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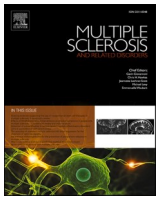

Long-term safety of satralizumab in neuromyelitis optica spectrum disorder (NMOSD) from SAkuraSky and SAkuraStar

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ABSTRACT

Background: This analysis evaluated long-term safety findings from the SAkuraSky and SAkuraStar studies with satralizumab in patients with neuromyelitis optica spectrum disorder (NMOSD).
Methods: SAkuraSky (satralizumab in combination with baseline immunosuppressive therapy; IST) and SAkuraStar (satralizumab monotherapy) are international, multicenter, randomized, placebo-controlled, phase 3 studies consisting of a double-blind (DB) period followed by an open-label extension (OLE). The overall satralizumab treatment (OST) period safety population comprised patients receiving ≥1 dose of satralizumab in the DB and/or OLE periods (cut-off date: 22 February 2021). Safety was evaluated in the DB and OST periods.
Results: In the SAkuraSky DB period, patients received satralizumab ($n = 41$) or placebo ($n = 42$) in addition to stable baseline IST; 75 patients were included in the OST population. In the SAkuraStar DB period, 63 patients received satralizumab monotherapy and 32 received placebo; 91 patients were included in the OST population. Median treatment exposure in the OST period was 4.4 years (range 0.1–7.0) in SAkuraSky and 4.0 years (range 0.1–6.1) in SAkuraStar. Rates of adverse events (AEs per 100 patient-years) and serious AEs in the OST period were comparable with satralizumab and placebo in the DB periods of both studies. Similarly, overall rates of infections and serious infections were consistent between the OST and DB periods with satralizumab, with no increase in rates of infections or serious infections over time. In the OST periods, longer exposure to satralizumab was not associated with a higher risk of severe (grade ≥3) laboratory changes versus the DB periods. No deaths or anaphylactic reactions to treatment with satralizumab were reported during the OST periods of both studies.
Conclusion: The safety profile of satralizumab as a monotherapy or in combination with IST was maintained in the OLE, and no new safety concerns versus the DB period were observed.
Clinical trial registration: ClinicalTrials.gov identifiers: NCT02028884 (SAkuraSky) and NCT02073279 (SAkuraStar).

1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a rare, often debilitating autoimmune disease of the central nervous system (Borisow et al., 2018; Oh and Levy, 2012; Papadopoulos et al., 2014), primarily characterized by inflammatory lesions in the optic nerves, spinal cord, brainstem, and cerebrum (Kessler et al., 2016; Oh and Levy, 2012; Papadopoulos et al., 2014; Wingerchuk et al., 2015). Most patients

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experience relapses characterized by frequent attacks of variable severity (Kawachi and Lassmann, 2017; Wingerchuk et al., 2015; Wingerchuk et al., 2007). Incomplete recovery from relapse is common, leading to accrual of permanent, residual disability (Kessler et al., 2016; Oh and Levy, 2012). Disease management focuses on preventing relapses and minimizing safety risks associated with long-term therapy (Kleiter and Gold, 2016; Kowarik et al., 2014; Papadopoulos et al., 2014).

Interleukin-6 (IL-6), a multifunctional cytokine, is thought to play a key role (Fujihara et al., 2020; Uzawa et al., 2010) in NMOSD pathophysiology. IL-6 signaling stimulates B-cell differentiation into plasmablasts that produce pathogenic aquaporin-4 autoantibodies (AQP4-IgG) (Chihara et al., 2011; Fujihara et al., 2020; Lin et al., 2016) present in over two-thirds of patients with NMOSD (Lennon et al., 2004). IL-6 also promotes differentiation of naïve T cells into inflammatory T-helper-17 cells (Agasing et al., 2020; Fujihara et al., 2020; Kimura and Kishimoto, 2010; Lin et al., 2016). Furthermore, IL-6 increases blood–brain barrier permeability, facilitating AQP4-IgG and proinflammatory cell infiltration into the central nervous system (Fujihara et al., 2020; Takeshita et al., 2017).

Until 2019, no treatments were approved for NMOSD (Selmaj and Selmaj, 2019), and off-label non-specific immunosuppressive therapies (ISTs) have historically been the mainstay of maintenance treatment (Brod, 2020; Held et al., 2021; Jarius et al., 2020). IST discontinuation in NMOSD can increase relapse risk (Kim et al., 2021), and therefore improving our understanding of treatment in patients receiving IST is crucial. Since then, three biologic treatments have been approved for patients with AQP4-IgG–seropositive NMOSD in various countries/regions: eculizumab, inebilizumab, and satralizumab (Cree et al., 2019; Holmøy et al., 2021; Pittock et al., 2019; Yamamura et al., 2019).

Satralizumab is a humanized monoclonal recycling antibody targeting both membrane-bound and soluble IL-6 receptors (IL-6R) (Traboulsee et al., 2020; Yamamura et al., 2019). Satralizumab inhibits inflammatory IL-6 signaling pathways (Traboulsee et al., 2020; Yamamura et al., 2019), and may intervene in AQP4-IgG production and T-cell activation (Chihara et al., 2011; Lin et al., 2016). In the SAkuraSky and SAkuraStar studies, satralizumab monotherapy or in combination with baseline IST significantly reduced relapse risk in patients with AQP4-IgG–seropositive NMOSD versus placebo. Satralizumab had a favorable safety profile in the double-blind periods of SAkuraSky and SAkuraStar (Traboulsee et al., 2020; Yamamura et al., 2019). Here, we report long-term satralizumab safety data from the SAkura studies, comparing outcomes from the overall satralizumab treatment (OST) periods with the double-blind periods.

2. Methods

2.1. Study design and participants

SAkuraSky and SAkuraStar were phase 3, multicenter, randomized, double-blind, placebo-controlled trials of satralizumab in patients with NMOSD, with ongoing open-label extension (OLE) periods. Detailed methodologies have been previously published (Traboulsee et al., 2020; Yamamura et al., 2019). Briefly, SAkuraSky had an add-on design, with patients randomized 1:1 to receive satralizumab or placebo plus their baseline IST (Yamamura et al., 2019). SAkuraStar had a monotherapy design, with patients randomized 2:1 to receive satralizumab or placebo (Traboulsee et al., 2020).

Participants who experienced a Clinical Endpoint Committee (CEC)-adjudicated protocol-defined relapse (PDR), or who reached the end of the double-blind period, could enter the ongoing OLE period of their respective study. In SAkuraSky, patients who experienced a relapse treated with rescue therapy could also enter the OLE (Yamamura et al., 2019). The SAkuraSky double-blind period ended after the total number of PDRs reached 26 (clinical cut-off date of 6 June 2018) (Yamamura et al., 2019), while the SAkuraStar double-blind period ended after 1.5 years (clinical cut-off date of 12 October 2018) (Traboulsee et al., 2020).

Eligible patients were aged 12–74 years in SAkuraSky and 18–74 years in SAkuraStar. Additional inclusion criteria included (Traboulsee et al., 2020; Yamamura et al., 2019) a diagnosis of AQP4-IgG–seropositive or AQP4-IgG–seronegative neuromyelitis optica per the 2006 Wingerchuk criteria (Wingerchuk et al., 2006) or AQP4-IgG–seropositive NMOSD at screening with idiopathic single or recurrent events of longitudinally extensive myelitis or recurrent or simultaneous optic neuritis in both eyes (the term NMOSD is used throughout this study to refer to both groups in accordance with 2015 guidelines (Wingerchuk et al., 2015)); an Expanded Disability Status Scale score $\leq$6.5; and clinical evidence of $\geq$2 relapses 2 years before screening, with at least 1 relapse occurring in the previous 12 months in SAkuraSky or 1 attack in the 12 months before screening in SAkuraStar. The proportion of AQP4-IgG–seronegative patients was limited to approximately 30% of adults in the studies to reflect the global population (Sepúlveda et al., 2016; Wingerchuk et al., 2007). Key exclusion criteria are reported elsewhere (Traboulsee et al., 2020; Yamamura et al., 2019).

