RESEARCH ARTICLE OPEN ACCESS

Long-Term Efficacy and Safety of Satralizumab in Patients With Neuromyelitis Optica Spectrum Disorder From the SAkuraMoon Open-Label Extension Study

Jeffrey L. Bennett,[1] Kazuo Fujihara,[2,3] Albert Saiz,[4] Anthony L. Traboulsee,[5] Benjamin M. Greenberg,[6] Brian G. Weinshenker,[7] Francesco Patti,[8] Ingo Kleiter,[9,10] Jacqueline Palace,[11] Jerome De Seze,[12] Rachael Evans,[13] Kathleen Blondeau,[14] Gaëlle Klingelschmitt,[14] Ivana Vodopivec,[14] Masouda Rahim,[15] and Takashi Yamamura[16]

Correspondence
Prof. Bennett
jeffrey.bennett@cuanschutz.edu

Neurol Neuroimmunol Neuroinflamm 2025;12:e200450. doi:10.1212/NXI.0000000000200450

Abstract

Background and Objectives

Satralizumab (SAT), an interleukin-6 receptor inhibitor, reduced the risk of protocol-defined relapse (PDR) vs placebo (PBO) with a favorable safety profile in patients with neuromyelitis optica spectrum disorder (NMOSD) in 2 pivotal phase 3 trials, SAkuraSky and SAkuraStar. We evaluated the long-term safety and efficacy of SAT in patients with NMOSD in the single-arm, open-label, rollover study SAkuraMoon.

Methods

Patients who completed the double-blind periods (DBPs) and open-label extensions (OLEs) of SAkuraSky and SAkuraStar were enrolled in SAkuraMoon, where they continued receiving subcutaneous SAT 120 mg 4 times a week (Q4W) ± immunosuppressive therapy. Safety analyses included all patients who received ≥1 dose of SAT in the overall SAT treatment (OST) period. The rates of adverse events (AEs) and infections per 100 patient-years (PYs) in the OST vs the DBPs were compared. Efficacy analyses were performed in the aquaporin-4 immunoglobulin-G–seropositive (AQP4-IgG+) population. Annualized investigator-assessed PDR rate (i.e., annualized relapse rate, ARR), time to first investigator-reported PDR (iPDR), severe iPDR (increase of ≥2 points in the Expanded Disability Status Scale [EDSS] score), and sustained EDSS score worsening were reported. The data cutoff date of these analyses was May 28, 2024.

Results

Overall, 166 patients with NMOSD were included in the analysis. The median (range) SAT exposure in the OST period was 6.9 years (0–10). Rates of AEs and serious AEs (95% CI) in the OST period (AEs: 299.4 (288.8–310.2)/100 PYs; serious AEs: 8.1 (6.4–10.0)/100 PYs) were lower compared with the DBP. Rates of infections (87.5 [81.9–93.5]/100 PYs) and serious infections (2.4 [1.5–3.5]/100 PYs) in the OST period were comparable with those of the DBP and did not increase over time. No fatalities occurred. In the AQP4-IgG+ population (n = 111), the overall adjusted ARR (95% CI) was 0.07 (0.05–0.10). At Week 456 (8.8 years), 67% (56%–76%), 89% (80%–94%), and 82% (72%–89%) of SAT-treated patients were free from iPDR, severe iPDR, and sustained EDSS score worsening, respectively.

MORE ONLINE

Class of Evidence
Criteria for rating therapeutic and diagnostic studies
NPub.org/coe

Supplementary Material

[1]Departments of Neurology and Ophthalmology, University of Colorado School of Medicine, Aurora, CO; [2]Department of Multiple Sclerosis Therapeutics, Fukushima Medical University School of Medicine, Japan; [3]Multiple Sclerosis and Neuromyelitis Optica Center, Southern TOHOKU Research Institute for Neuroscience, Fukushima, Japan; [4]Service of Neurology, Hospital Clinic de Barcelona, Spain; [5]University of British Columbia, Vancouver, Canada; [6]Department of Neurology, University of Texas Southwestern Medical Center, Dallas; [7]University of Virginia, Charlottesville; [8]AOU Policlinico Vittorio Emanuele, Università di Catania, Italy; [9]Marianne-Strauß-Klinik, Behandlungszentrum Kempfenhausen für Multiple Sklerose Kranke GmbH, Berg, Germany; [10]Ruhr University Bochum, Germany; [11]John Radcliffe Hospital, Oxford, United Kingdom; [12]Hôpital de Hautepierre, Strasbourg, France; [13]Roche Products Ltd, Welwyn Garden City, United Kingdom; [14]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [15]ApotheCom, London, United Kingdom; and [16]Department of Neurology, National Center of Neurology and Psychiatry, Tokyo, Japan.

The Article Processing Charge was funded by F. Hoffmann La Roche.

Glossary

ADA = anti-drug antibody; **AE** = adverse event; **ALT** = alanine transaminase; **ARR** = assessed PDR rate; **AST** = aspartate transaminase; **CCOD** = clinical cutoff date; **DBP** = double-blind period; **EDSS** = Expanded Disability Status Scale; **FSS** = Functional Systems Score; **iPDR** = investigator-reported PDR; **IRR** = injection-related reaction; **IST** = immunosuppressive therapy; **MedDRA** = Medical Dictionary for Regulatory Activities; **NCI-CTCAE** = National Cancer Institute Common Terminology Criteria for Adverse Events; **NMOSD** = neuromyelitis optica spectrum disorder; **OLE** = open-label extension; **OST** = overall SAT treatment; **PBO** = placebo; **PDR** = protocol-defined relapse; **PK** = pharmacokinetic; **PY** = patient-year; **SAT** = satralizumab; **ULN** = upper limit of normal.

Discussion

The safety and efficacy of SAT (±IST) is sustained with long-term treatment, supporting SAT as an effective maintenance therapy option for patients with AQP4-IgG+ NMOSD.

Trial Registration Information

ClinicalTrials.gov registration numbers: NCT02028884 (SAkuraSky), NCT02073279 (SAkuraStar), and NCT04660539 (SAkuraMoon); EudraCT: 2020-003413-35 (SAkuraMoon).

Classification of Evidence

This study provides Class IV evidence that SAT is safe and effective in patients with NMOSD.

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a rare, chronic, autoimmune disease, characterized by demyelinating lesions in the optic nerves, spinal cord, brainstem, and cerebrum.[1,2] The hallmark clinical manifestations of NMOSD are optic neuritis, resulting in vision loss, and longitudinally extensive transverse myelitis resulting in weakness, sensory impairment, and bladder and bowel dysfunction.[1,3]

Aquaporin-4 immunoglobulin-G–seropositive (AQP4-IgG+) NMOSD generally follows a relapsing disease course, and patients are at persistent risk of relapse regardless of disease duration.[1] Disability and health-related quality-of-life worsening are driven by attacks/relapses, and chronic neurologic disability develops incrementally after attacks.[4]

Therefore, NMOSD management focuses on the treatment of acute attacks and aims to prevent future relapses, meaning that patients require lifelong preventative therapeutic options that are both safe and effective.[5,6] Since 2019, several monoclonal antibodies have been approved for patients with AQP4-IgG+ NMOSD, namely eculizumab and ravulizumab (2 complement C5 inhibitors), inebilizumab (an anti-CD19 B cell–depleting antibody), and satralizumab (SAT) (an anti-interleukin-6 [IL-6] receptor monoclonal antibody).[7-9]

IL-6, a pleiotropic cytokine implicated in the pathophysiology of AQP4-IgG+ NMOSD, plays a role in the immunopathogenic mechanisms upstream of AQP4-IgG–related effects, mediated through B cell–related and T cell–related pathways.[10,11] IL-6 induces T-cell polarization toward an inflammatory Th17 phenotype, inhibits T regulatory cell development, promotes B-cell differentiation into plasmablasts, and contributes to impaired integrity of the blood-brain barrier, thus enabling pathogenic antibodies and proinflammatory cells to enter the CNS.[10,11]

SAT is a subcutaneously administered, humanized IgG2 monoclonal antibody that inhibits the IL-6 signaling pathway by targeting the membrane-bound and soluble forms of the IL-6 receptor (IL-6R).[12-16] SAT was designed using pH-dependent recycling antibody technology to allow for prolonged plasma half-life compared with conventional monoclonal antibodies, maximum inhibition of IL-6 signaling, and a 4-week dosing regimen.[13-16]

In the double-blind (DB) periods of the 2 pivotal phase 3 studies, treatment with SAT in combination with background immunosuppressive therapy (IST) (SAkuraSky) or as a monotherapy (SAkuraStar) significantly reduced relapse risk in adult and adolescent patients with AQP4-IgG+ NMOSD vs placebo (PBO).[13,14] At Week 192, 71% (95% CI 55%–83%) of patients in SAkuraSky and 73% (95% CI 59%–83%) of patients in SAkuraStar remained free from protocol-defined relapses.[16] Overall, SAT treatment was well tolerated in the DB periods of both SAkura studies and showed a favorable safety profile.[13-16]

In this article, we present data from the SAkuraMoon study (NCT04660539), a single-arm, open-label, rollover study including participants who completed the DB and open-label extension (OLE) periods of the SAkuraSky and SAkuraStar trials. Considering the chronic nature of NMOSD and the

need for life-long maintenance therapy, the main research question addressed by this study was the long-term safety and efficacy of SAT in patients with NMOSD.

