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Long-term Efficacy of Satralizumab in AQP4-IgG–Seropositive Neuromyelitis Optica Spectrum Disorder From SAkuraSky and SAkuraStar

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Abstract

Background and Objectives

Satralizumab, an interleukin 6 receptor inhibitor, reduced the risk of protocol-defined relapse (PDR) vs placebo in 2 independent, double-blind studies in patients with neuromyelitis optica spectrum disorder (NMOSD). We assessed the long-term efficacy of satralizumab in patients with aquaporin-4-immunoglobulin G (IgG)–seropositive (AQP4-IgG+) NMOSD.

Methods

Following the double-blind periods of SAkuraSky (satralizumab + baseline immunosuppressive treatment [IST]) and SAkuraStar (satralizumab monotherapy), patients could enter the open-label extension (OLE, satralizumab 120 mg Q4W ± IST). This analysis included all AQP4-IgG+ patients who received ≥1 dose of satralizumab in the double-blind and/or OLE periods, from patients' first dose to the data cutoff (February 22, 2021). PDR in the OLE period was determined by the investigator without external adjudication. We evaluated time to first investigator-reported PDR (iPDR), severe iPDR (≥2 point increase in the Expanded Disability Status Scale [EDSS] score), and sustained EDSS worsening (EDSS score increase of ≥2, ≥1, or ≥0.5 points for patients with baseline scores of 0, 1–5, or ≥5.5, respectively, confirmed ≥24 weeks post–initial worsening), plus the annualized iPDR rate (ARR).

Results

Forty-six of 55 AQP4-IgG+ patients (84%) in SAkuraSky and 57/64 patients in SAkuraStar (89%) continued from the double-blind periods into the OLEs. In total, 111 AQP4-IgG+ patients received ≥1 dose of satralizumab in the double-blind and/or OLE periods and were included in these analyses (SAkuraSky: 49; SAkuraStar: 62). The median (range) duration of satralizumab exposure was 4.4 (0.1–7.0) years in SAkuraSky and 4.0 (0.1–6.0) years in SAkuraStar, with a combined 440.1 patient-years of treatment. Seventy-one of 111 patients (64%) received satralizumab for ≥192 weeks (3.7 years). At this time point, 71% (SAkuraSky) and 73% (SAkuraStar) of satralizumab-treated patients were free from iPDR, 91% (SAkuraSky) and 90% (SAkuraStar) were free from severe iPDR, and 90% (SAkuraSky) and 86% (SAkuraStar) had no sustained EDSS worsening. The overall adjusted ARR (95% CI) was 0.12 (0.08–0.18) in SAkuraSky and 0.08 (0.05–0.13) in SAkuraStar and remained stable over time.

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Class of Evidence
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Glossary

ARR = annualized iPDR rate; **AQP4-IgG+** = aquaporin-4–immunoglobulin G seropositive; **AZA** = azathioprine; **CEC** = Clinical Endpoint Committee; **EDSS** = Expanded Disability Status Scale; **HR** = hazard ratio; **IL-6** = interleukin 6; **iPDR** = investigator-reported protocol-defined relapse; **IST** = immunosuppressive treatment; **MMF** = mycophenolate mofetil; **NMOSD** = neuromyelitis optica spectrum disorder; **OCS** = oral corticosteroid; **OLE** = open-label extension; **PDR** = protocol-defined relapse; **PY** = patient-year.

Discussion

These long-term results from the OLE periods of the SAkura studies demonstrate the continued efficacy of satralizumab over more than 3.5 years of treatment. High proportions of patients remained free from relapse, severe relapse, or worsening disease, with a consistently low ARR.

Trial Registration Information

ClinicalTrials.gov registration numbers: NCT02028884 (SAkuraSky) and NCT02073279 (SAkuraStar).

Classification of Evidence

This study provides Class II evidence that satralizumab reduces the risk of relapse in patients with AQP4-IgG+ NMOSD beyond the first 96 weeks of treatment.

Neuromyelitis optica spectrum disorder (NMOSD) is a chronic, neuroinflammatory, autoimmune disease of the CNS.[1-4] Patients typically experience a relapsing disease course, with acute, unpredictable attacks affecting the optic nerve, spinal cord, and brain.[1,5]

Frequently observed symptoms include visual impairment due to optic neuritis and paralysis, sensory loss, and bladder dysfunction due to longitudinally extensive transverse myelitis. Lesions targeting the area postrema can cause nausea, vomiting, and severe hiccups.[3,5]

Relapses carry a risk of severe, permanent neurologic disability, which accumulates over time with subsequent attacks.[1,6,7] Management of NMOSD is centered around reducing the frequency and severity of attacks.[8,9] Because of the chronic nature of NMOSD, it is essential that a patient's maintenance therapy remains highly effective, safe, and tolerable with long-term use.

The exact mechanisms through which NMOSD relapses occur are not fully understood, but a number of inflammatory processes drive NMOSD disease activity. More than 80% of patients with NMOSD are seropositive for aquaporin-4-immunglobulin G (AQP4-IgG), a pathologic autoantibody against the water channel protein AQP4, which is expressed primarily on astrocyte end foot processes.[5] One of the key mechanisms of injury among several others in NMOSD is binding of the AQP4-IgG to AQP4 and initiating the formation of membrane attack complex through the complement cascade, resulting in astrocytic damage and secondary damage to the oligodendrocytes and neurons. Hence, NMOSD pathology is considered a form of astrocytopathy.[5,10]

Interleukin 6 (IL-6), a pleiotropic cytokine, is considered to play an integral role in NMOSD pathophysiology.[2,11] IL-6 promotes the differentiation and survival of B cells and specifically plasmablasts, including those specific for AQP4-IgG. Moreover, IL-6 shifts the balance of T cells from Treg cells and polarizes them toward the inflammatory Th17 phenotype and is thought to increase the permeability of the blood-brain barrier, allowing both humoral and cellular mediators of injury to penetrate the CNS.[11,12]

Satralizumab, approved for the treatment of AQP4-IgG+ NMOSD, is a subcutaneously administered, humanized, IgG2 monoclonal recycling antibody that inhibits the IL-6 signaling pathways by binding to and blocking membrane-bound and soluble IL-6 receptors.[13,14] Satralizumab was designed with pH-dependent recycling antibody technology, which provides improved persistence in the plasma vs conventional, non-recycling antibodies and enables dosing every 4 weeks.[15] In the double-blind periods of the pivotal phase 3 SAkuraSky and SAkuraStar studies, satralizumab significantly reduced the risk of NMOSD relapse vs placebo in AQP4-IgG+ patients when used as a monotherapy or in combination with baseline immunosuppressive treatments (ISTs).[13,14] Overall, 92% and 77% of AQP4-IgG+ patients treated with satralizumab remained relapse free at week 96, compared with 53% and 41% treated with placebo in the SAkuraSky and SAkuraStar studies, respectively. Satralizumab was well tolerated, with an overall favorable safety profile.[13,14]

Here, we used data from the double-blind and open-label extension (OLE) periods of the SAkura studies to assess the long-term efficacy of satralizumab in patients with AQP4-IgG+ NMOSD. The main research questions addressed by the analysis were the effect of long-term satralizumab treatment (192 weeks) on time to first relapse (primary outcome), severe relapse, and sustained worsening in disability, plus changes in the annualized relapse rate over time.