2.2. Procedures

Patients received subcutaneous satralizumab (120 mg) or placebo at weeks 0, 2, and 4, and every 4 weeks thereafter in the double-blind periods of both studies. During the SAkuraSky double-blind period, patients continued baseline treatment with a stable dose of azathioprine (maximum, 3 mg/kg/day), mycophenolate mofetil (maximum, 3000 mg/day), or oral corticosteroids (maximum 15 mg/day; prednisolone equivalent) in addition to study drug; dose increases/changes were not permitted. Adolescents (aged 12–17 years) could receive oral corticosteroids in addition to either azathioprine or mycophenolate mofetil. During the OLE periods, all patients received satralizumab administered on the same dosing schedule as the double-blind period (including loading doses of satralizumab for patients who received placebo in the double-blind period). Patients in SAkuraSky could discontinue or change their baseline IST upon entry to the OLE; however, IST dosing increases were not permitted. No concomitant ISTs were permitted during the double-blind or OLE periods of SAkuraStar.

Throughout both studies, patients could receive acute relapse rescue therapy (e.g., pulse intravenous corticosteroids, intravenous immunoglobulin, and/or apheresis) and analgesics for pain management.

Patients entering the OLE after a relapse could start satralizumab after $\geq$31 days from relapse onset, while those completing the double-blind period started satralizumab 4 weeks after the last dose. In both studies, patients experiencing a relapse during the OLE continued satralizumab per the investigator's discretion.

2.3. Outcomes

The primary objective of this analysis was to evaluate the long-term safety of satralizumab during the OST period. The OST period safety population comprised patients receiving $\geq$1 dose of satralizumab in the double-blind and/or OLE periods up to the clinical cut-off date (22 February 2021). Adverse events (AEs) were assessed by study investigators at each patient contact until withdrawal visit/last observation visit (12–48 weeks after the last treatment dose).

Safety assessments consisted of monitoring and recording AEs, including AE severity and seriousness and laboratory parameters (including neutrophils, platelets, liver enzymes [alanine aminotransferase and aspartate aminotransferase] and total bilirubin, total cholesterol, triglycerides, fibrinogen, and complement [C3 and C4], etc.). Infection AEs (including serious and potential opportunistic infections) and injection-related reactions (IRRs) were specifically evaluated. Relapses were not categorized as AEs. AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 and reported by Preferred Term (PT).

AEs were identified as infections when coded to the MedDRA system organ class Infections and Infestations. Infection AEs with similar medical concepts were grouped by MedDRA Preferred Term into baskets. This approach enables a more comprehensive assessment of infections, without being restricted to fragmentation of AEs based on individual investigator-reported Preferred Terms. Baskets of Preferred Terms selected for safety analyses of infection events in both studies included upper respiratory tract infections, lower respiratory tract infections, skin infections, urinary tract infections, gastrointestinal tract infections, and sepsis. Additionally, potential opportunistic infections selected using the standardized MedDRA query (SMQ narrow) 'opportunistic infections' were analyzed.

Laboratory assessments were conducted at weeks 0, 2, and 4, and every 4 weeks thereafter during the double-blind periods, and followed a similar assessment schedule during the OLE periods. For all laboratory parameters reported except complement, patients with a post-baseline worsening in laboratory value grade severity compared to baseline were reported. Grade severity was determined using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4 (NIH, 2009). For complement, lowest complement level throughout the study was classified as mild to moderate (≥0.5 x the lower limit of normal [LLN]) or severe (<0.5 x LLN). For alanine aminotransferase (ALT)/aspartate aminotransferase (AST), the finding of elevated (>3 x the upper limit of normal [ULN]) ALT or AST in combination with either total bilirubin >2 x ULN or clinical jaundice was defined as an indicator of severe drug-induced liver injury.

2.4. Statistical analysis

The safety analysis population included all patients who received at least 1 dose of study treatment. 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) x 100. 95% confidence intervals (CIs) were calculated using the exact method based on the Poisson distribution.

Safety was also assessed in patients who were AQP4-IgG–seropositive at screening, with AQP4-IgG serological status tested using the M23-based enzyme-linked immunosorbent assay (ELISA). Duration of exposure to study drug (years) varied by patient and was defined as: (number of days between the first treatment dose and last treatment dose) / 365.25.

2.5. Standard protocol approvals, registrations, and patient consents

Approval was obtained from the local ethics committee or institutional review board at each trial center, and all patients provided written informed consent. The trials were conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. The trials are registered with ClinicalTrials.gov, NCT02028884 (SAkuraSky) and NCT02073279 (SAkuraStar).

3. Results

3.1. Cohort

In the double-blind periods, 83 patients were randomly assigned to placebo (n = 42) or satralizumab (n = 41) plus baseline IST in SAkuraSky, and 95 patients were randomly assigned to placebo (n = 32) or satralizumab (n = 63) monotherapy in SAkuraStar. Two additional patients were enrolled into SAkuraSky; the first was enrolled on the clinical cut-off date (6 June 2018) to receive satralizumab, and the second was enrolled directly into the OLE. Both patients were included in analyses for the OST period, but not the double-blind period.

In this analysis, 75 patients in SAkuraSky and 91 patients in SAkuraStar received at least 1 dose of satralizumab in the double-blind/OLE periods and were included in the safety analysis population.

Disease history and baseline characteristics were balanced overall for patients in the double-blind and OST periods of both studies, apart from a numerically higher proportion of women in the placebo group and a numerically higher proportion of African Americans in the satralizumab group, both in SAkuraStar (Table 1).

In SAkuraSky, median satralizumab exposure was 2.1 years (range 0.0–4.3; IQR 0.4–2.8) in the double-blind period and 4.4 years (range 0.1–7.0; IQR 2.6–5.8) in the OST period; the median placebo exposure in the double-blind period was 0.6 years (range 0.0–3.5; IQR 0.2–2.2). In SAkuraStar, the median satralizumab exposure was 1.8 years (range 0.0–3.9; IQR 0.8–2.3) in the double-blind period and 4.0 years (range 0.1–6.1; IQR 2.3–5.0) in the OST period; median placebo exposure in the double-blind period was 1.1 years (range 0.0–4.1; IQR 0.3–1.8).

3.2. Overall safety profile

The rates of AEs and serious AEs were comparable between placebo and satralizumab in the double-blind periods of SAkuraSky and SAkuraStar (Tables 2 and 3). Similarly, in the OST periods, rates of AEs and serious AEs were consistent with the satralizumab group in the double-blind periods (Table 2 and 3). Most AEs with satralizumab were mild or moderate in severity, and no deaths or anaphylactic reactions related to study treatment were reported throughout either study. In both studies, the incidence of AEs leading to treatment discontinuation with satralizumab was low (Tables 2 and 3). No pattern of AEs leading to satralizumab discontinuation was observed.

In patients with AQP4-IgG–seropositive NMOSD, the safety profile of satralizumab was consistent with the overall SAkuraSky and SAkuraStar safety analysis populations, which enrolled both AQP4-IgG–seropositive and AQP4-IgG–seronegative patients (Appendix Tables A1 and A2).