Methods

Study Design and Participants

SAkuraMoon was a multicenter, single-arm, open-label, rollover phase 3b study of SAT ± IST for patients with NMOSD who had completed the DB and OLE periods of the SAkuraSky (NCT02028884) or SAkuraStar (NCT02073279) trials (eFigure 1). Detailed methodology for the SAkuraSky and SAkuraStar studies has been published previously.[13-16]

Patients with AQP4-IgG+ NMOSD who participated in SAkuraSky or SAkuraStar were eligible to enroll in SAkuraMoon. Patients with NMOSD who were AQP4-IgG– at screening in SAkuraSky and SAkuraStar could enroll in SAkuraMoon if the investigator considered continued treatment with SAT to be beneficial for the patient. Full inclusion/exclusion criteria have been included in the supplement (eAppendix 1).

The treatment period in SAkuraMoon was up to 3 years from the date of first patient enrollment. If patients experienced a relapse during the study, they underwent Expanded Disability Status Scale (EDSS) assessment and were treated with acute relapse/rescue therapy at the investigator's discretion. After the last SAT dose, a 12-week safety follow-up was conducted for all patients who received at least 1 dose of SAT, except for patients who continued with SAT treatment outside this study.

Procedures

Patients were transitioned from their ongoing OLE of SAkuraSky or SAkuraStar at a planned dosing visit to allow for continuous dosing with subcutaneous SAT at a dose of 120 mg every 4 weeks. Patients received SAT as monotherapy or in combination with one of the following background immunosuppressive treatments: azathioprine (AZA; maximum 3 mg/kg/d), mycophenolate mofetil (MMF; maximum 3,000 mg/d), or oral corticosteroids (OCS; maximum 15 mg/d; prednisolone equivalent). Patients aged younger than 18 years at the time of informed consent for SAkuraSky could continue treatment with a combination of OCS and either AZA or MMF. Background treatment could be modified at the investigator's discretion.

In accordance with local regulations, administration of SAT using prefilled syringes outside the study site (e.g., self-administration or administration by a caregiver after completing training) was permitted on scheduled dosing days that did not require additional assessments.

Pain medication and acute relapse/rescue therapy (pulse IV or OCS, IV immunoglobulin, and/or apheresis, including plasma exchange or plasmapheresis) were permitted during the study. SAT treatment continued as scheduled, concurrently with acute relapse therapy at the discretion of the investigator. Patients who terminated the study early were required to complete an end-of-treatment visit and a safety follow-up visit 12 weeks after administration of the final dose of the study drug.

Outcomes

The primary objective was to investigate the long-term safety of SAT in patients with NMOSD. Safety outcomes included the incidence and severity of adverse events (AEs), serious AEs, infections (including serious and opportunistic infections [eAppendix 2 provides a glossary of SAT-specific potential opportunistic infections]), hepatotoxicity, and injection-related reactions (IRRs). A severe AE was defined as an AE that is incapacitating, resulting in the inability to work or to perform normal daily activity. In addition, the changes from baseline in targeted vital signs, targeted clinical laboratory tests, ECG results, and suicidality were monitored. AEs of special interest for this study were as follows: (1) cases of potential drug-induced liver injury that included elevated alanine transaminase (ALT) or aspartate transaminase (AST) in combination with either an elevated bilirubin or clinical jaundice and (2) suspected transmission of an infectious agent related to the study drug. AEs of special interest were required to be reported by the investigator immediately. Relapses were not categorized as AEs. AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 27.0 and reported by Preferred Term. AEs were identified as infections when coded to the MedDRA system organ class "Infections and Infestations."

Based on the outcomes of the DB periods in the SAkuraSky and SAkuraStar studies, SAT was approved for the treatment of patients with AQP4-IgG+ NMOSD. As such, this study exclusively analyzed efficacy outcomes in this patient population. Efficacy assessments included the time to first PDR as assessed by the investigator (iPDR) that occurred during the parent studies or this study, the proportion of relapse-free patients, and the annualized iPDR rate (ARR). iPDRs were defined as new or worsening objective neurologic symptoms attributable to NMOSD and persisting for >24 hours, with at least one of the following: increase of at least 1.0 point in the EDSS score or increase of ≥2.0 EDSS points from a baseline EDSS score of 0 in the parent study; an increase of at least 2.0 points in one of the appropriate Functional Systems Scores (FSSs) affecting either pyramidal, cerebellar, brainstem, sensory, bowel, or bladder function, or a single eye function; increase of at least 1.0 point in 2 or more of the appropriate FSS if the score at baseline in the parent study was 1.0 or more; increase of at least 1.0 point in single eye FSSs when the score at baseline in the parent study in that eye was 1.0 or more. The time to severe iPDR (increase of ≥2 points in the EDSS score regardless of the baseline EDSS score in the parent study) was also evaluated. The base of comparison for the increase was the score at the most recent scheduled

EDSS/FSS assessment visit before the relapse. EDSS and FSS scores were assessed within 7 days of a patient reporting their symptoms to the clinical trial coordinating center. Additional predefined secondary efficacy outcomes were the change in EDSS score, time to EDSS score worsening, proportion of patients without EDSS score worsening, proportion of patients who received rescue therapy, and change in visual acuity.

In SAkuraMoon, laboratory assessments were conducted every 12 weeks, and a postbaseline worsening in laboratory value grade severity compared with baseline was reported. Baseline values were the patient's last observation on or before receiving the first SAT dose. Grade severity was determined using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4 (NIH, 2009). For ALT/AST, the finding of elevated (>3 × the upper limit of normal [ULN]) ALT or AST in combination with either total bilirubin >2 × ULN or clinical jaundice was defined as an indicator of severe drug-induced liver injury. Finally, the pharmacokinetic (PK) end point was the serum concentration of SAT to characterize the PK profile of SAT further.

Statistical Analysis

Patients who were enrolled in the parent studies (SAkuraSky and SAkuraStar) were included in the statistical analyses even if they were not enrolled in SAkuraMoon. The reported analyses are based on data from the overall SAT treatment (OST) period, defined from the patient's first dose in the DB or OLE period to the clinical cutoff date (CCOD) of May 28, 2024.

The safety analysis population included all randomized or enrolled patients who received at least 1 dose of SAT during either the parent SAkura studies or SAkuraMoon. AEs were evaluated descriptively as the proportion of patients who experienced the AE and as rates (number of events per 100 patient-years [PYs] of safety observation) to adjust for treatment exposure differences. The rate of AEs per 100 PYs was calculated as (total number of AEs/total number of PYs of safety observation) × 100, with 95% CIs calculated using the exact method based on the Poisson distribution.

Efficacy analyses included all AQP4-IgG+ patients who received at least 1 dose of SAT at any time during either the parent studies or this study. The Kaplan-Meier method was used to estimate the distribution of time to first iPDR, time to first severe iPDR, time to EDSS score worsening (relapse-free proportions), and 95% CIs. The ARR was calculated as the total number of iPDRs divided by the total number of PYs of the whole study period starting from the first dose of SAT. The adjusted ARR over time was calculated using estimates from analyses based on a generalized estimating equation Poisson regression model with repeated measurements using an unstructured covariance matrix, adjusted by study identifier of the parent study and exposure year; log-transformed PYs were included as an offset variable. The adjusted overall ARR for the whole period was estimated using a Poisson regression model. SAS version 9.4 was used to perform the statistical analyses.

Standard Protocol Approvals, Registrations, and Patient Consents

Approval was obtained from the local ethics committee or institutional review board at each participating trial center (eTable 1), and all patients provided written informed consent. SAkuraMoon (NCT04660539) and the parent SAkura studies (SAkuraSky: NCT02028884; SAkuraStar: NCT02073279) were conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. The study protocol and statistical analysis plan are available in eSAP 1 and eSAP 2, respectively.

Data Availability

Qualified researchers may request access to individual patient-level clinical data through a data request platform. At the time of writing this, the request platform is Vivli (vivli.org/ourmember/roche/). Up-to-date details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents are available at go.roche.com/data_sharing. Anonymized records for individual patients across more than 1 data source external to Roche cannot, and should not, be linked because of a potential increase in the risk of patient reidentification.