Methods

Study Design and Participants

SAkuraSky and SAkuraStar are phase 3, multicenter, randomized, double-blind, placebo-controlled trials of satralizumab in patients with NMOSD, with ongoing OLE periods. Detailed methodology for the SAkuraSky and SAkuraStar studies has been reported previously.[13,14]

In SAkuraSky, patients were randomized in a 1:1 ratio to receive satralizumab or placebo in combination with their stable baseline IST.[14] In SAkuraStar, patients were randomized 2:1 to receive satralizumab or placebo monotherapy (no concomitant ISTs permitted).[13]

Patients with AQP4-IgG–seropositive or –seronegative NMOSD and a documented attack history were eligible. Adolescents and adults could enter SAkuraSky (12–74 years), whereas SAkuraStar enrolled adults only (18–74 years). Full inclusion/exclusion criteria have been included in the supplement. The current analysis focused on AQP4-IgG+ patients only, in accordance with approved treatment indications worldwide.

The primary end point of both studies was time to first protocol-defined relapse (PDR). PDRs were new or worsening objective neurologic symptoms meeting the prespecified Expanded Disability Status Scale (EDSS)/functional system score criteria (full criteria provided in the supplement). PDRs were adjudicated by an independent Clinical Endpoint Committee (CEC) during the double-blind periods. Relapse adjudication by the CEC was not performed during the OLEs. Therefore, relapses meeting the PDR criteria, as determined and reported by the investigators as iPDR, were considered for the current analyses.

Patients were eligible to enter the OLE of their respective study if they experienced a PDR, a relapse treated with rescue therapy (SAkuraSky only), or when the double-blind period ended.[13,14] Commencement of the OLE took place 4 weeks after the final dosing in the double-blind period. Patients who entered the OLE due to a relapse initiated open-label satralizumab, with or without concomitant IST, ≥ 30 days after the onset of the relapse.

The double-blind periods of both studies ended as planned: after 26 PDRs were reached in SAkuraSky (clinical cutoff date of June 6, 2018)[14] and 1.5 years after the last patient was enrolled in SAkuraStar (clinical cutoff date of October 12, 2018).[13] The cutoff date used for the current analysis, which includes data from the ongoing OLE periods, was February 22, 2021.

Procedures

Patients received subcutaneous satralizumab 120 mg or placebo at weeks 0, 2, and 4, and Q4W thereafter in the double-blind periods (eFigure 1, links.lww.com/NXI/A783). The same satralizumab dosing regimen was applied in the OLEs.

During the double-blind period of SAkuraSky, patients continued baseline IST with a stable dose of 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). Adolescent patients (aged 12–17 years) could receive OCS in addition to either AZA or MMF. Patients could not change their IST dose in the SAkuraSky double-blind period with the exception of dose decreases for safety reasons; however, in the OLE, patients could reduce or discontinue their baseline treatment.

No concomitant ISTs were permitted during the double-blind period of SAkuraStar. Acute relapse rescue therapy (pulse IV corticosteroids, intravenous immunoglobulin G and/or apheresis) was permitted in the double-blind and OLE periods of both studies. Patients who entered the OLE due to a relapse in the double-blind period could receive satralizumab injections in the OLE once their condition had stabilized (between day 31–60 postrelapse). Patients who experienced a relapse during the OLE period continued satralizumab at the discretion of the study site investigator.

Outcomes

The current analyses assessed all AQP4-IgG+ patients who received ≥1 dose of satralizumab in the double-blind and/or OLE periods of the SAkura studies, referred to as the total satralizumab treatment period. The total satralizumab treatment period comprises the combined double-blind and OLE periods for patients originally randomized to satralizumab and the OLE period only for patients originally randomized to placebo. Results from the total satralizumab treatment period are based on patients' first day of satralizumab treatment (i.e., patients switching from placebo to satralizumab were rebaselined on receiving their first satralizumab dose).

We investigated the long-term efficacy of satralizumab, measured by time to first iPDR in the total satralizumab treatment period. The effect of satralizumab on severe relapses was also evaluated using time to first severe PDR (double-blind period) and severe iPDR (total satralizumab treatment period). Severe relapses were those associated with a ≥2-point increase in the EDSS score at the relapse assessment regardless of the prerelapse score, compared with the last scheduled assessment prior to the relapse. This threshold was selected post hoc based on published data, which showed that relapses causing EDSS increases of ≥2 points frequently result in lasting disability.[16]

The proportions of patients who received rescue therapy in the double-blind and total satralizumab treatment periods of the SAkura studies were assessed. Physicians could treat patients with rescue therapy for any suspected relapse.

An investigation was performed into the effect of satralizumab on lasting disability, measured by time to first sustained worsening of the EDSS score in the total satralizumab treatment period. Sustained EDSS worsening was defined as an increase in the EDSS score from a patient's last scheduled assessment that was confirmed ≥24 weeks post–initial worsening. The

required increase in the EDSS score was ≥2 points in patients with a baseline EDSS score of 0, ≥1 point in those with a baseline of 1–5, or ≥0.5 points in those with a baseline of ≥5.5.

For all time to first event analyses, the proportions free from relapse/EDSS worsening at week 192 (3.7 years) are presented. The annualized iPDR rate (ARR) was also assessed.

A detailed analysis of the long-term safety of satralizumab has been published.[17] Top-line safety results from this analysis have been presented here.

Statistical Analysis

The ARR was calculated as the total number of iPDRs divided by the total number of patient-years (PYs). The adjusted overall ARR was calculated using a Poisson regression model adjusted by study identifier. The adjusted ARR over time (years 1–3 in SAkuraSky and 1–4 in SAkuraStar) was calculated using estimates from analysis based on a GEE Poisson regression model with repeated measurements using unstructured covariance matrix, adjusted by study identifier and year; log-transformed PYs were included as an offset variable. Estimated relapse-free proportions and 95% CIs were calculated as Kaplan-Meier estimates. 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 trial center for both studies, and all patients provided written informed consent. The trials (SAkuraSky: NCT02028884; SAkuraStar: NCT02073279) were conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki.

Data Availability

For 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, see here: go.roche.com/data_sharing. Qualified researchers may request access to individual patient-level data through the clinical study data request platform (clinicalstudydatarequest.com). Anonymized records for individual patients across more than one data source external to Roche cannot, and should not, be linked due to a potential increase in risk of patient reidentification.