Rates of IRRs in the double-blind period were higher with satralizumab versus placebo in SAkuraSky and were comparable between satralizumab and placebo in SAkuraStar (Tables 2 and 3). In the SAkuraSky OST period, the rate of IRRs was lower than with satralizumab during the double-blind period (Table 2). In the SAkuraStar OST period, the rate of IRRs was consistent with satralizumab during the double-blind period (Table 3). Additionally, no IRRs with satralizumab were serious and none led to treatment discontinuation/interruption.

During the double-blind period of both studies, infection and serious infection rates with satralizumab were comparable or not higher than with placebo (Tables 2 and 3). Infection and serious infection rates in the OST periods were consistent with the satralizumab group in the double-blind periods (Tables 2 and 3).

The most common AEs in the OST period of SAkuraSky were nasopharyngitis (27.2 events/100 PYs [95% CI, 21.7–33.5]) and upper respiratory tract infection (22.4 events/100 PYs [95% CI, 17.5–28.3]), reported in 35% (n = 26) and 25% of patients (n = 19), respectively. In the placebo group during the double-blind period, rates of nasopharyngitis and upper respiratory tract infection were 21.9 events/100 PYs (95% CI, 11.6–37.4) and 18.5 events/100 PYs (95% CI, 9.2–33.1), reported in 17% (n = 7) and 14% of patients (n = 6), respectively.

The most common AEs in the SAkuraStar OST period were upper respiratory tract infection (20.9 events/100 PYs [95% CI, 16.3–26.3]) and urinary tract infection (19.1 events/100 PYs [95% CI, 14.7–24.3]), reported in 26% (n = 24) and 22% of patients (n = 20), respectively. Upper respiratory tract infection and urinary tract infection were reported in 19% (n = 6; 37.0 events/100 PYs [95% CI, 20.7–61.0]) and 25% of patients (n = 8; 59.1 events/100 PYs [95% CI, 37.9–88.0]), respectively, in the placebo group during the double-blind period.

Table 1
Demographics and baseline characteristics of the safety analysis population in the double-blind and OST periods of SAkuraSky and SAkuraStar.

	SAkuraSky			SAkuraStar		
	DB period		OST period	DB period		OST period
	Placebo (*n* = 42)	**Satralizumab (*n* = 41)**	**Satralizumab (*n* = 75)**	**Placebo (*n* = 32)**	**Satralizumab (*n* = 63)**	**Satralizumab (*n* = 91)**
Age, years						
Mean (SD)	43.4 (12.0)	40.8 (16.1)	41.1 (14.9)	40.5 (10.5)	45.3 (12.0)	43.9 (11.7)
Range	14–65	13–73	13–73	20–56	21–70	21–70
Female sex, n (%)	40 (95)	37 (90)	69 (92)	31 (97)	46 (73)	73 (80)
Race or ethnicity, n (%)						
American Indian/Alaska Native	0	0	0	0	2 (3)	2 (2)
Asian	18 (43)	17 (41)	33 (44)	6 (19)	8 (13)	14 (15)
Black/African American	2 (5)	0	2 (3)	3 (9)	13 (21)	15 (16)
White	21 (50)	24 (59)	39 (52)	22 (69)	37 (59)	56 (62)
Other	1 (2)	0	1 (1)	1 (3)	3 (5)	4 (4)
Treatment at baseline, n (%)						
Oral corticosteroids	20 (48)	17 (41)	35 (47)	–	–	–
Azathioprine	13 (31)	16 (39)	24 (32)	–	–	–
MMF	8 (19)	4 (10)	11 (15)	–	–	–
Azathioprine plus corticosteroids[a]	0	3 (7)	3 (4)	–	–	–
MMF plus oral corticosteroids[a]	1 (2)	1 (2)	2 (3)	–	–	–
Previous treatment, n (%)[b]						
B-cell-depleting therapy	–	–	–	4 (13)	8 (13)	11 (12)
ISTs or other	–	–	–	28 (88)	55 (87)	80 (88)

Abbreviations: DB, double-blind; IST, immunosuppressive therapy; MMF, mycophenolate mofetil; NMOSD, neuromyelitis optica spectrum disorder; OST, overall satralizumab treatment; SD, standard deviation.

[a] Adolescent patients (aged 12–17 years) only.

[b] Patients in SAkuraStar were not permitted to continue baseline immunosuppressants but were stratified by previous therapy for the prevention of an NMOSD attack (B-cell-depleting therapy vs. immunosuppressants or other).

Table 2
Adverse events in the safety analysis population during the DB and OST periods of SAkuraSky.

	DB period				OST period	
	Placebo (*n* = 42; PYs = 59.5)		Satralizumab + IST (*n* = 41; PYs = 78.5)		Satralizumab ± IST (*n* = 75; PYs = 316.7)	
	Patients, *n* (%)	**AEs per 100 PYs (95% CI)**	**Patients, *n* (%)**	**AEs per 100 PYs (95% CI)**	**Patients, *n* (%)**	**AEs per 100 PYs (95% CI)**
All AEs	40 (95.2)	514.3 (458.2–575.2)	37 (90.2)	485.2 (437.7–536.5)	71 (94.7)	365.6 (344.9–387.3)
Serious AEs	9 (21.4)	20.2 (10.4–35.2)	7 (17.1)	11.5 (5.2–21.8)	21 (28.0)	10.4 (7.2–14.6)
Severe AEs	5 (11.9)	11.8 (4.7–24.2)	5 (12.2)	6.4 (2.1–14.9)	15 (20.0)	7.3 (4.6–10.9)
AEs leading to treatment discontinuation	4 (9.5)	6.72 (1.8–17.2)	3 (7.3)	5.1 (1.4–13.0)	7 (9.3)	2.5 (1.1–5.0)
Infections[a]	26 (61.9)	149.6 (120.1–184.1)	28 (68.3)	132.5 (108.2–160.5)	60 (80.0)	125.0 (113.0–138.0)
Serious infections[a]	3 (7.1)	5.0 (1.0–14.7)	2 (4.9)	2.6 (0.3–9.2)	8 (10.7)	2.8 (1.3–5.4)
Injection-related reactions	2 (4.8)	3.4 (0.4–12.1)	5 (12.2)	21.7 (12.6–34.7)	10 (13.3)	8.5 (5.6–12.4)
Fatal AEs	0	0 (NE–6.2)	0	0 (NE–4.7)	0	0 (NE–1.2)

Abbreviations: AE, adverse event; CI, confidence interval; DB, double-blind; IST, immunosuppressive therapy; NE, not evaluable; OST, overall satralizumab treatment; PYs, patient-years.

[a] MedDRA system organ class 'infections and infestations.'

Table 3
Adverse events in the safety analysis population during the DB and OST periods of SAkuraStar.