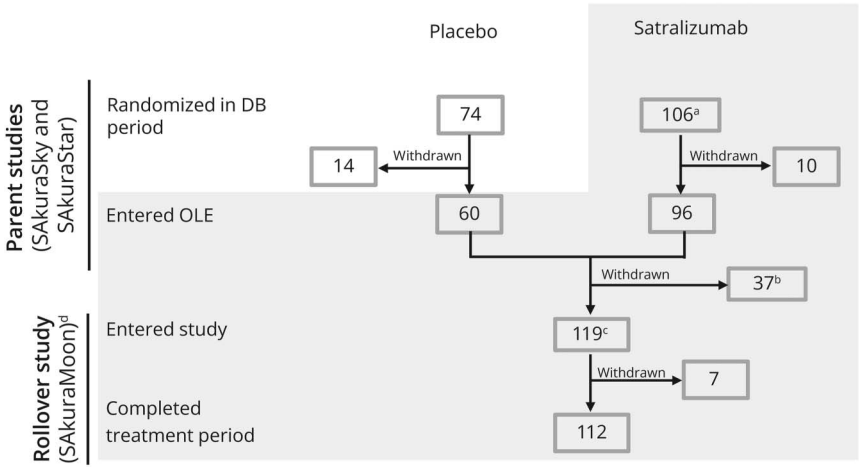
Results

Patient Population

SAkuraSky and SAkuraStar enrolled a total of 180 patients, with 74 randomly assigned to PBO and 106 randomly assigned to SAT (Figure 1). Of these, 60 patients receiving PBO and 96 patients receiving SAT entered the OLE period of their respective study. Of the 180 patients enrolled in the parent studies, 119 patients were subsequently enrolled in SAkuraMoon. Seven patients discontinued participation in SAkuraMoon because of the following reasons: pregnancy (n = 2), loss to follow-up (n = 1), patient withdrawal (n = 2), and switch to commercial SAT (n = 2). The SAkuraMoon study took place across 53 study centers in 17 participating countries worldwide.

Overall, 166 patients who received at least 1 dose of SAT during either the parent SAkura studies or SAkuraMoon were included in the safety analysis population. Most patients were women (n = 142, 86%) (Table 1). The mean (SD) age when patients received their first dose of SAT was 42.7 (13.3) years. In total, 81 patients (49%) received previous treatments for relapse prevention, primarily with systemic corticosteroids (prednisolone, methylprednisolone; n = 41, 24%) and immunosuppressants (azathioprine [n = 24, 15%], mycophenolate mofetil [n = 9, 5%]). The efficacy analyses included

Figure 1 Patient Disposition From the Parent Studies of SAkuraSky and SAkuraStar to the Rollover Study, SAkuraMoon



[a]One patient was randomly assigned on the day of the CCOD of SAkuraSky, and 1 patient was enrolled directly into the OLE period of SAkuraSky and is included in the satralizumab treatment arm of the intent-to-treat population. [b]Two patients were reported as discontinued from the parent study OLE on the day they enrolled to SAkuraMoon. [c]Of the 119 patients who entered the rollover study, SAkuraMoon, 78 were AQP4-IgG+ and 41 were AQP4-IgG−. [d]Analyses in SAkuraMoon were based on data from the OST period, represented as the shaded gray area, and defined from the patients' first dose of satralizumab in the DB or OLE periods of the parent studies (SAkuraSky or SAkuraStar) to the clinical cutoff date of May 28, 2024. Efficacy analyses included all AQP4-IgG+ patients (n = 111) who received at least 1 dose of satralizumab at any time during either the parent studies or SAkuraMoon. The safety analysis population included all randomized or enrolled patients (n = 166) who received at least 1 dose of satralizumab during either the parent studies or SAkuraMoon, including patients not participating in SAkuraMoon. AQP4-IgG+ = aquaporin-4 immunoglobulin G–seropositive; AQP4-IgG− = aquaporin-4 immunoglobulin G–seronegative; CCOD = clinical cutoff date; DB = double-blind; OLE = open-label extension; OST = overall satralizumab treatment.

111 of the 121 AQP4-IgG+ patients (92%) enrolled in the parent studies, with a mean (SD) baseline ARR and EDSS score of 1.14 (0.53) and 3.96 (1.62), respectively.

A total of 59 AQP4-IgG− patients were randomly assigned to study treatment in the parent studies and received at least 1 dose of the study drug. Of these, 41 patients (70%) entered the rollover study, SAkuraMoon, and were included in all safety analyses.

The median duration of SAT exposure in the OST period was 6.9 years (range: 0–10), with 80 patients (48%) receiving SAT for at least 7 years and 16 patients (10%) reaching up to 10 years of SAT treatment. The total SAT exposure was 1,014 PYs.

Safety Analyses

Overall Safety Profile

The safety profile of SAT in the SAkura studies has been published previously; overall, a higher rate of AEs was reported in the PBO group compared with the SAT group during the DB periods.[13-15] Most patients (98%) reported at least 1 AE during the OST period; most were mild or

Table 1 Demographics and Baseline Characteristics of Patients in the SAkuraMoon Study

	AQP4-IgG+ patients (n = 111)	All patients (n = 166)
Age, y		
Mean (SD; min–max)	43.2 (13.5; 13–73)	42.7 (13.3; 13–73)
Female sex, n (%)	100 (90)	142 (86)
Geographic region, n (%)		
Asia	36 (32)	42 (25)
Europe/other	35 (32)	67 (40)
North America	40 (36)	57 (34)
Baseline ARR, mean (SD)	1.14 (0.53)	1.18 (0.55)
Baseline EDSS score, mean (SD)	3.96 (1.62)	3.80 (1.57)

Abbreviations: AQP4-IgG+ = aquaporin-4 immunoglobulin G–seropositive; ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale.
Data are mean (SD; min–max) or n (%).
Efficacy analyses included all patients with AQP4-IgG+ (n = 111) who received at least 1 dose of satralizumab at any time during either the parent studies (SAkuraSky or SAkuraStar) or SAkuraMoon. The safety analysis population included all randomized or enrolled patients (n = 166) who received at least 1 dose of satralizumab during either the parent studies or SAkuraMoon, including patients not participating in SAkuraMoon.

Table 2 Adverse Events in the Safety Analysis Population During the DB Periods of SAkuraSky and SAkuraStar, Until the End of the OST Period in SAkuraMoon