Results

Patient Population

In total, 119 AQP4-IgG+ patients took part in the double-blind periods of the phase 3 studies (SAkuraSky: satralizumab + IST, n = 27, placebo + IST, n = 28; SAkuraStar: satralizumab, n = 41, placebo n = 23) (Figure 1). Of these, 44 patients (80%) entered the SAkuraSky OLE, and 57 (89%) entered the SAkuraStar OLE; reasons for drop out are shown in Figure 1. Two additional adolescent patients were enrolled into the SAkuraSky OLE; one entered on the day after the double-blind period cutoff date (June 6, 2018), and the other entered directly into the OLE. Both patients were included in analyses for the total satralizumab treatment period.

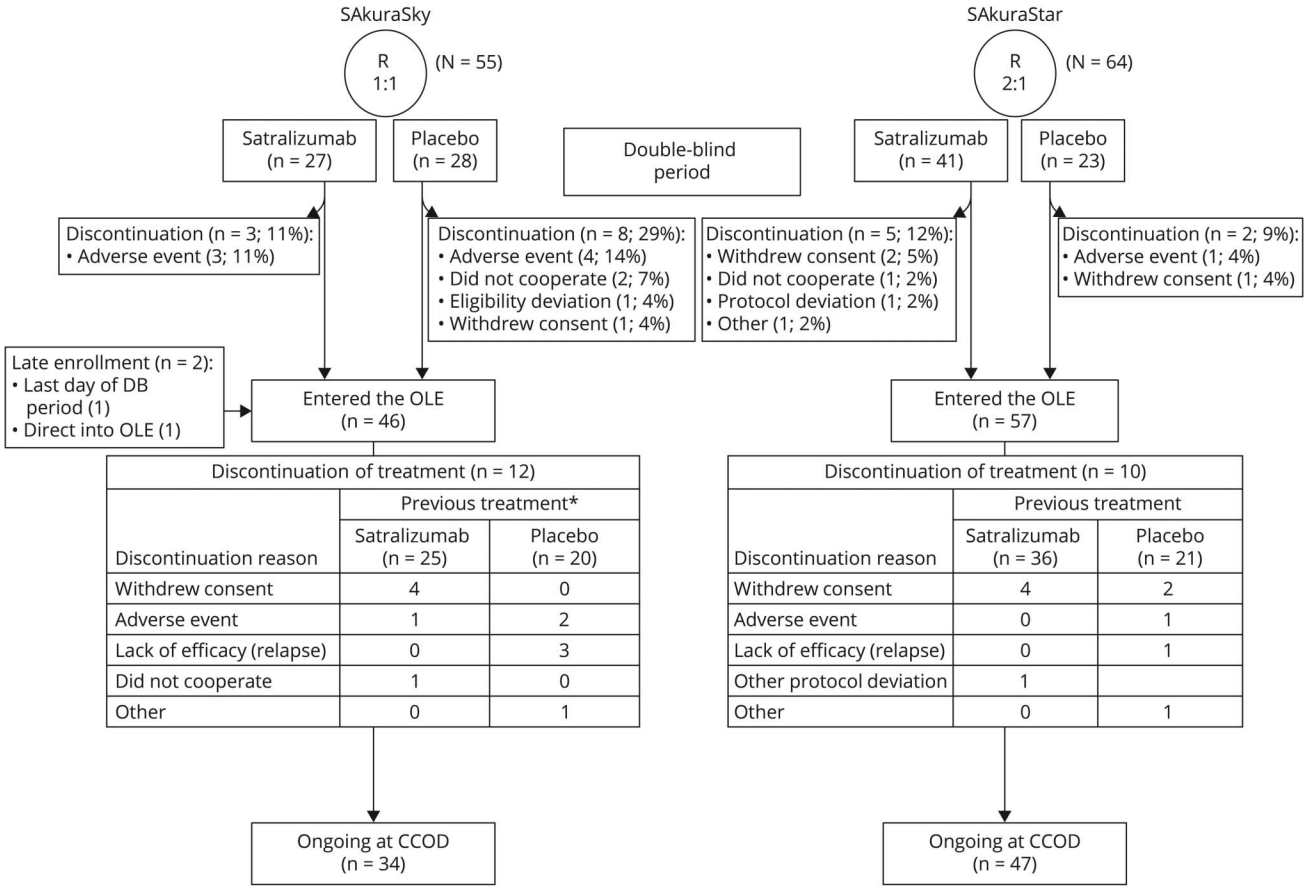
Twelve patients in SAkuraSky and 10 in SAkuraStar dropped out during the OLE. Of these, 3 patients in SAkuraSky and 1 patient in SAkuraStar discontinued treatment due to a lack of efficacy (Figure 1); all 4 patients had been receiving placebo in the double-blind period, had entered the OLE due to a relapse, and had discontinued from the OLE before the clinical cutoff dates at the end of each double-blind period. Four patients in SAkuraSky and 6 patients in SAkuraStar discontinued after withdrawing consent. Adverse events leading to discontinuation occurred in 3 patients in SAkuraSky (endocarditis, large intestine infection, and colon cancer) and 1 patient in SAkuraStar (spinal compression fracture). One patient in SAkuraSky discontinued treatment due to lack of cooperation with study requirements, 1 patient in SAkuraStar discontinued after a protocol deviation, and 2 patients discontinued for other reasons.

Overall, 111 AQP4-IgG+ patients received ≥1 dose of satralizumab in the double-blind and/or OLE periods and were included in the total satralizumab treatment period (SAkuraSky: n = 49; SAkuraStar: n = 62). Of those 111 patients, 69 were originally randomized to satralizumab, 41 to placebo and then went on to enter the OLE, and 1 patient directly entered the OLE. The mean (SD) age of these patients at randomization was 42.0 (15.1) years in SAkuraSky and 44.1 (12.0) in SAkuraStar. Most patients were female (100% in SAkuraSky and 82% in SAkuraStar) (Table 1). Because of differences in the studies' inclusion criteria, the mean [SD] ARR at baseline was higher in SAkuraSky (1.38 [0.47]) than SAkuraStar (0.95 [0.50]).

OCS and AZA were the most common baseline ISTs used in the AQP4-IgG+ population of SAkuraSky (Table 1). In the double-blind period, 27 (49%) were receiving OCS, 22 (40%) were receiving AZA, 4 (7%) were receiving MMF, and 2 (4%) adolescents were receiving MMF plus OCS. Baseline ISTs for the 49 AQP4-IgG+ patients included in the total satralizumab treatment period were OCS (n = 27, 55%), AZA (n = 17, 35%), MMF (n = 3, 6%), and MMF + OCS (n = 2, 4%). Of the 46 patients who entered the SAkuraSky OLE, 12 (26%) had stopped using their background IST by the cutoff date. No patients in SAkuraStar began using any background ISTs during the OLE.