	DB period				OST period	
	Placebo (*n* = 32; PYs = 40.6)		Satralizumab monotherapy (*n* = 63; PYs = 115.2)		Satralizumab monotherapy (*n* = 91; PYs = 340.4)	
	Patients, *n* (%)	**AEs per 100 PYs (95% CI)**	**Patients, *n* (%)**	**AEs per 100 PYs (95% CI)**	**Patients, *n* (%)**	**AEs per 100 PYs (95% CI)**
All AEs	24 (75.0)	495.2 (429.1–568.6)	58 (92.1)	473.9 (435.0–515.4)	90 (98.9)	351.7 (332.0–372.2)
Serious AEs	5 (15.6)	14.8 (5.4–32.2)	12 (19.0)	17.4 (10.6–26.8)	20 (22.0)	10.9 (7.7–15.0)
Severe AEs	2 (6.2)	9.9 (2.7–25.2)	17 (27.0)	32.1 (22.6–44.3)	24 (26.4)	16.5 (12.4–21.4)
AEs leading to treatment discontinuation	1 (3.1)	2.5 (0.1–13.7)	1 (1.6)	0.9 (0.0–4.8)	2 (2.2)	0.6 (0.1–2.1)
Infections[a]	14 (43.8)	162.6 (125.8–206.9)	34 (54.0)	99.8 (82.4–119.8)	60 (65.9)	82.3 (72.9–92.5)
Serious infections[a]	3 (9.4)	9.9 (2.7–25.2)	6 (9.5)	5.2 (1.9–11.3)	8 (8.8)	3.2 (1.6–5.8)
Injection-related reactions	5 (15.6)	17.3 (6.9–35.5)	9 (14.3)	13.9 (7.9–22.6)	12 (13.2)	7.9 (5.2–11.5)
Fatal AEs	0	0 (NE–9.1)	0	0 (NE–3.2)	0	0 (NE–1.1)

Abbreviations: AE, adverse event; CI, confidence interval; DB, double-blind; NE, not evaluable; OST, overall satralizumab treatment; PYs, patient-years.

[a] MedDRA system organ class 'infections and infestations.'

3.3. Infections

When comparing infections by basket, the most common infections during the double-blind and OST periods of both studies were under the upper respiratory tract infection and urinary tract infection baskets with satralizumab and placebo, with comparable rates observed between the satralizumab and placebo groups (Tables 4 and 5).

Infection and serious infection rates by basket with satralizumab in the OST period were consistent with those observed with satralizumab and placebo during the double-blind period (Tables 4 and 5; Appendix Tables A3 and A4).

Overall, infection and serious infection rates did not increase over time in either study (Fig. 1). However, data beyond year 4 should be interpreted with caution due to the limited number of PYs of exposure. Most infections reported during years 5–7 of the studies were non-serious (96%), of mild or moderate severity (98%), and the rates of serious infections in these years were consistent with those reported during years 1–4.

Throughout both studies, there were no cases of progressive multifocal leukoencephalopathy. No cases of opportunistic infections (identified by the MedDRA SMQ [narrow] 'opportunistic infections') were identified in patients treated with satralizumab throughout both studies.

Five cases of COVID-19 infection were reported during the OST periods of SAkuraSky (n = 3) and SAkuraStar (n = 2). All COVID-19 infections were non-serious, mild to moderate in severity, and were resolved with/without treatment. No patients who reported COVID-19 infections received the SARS-CoV-2 vaccine, since these cases occurred before widespread vaccination rollout.

3.4. Laboratory value changes

Overall, longer exposure to satralizumab in the OST periods of both studies was not associated with a higher risk of severe (grade ≥3) laboratory changes compared with satralizumab treatment in the double-blind period (Table 6). Most decreases in neutrophil count were grade 1 or 2 throughout the studies and were transient/intermittent. Grade 3 or 4 decreases in neutrophil counts with satralizumab were not associated with severe or serious infections. No neutrophil count decreases necessitated the use of colony-stimulating factor treatment. No decreases in platelet counts (all grade 1 or 2) with satralizumab were associated with bleeding events, and most platelet decreases were transient/intermittent. Similarly, most elevations in liver enzymes (ALT

Table 4
Rate of infections by basket in the safety analysis population during the DB and OST periods of SAkuraSky.

	DB period				OST period	
	Placebo (n = 42; PYs = 59.5)		Satralizumab + IST (n = 41; PYs = 78.5)		Satralizumab ± IST (n = 75; PYs = 316.7)	
	Patients, *n* (%)	**AEs per 100 PYs (95% CI)**	**Patients, *n* (%)**	**AEs per 100 PYs (95% CI)**	**Patients, *n* (%)**	**AEs per 100 PYs (95% CI)**
Upper respiratory tract infections	16 (38.1)	72.3 (52.3–97.3)	20 (48.8)	84.1 (65.0–106.9)	45 (60.0)	64.1 (55.6–73.5)
Urinary tract infections	10 (23.8)	23.5 (12.9–39.5)	10 (24.4)	16.6 (8.8–28.3)	24 (32.0)	18.3 (13.9–23.7)
Skin infections	6 (14.3)	11.8 (4.7–24.2)	3 (7.3)	3.8 (0.8–11.2)	13 (17.3)	6.0 (3.6–9.4)
Lower respiratory tract infections	2 (4.8)	3.4 (0.4–12.1)	3 (7.3)	7.6 (2.8–16.6)	8 (10.7)	4.1 (2.2–7.0)
Gastrointestinal infections	2 (4.8)	3.4 (0.4–12.1)	2 (4.9)	3.8 (0.8–11.2)	7 (9.3)	4.4 (2.4–7.4)
Sepsis[a]	1 (2.4)	1.7 (0–9.4)	0	0 (0–4.7)	1 (1.3)	0.6 (0.1–2.3)

Abbreviations: AE, adverse event; CI, confidence interval; DB, double-blind; IST, immunosuppressive therapy; OST, overall satralizumab treatment; PYs, patient-years.
Infection events by Preferred Term may be classified under more than one basket. Baskets for safety analyses of infection events included upper respiratory tract infections, lower respiratory tract infections, skin infections, urinary tract infections, gastrointestinal tract infections, sepsis, and an opportunistic infection screening basket.

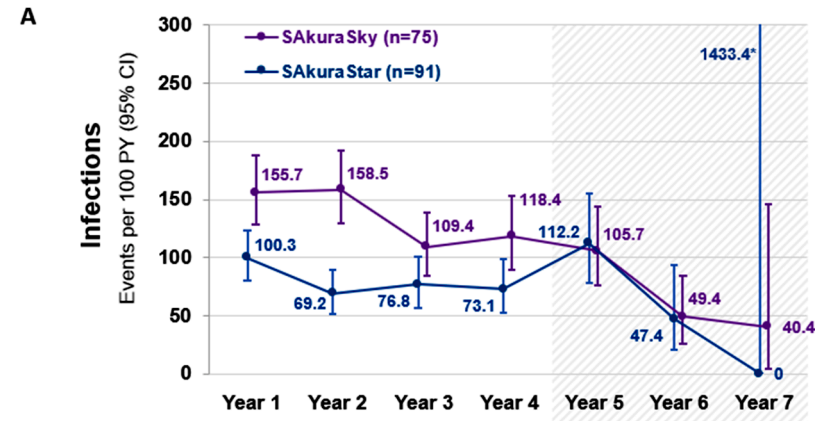
[a] One patient experienced a severe, serious sepsis event with placebo due to *Escherichia coli* infection during the double-blind period. One patient experienced two sepsis events during the OST period: one non-serious sepsis event of mild severity and one serious urosepsis event of moderate severity, both due to *Escherichia coli* infection. Both events were resolved with treatment, and no dose change in satralizumab was required. Both patients were receiving concomitant immunosuppressive treatment with azathioprine.

Table 5
Rate of infections by basket in the safety analysis population during the DB and OST periods of SAkuraStar.

