.

B. G. Weinshenker reports consulting fees from UCB Biosciences, Mitsubishi Tanabe, Genentech, and Roche and speaking fees from Genentech, Roche, and Novartis; he participated on the Attack Adjudication Committee for Alexion and Horizon Therapeutics (formerly MedImmune/Viela Bio). He reports personal fees from Chugai. He has a patent NMO-IgG for diagnosis of neuromyelitis optica with royalties paid to RSR Ltd, Oxford University, Hospices Civils de Lyon, and MVZ Labor PD Dr. Volkmann und Kollegen GbR.

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