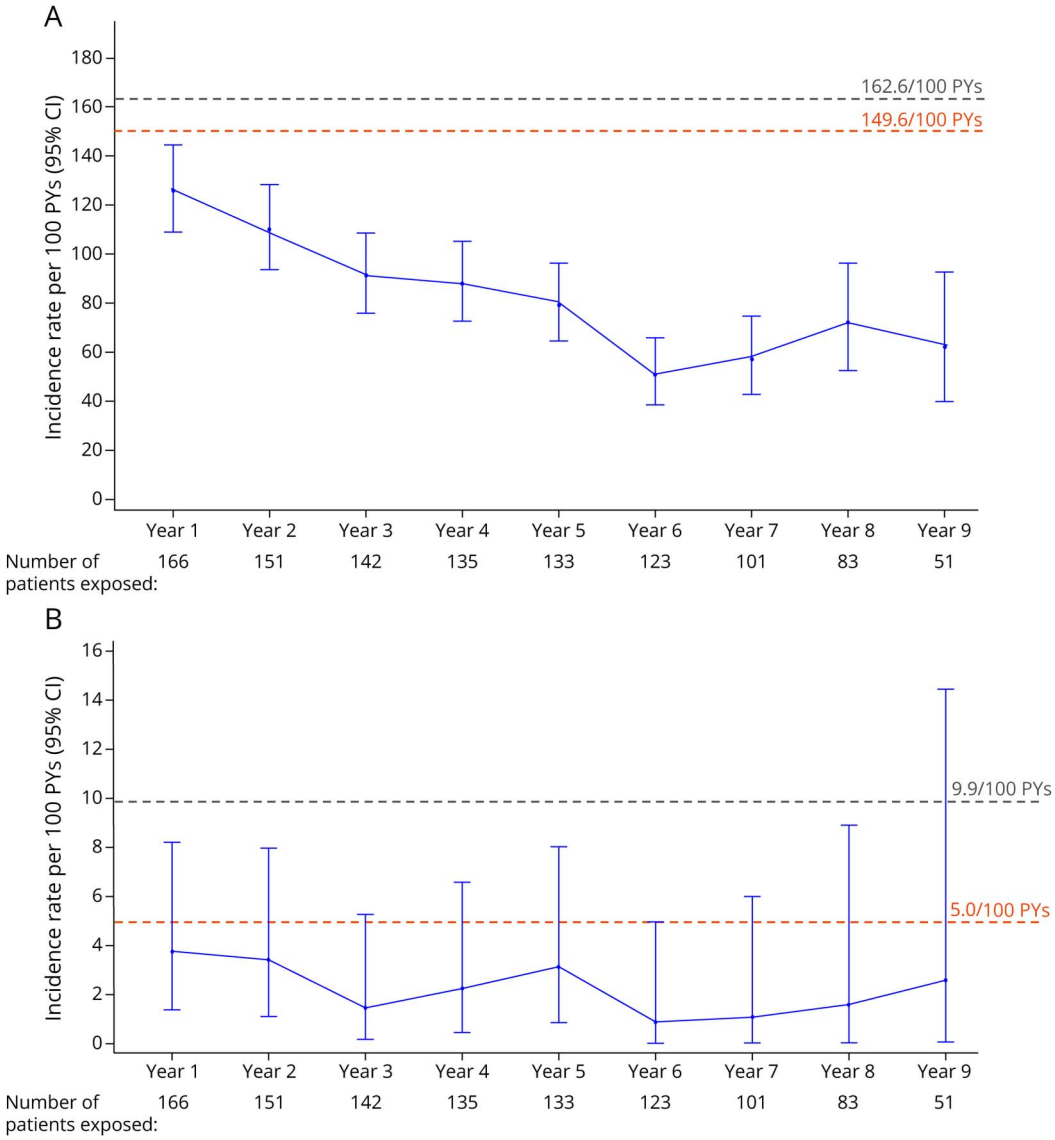
	SAkuraSky and SAkuraStar DB periods								SAkuraMoon OST period	
	SAkuraStar: Placebo (n = 32; PY = 40.6)		SAkuraSky: Placebo + IST (n = 42; PY = 59.5)		SAkuraStar: Satralizumab (n = 63; PY = 115.2)		SAkuraSky: Satralizumab + IST (n = 41; PY = 78.5)		Satralizumab ± IST (n = 166; PY = 1014.4)	
	Patients, n (%)	AEs/100 PYs (95% CI)	Patients, n (%)	AEs/100 PYs (95% CI)	Patients, n (%)	AEs/100 PYs (95% CI)	Patients, n (%)	AEs/100 PYs (95% CI)	Patients, n (%)	AEs/100 PYs (95% CI)
All AEs	24 (75.0)	495.2 (429.1–568.6)	40 (95.2)	514.3 (458.2–575.2)	58 (92.1)	473.9 (435.0–515.4)	37 (90.2)	485.2 (437.7–536.5)	162 (97.6)	299.4 (288.8–310.2)
Serious AEs[a]	5 (15.6)	14.8 (5.4–32.2)	9 (21.4)	20.2 (10.4–35.2)	12 (19.0)	17.4 (10.6–26.8)	7 (17.1)	11.5 (5.2–21.8)	44 (26.5)	8.1 (6.4–10.0)
Severe AEs[a]	2 (6.2)	9.9 (2.7–25.2)	5 (11.9)	11.8 (4.7–24.2)	17 (27.0)	32.1 (22.6–44.3)	5 (12.2)	6.4 (2.1–14.9)	46 (27.7)	9.6 (7.8–11.7)
Fatal AEs	0	0 (NE–9.1)	0	0 (NE–6.2)	0	0 (NE–3.2)	0	0 (NE–4.7)	0	0 (NE–0.4)
AEs leading to treatment discontinuation	1 (3.1)	2.5 (0.1–13.7)	4 (9.5)	6.7 (1.8–17.2)	1 (1.6)	0.9 (0.0–4.8)	3 (7.3)	5.1 (1.4–13.0)	9 (5.4)	1.0 (0.5–1.8)
Infections[b]	14 (43.8)	162.6 (125.8–206.9)	26 (61.9)	149.6 (120.1–184.1)	34 (54.0)	99.8 (82.4–119.8)	28 (68.3)	132.5 (108.2–160.5)	132 (79.5)	87.5 (81.9–93.5)
Serious infections[b]	3 (9.4)	9.9 (2.7–25.2)	3 (7.1)	5.0 (1.0–14.7)	6 (9.5)	5.2 (1.9–11.3)	2 (4.9)	2.6 (0.3–9.2)	19 (11.4)	2.4 (1.5–3.5)
Injection-related reactions	5 (15.6)	17.3 (6.9–35.5)	2 (4.8)	3.4 (0.4–12.1)	9 (14.3)	13.9 (7.9–22.6)	5 (12.2)	21.7 (12.6–34.7)	24 (14.5)	5.6 (4.3–7.3)
Anaphylactic reactions	0	0 (NE–9.1)	0	0	0	0 (NE–3.2)	0	0	1 (0.6)	0.1 (0–0.6)
Neoplasms	1 (3.1)	2.5 (0.1–13.7)	3 (7)	5.0 (1.0–14.7)	2 (3.2)	1.7 (0.2–6.3)	3 (7)	3.8 (0.8–11.2)	21 (12.7)	2.3[c] (1.4–3.4)

Abbreviations: AE = adverse event; DB = double-blind; IST = immunosuppressive therapy; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NE = not evaluable; OST = overall satralizumab treatment; PYs = patient-years.
NCI-CTCAE (v4·0) was used for assessing AE severity.
[a] A serious AE was defined as any AE that is life-threatening or fatal, requires or prolongs inpatient hospitalization, results in persistent or significant disability, results in a congenital anomaly in a neonate born to a mother exposed to the study drug, or is a significant medical event in the investigator's judgment. A severe AE was defined as an AE that is incapacitating, resulting in the inability to work or to perform normal daily activity.
[b] MedDRA system organ class "Infections and Infestations."
[c] Overall, 23 AEs of neoplasms were observed in 21 patients, including uterine leiomyoma (n = 6, 4%), colorectal adenoma (n = 2, 1%), colon cancer, ovarian adenoma, and benign ovarian germ cell teratoma (all n = 1, 0.6% each).

moderate in severity. Overall, 82 serious AEs were reported among 44 patients (27%). In the OST period, the rates of AEs and serious AEs (95% CI) were 299.4 (288.8–310.2)/100 PYs and 8.1 (6.4–10.0)/100 PYs, respectively, and were lower compared with the DB periods of the parent studies (Table 2). Most severe AEs were resolved by study completion. Most AEs were reported in the "Infections and Infestations" system organ class (80% of patients reported at least 1 AE) and were mainly events of upper respiratory tract infection, urinary tract infection, and nasopharyngitis. Regarding individual AEs, the most frequently reported AEs were nasopharyngitis (29%), upper respiratory tract infection (28%), headache (27%), urinary tract infection (25%), arthralgia (21%), COVID-19 (19%), and pain in extremity (16%). One patient (1%) experienced an anaphylactic reaction in SAkuraMoon unrelated to SAT treatment. There were no reports of serious hypersensitivity reactions related to SAT. Overall, 10 AEs leading to treatment discontinuation were reported in 9 patients (5%): ALT increase (resolved), AST increase (resolved), neutrophil count decrease (resolved), large intestine infection (resolved), pneumonia (resolved), metastatic colon cancer (unknown outcome), septic endocarditis (resolved with sequelae), spinal compression fracture (resolved), urticaria (resolved), and vasculitis (resolved). A total of 57 IRRs were reported in 24 patients (15%) during the OST period; the rate of reported IRRs was lower than with SAT during the DB periods of SAkuraSky and SAkuraStar (Table 2). All IRRs were nonserious, most were mild or moderate in severity, and none led to treatment discontinuation or interruption. No deaths or AEs of special interest occurred during the study.

In the OST period, the incidence rate of neoplasms (95% CI) was 2.3 (1.4–3.4)/100 PYs, which was comparable with the rates observed during the DB periods of the primary studies (Table 2). In total, 26 AEs of fractures occurred in 18 patients (11%); rib and spinal compression (both n = 3, 2%) fractures were the most common. Two patients with AEs of fractures were receiving chronic OCS.

Figure 2 Rates of (A) Infections and (B) Serious Infections in Patients Receiving Satralizumab by Year During the OST Period (Safety Analysis Population)



Dashed lines indicate reference rates from the DB periods of SAkuraSky (placebo+IST, orange line) and SAkuraStar (placebo monotherapy, gray line). OST = overall satralizumab treatment; PYs = patient-years.

Infections

The rates of infections (87.5 [81.9–93.5]/100 PYs) and serious infections (2.4 [1.5–3.5]/100 PYs) in the OST period were comparable with those of the DB periods and decreased over time (Figure 2). Most infections were nonserious and of mild or moderate severity. The most common infections were respiratory tract infections (n = 85, 51%) and urinary tract infections (n = 52, 31%) (eTable 2). A total of 24 patients experienced potential opportunistic infections (8.6 [95% CI 6.9–10.6]/100 PYs), the most common being oral herpes in 9 patients (5%) (6.9 [95% CI 5.4–8.7]/100 PYs) and herpes zoster in 7 patients (4%) (0.7 [95% CI 0.3–1.4]/100 PYs). The cases of herpes zoster were mild (5/7) or moderate (2/7) in severity; 4 of 7 patients were using concomitant ISTs, and 3 of 7 patients were older than 50 years. The rate of herpes zoster did not increase with time. Other potential opportunistic infections included herpes virus infection (not otherwise specified) in 1 patient, genital herpes simplex in 1 patient, oral candidiasis in 3 patients, atypical mycobacterial infection in 1 patient, and fungal sinusitis in 1 patient. No cases of meningococcal infection or encephalitis were reported during the OST period. The most common serious infections were urinary tract infections (n = 7, 4%) and sepsis (n = 4, 2%) (eTable 3). Of the 166 patients evaluated, events of serious infections were recorded in 19 patients (2.4 [95% CI 1.5–3.5]/100 PYs), all of whom received SAT.