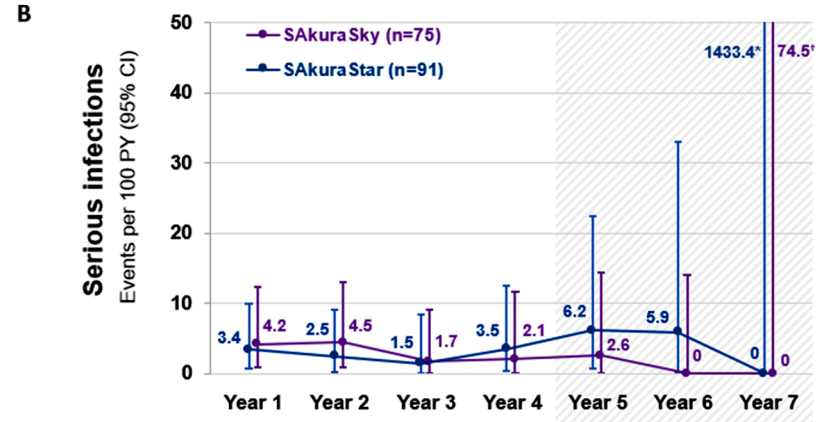
	DB period				OST period	
	Placebo (n = 32; PYs = 40.6)		Satralizumab monotherapy (n = 63; PYs = 115.2)		Satralizumab monotherapy (n = 91; PYs = 340.4)	
	Patients, *n* (%)	**AEs per 100 PYs (95% CI)**	**Patients, *n* (%)**	**AEs per 100 PYs (95% CI)**	**Patients, *n* (%)**	**AEs per 100 PYs (95% CI)**
Upper respiratory tract infections	9 (28.1)	49.3 (30.1–76.1)	22 (34.9)	35.6 (25.5–48.3)	46 (50.5)	37.9 (31.6–45.0)
Urinary tract infections	8 (25.0)	61.6 (39.9–90.9)	12 (19.0)	33.9 (24.1–46.3)	24 (26.4)	21.7 (17.1–27.3)
Skin infections	2 (6.3)	4.9 (0.6–17.8)	6 (9.5)	6.9 (3.0–13.7)	8 (8.8)	5.6 (3.4–8.7)
Gastrointestinal infections	2 (6.3)	7.4 (1.5–21.6)	5 (7.9)	4.3 (1.4–10.1)	7 (7.7)	2.6 (1.2–5.0)
Lower respiratory tract infections	2 (6.3)	4.9 (0.6–17.8)	5 (7.9)	4.3 (1.4–10.1)	9 (9.9)	3.2 (1.6–5.8)
Sepsis[a]	0	0 (0–9.1)	2 (3.2)	1.7 (0.2–6.3)	2 (2.2)	0.6 (0.1–2.1)

Abbreviations: AE, adverse event; CI, confidence interval; DB, double-blind; OST, overall satralizumab treatment; PYs, patient-years.
Infection events by Preferred Term may be classified under more than one basket. Baskets for safety analyses of infection events included upper respiratory tract infections, lower respiratory tract infections, skin infections, urinary tract infections, gastrointestinal tract infections, sepsis, and an opportunistic infection screening basket.

[a] Two patients experienced sepsis events during the OST period. The first patient experienced a urosepsis event (serious and moderate severity) due to an *Escherichia coli* infection. The second patient experienced a pulmonary sepsis event (serious and severe severity), which the investigator deemed may have been community acquired. Both events were resolved with treatment, and necessitated interruption to satralizumab treatment. The first patient had the following concomitant disorders: elevated blood pressure, asthma, dyslipidemia, depression, neurogenic bladder, type 2 diabetes, constipation, muscle spasms, and gastroesophageal reflux disease. The second patient had the following concomitant disorders: type 1 diabetes, depression, deep vein thrombosis, osteopenia, hypothyroid, hyperlipidemia, and elevated leukocyte levels.



	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
SAkuraSky							
PY	71.3	66.9	60.4	48.1	38.8	26.3	5.0
Patients exposed	75	68	66	52	46	35	16
SAkuraStar							
PY	87.7	79.5	66.4	57.5	32.1	16.9	0.3
Patients exposed	91	83	76	61	50	24	3



	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
SAkuraSky							
PY	71.3	66.9	60.4	48.1	38.8	26.3	5.0
Patients exposed	75	68	66	52	46	35	16
SAkuraStar							
PY	87.7	79.5	66.4	57.5	32.1	16.9	0.3
Patients exposed	91	83	76	61	50	24	3

Fig. 1. Rates of (a) infections and (b) serious infections in patients receiving satralizumab by year during the OST periods in SAkuraSky and SAkuraStar (safety analysis population).
Abbreviations: CI, confidence interval; OST, overall satralizumab treatment; PY, patient-years.
*Upper CI limits for rates of infection and serious infection in SAkuraStar at year 7. †Upper CI limit for rate of serious infection in SAkuraSky at year 7.

or AST) with satralizumab throughout the studies were grade 1, transient/intermittent, and resolved without treatment disruption. No patients had liver function tests indicative of drug-induced liver injury or met the criteria for Hy's law. Most elevations in triglyceride and cholesterol levels with satralizumab were also grade 1 or grade 2, and none of these elevations necessitated dose interruptions. Decreases in fibrinogen levels (mainly grade 1 or 2) with satralizumab were not associated with bleeding events. Three patients in SAkuraStar experienced a grade ≥3 decrease in fibrinogen levels at a single time point during the OST period; none of these patients experienced a bleeding event. Most decreases in complement levels with satralizumab in both studies were mild to moderate in severity.

4. Discussion

SAkuraSky and SAkuraStar enrolled patients with both AQP4-IgG–seropositive and AQP4-IgG–seronegative NMOSD, consistent with real-world clinical practice (Hamid et al., 2017; Traboulsee et al., 2020; Yamamura et al., 2019). This long-term safety analysis of satralizumab, with a median of 4 years of treatment exposure in the SAkuraSky and SAkuraStar OST periods, demonstrates that satralizumab treatment is well tolerated in patients with NMOSD, with no new or unexpected safety findings over time. The safety profile of satralizumab previously reported in the double-blind periods of SAkuraSky and SAkuraStar was maintained with up to 7 years follow-up. Similarly, evidence from recent prospective and retrospective studies supports the long-term safety of tocilizumab, another IL-6R antagonist, in patients with NMOSD and

Table 6
Laboratory events (worsened from baseline) in patients receiving satralizumab by highest NCI-CTCAE grade post-baseline in the DB and OST periods of SAkuraSky and SAkuraStar (safety analysis population).