The median (range) duration of satralizumab exposure in the total satralizumab treatment period was 4.4 (0.1–7.0) years in SAkuraSky and 4.0 (0.1–6.0) years in SAkuraStar. The total satralizumab exposure was 203.9 years in SAkuraSky and 236.2 years in SAkuraStar. Compared with the double-blind periods, the duration of exposure to satralizumab in the total satralizumab treatment period was 3.8 times longer in SAkuraSky and 2.9 times greater in SAkuraStar. Seventy-one of 111 patients (64%) received satralizumab for ≥192 weeks (3.7 years). Nine patients (8%) discontinued satralizumab therapy after less than 1 year of treatment.

Figure 1 Flowchart of AQP4-IgG Seropositive Patients in the SAkura Studies



Discontinuation of treatment (n = 12)		
	Previous treatment*	
Discontinuation reason	Satralizumab (n = 25)	Placebo (n = 20)
Withdrew consent	4	0
Adverse event	1	2
Lack of efficacy (relapse)	0	3
Did not cooperate	1	0
Other	0	1

Discontinuation of treatment (n = 10)		
	Previous treatment	
Discontinuation reason	Satralizumab (n = 36)	Placebo (n = 21)
Withdrew consent	4	2
Adverse event	0	1
Lack of efficacy (relapse)	0	1
Other protocol deviation	1	
Other	0	1

*One patient joined directly into the OLE and remained in the trial at the cutoff for the current analysis (February 22, 2021). Where patients withdrew consent, this applied to all data collection from that point onward, not prior. AQP4-IgG = aquaporin-4-immunoglobulin G; CCOD = clinical cutoff date; DB = double-blind; OLE = open-label extension; R = randomization.

There was good concordance between iPDRs and CEC-adjudicated PDRs. Across the 73 relapses in the SAkura studies' double-blind periods (intention-to-treat population) that were judged by investigators to meet the PDR criteria, 64 (88%) went on to be confirmed by the CEC.

Efficacy Analyses

Effect on Relapse Risk and the Annualized Relapse Rate

Double-Blind Period

Primary efficacy results from the SAkura studies have been published previously.[13,14] In AQP4-IgG+ patients, satralizumab reduced the risk of PDR vs placebo when administered in combination with baseline IST in SAkuraSky [hazard ratio [HR] (95% CI): 0.21 (0.06–0.75)] and when given as monotherapy in SAkuraStar (HR [95% CI]: 0.26 [0.11–0.63]). PDRs were experienced by 3 patients in the satralizumab group vs 12 in the placebo group of SAkuraSky (11% vs 43%) and by 9 patients in the satralizumab group vs 13 in the placebo group of SAkuraStar (22% vs 57%).

Total Satralizumab Treatment Period

Long-term results showed that 12 patients (24%) experienced an iPDR in the total satralizumab treatment period of SAkuraSky; of those, 6 patients experienced more than 1 relapse over the course of the study (Table 2). In SAkuraStar, 17 patients (27%) experienced an iPDR, of whom 1 experienced more than 1 relapse (Table 2). The estimated proportion of iPDR-free patients (95% CI) at week 192 was 71% (55–83%) in SAkuraSky and 73% (59–83%) in SAkuraStar (Figure 2). The median time to first iPDR (95% CI) was not evaluable in either study. Figure 3 shows relapse events in AQP4-IgG+ patients reported during the SAkura studies and during the 2 years prior to enrollment.

The overall adjusted ARR (95% CI) was 0.12 (0.08–0.18) in SAkuraSky and 0.08 (0.05–0.13) in SAkuraStar. When observed longitudinally, the yearly ARR remained consistently at or below 0.20 for the duration of the total satralizumab treatment period (Table 2). In the OLE periods alone, the overall ARR was numerically lower in patients originally randomized to satralizumab than those who had switched

Table 1 Demographics and Baseline Characteristics AQP4-IgG+ Patients in the Double-Blind and Total Satralizumab Treatment Periods of SAkuraSky and SAkuraStar

	SAkuraSky (add-on study)			SAkuraStar (monotherapy study)		
	Double-blind period		Total satralizumab treatment period	Double-blind period		Total satralizumab treatment period
	Placebo + IST (n = 28)	Satralizumab + IST (n = 27)	Satralizumab + IST (n = 49)	Placebo (n = 23)	Satralizumab (n = 41)	Satralizumab (n = 62)
Age, y						
Mean (SD; min–max)	43.4 (12.9; 14–65)	44.4 (15.7; 13–73)	42.0 (15.1; 13–73)	40.1 (11.5; 20–56)	46.0 (12.0; 22–70)	44.1 (12.0; 21–70)
Sex, female, n (%)	28 (100)	27 (100)	49 (100)	22 (96)	31 (76)	51 (82)
Geographic region, n (%)						
Asia	13 (46)	13 (48)	26 (53)	5 (22)	5 (12)	10 (16)
Europe/other	15 (54)	14 (52)	23 (47)	18 (78)	36 (88)	52 (84)
Baseline ARR, mean (SD)	1.33 (0.41)	1.41 (0.52)	1.38 (0.47)	1.02 (0.51)	0.91 (0.50)	0.95 (0.50)
Baseline EDSS score, mean (SD)	3.70 (1.44)	4.30 (1.58)	4.06 (1.68)	3.43 (1.55)	4.02 (1.50)	3.88 (1.59)
Baseline treatment, n (%)				N/A	N/A	N/A
Oral corticosteroids	13 (46)	14 (52)	27 (55)			
Azathioprine	11 (39)	11 (41)	17 (35)			
Mycophenolate mofetil	3 (11)	1 (4)	3 (6)			
MMF + OCS	1 (4)	1 (4)	2 (4)			
Most recent attack was onset	N/A	N/A	N/A	4 (17)	5 (12)	9 (15)

Abbreviations: AQP4-IgG+ = aquaporin-4-IgG–seropositive; ARR = annualized relapse rate; IST = immunosuppressive therapy; MMF = mycophenolate mofetil; OCS = oral corticosteroid.

from placebo (SAkuraSky: 0.04 vs 0.14; SAkuraStar: 0.02 vs 0.03).

Effect on Relapse Severity

Double-Blind Period

Satralizumab significantly reduced the risk of severe PDR vs placebo by 85% in the double-blind period of SAkuraSky (HR [95% CI]: 0.15 [0.02–1.25]; $p = 0.044$) and by 79% in SAkuraStar (HR [95% CI]: 0.21 [0.05–0.91]); $p = 0.023$) (eFigure 2, links.lww.com/NXI/A783). The proportion of patients free from severe PDR at week 96 of SAkuraSky (double-blind period) was 100% in the satralizumab group vs 76% in the placebo group. For SAkuraStar, these values were 92% and 71%, respectively. In SAkuraSky, 1 of 3 (33%) PDRs in the satralizumab group were severe vs 6 of 12 (50%) in the placebo group. In SAkuraStar, 3 of 9 PDRs (33%) in the satralizumab group were severe vs 5 of 13 (38%) in the placebo group.