Laboratory Values

In the OST period, longer exposure to SAT was not associated with a higher risk of severe (grade ≥3) laboratory changes

compared with the DB periods of SAkuraSky and SAkuraStar (eTable 4). Most decreases in neutrophil counts were grade 2 and transient/intermittent in nature, with 26 events of neutropenia recorded at an incidence rate of 2.6 (95% CI 1.7–3.8)/100 PYs. SAT treatment was interrupted in 7 patients because of 8 events of neutropenia, and 1 patient discontinued treatment. No neutrophil count decreases necessitated the use of granulocyte colony-stimulating factor treatment. Platelet count decreases were mainly grade 1 and transient/intermittent, with no bleeding events. Six patients experienced thrombocytopenia, and the overall incidence rate was 0.6 (95% CI 0.2–1.3)/100 PYs. One case of thrombocytopenia resulted in dose interruption. Most cases of hepatic enzyme elevations (ALT or AST) were also grade 1, and no patients had liver function tests indicative of drug-induced liver injury. Two patients had grade 3 ALT increase, and 1 patient had grade 3 AST increase; both cases occurred during the parent study SAkuraStar. One patient met the protocol-defined criteria for dose discontinuation for liver abnormalities defined as isolated AST and/or ALT >5 × ULN. The second patient had already discontinued study treatment (due to lack of efficacy) before the liver enzyme elevations. Most increases in triglyceride and cholesterol levels were grade 1 or grade 2 (eTable 4). Decreases in fibrinogen levels were mainly grade 1 or 2, and there were no associations with bleeding events.

Vital Signs

There was an increase in postbaseline values of vital signs when compared with baseline values; however, most of these changes were not considered clinically significant. Changes in vital signs that were considered clinically significant were reported as AEs; none resulted in changes in study treatment. Changes in body weight (increase and/or decrease) were common in the OST period: overall, 133 patients had an increase or decrease in body weight of ≥7%, and 49 patients had an increase or decrease in body weight of ≥15% (eTable 5).

PKs and Immunogenicity

The PK profile of SAT during the OST period was consistent with the PK profile observed during the DB periods of SAkuraSky and SAkuraStar. At baseline, 3 of 164 evaluable patients (2%) had a positive result for anti-drug antibodies (ADAs). At the time of CCOD, 99 of 166 evaluable patients (60%) tested positive for treatment-emergent ADAs, of whom 16 had transient ADAs and 76 had persistent ADAs. There was no temporal relationship between the presence of ADAs and the occurrence of AEs.

Efficacy Analyses

Effect on Relapse Risk and the Annualized Relapse Rate

Efficacy results in the AQP4-IgG+ population from the DB and OLE periods of the SAkura studies have been published previously.[13,14,16] In the OST period, 32 patients (29%) experienced 48 iPDRs (Table 3). The estimated proportion of iPDR-free patients at Week 456 was 67% (95% CI 56%–76%) (Figure 3A). Owing to low patient exposure beyond Week 456 (year 9), results beyond this point should be interpreted with caution. The median time to first iPDR was not evaluable in this analysis. Relapse events in AQP4-IgG+ patients during their participation in the SAkura studies and during the 2 years before enrollment are illustrated in Figure 4. A greater number of patients randomly assigned to SAT in the primary studies were relapse-free and were less likely to experience multiple relapses compared with patients who were originally randomly assigned to PBO; the protective effect of SAT was sustained with long-term treatment.

The overall adjusted ARR (95% CI) was 0.12 (0.08–0.18) in SAkuraSky and 0.08 (0.05–0.13) in SAkuraStar.[13,14] In this study, in the OST period, the adjusted ARR (95% CI) was 0.07 (0.05–0.10). When observed longitudinally, the adjusted ARR remained consistently at or below 0.20 for the duration of the OST period. After the third year of treatment, the yearly ARR was consistently below 0.10 (Table 3).

Effect on Relapse Severity and Use of Rescue Therapy

In SAkuraMoon, 10 patients experienced severe iPDRs during the OST period. The estimated proportion of severe iPDR-free patients at Week 456 was 89% (95% CI 80%–94%) (Table 2, Figure 3B). In total, 71 AQP4-IgG+ patients (64%) did not receive rescue therapy for an acute relapse during the OST period.

Effect on Sustained Disability Accrual

In the OST period, 16 patients (15%) experienced EDSS score worsening lasting ≥24 weeks (Table 3). By week 456, an estimated 82% (95% CI 72%–89%) of SAT-treated patients did not experience sustained worsening of EDSS score (Figure 3C).

Discussion

These results from the rollover SAkuraMoon study demonstrate that the safety and efficacy profile of SAT treatment (±IST) observed during the pivotal SAkuraSky and SAkuraStar studies was sustained with long-term treatment, over a median treatment exposure of 6.9 years. Overall, SAT was well tolerated, as an add-on to background ISTs or as monotherapy, in patients with NMOSD, with no new or unexpected safety findings and no fatalities recorded during the study. Most AEs in the OST period were mild or moderate in severity, and rates were lower than in the DB periods of the primary studies.[13-15] Furthermore, most severe AEs were resolved by study completion.

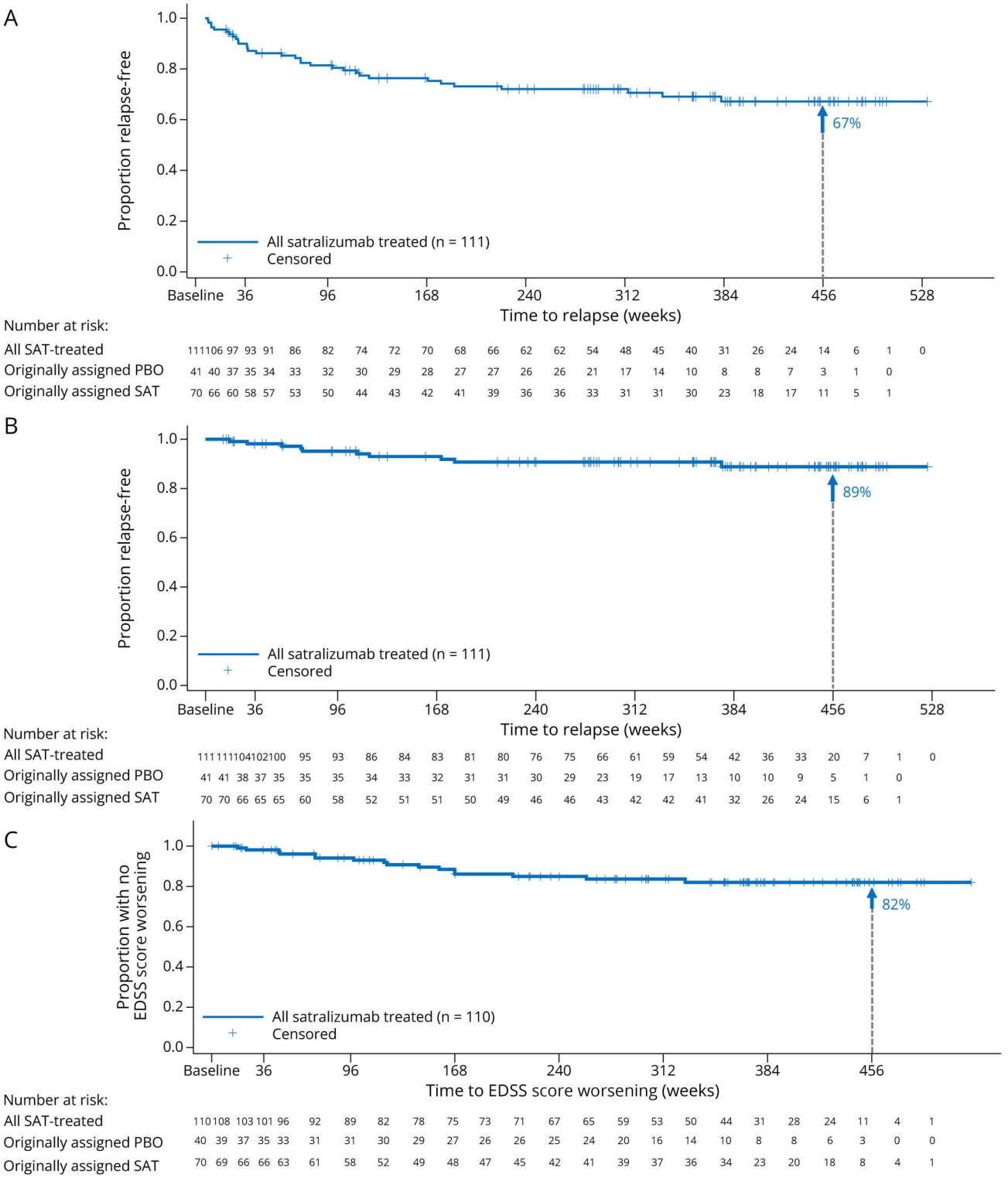
One of the main clinical considerations when inhibiting the IL-6 signaling pathway, particularly in combination with other ISTs, is the occurrence and severity of infections.[17,18] Infections were the most common AEs observed in this study, especially infections of the upper respiratory tract and the urinary tract, with the latter being a common complication of bladder dysfunction in the context of NMOSD.[19,20] Despite the high number of patients