	SAkuraSky		SAkuraStar	
	DB period ($n = 41$)	OST period ($n = 75$)	DB period ($n = 63$)	OST period ($n = 91$)
Neutrophil decrease, *n* (%)				
Any	12/41 (29.3)	31/75 (41.3)	21/63 (33.3)	36/91 (39.6)
Grade 1	2/41 (4.9)	3/75 (4.0)	3/61 (4.9)	6/88 (6.8)
Grade 2	5/41 (12.2)	18/75 (24.0)	13/61 (21.3)	20/88 (22.7)
Grade 3	5/41 (12.2)	9/75 (12.0)	3/63 (4.8)	8/91 (8.8)
Grade 4	–	1/75 (1.3)	2/63 (3.2)	2/91 (2.2)
Alanine aminotransferase increase, *n* (%)				
Any	6/41 (14.6)	26/75 (34.7)	23/63 (36.5)	35/91 (38.5)
Grade 1	5/38 (13.2)	24/72 (33.3)	21/62 (33.9)	32/90 (35.6)
Grade 2	–	–	2/63 (3.2)	3/91 (3.3)
Grade 3	1/41 (2.4)	2/75 (2.7)	–	–
Aspartate aminotransferase increase, *n* (%)				
Any	6/41 (14.6)	18/75 (24.0)	13/63 (20.6)	27/91 (29.7)
Grade 1	5/40 (12.5)	16/74 (21.6)	12/62 (19.4)	25/90 (27.8)
Grade 2	1/41 (2.4)	1/75 (1.3)	1/63 (1.6)	2/91 (2.2)
Grade 3	–	1/75 (1.3)	–	–
Cholesterol increase, *n* (%)				
Any	15/41 (36.6)	31/75 (41.3)	29/63 (46.0)	50/91 (54.9)
Grade 1	9/21 (42.9)	20/34 (58.8)	24/37 (64.9)	41/52 (78.8)
Grade 2	6/39 (15.4)	10/73 (13.7)	5/63 (7.9)	9/90 (10.0)
Grade 3	–	1/75 (1.3)	–	–
Triglyceride increase, *n* (%)				
Any	24/41 (58.5)	46/75 (61.3)	42/63 (66.7)	62/91 (68.1)
Grade 1	19/38 (50.0)	33/66 (50.0)	26/43 (60.5)	39/62 (62.9)
Grade 2	5/41 (12.2)	12/75 (16.0)	14/60 (23.3)	18/88 (20.5)
Grade 3	–	1/75 (1.3)	2/63 (3.2)	5/91 (5.5)
Platelet decrease, *n* (%)				
Any	11/41 (26.8)	25/75 (33.3)	14/63 (22.2)	26/91 (28.6)
Grade 1	11/40 (27.5)	24/72 (33.3)	12/60 (20.0)	24/85 (28.2)
Grade 2	–	1/75 (1.3)	2/63 (3.2)	2/91 (2.2)
Fibrinogen decrease, *n* (%)				
Any	27/41 (65.9)	58/75 (77.3)	48/63 (76.1)	76/91 (83.5)
Grade 1	11/41 (26.8)	23/75 (30.7)	15/63 (23.8)	24/90 (26.7)
Grade 2	16/41 (39.0)	35/75 (46.7)	32/63 (50.8)	49/90 (54.4)
Grade 4	–	–	1/63 (1.6)[a]	3/91 (3.3)

Abbreviations: DB, double-blind; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; OST, overall satralizumab treatment.

[a] This grade 4 fibrinogen decrease is believed to be a data error; this error has been corrected retrospectively, and the fibrinogen levels in this patient were within the normal range during the double-blind period of SAkuraStar.

Table entries show the number of patients with the grade as their highest post-baseline NCI-CTCAE grade for the test. Baseline is the patient's last observation on or before first study drug administration. For the 'any' grade row, denominators include patients with either a baseline value or at least one post-baseline value for the laboratory test, as well as a baseline NCI grade <4 or missing. For a specific NCI grade row (e.g., grade 2) the denominator includes patients who have a baseline grade lower than the post-baseline grade being tabulated (i.e., lower than grade 2) or a missing baseline grade. 'Any' equals the number of patients with any increase in grade for the specified laboratory test. Grading is based on numeric ranges within NCI-CTCAE v4, except for fibrinogen, which excludes the percentage change criteria from grading.

myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) (Ringelstein et al., 2022; Zhang et al., 2020).

Patients in SAkuraSky could receive satralizumab as an add-on therapy to their baseline IST, whereas patients in SAkuraStar received satralizumab monotherapy. The rates of AEs and serious AEs with satralizumab treatment in the double-blind and OST periods were similar between the two studies and were comparable with placebo during the double-blind periods, suggesting that satralizumab is well tolerated as an add-on or as monotherapy. Consistent with these findings, a separate analysis of 16 patients who tapered their oral corticosteroid dose during the OLE period of SAkuraSky showed that the satralizumab safety profile in steroid-tapered patients was comparable with the overall study population during the double-blind period (Yamamura, 2022).

Satralizumab may be subcutaneously self-administered by patients following guidance and assessment for suitability by a healthcare professional (FDA, 2020). Therefore, IRRs with satralizumab are of interest, particularly as home administration is an increasingly important consideration (e.g., during the ongoing COVID-19 pandemic, to reduce the need to travel to clinical settings). In this analysis, IRRs with satralizumab were generally mild to moderate and none led to treatment discontinuation/interruption.

Rates of serious infections during the OST periods were comparable with those observed in patients receiving either satralizumab or placebo during the double-blind study periods. The most common AEs were nasopharyngitis and upper respiratory tract infection during the OST period of SAkuraSky, and upper respiratory tract infection and urinary tract infection during the OST period of SAkuraStar. Similarly, when rates of infection and serious infection by basket were analyzed, the most common infections during the double-blind and OST periods of both studies were under the upper respiratory tract infection and urinary tract infection baskets in patients receiving satralizumab and placebo, with comparable rates observed between the satralizumab and placebo groups. No opportunistic infections were reported in SAkuraSky or SAkuraStar. Overall, rates of infections and serious infections did not increase over time in either study. However, given the mechanism of action of IL-6R inhibition, vigilance for timely detection of infection is recommended for patients receiving satralizumab, and satralizumab administration should be delayed in patients with an active infection until the infection is controlled.

In this analysis, laboratory changes were reported in some patients receiving satralizumab, including decreases in neutrophil and platelet counts, elevations in liver enzymes and lipids, and decreases in fibrinogen and complement. The mechanisms behind these laboratory changes may be due to the mechanism of action of satralizumab, the expected pharmacodynamic effects of IL-6R inhibition, and the direct changes to levels of inflammation-mediating acute phase proteins (Romano et al., 2018; Smolen and Aletaha, 2011). In all cases, laboratory changes reported with satralizumab treatment were in line with those observed with other IL-6R antagonists, and most laboratory changes were mild or moderate in severity throughout the OST periods of both studies.

Limitations of this analysis include potential bias associated with the OLE periods. Furthermore, these analyses combine data from the double-blind and OLE periods, which have inherent differences in study design. Since more than 90% of patients from the double-blind periods of both studies were enrolled in the OST period, selection bias based on inclusion in the OLE period is unlikely; however, the open-label study design may have yielded unconscious bias in AE reporting.

5. Conclusion

In conclusion, this analysis of safety data from the SAkura studies provides evidence that the favorable safety profile and tolerability of satralizumab are sustained with long-term treatment both as monotherapy and in combination with baseline IST in patients with AQP4-IgG–seropositive and AQP4-IgG–seronegative NMOSD. These results are promising, given the need for minimizing safety risks associated with long-term therapy use in patients with NMOSD. This study adds to the current experience of IL-6R inhibition in patients with NMOSD and other inflammatory diseases; knowledge obtained from this analysis will aid in optimizing the clinical benefit for patients. The long-term safety and efficacy of satralizumab continues to be monitored in the ongoing OLE study, SAkuraMoon (NCT04660539), which will evaluate patients with NMOSD who have completed the SAkuraSky and SAkuraStar OLE periods.

Data sharing statement

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: https://go.roche.com/data_sharing. Qualified researchers may request access to individual patient-level data through the clinical study data request platform (http://www.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 re-identification.