Total Satralizumab Treatment Period

Overall, 3 patients (6%) in SAkuraSky and 6 patients (10%) in SAkuraStar experienced a severe iPDR. Two patients in SAkuraSky experienced more than 1 severe relapse over the course of the study, whereas no patients in SAkuraStar experienced more than 1 severe relapse (Table 2). The estimated proportions (95% CI) of satralizumab-treated patients who remained free from severe relapse at week 96 were 100% (100–100%) in SAkuraSky and 92% (81–96%) in SAkuraStar (Figure 4). By week 192, these values were 91% (75–97%) in SAkuraSky and 90% (78–95%) in SAkuraStar. Consistent with the satralizumab groups in the double-blind periods, 8/24 iPDRs (33%) in SAkuraSky and 6/19 (32%) iPDRs in SAkuraStar were severe in the total satralizumab treatment period.

Rescue Therapy Use

Double-Blind Period

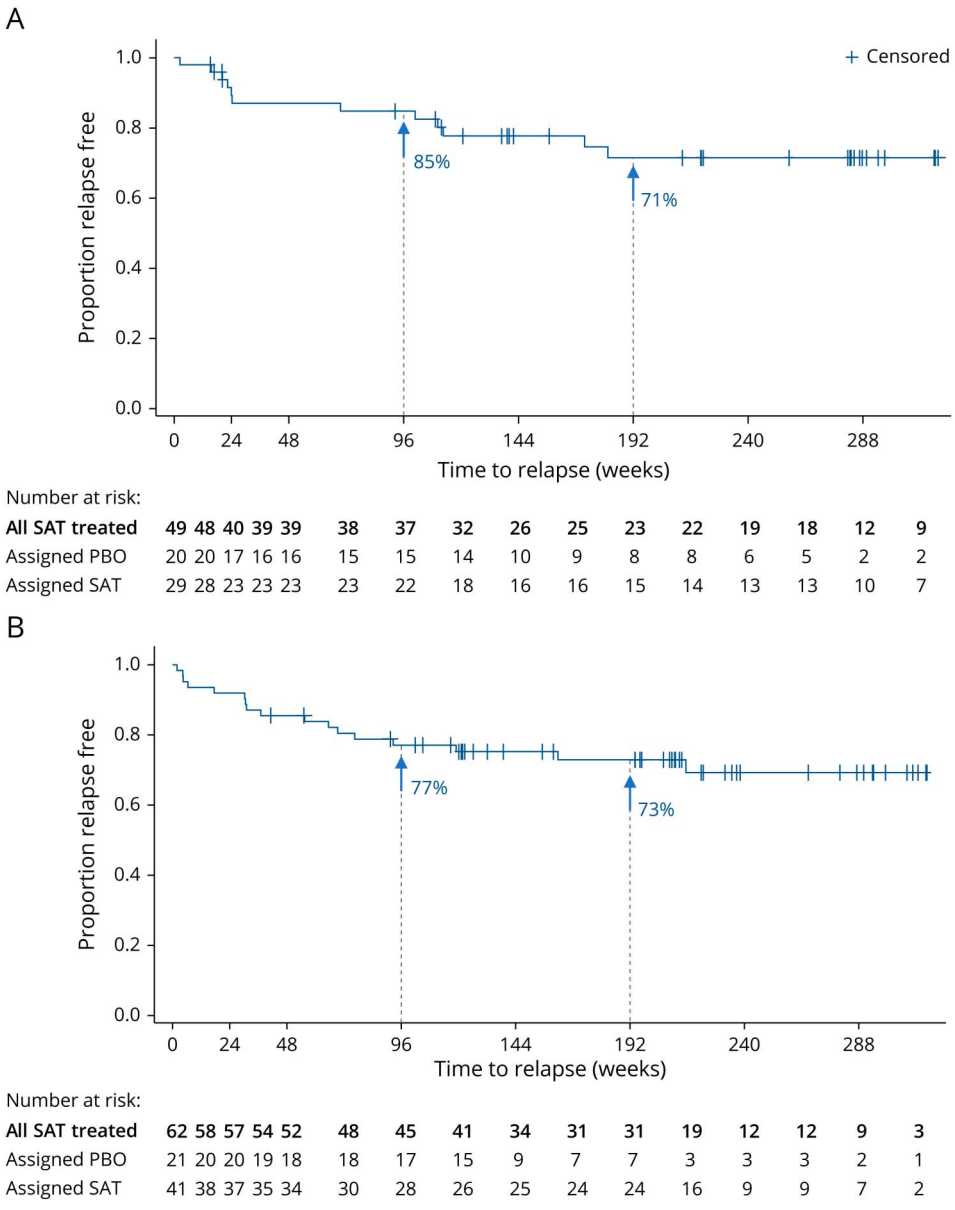
In total, 56 AQP4-IgG+ patients received acute relapse rescue therapy across the double-blind periods of both trials. The proportions of patients who received rescue therapy were lower with satralizumab vs placebo (11 [41%] vs 18 [64%] patients in SAkuraSky; 13 [32%] vs 14 [61%] patients in SAkuraStar). The OR (95% CI) for receiving rescue therapy with satralizumab vs placebo was 0.39 (0.13–1.15; $p = 0.088$) in SAkuraSky and 0.26 (0.09–0.79; $p = 0.018$) in SAkuraStar. The most common rescue therapy was systemic corticosteroids, administered to 53 of 56 patients (95%) who were treated for a relapse. Nine patients

Table 2 Summary of Efficacy Analyses (Total Satralizumab Treatment Period)

	SAkuraSky: Satralizumab + IST (n = 49)	SAkuraStar: Satralizumab (n = 62)
iPDR		
Patients with ≥1 event	12 (24%)	17 (27%)
Number of events	24	19
Relapse free at week 96 (95% CI)	85% (71–92%)	77% (64–86%)
Relapse free at week 192 (95% CI)	71% (55–83%)	73% (59–83%)
Number of patients with relapses		
1 iPDR	6	16
2 iPDRs	3	0
3 iPDRs	1	1
4 iPDRs	1	0
5 iPDRs	1	0
Severe iPDR		
Patients with ≥1 event	3 (6%)	6 (10%)
Number of events	8	6
Severe relapse free at week 96 (95% CI)	100% (100–100%)	92% (81–96%)
Severe relapse free at week 192 (95% CI)	91% (75–97%)	90% (78–95%)
Number of patients with relapses		
1 severe iPDR	1	6
2 severe iPDRs	0	0
3 severe iPDRs	1	0
4 severe iPDRs	1	0
Sustained EDSS worsening		
Patients with ≥1 event	5 (10%)	7 (11%)
Event free at week 96 (95% CI)	93% (80–98%)	95% (85–98%)
Event free at week 192 (95% CI)	90% (75–96%)	86% (73–93%)
Adjusted ARR (95% CI)		
Overall ARR	0.12 (0.08–0.18)	0.08 (0.05–0.13)
Year 1	0.20 (0.09–0.44) [n = 49]	0.15 (0.08–0.27) [n = 62]
Year 2	0.05 (0.01–0.19) [n = 43]	0.13 (0.06–0.28) [n = 59]
Year 3	0.08 (0.02–0.34) [n = 41]	0.02 (0.00–0.15) [n = 54]
Year 4	0.19[a] [n = 32]	0.02 (0.00–0.18) [n = 42]
Year 5	0.08[a] [n = 32]	0.05[a] [n = 33]
Year 6	0.11[a] [n = 23]	0.00[a] [n = 16]
Rescue therapy use		
Patients receiving rescue therapy	20 (41%)	19 (31%)

Abbreviations: ARR = annualized iPDR rate; EDSS = Expanded Disability Status Scale; iPDR = investigator-reported protocol-defined relapse; IST = immunosuppressive therapy.
[a] Unadjusted value.