Table 3 Summary of Efficacy Analyses in AQP4-IgG+ Patients During the OST Period

	SAkuraSky OST	SAkuraStar OST	SAkuraMoon OST
	Satralizumab + IST (n = 49)	Satralizumab (n = 62)	Satralizumab ± IST (n = 111)
iPDR			
Number of events	24	19	48
Patients with ≥1 event	12	17	32
Relapse free at Week 96, % (95% CI)	85 (71–92)	77 (64–86)	80 (72–87)
Relapse free at Week 192, % (95% CI)	71 (55–83%)	73 (59–83)	73 (63–81)
Relapse free at Week 456, % (95% CI)	-	-	67 (56–76)
Severe iPDR			
Number of events	8	6	20
Patients with ≥1 event	3	6	10
Severe relapse free at Week 96, % (95% CI)	100 (100–100)	92 (81–96)	95 (89–98)
Severe relapse free at Week 192, % (95% CI)	91 (75–97)	90 (78–95)	91 (83–95)
Severe relapse free at Week 456 %, (95% CI)	-	-	89 (80–94)
Sustained EDSS score worsening, (%)			
Event free at Week 96 (95% CI)	93 (80–98)	95 (85–98)	94 (87–97)
Event free at Week 192 (95% CI)	90 (75–96)	86 (73–93)	86 (77–92)
Event free at Week 456 (95% CI)	-	-	82 (72–89)
Adjusted ARR (95% CI)			
Overall ARR	0.12 (0.08–0.18)	0.08 (0.05–0.13)	0.07 (0.05–0.10)
Y 1	0.20 (0.09–0.44) (n = 49)	0.15 (0.08–0.27) (n = 62)	0.17 (0.10–0.28) (n = 111)
Y 2	0.05 (0.01–0.19) (n = 43)	0.13 (0.06–0.28) (n = 59)	0.10 (0.05–0.19) (n = 102)
Y 3	0.08 (0.02–0.34) (n = 41)	0.02 (0.00–0.15) (n = 54)	0.04 (0.01–0.14) (n = 95)
Y 4	0.19[a] (n = 32)	0.02 (0.00–0.18) (n = 42)	0.08 (0.02–0.26) (n = 89)
Y 5	0.08[a] (n = 32)	0.05[a] (n = 33)	0.05 (0.01–0.15) (n = 88)
Y 6	0.11[a] (n = 23)	0.00[a] (n = 16)	0.04[a] (n = 80)
Y 7	-	-	0.03[a] (n = 66)
Y 8	-	-	0.02[a] (n = 56)
Y 9	-	-	0.04[a] (n = 33)
Y 10	-	-	0.0[a] (n = 13)
Y 11	-	-	0.0[a] (n = 1)
Rescue therapy use, n (%)			
Patients receiving rescue therapy	20 (41)	19 (31)	40 (36)

Abbreviations: AQP4-IgG+ = aquaporin-4 immunoglobulin G–seropositive; ARR = annualized relapse rate; DB = double-blind; EDSS = Expanded Disability Status Scale; iPDR = investigator-reported protocol-defined relapse; IST = immunosuppressive therapy; OLE = open-label extension; OST = overall satralizumab treatment.
Data reported are for AQP4-IgG+ patients who received at least 1 dose of satralizumab at any time either during the overall satralizumab treatment (OST) periods of the parent studies (SAkuraSky and SAkuraStar) or during the OST period of SAkuraMoon. The OST period of SAkuraSky and SAkuraStar was defined from the patient's first dose of satralizumab in the DB or OLE period to the clinical cutoff date of Febuary 22, 2021.[16] The OST period of SAkuraMoon was defined from the patient's first dose of satralizumab in the DB or OLE period to the clinical cutoff date of May 28, 2024. Patients who were enrolled in the parent studies were included in the statistical analyses even if they were not enrolled in SAkuraMoon.
[a] Unadjusted value.

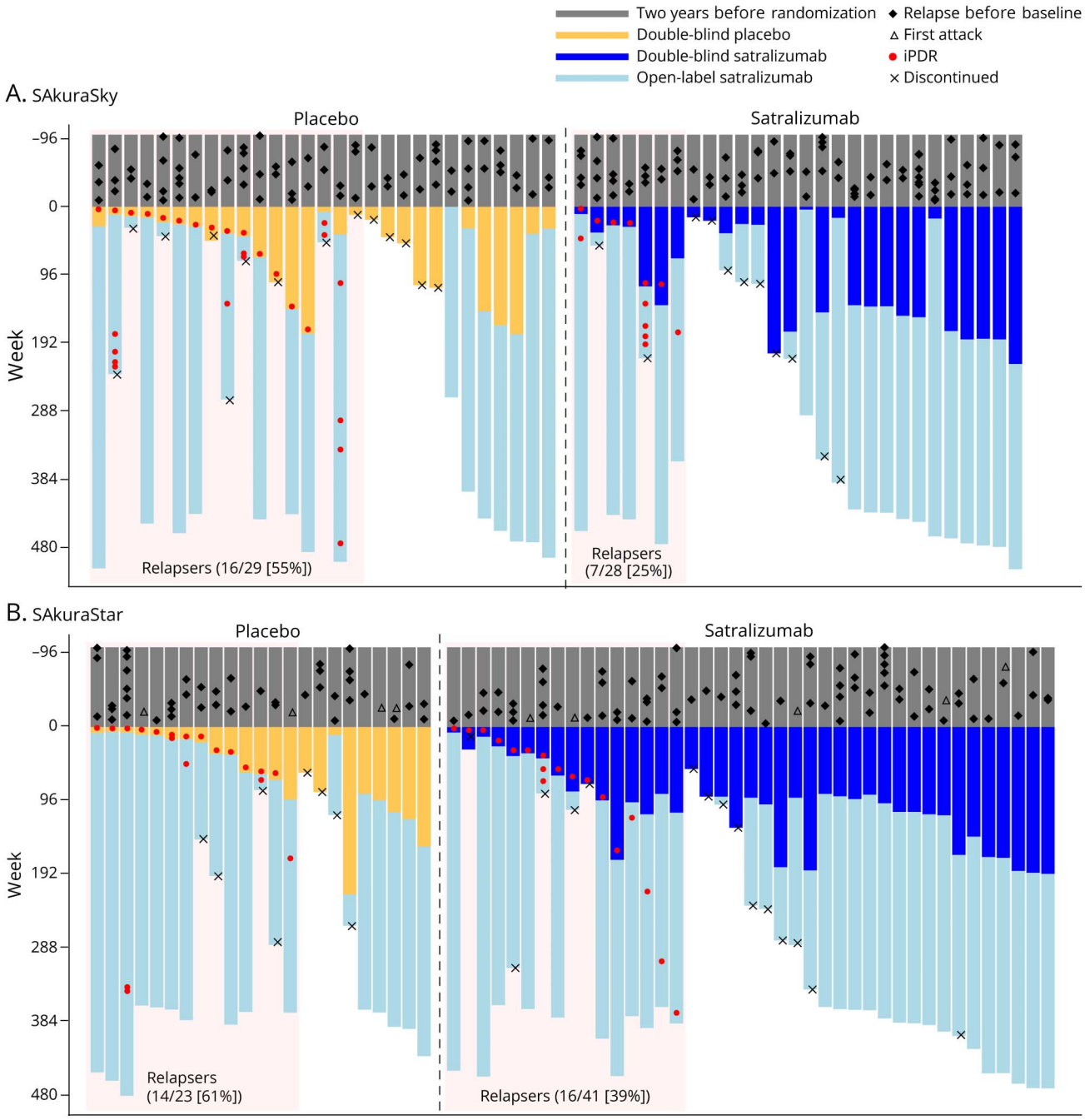
Figure 3 Kaplan-Meier Analysis of (A) Time to First iPDR, (B) Time to First Severe iPDR, and (C) Time to First Sustained EDSS Score Worsening, in the Overall Satralizumab Treatment Period for the AQP4-IgG–Positive Cohort