CRediT authorship contribution statement

Takashi Yamamura: Conceptualization, Investigation, Writing – original draft, Writing – review & editing, Visualization. **Brian Weinshenker:** Conceptualization, Writing – original draft, Writing – review & editing, Visualization. **Michael R. Yeaman:** Conceptualization, Writing – original draft, Writing – review & editing, Visualization. **Jerome De Seze:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing, Visualization. **Francesco Patti:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing, Visualization. **Patricia Lobo:** Writing – original draft, Writing – review & editing, Visualization. **H.-Christian von Büdingen:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Visualization. **Xiujing Kou:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Visualization. **Kristina Weber:** Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing, Visualization. **Benjamin Greenberg:** Conceptualization, Writing – original draft, Writing – review & editing, Visualization.

Declaration of Competing Interest

This study was sponsored by F. Hoffmann-La Roche. **Takashi Yamamura** served on scientific advisory boards for Biogen, Takeda, Sumitomo, Novartis, and Chugai. He receives consulting fees from Biogen, Takeda, Mitsubishi Tanabe, Novartis, Roche, and Chugai. He carried out contracted research in Mitsubishi Tanabe, Novartis, Chugai, Sanofi, Chiome Bioscience, and Miraca Holdings (within the contract period but no deposit). He received speaker honoraria from Chugai, Takeda, Biogen, and Sumitomo. **Brian G. Weinshenker** reports consulting fees from UCB Biosciences, Mitsubishi Tanabe, Genentech, and Roche, and speaking fees from Genentech, Roche, and Novartis; he participated on the Attack Adjudication Committee for Alexion and Horizon Therapeutics (formerly MedImmune/Viela Bio). He reports personal fees from Chugai. He has a patent NMO-IgG for diagnosis of neuromyelitis optica with royalties received from RSR Ltd, Oxford University, Hospices Civils de Lyon, and MVZ Labor PD Dr. Volkmann und Kollegen GbR. **Michael R. Yeaman** received grants from the US National Institutes of Health and the US Department of Defense, and consulting fees from Roche, Horizon, and Alexion. He is a founder and shareholder in NovaDigm Therapeutics, Inc. and Metacin, Inc. He serves on the Genentech-Roche Strategic Scientific Committee for NMOSD and is Chair Medical Advisor to the Guthy-Jackson Charitable Foundation for NMOSD. **Jerome De Seze** received grants and personal fees from Roche, personal fees from Chugai, and has served on advisory boards in the expert committee for the clinical trial conducted by Chugai. **Francesco Patti** has served on the scientific advisory boards for Almirall, Bayer, Biogen, Calgene, Merck, Novartis, Roche, Sanofi, and TEVA; he also received speaker honoraria from the aforementioned companies and research grants for his department from Biogen and Merck. **Patricia Lobo** is an employee of ApotheCom, who is paid to provide medical writing assistance for F. Hoffmann-La Roche Ltd. **H.-Christian von Büdingen, Xiujing Kou**, and **Kristina Weber** are employees of F. Hoffmann-La Roche Ltd. **Benjamin Greenberg** received consulting fees from Alexion, Novartis, EMD Serono, Viela Bio, Genentech/Roche, Greenwich Biosciences, Axon Advisors, Rubin Anders, ABCAM, Signant, IQVIA, Sandoz, Druggability Technologies, Genzyme, and Immunovant. He receives contracted research fees from Clene Nanomedicine. He receives royalties from UpToDate.

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F. Hoffmann-La Roche Ltd. contributed to writing of the report. All authors, including those employed by Roche, had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2022.104025.

References

Agasing, A.M., Wu, Q., Khatri, B., Borisow, N., Ruprecht, K., Brandt, A.U., Gawde, S., Kumar, G., Quinn, J.L., Ko, R.M., Mao-Draayer, Y., Lessard, C.J., Paul, F., Axtell, R. C., 2020. Transcriptomics and proteomics reveal a cooperation between interferon and T-helper 17 cells in neuromyelitis optica. Nat. Commun. 11 (1), 2856.

Borisow, N., Mori, M., Kuwabara, S., Scheel, M., Paul, F., 2018. Diagnosis and treatment of NMO spectrum disorder and MOG-encephalomyelitis. Front. Neurol. 9, 888.

Brod, S.A., 2020. Review of approved NMO therapies based on mechanism of action, efficacy and long-term effects. Mult. Scler. Relat. Disord. 46, 102538.

Chihara, N., Aranami, T., Sato, W., Miyazaki, Y., Miyake, S., Okamoto, T., Ogawa, M., Toda, T., Yamamura, T., 2011. Interleukin 6 signaling promotes anti-aquaporin 4 autoantibody production from plasmablasts in neuromyelitis optica. Proc. Natl. Acad. Sci. U. S. A. 108 (9), 3701–3706.

Cree, B.A.C., Bennett, J.L., Kim, H.J., Weinshenker, B.G., Pittock, S.J., Wingerchuk, D.M., Fujihara, K., Paul, F., Cutter, G.R., Marignier, R., Green, A.J., Aktas, O., Hartung, H. P., Lublin, F.D., Drappa, J., Barron, G., Madani, S., Ratchford, J.N., She, D., Cimbora, D., Katz, E., 2019. Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): a double-blind, randomised placebo-controlled phase 2/3 trial. Lancet 394 (10206), 1352–1363.

FDA, 2020. US Food and Drug Administration. ENSPRYNG™ prescribing information.

Fujihara, K., Bennett, J.L., de Seze, J., Haramura, M., Kleiter, I., Weinshenker, B.G., Kang, D., Mughal, T., Yamamura, T., 2020. Interleukin-6 in neuromyelitis optica spectrum disorder pathophysiology. Neurol. Neuroimmunol. Neuroinflamm. 7 (5).

Hamid, S.H.M., Whittam, D., Mutch, K., Linaker, S., Solomon, T., Das, K., Bhojak, M., Jacob, A., 2017. What proportion of AQP4-IgG-negative NMO spectrum disorder patients are MOG-IgG positive? A cross sectional study of 132 patients. J. Neurol. 264 (10), 2088–2094.

Held, F., Klein, A.K., Berthele, A., 2021. Drug treatment of neuromyelitis optica spectrum disorders: out with the old, in with the new? Immunotarget. Ther. 10, 87–101.

Holmøy, T., Høglund, R.A., Illes, Z., Myhr, K.M., Torkildsen, Ø., 2021. Recent progress in maintenance treatment of neuromyelitis optica spectrum disorder. J. Neurol. 268 (12), 4522–4536.

Jarius, S., Paul, F., Weinshenker, B.G., Levy, M., Kim, H.J., Wildemann, B., 2020. Neuromyelitis optica. Nat. Rev. Dis. Primers 6 (1), 85.

Kawachi, I., Lassmann, H., 2017. Neurodegeneration in multiple sclerosis and neuromyelitis optica. J. Neurol. Neurosurg. Psychiatry 88 (2), 137–145.

Kessler, R.A., Mealy, M.A., Levy, M., 2016. Treatment of neuromyelitis optica spectrum disorder: acute, preventive, and symptomatic. Curr. Treat. Option. Neurol. 18 (1), 2.

Kim, S.H., Jang, H., Park, N.Y., Kim, Y., Kim, S.Y., Lee, M.Y., Hyun, J.W., Kim, H.J., 2021. Discontinuation of immunosuppressive therapy in patients with neuromyelitis optica spectrum disorder with aquaporin-4 antibodies. Neurol. Neuroimmunol. Neuroinflamm. 8 (2).

Kimura, A., Kishimoto, T., 2010. IL-6: regulator of Treg/Th17 balance. Eur. J. Immunol. 40 (7), 1830–1835.

Kleiter, I., Gold, R., 2016. Present and future therapies in neuromyelitis optica spectrum disorders. Neurotherapeutics 13 (1), 70–83.