Figure 2 Kaplan-Meier Analysis of Time to First iPDR in the Total Satralizumab Treatment Periods of (A) SAkuraSky and (B) SAkuraStar



PBO = placebo; SAT = satralizumab.

received plasma exchange, distributed evenly between the satralizumab and placebo groups (SAkuraSky: 3 vs 4 patients, respectively; SAkuraStar: 2 vs 0 patients, respectively). Other acute immunosuppressive rescue therapies were rituximab (1 patient in the placebo group of SAkuraSky) and cyclophosphamide (1 patient in the satralizumab group of SAkuraStar).

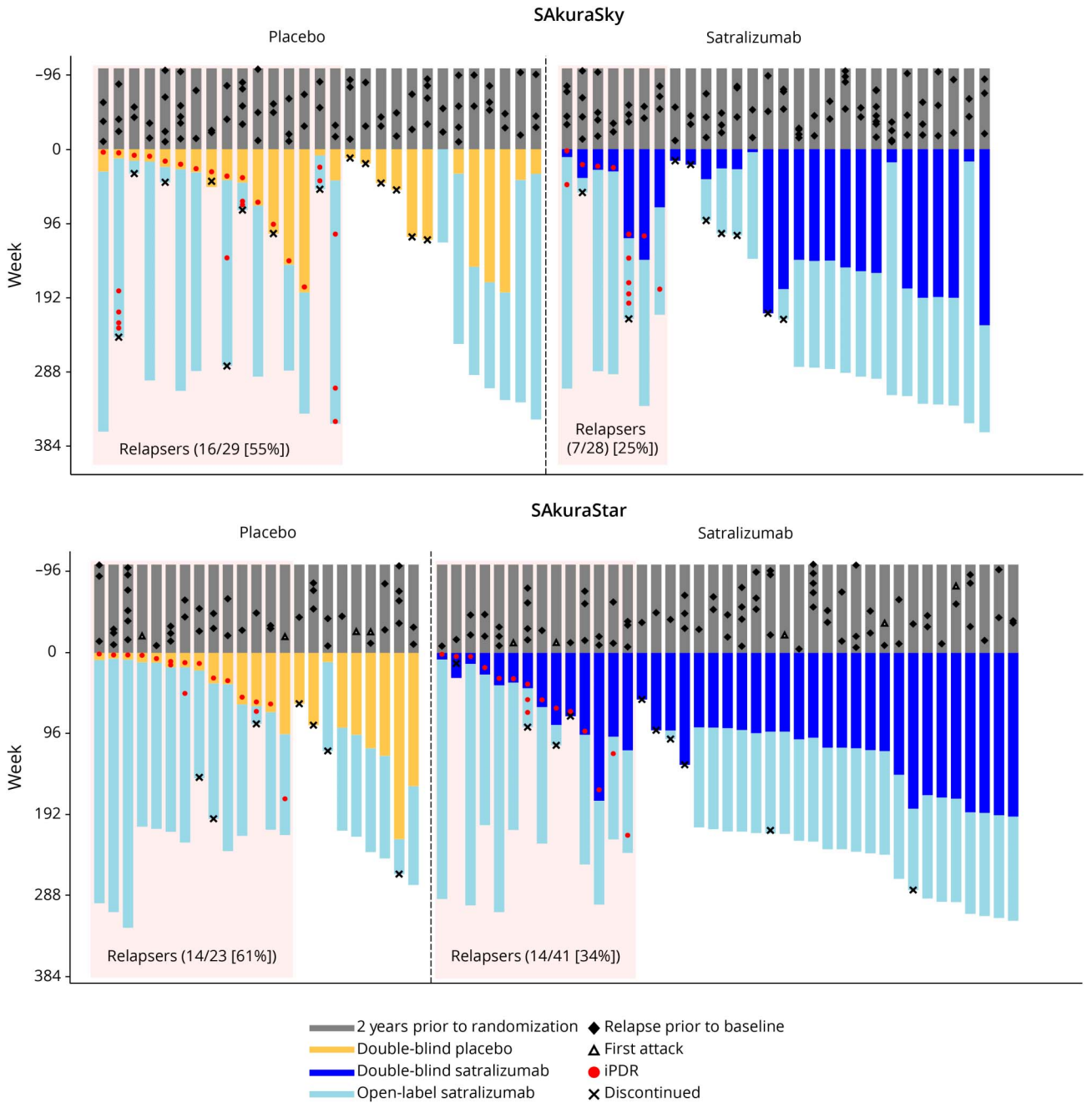
Total Satralizumab Treatment Period

A total of 20 patients (41%) in SAkuraSky and 19 patients (31%) in SAkuraStar were treated for an acute relapse while receiving satralizumab in the total satralizumab treatment period. All patients who received rescue therapy were treated with systemic corticosteroids, with the exception of 1 patient in SAkuraSky. Beyond the double-blind periods, 4 additional patients received plasma exchange and 1 patient received IV immunoglobulin G, all during the SAkuraSky total satralizumab treatment period.

Effect on Sustained Disability Accrual

In the total satralizumab treatment period, 5 patients (10%) in SAkuraSky and 7 patients (11%) in SAkuraStar experienced EDSS worsening lasting ≥24 weeks (Table 2). An estimated 90% (75–96%) of satralizumab-treated patients in SAkuraSky and 86% (73–93%) in SAkuraStar did not experience sustained worsening of EDSS by week 192 (Figure 5). Change from baseline in the mean (SD) EDSS score at week 192 was −0.21 (0.95) in SAkuraSky (from 4.06 [1.68] to 3.88 [1.80]) and −0.29 (1.02) in SAkuraStar (from 3.88 [1.59] to 3.46 [1.38]).

Figure 3 Swim Plot of iPDR Events in All Patients Who Received Satralizumab in SAkuraSky and SAkuraStar



iPDR = investigator-reported protocol-defined relapse.