AQP4-IgG+ = aquaporin-4 immunoglobulin G–seropositive; EDSS = Expanded Disability Status Scale; iPDR = investigator-reported protocol-defined relapse; PBO = placebo; SAT = satralizumab.

experiencing infections, the number of cases of serious or opportunistic infections was low, and no cases of viral or bacterial meningitis/encephalitis or serious herpes virus–associated infections were reported. In addition, the rates of infections and serious infections in the OST period were often lower than in the PBO and PBO + IST arms from the DB periods and did not

Figure 4 Swim Plot of iPDR Events in All Patients Who Received Satralizumab in (A) SAkuraSky and (B) SAkuraStar, Pooled With Patients Who Were Rolled Over in SAkuraMoon



Swim plots were generated for all randomized patients in the DB period of the parent SAkura studies, including patients not participating in SAkuraMoon. DB = double-blind; iPDR = investigator-reported protocol-defined relapse.

increase over time, suggesting that there is no aggravating effect of long-term treatment with SAT.[13-15]

Additional clinical considerations of IL-6R inhibition include changes in laboratory values, including the neutrophil counts, the level of hepatic enzymes, and lipids.[17,18] In our study, most laboratory changes were mild or moderate in severity throughout the OST period and did not lead to treatment interruption. It should be noted that there are currently no reliable neutralizing anti-SAT antibody assays available. Although a high rate of ADAs were observed in this study, no safety signals were observed in this and the parent studies that may suggest an association with SAT over the long-term follow-up.[21] Furthermore, data from the parent studies showed no clear impact of ADAs on the efficacy of SAT.[21]

Relapses are a primary driver of neurologic and physical disability accumulation in patients with NMOSD, and EDSS

score worsening has been shown to be associated with a decrease in patients' quality of life.[4,22] In AQP4-IgG+ NMOSD, patients on ISTs still have a 54% chance of relapse in 2 years.[23] In this study, approximately 7 of 10 patients remained iPDR free at Week 456 (8.8 years). Relapses that only occurred in 29% of patients were relatively mild and associated with good recovery, thus highlighting the clinical benefit of SAT for most patients during the OST period. In comparison with the mean (SD) ARR of 1.14 (0.53) at baseline, long-term treatment with SAT resulted in a consistently low ARR (≤0.2) over a period of 9 years.

Furthermore, 9 of 10 patients (89%) with AQP4-IgG+ NMOSD did not experience any severe iPDRs, defined as an increase of ≥2 points in the EDSS score, and 82% of patients did not experience sustained worsening of EDSS score by Week 456. Moreover, there was a relatively low proportion of patients requiring rescue therapy during the OST period, demonstrating the efficacy of SAT in relapse prevention.

SAkuraMoon enrolled a population with active NMOSD that was largely representative of usual clinical practice and is encountered in real-world studies.[24-26] A further strength of this study is the large proportion of patients who chose to continue with SAT treatment from the original studies, reaching a maximum of 11 years of follow-up for 1 patient. The low dropout rate supports the integrity of the conclusions regarding the safety and efficacy of SAT treatment. Patients with NMOSD who were AQP4-IgG–negative at screening in SAkuraSky and SAkuraStar could enroll in SAkuraMoon, if the investigator considered continued treatment with SAT to be beneficial for the patient. Considering the lower proportion of patients with AQP4-IgG–NMOSD in our cohort and the inherent heterogeneity of this population, reporting the efficacy of SAT in the AQP4-IgG– NMOSD was beyond the scope of this study, but these patients were included in all safety analyses. As understanding of seronegative NMOSD advances, future studies should evaluate the safety and efficacy of currently available treatments in this patient group.

A limitation of this analysis was the potential bias associated with the open-label design of the study. To mitigate this bias, prespecified and objective criteria were used to define and assess iPDRs. Of 180 patients randomly assigned to the parent studies, 119 patients (66%) rolled over to SAkuraMoon. With up to one-third of patients withdrawing, there may be a selection bias toward a more SAT-responsive sample.[15,16] The absence of an external control may also be considered a limitation of this analysis. However, this is minimized when considering the significant effect in relapse prevention observed when comparing the SAT and PBO groups during the DB periods of the original studies and the consistently low ARR during the OST period.[13-16]

Evaluating the long-term safety and efficacy of an approved therapy is important to help clinicians make informed decisions on the most appropriate treatment for their patients with NMOSD, a chronic disease requiring long-term maintenance relapse prevention therapy. To the authors' knowledge, SAkuraMoon provides the longest follow-up of a phase 3 cohort investigating the therapeutic value of disease-modifying therapy for patients with AQP4-IgG+ NMOSD. Overall, this study provides reliable, consistent, long-term data highlighting the favorable safety and efficacy profile of SAT treatment, as monotherapy or in combination with ISTs, for patients with AQP4-IgG+ NMOSD.

Acknowledgment

The authors thank the patients and their care partners, in addition to the investigators and their teams, who contributed to this study. The authors also thank the project team member at F. Hoffmann La Roche, Elizaveta Kulcsar (F. Hoffmann-La Roche Ltd, Basel, Switzerland), for support with statistical analysis.

Author Contributions

J.L. Bennett: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. K. Fujihara: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. A. Saiz: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. A.L. Traboulsee: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. B.M. Greenberg: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. B.G. Weinshenker: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. F. Patti: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. I. Kleiter: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. J. Palace: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. J. De Seze: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. R. Evans: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. K. Blondeau: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. G. Klingelschmitt: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. I. Vodopivec: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. M. Rahim: drafting/revision of the manuscript for content, including medical writing for content. T Yamamura: drafting/

revision of the manuscript for content, including medical writing for content; analysis or interpretation of data.

Study Funding

This research was funded by F. Hoffmann La Roche. Medical writing support was provided by Sofia Thomaidou and Masouda Rahim of ApotheCom, London, United Kingdom, funded by F. Hoffmann La Roche, in accordance with Good Publication Practice 3 guidelines. Authors were neither paid to participate nor precluded from accessing data in the study.

Disclosure

J.L. Bennett has performed consultative services for Amgen, Genentech, TG Therapeutics, Alexion, Reistone Bio, Roche, Antigenomycs, Chugai, Mitsubishi Tanabe, EMD Serono, Beigene, Novartis, CorEvitas, Immpact Bio, and ImCyse. He has served on Scientific Advisory or Data Safety Monitoring boards for Clene Nanomedicine and Roche. He has served on a speaker's bureau for Alexion; has received research support from the NIH and the National MS Society; and has received intellectual property interests from a patent on Aquaporumab. K. Fujhara received grants from Ministry of Health, Welfare and Labour of Japan; received personal fees from Roche/Chugai, Alexion, Argenx, Amgen, Biogen, Eisai, Mitsubishi-Tanabe, Novartis, UCB, Sanofi, Teijin, and Asahi Kasei Medical. A. Saiz received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Merck, Sanofi, Biogen, Roche, Novartis, Janssen, and Horizon Therapeutics. A. Traboulsee received consulting fees from Genzyme, Roche, and Novartis and is part of a speakers bureau for Genzyme and Roche. B.M. Greenberg received consulting fees from Alexion, Novartis, EMD Serono, Amgen, Abcuro, Genentech/Roche, Signant, IQVIA, Sandoz, Sanofi/Genzyme, Immunovant, TG Therapeutics, Clene, Arialys, and Syneos. He receives royalties from UpToDate. He has received research grants from Anokion and Regeneron; has received speaker honoraria from PRIME; and holds a patent for GenrAb. He has equity in Clene Nanomedicine and GenrAb. He is a board member of the Siegel Rare Neuroimmune Association. B. Weinshenker reports consulting fees from UCB Biosciences, Horizon, Mitsubishi Tanabe, Genentech, and Roche, and speaking fees from Genentech, Roche, and Novartis; he participated or participates on the Attack Adjudication Committee for Alexion, Horizon Therapeutics (formerly MedImmune/Viela Bio) and UCB Biosciences. He has a patent NMO-IgG for diagnosis of neuromyelitis optica with royalties received from RSR Ltd., Oxford University, Hospices Civils de Lyon, and MVZ Labor PD Dr Volkmann und Kollegen GbR. F. Patti received research grants, fees for speaking activities, consultation or serving on advisory boards from Alexion, Amirall, Biogen, Bristol Meyers, and Squibb, Janssen, Merck, Novartis, Roche, and Sanofi. I. Kleiter has received personal compensation for consulting, serving on a scientific advisory board, speaking or other activities from Alexion, Almirall, Biogen, GlaxoSmithKline, Hexal, Horizon, Merck, Neuraxpharm, Roche/Chugai, and Sanofi. J. Palace has received support for scientific meetings and honorariums for advisory work from Merck Serono, Novartis, Chugai, Alexion, Roche, Medimmune/Horizon, Argenx, Sanofi, UCB, Mitsubishi, Amplo Biotechnology, and Janssen; and research grants from Alexion, Argenx, Roche, Medimmune, UCB, and Amplo biotechnology, Patent ref P37347WO and licence agreement Numares multimarker MS diagnostics. She acknowledges partial funding to the trust by highly specialized services from National Health Service (NHS) England. She is on the medical advisory boards of the Sumaira Foundation and MOG Project charities, is a member of the Guthy Jackon Foundation Charity, and is on the Board of the European Charcot Foundation, a member of MAGNIMS (steering member until February 2024) and the UK NHS England IVIG Committee, and chairman of the NHS England neuroimmunology patient pathway and ECTRIMS Council member on the educational committee since June 2023, current Association of British Neurologists (ABN) advisory groups for MS and neuroinflammation and previous neuromuscular diseases ABN advisory member until April 2024. J. De Seze received grants and personal fees from Roche, received personal fees from Chugai, and has served on advisory boards in the expert committee for the clinical trial conducted by Chugai. R. Evans is an employee of Roche Products Ltd. K. Blondeau is an employee of F. Hoffmann-La Roche Ltd and Parexel Belgium SRL. G. Klingelschmitt and I. Vodopivec are employees of F. Hoffmann-La Roche Ltd. M. Rahim is an employee of ApotheCom, London, United Kingdom, who received funding from F. Hoffman-La Roche for medical writing assistance. T. Yamamura served on scientific advisory boards for Chugai, Roche, Biogen Japan, Biogen Massachusetts, Novartis, and Mitsubishi Tanabe; received research grants from Chugai, Novartis, Biogen Japan, Chiome Bioscience, Sanofi, UCB Japan, and Mebix; received speaker honoraria from Chugai, Biogen Japan, Novartis, Mitsubishi Tanabe, Takeda, Miyarisan, Alexion, Sumitomo, and Teijin. Go to Neurology.org/NN for full disclosures.