Kowarik, M.C., Soltys, J., Bennett, J.L., 2014. The treatment of neuromyelitis optica. J. Neuroophthalmol. 34 (1), 70–82.

Lennon, V.A., Wingerchuk, D.M., Kryzer, T.J., Pittock, S.J., Lucchinetti, C.F., Fujihara, K., Nakashima, I., Weinshenker, B.G., 2004. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. Lancet 364 (9451), 2106–2112.

Lin, J., Li, X., Xia, J., 2016. Th17 cells in neuromyelitis optica spectrum disorder: a review. Int. J. Neurosci. 126 (12), 1051–1060.

NIH, 2009. National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Oh, J., Levy, M., 2012. Neuromyelitis optica: an antibody-mediated disorder of the central nervous system. Neurol. Res. Int. 2012, 460825.

Papadopoulos, M.C., Bennett, J.L., Verkman, A.S., 2014. Treatment of neuromyelitis optica: state-of-the-art and emerging therapies. Nat. Rev. Neurol. 10 (9), 493–506.

Pittock, S.J., Berthele, A., Fujihara, K., Kim, H.J., Levy, M., Palace, J., Nakashima, I., Terzi, M., Totolyan, N., Viswanathan, S., Wang, K.C., Pace, A., Fujita, K.P., Armstrong, R., Wingerchuk, D.M., 2019. Eculizumab in aquaporin-4-positive neuromyelitis optica spectrum disorder. N. Engl. J. Med. 381 (7), 614–625.

Ringelstein, M., Ayzenberg, I., Lindenblatt, G., Fischer, K., Gahlen, A., Novi, G., Hayward-Könnecke, H., Schippling, S., Rommer, P.S., Kornek, B., Zrzavy, T., Biotti, D., Ciron, J., Audoin, B., Berthele, A., Giglhuber, K., Zephir, H., Kümpfel, T., Berger, R., Röther, J., Häußler, V., Stellmann, J.P., Whittam, D., Jacob, A., Kraemer, M., Gueguen, A., Deschamps, R., Bayas, A., Hümmert, M.W., Trebst, C., Haarmann, A., Jarius, S., Wildemann, B., Grothe, M., Siebert, N., Ruprecht, K., Paul, F., Collongues, N., Marignier, R., Levy, M., Karenfort, M., Deppe, M., Albrecht, P., Hellwig, K., Gold, R., Hartung, H.P., Meuth, S.G., Kleiter, I., Aktas, O., 2022. Interleukin-6 receptor blockade in treatment-refractory MOG-IgG-associated disease and neuromyelitis optica spectrum disorders. Neurol. Neuroimmunol. Neuroinflamm. 9 (1), e100.

Romano, C., Del Mastro, A., Sellitto, A., Solaro, E., Esposito, S., Cuomo, G., 2018. Tocilizumab reduces complement C3 and C4 serum levels in rheumatoid arthritis patients. Clin. Rheumatol. 37 (6), 1695–1700.

Selmaj, K., Selmaj, I., 2019. Novel emerging treatments for NMOSD. Neurol. Neurochir. Pol. 53 (5), 317–326.

Sepúlveda, M., Armangué, T., Sola-Valls, N., Arrambide, G., Meca-Lallana, J.E., Oreja-Guevara, C., Mendibe, M., Alvarez de Arcaya, A., Aladro, Y., Casanova, B., Olascoaga, J., Jiménez-Huete, A., Fernández-Fournier, M., Ramió-Torrentà, L., Cobo-Calvo, A., Viñals, M., de Andrés, C., Meca-Lallana, V., Cervelló, A., Calles, C., Rubio, M.B., Ramo-Tello, C., Caminero, A., Munteis, E., Antigüedad, A.R., Blanco, Y., Villoslada, P., Montalban, X., Graus, F., Saiz, A., 2016. Neuromyelitis optica spectrum disorders: comparison according to the phenotype and serostatus. Neurol. Neuroimmunol. Neuroinflamm. 3 (3), e225.

Smolen, J.S., Aletaha, D., 2011. Interleukin-6 receptor inhibition with tocilizumab and attainment of disease remission in rheumatoid arthritis: the role of acute-phase reactants. Arthritis Rheum. 63 (1), 43–52.

Takeshita, Y., Obermeier, B., Cotleur, A.C., Spampinato, S.F., Shimizu, F., Yamamoto, E., Sano, Y., Kryzer, T.J., Lennon, V.A., Kanda, T., Ransohoff, R.M., 2017. Effects of neuromyelitis optica-IgG at the blood-brain barrier in vitro. Neurol. Neuroimmunol. Neuroinflamm. 4 (1), e311.

Traboulsee, A., Greenberg, B.M., Bennett, J.L., Szczechowski, L., Fox, E., Shkrobot, S., Yamamura, T., Terada, Y., Kawata, Y., Wright, P., Gianella-Borradori, A., Garren, H., Weinshenker, B.G., 2020. Safety and efficacy of satralizumab monotherapy in neuromyelitis optica spectrum disorder: a randomised, double-blind, multicentre, placebo-controlled phase 3 trial. Lancet Neurol. 19 (5), 402–412.

Uzawa, A., Mori, M., Arai, K., Sato, Y., Hayakawa, S., Masuda, S., Taniguchi, J., Kuwabara, S., 2010. Cytokine and chemokine profiles in neuromyelitis optica: significance of interleukin-6. Mult. Scler. 16 (12), 1443–1452.

Wingerchuk, D.M., Banwell, B., Bennett, J.L., Cabre, P., Carroll, W., Chitnis, T., de Seze, J., Fujihara, K., Greenberg, B., Jacob, A., Jarius, S., Lana-Peixoto, M., Levy, M., Simon, J.H., Tenembaum, S., Traboulsee, A.L., Waters, P., Wellik, K.E., Weinshenker, B.G., 2015. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 85 (2), 177–189.

Wingerchuk, D.M., Lennon, V.A., Lucchinetti, C.F., Pittock, S.J., Weinshenker, B.G., 2007. The spectrum of neuromyelitis optica. Lancet Neurol. 6 (9), 805–815.

Wingerchuk, D.M., Lennon, V.A., Pittock, S.J., Lucchinetti, C.F., Weinshenker, B.G., 2006. Revised diagnostic criteria for neuromyelitis optica. Neurology 66 (10), 1485–1489.

Yamamura, T., 2022. Exploring steroid tapering in patients with neuromyelitis optica spectrum disorder treated with satralizumab in SAkuraSky: a case series. Mult. Scler. Relat. Disord. 61, 103772. https://doi.org/10.1016/j.msard.2022.103772.

Yamamura, T., Kleiter, I., Fujihara, K., Palace, J., Greenberg, B., Zakrzewska-Pniewska, B., Patti, F., Tsai, C.P., Saiz, A., Yamazaki, H., Kawata, Y., Wright, P., De Seze, J., 2019. Trial of satralizumab in neuromyelitis optica spectrum disorder. N. Engl. J. Med. 381 (22), 2114–2124.

Zhang, C., Zhang, M., Qiu, W., Ma, H., Zhang, X., Zhu, Z., Yang, C.S., Jia, D., Zhang, T.X., Yuan, M., Feng, Y., Yang, L., Lu, W., Yu, C., Bennett, J.L., Shi, F.D., 2020. Safety and efficacy of tocilizumab versus azathioprine in highly relapsing neuromyelitis optica spectrum disorder (TANGO): an open-label, multicentre, randomised, phase 2 trial. Lancet Neurol. 19 (5), 391–401.