Safety Analyses

A detailed analysis of the long-term safety of satralizumab has been published.[17] Rates of AEs, serious AEs, infections, and serious infections in the total satralizumab treatment periods were consistent with the satralizumab groups in the double-blind periods. Rates of serious infections were low, and the rates of infections and serious infections did not increase over time. Most AEs in the total satralizumab treatment period were mild or moderate in severity, and there were no reported deaths and no anaphylactic reactions related to satralizumab.[17]

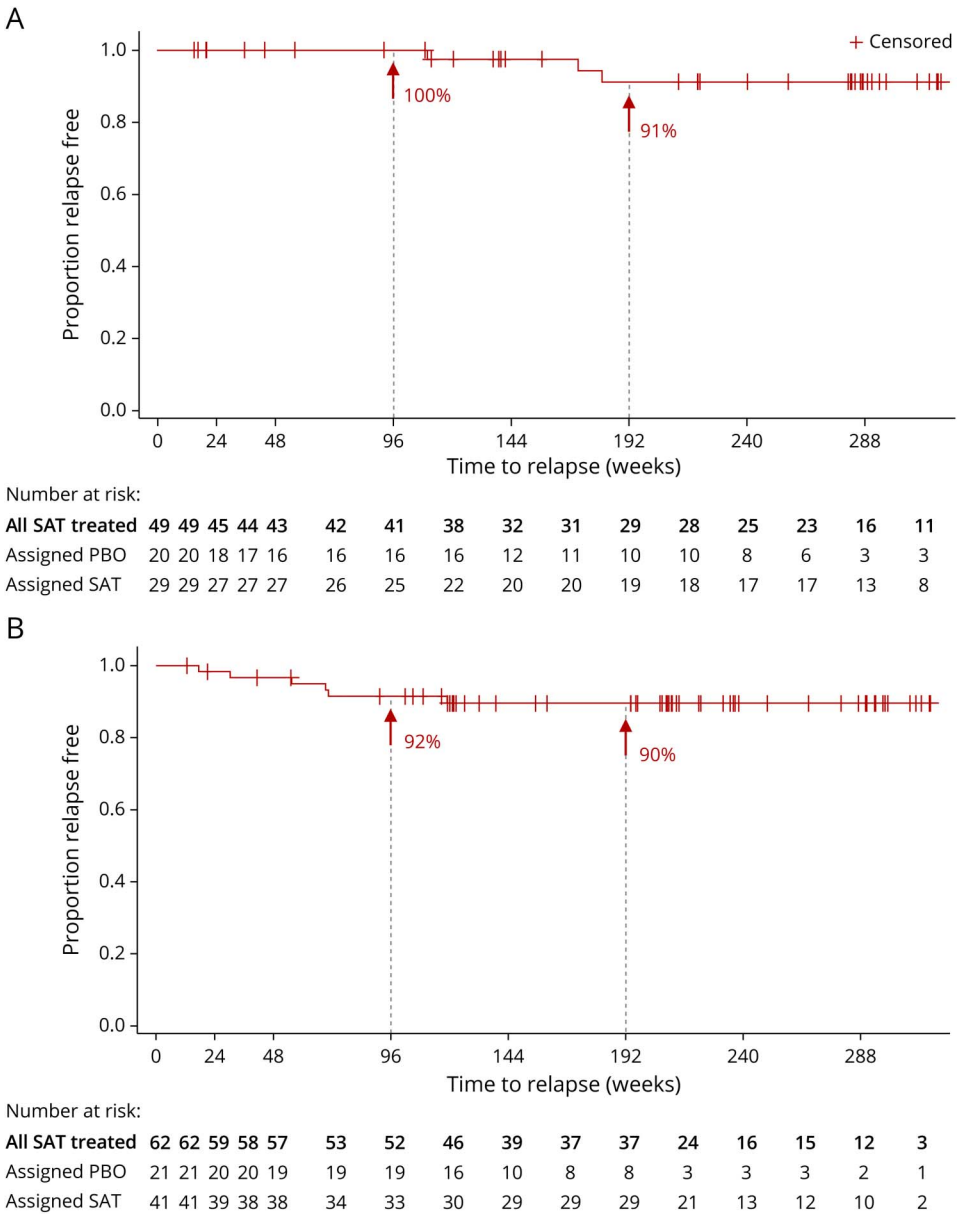
Classification of Evidence

This study provides Class II evidence that satralizumab reduces the risk of relapse in patients with AQP4-IgG+ NMOSD beyond the first 96 weeks of treatment.

Discussion

These analyses explored the long-term efficacy of satralizumab in patients with AQP4-IgG-seropositive NMOSD, using data from all patients who received ≥1 dose of satralizumab across the double-blind and OLE periods of SAkuraSky and

Figure 4 Kaplan-Meier Analysis of Time to First Severe iPDR in the Total Satralizumab Treatment Periods of (A) SAkuraSky and (B) SAkuraStar