Publication History

Received by *Neurology® Neuroimmunology & Neuroinflammation* February 11, 2025. Accepted in final form June 4, 2025. Submitted and externally peer reviewed. The handling editor was Romana Höftberger, MD.

References

1. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology*. 2015;85(2):177-189. doi:10.1212/WNL.0000000000001729
2. Kawachi I, Lassmann H. Neurodegeneration in multiple sclerosis and neuromyelitis optica. *J Neurol Neurosurg Psychiatry*. 2017;88(2):137-145. doi:10.1136/jnnp-2016-313300
3. Noori H, Marsool MDM, Gohil KM, et al. Neuromyelitis optica spectrum disorder: exploring the diverse clinical manifestations and the need for further exploration. *Brain Behav*. 2024;14(8):e3644. doi:10.1002/brb3.3644
4. Berthele A, Levy M, Wingerchuk DM, et al. A single relapse induces worsening of disability and health-related quality of life in patients with neuromyelitis optica spectrum disorder. *Front Neurol*. 2023;14:141099376. doi:10.3389/fneur.2023.1099376
5. Costello F, Burton JM. Contemporary management challenges in seropositive NMOSD. *J Neurol*. 2022;269(10):5674-5681. doi:10.1007/s00415-022-11241-5
6. Hayes MTG, Adam RJ, McCombe PA, Walsh M, Blum S. Long-term efficacy and safety of rituximab in the treatment of neuromyelitis Optica Spectrum disorder. *Mult Scler J Exp Transl Clin*. 2024;10(2):20552173241257876. doi:10.1177/20552173241257876

7. Chu YC, Huang TL. What's new in neuromyelitis optica spectrum disorder treatment? *Taiwan J Ophthalmol*. 2022;12(3):249-263. doi:10.4103/2211-5056.355617
8. Thon JM, Sharkus R, Thakkar R, Hunter K, Siegler JE, Thon OR. Utilization of FDA approved treatments for neuromyelitis optica spectrum disorder in clinical practice: a survey study of academic neuroimmunologists. *Mult Scler Relat Disord*. 2023;80:80105076. doi:10.1016/j.msard.2023.105076
9. Pittock SJ, Barnett M, Bennett JL, et al. Ravulizumab in aquaporin-4-positive neuromyelitis optica spectrum disorder. *Ann Neurol*. 2023;93(6):1053-1068. doi:10.1002/ana.26626
10. Fujihara K, Bennett JL, de Seze J, et al. Interleukin-6 in neuromyelitis optica spectrum disorder pathophysiology. *Neurol Neuroimmunol Neuroinflamm*. 2020;7(5):e841. doi:10.1212/NXI.0000000000000841
11. Held F, Klein AK, Berthele A. Drug treatment of neuromyelitis optica spectrum disorders: out with the old, in with the new? *Immunotargets Ther*. 2021;10:1087-1101. doi:10.2147/ITT.S287652
12. Meher BR, Mohanty RR, Dash A. Review of satralizumab for neuromyelitis optica spectrum disorder: a new biologic agent targeting the interleukin-6 receptor. *Cureus*. 2024;16(2):e55100. doi:10.7759/cureus.55100
13. Yamamura T, Kleiter I, Fujihara K, et al. Trial of satralizumab in neuromyelitis optica spectrum disorder. *N Engl J Med*. 2019;381(22):2114-2124. doi:10.1056/NEJMoa1901747
14. Traboulsee A, Greenberg BM, Bennett JL, et al. Safety and efficacy of satralizumab monotherapy in neuromyelitis optica spectrum disorder: a randomised, double-blind, multicentre, placebo-controlled phase 3 trial. *Lancet Neurol*. 2020;19(5):402-412. doi:10.1016/S1474-4422(20)30078-8
15. Yamamura T, Weinshenker B, Yeaman MR, et al. Long-term safety of satralizumab in neuromyelitis optica spectrum disorder (NMOSD) from SAkuraSky and SAkuraStar. *Mult Scler Relat Disord*. 2022;66:66104025. doi:10.1016/j.msard.2022.104025
16. Kleiter I, Traboulsee A, Palace J, et al. Long-term efficacy of satralizumab in AQP4-IgG-seropositive neuromyelitis optica spectrum disorder from SAkuraSky and SAkuraStar. *Neurol Neuroimmunol Neuroinflamm*. 2023;10(1):e200071. doi:10.1212/NXI.0000000000200071
17. McElvaney OJ, Curley GF, Rose-John S, McElvaney NG. Interleukin-6: obstacles to targeting a complex cytokine in critical illness. *Lancet Respir Med*. 2021;9(6):643-654. doi:10.1016/S2213-2600(21)00103-X
18. Choy EH, De Benedetti F, Takeuchi T, Hashizume M, John MR, Kishimoto T. Translating IL-6 biology into effective treatments. *Nat Rev Rheumatol*. 2020;16(6):335-345. doi:10.1038/s41584-020-0419-z
19. Abna Z, Fazeli SA, Khanmoradi Z, Sahraian MA. Neuromyelitis Optica Spectrum Disorders (NMOSD) and structural renal diseases: a literature review. *Neuroimmunology Rep*. 2024;6:100220. doi:10.1016/j.nerep.2024.100220
20. de Carvalho FL, Gomes CM, Apostolos-Pereira SL, et al. Voiding dysfunction in patients with neuromyelitis optica spectrum disorders. *Neurourol Urodyn*. 2016;35(1):39-43. doi:10.1002/nau.22667
21. *Enspyng PI*. 2020. Accessed March 2022. accessdata.fda.gov/drugsatfda_docs/label/2020/761149s000lbl.pdf
22. Levy M, Haycox AR, Becker U, et al. Quantifying the relationship between disability progression and quality of life in patients treated for NMOSD: insights from the SAkura studies. *Mult Scler Relat Disord*. 2022;57:57103332. doi:10.1016/j.msard.2021.103332
23. Palace J, Lin DY, Zeng D, et al. Outcome prediction models in AQP4-IgG positive neuromyelitis optica spectrum disorders. *Brain*. 2019;142(5):1310-1323. doi:10.1093/brain/awz054
24. Kessler RA, Mealy MA, Levy M. Early indicators of relapses vs pseudorelapses in neuromyelitis optica spectrum disorder. *Neurol Neuroimmunol Neuroinflamm*. 2016;3(5):e269. doi:10.1212/NXI.0000000000000269
25. Hamid SHM, Whittam D, Mutch K, et al. What proportion of AQP4-IgG-negative NMO spectrum disorder patients are MOG-IgG positive? A cross sectional study of 132 patients. *J Neurol*. 2017;264(10):2088-2094. doi:10.1007/s00415-017-8596-7
26. Lennon VA, Wingerchuk DM, Kryzer TJ, et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. *Lancet*. 2004;364(9451):2106-2112. doi:10.1016/S0140-6736(04)17551-X