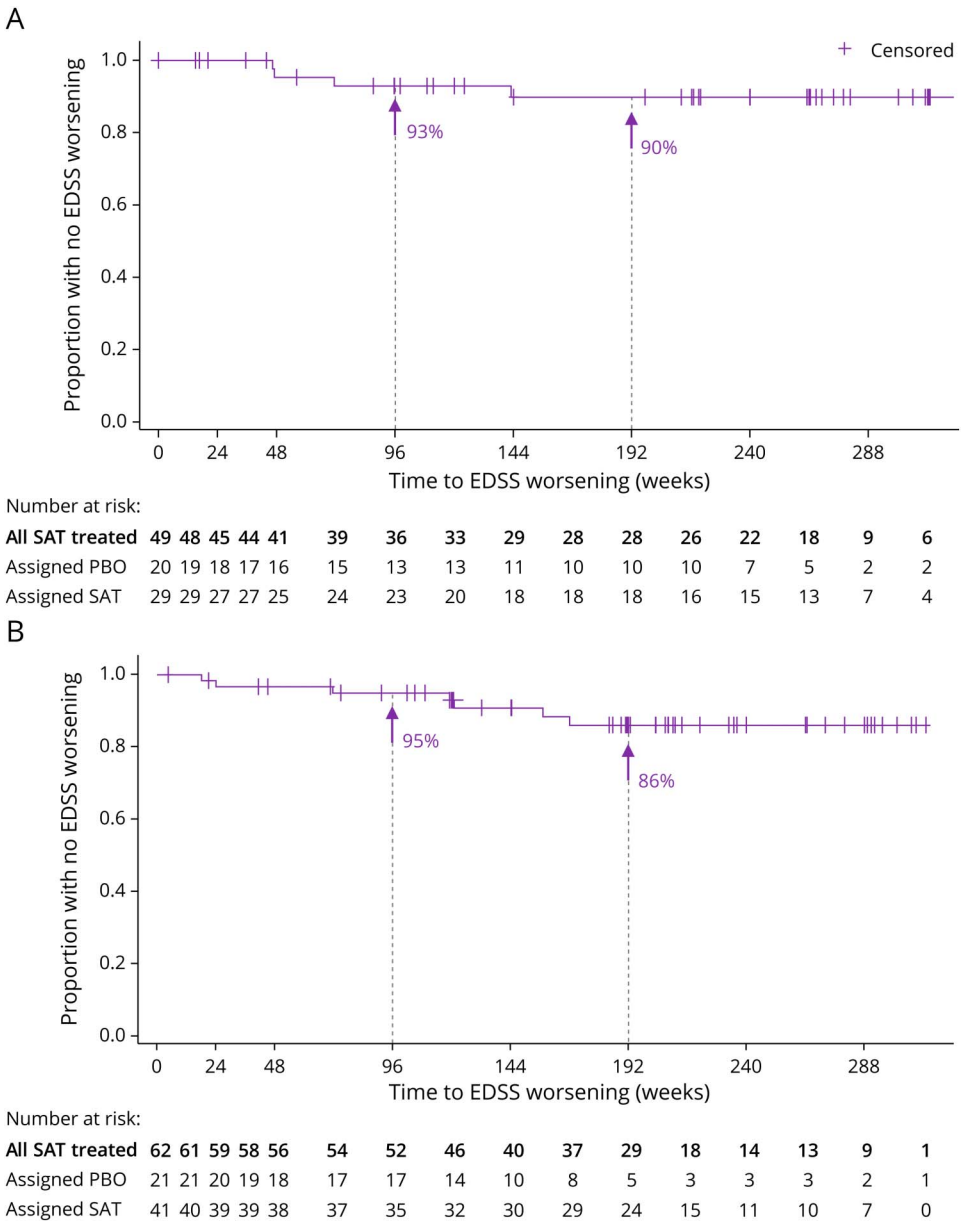


iPDR = investigator-reported protocol-defined relapse; PBO = placebo; SAT = satralizumab.

SAkuraStar. Satralizumab, administered as monotherapy or in combination with add-on IST, significantly reduced the risk of PDR in the double-blind periods of the SAkura studies. The current analyses showed that the protective effect of satralizumab was sustained throughout the total satralizumab treatment period, with high proportions of patients free from iPDR at week 192 (3.7 years). It is important to note that 88% of iPDRs in the double-blind period were confirmed as PDRs by the independent CEC, supporting the use of iPDR as a robust, objective measure of relapse.

Disability accrual following an NMOSD relapse correlates strongly with the severity of attack, and attacks crossing a certain point of no return, associated with an EDSS change of 2–3 points, are significantly more likely to result in lasting neurologic deficits.[16,18] The risk of experiencing a severe relapse, associated with an EDSS change of ≥2 points, was significantly lower in the satralizumab group compared with the placebo group in the double-blind period. Of patients receiving double-blind satralizumab, 100% in SAkuraSky and more than 90% in SAkuraStar remained free from severe PDR at week 96 (1.8 years). Long-term data from the total satralizumab treatment period showed that the protection from severe relapse was maintained, with 91% of patients in SAkuraSky and 90% of patients in SAkuraStar free from severe iPDR after 192 weeks (3.7 years) of satralizumab treatment. These results support that treatment with satralizumab, whether given alone or in addition to background ISTs,

Figure 5 Kaplan-Meier Analysis of Time to First Sustained EDSS Worsening in the Total Satralizumab Treatment Periods of (A) SAkuraSky and (B) SAkuraStar



EDSS = Expanded Disability Status Scale; PBO = placebo; SAT = satralizumab.

provided sustained, long-term protection from severe relapses, which carry a high risk of permanent disability.

These data are further supported by the reduced need for rescue therapy in patients receiving satralizumab. Acute relapse rescue therapy use may provide an insight into the relapses considered by treating investigators to be severe, and our analysis showed that the double-blind satralizumab group was less likely to require rescue therapy vs the placebo group.

One of the primary goals of maintenance therapy in NMOSD is to minimize the accumulation of lasting disability through relapse suppression.[8,9] Few patients accrued long-term disability while receiving satralizumab, with 90% of satralizumab-treated patients in SAkuraSky and 86% in SAkuraStar experiencing no sustained worsening of EDSS by week 192.

The overall ARR was low with long-term satralizumab treatment and remained consistent (≤0.2) over the course of the studies. Because frequently relapsing patients are more likely to discontinue treatment, ARR values are subject to potential bias. However, only 4 patients (3.9%) across both trials exited the OLE periods due to lack of efficacy, making the effect of their discontinuation on the overall ARR minimal.

Satralizumab was well tolerated and showed a favorable safety profile in the double-blind periods of both studies.[13,14] Long-term safety analyses from the SAkura studies showed that the favorable

safety profile and tolerability of satralizumab is sustained with long-term treatment when administered as a monotherapy or in combination with baseline IST.[17]

The positive, long-term efficacy results from this study were supported by the strong uptake for the OLE periods, with 103 of 119 AQP4-IgG–seropositive patients (87%) from the double-blind periods transitioning into the OLEs. More than 90% of patients who received satralizumab continued treatment for more than 1 year. Across the OLE periods of both studies, 21% of patients discontinued treatment. Among those who discontinued satralizumab after less than 1 year, reasons for stopping treatment included adverse events, lack of efficacy, and noncompliance.

The analyses were affected by low patient exposure beyond week 144 (2.8 years) in SAkuraSky and week 192 (3.7 years) in SAkuraStar, so results beyond this point should be interpreted with caution. In the OLE periods, all patients received open-label satralizumab and there was no direct comparator arm, so conclusions regarding the efficacy of satralizumab vs placebo beyond the double-blind period are limited. Nevertheless, each iPDR represents an impactful and clinically meaningful exacerbation of symptoms, and it is positive to see that patients maintain protection from such events with long-term satralizumab treatment.

A limitation of the relapse assessment process during the SAkura studies was that relapse phenotype (e.g., optic neuritis or transverse myelitis) was not captured, so it is not possible to assess the effect of satralizumab on attacks in different areas of the CNS. Similarly, MRI scans were not included as part of the study assessments, so MRI activity was not evaluated during iPDRs or during periods of clinical inactivity.

There are 2 limitations caused by the OLE design. First, as with all open-label studies, results from the OLE periods of SAkuraSky and SAkuraStar are subject to bias. This was minimized in the OLE by using prespecified, objective criteria to assess relapses and define an iPDR, making the likelihood of bias significantly affecting the results very low. Second, some patients from the original cohort withdrew from the double-blind period, or elected not to continue into the OLE, potentially biasing the OLE populations in favor of those more responsive to satralizumab.

In conclusion, these data from the ongoing OLE periods of the SAkura studies demonstrate that the efficacy of satralizumab observed in the double-blind periods is sustained over the long term. After more than 3.5 years of treatment, high proportions of patients remained free from relapse, severe relapse, and worsening in neurologic disability, with consistently low ARR. Based on the robust safety and efficacy profile, long-term satralizumab treatment as monotherapy or in combination with ISTs is a favorable maintenance therapy option for the management patients with AQP4-IgG–seropositive NMOSD.

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