Enspryng®

Satralizumab

Solution for injection

1. NAME OF THE MEDICINAL PRODUCT

Enspryng

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe (PFS) contains 120 mg of satralizumab in 1 mL.

Satralizumab is produced in Chinese hamster ovary cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

Colourless to slightly yellow liquid. The solution has a pH of approximately 6.0 and an osmolality of approximately 310 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Enspryng is indicated as a monotherapy or in combination with immunosuppressive therapy (IST) for the treatment of neuromyelitis optica spectrum disorders (NMOSD) in adult and adolescent patients from 12 years of age who are anti-aquaporin-4 IgG (AQP4-IgG) seropositive.

4.2 Posology and method of administration

Treatment should be initiated under the supervision of a physician experienced in the treatment of neuromyelitis optica (NMO) or NMOSD.

Posology

Enspryng can be used as a monotherapy or in combination with oral corticosteroids (OCs), azathioprine (AZA) or mycophenolate mofetil (MMF) (see section 5.1). The posology in adolescent patients ≥12 years of age with body weight ≥ 40 kg and adult patients is the same.

Loading doses

The recommended loading dose is 120 mg subcutaneous (SC) injection every two weeks for the first three administrations (first dose at week 0, second dose at week 2 and third dose at week 4).

Maintenance doses

The recommended maintenance dose is 120 mg SC injection every four weeks.

Duration of treatment

Enspryng is intended for long-term treatment.

Delayed or missed doses

If an injection is missed, for any reason other than increases in liver enzymes, it should be administered as described in table 1.

Table 1: Recommended dosage for delayed or missed doses

Last dose administered	**Recommended dosage for delayed or missed doses**
Missed a loading dose or less than 8 weeks during the maintenance period	The recommended dose should be administered as soon as possible without waiting until the next planned dose. Loading period If the second loading dose is delayed or missed, this dose should be administered as soon as possible and the third and final loading dose 2 weeks later. If the third loading dose is delayed or missed, this dose should be administered as soon as possible and the first maintenance dose 4 weeks later. Maintenance period After the delayed or missed dose is administered, the dosing schedule should be reset to every 4 weeks.
8 weeks to less than 12 weeks	The recommended dose should be administered at 0*, 2 weeks and every 4 weeks thereafter.
12 weeks or longer	The recommended dose should be administered at 0*, 2, 4 weeks and every 4 weeks thereafter.

* "0 weeks" refers to time of the first administration after the missed dose.

Dose modification advice for liver enzyme abnormalities

If the alanine aminotransferase (ALT) or aspartate transaminase (AST) elevation is >5 x upper limit of normal (ULN) and associated with any bilirubin elevation, treatment must be discontinued, and reinitiation is not recommended.

If the ALT or AST elevation is >5 x ULN and not associated with any bilirubin elevation, treatment should be discontinued. Treatment can be restarted at a dose of 120 mg SC injection every four weeks when the ALT and AST levels have returned to the normal range and based on assessment of benefit-

risk of treatment in the patient. If the decision is taken to restart treatment, liver parameters must be closely monitored, and if any subsequent increase in ALT/AST and/or bilirubin is observed, treatment must be discontinued, and reinitiation is not recommended (see sections 4.4 and 4.8).

Table 2: Recommended dose for restart of treatment after liver transaminase elevation

Last dose administered	**Recommended dose for restart of treatment**
Less than 12 weeks	Treatment should be restarted using the recommended dose, given every 4 weeks.
12 weeks or longer	Treatment should be restarted using the recommended dose, given at weeks 0*, 2, 4 and every 4 weeks thereafter.

* "0 weeks" refers to time of the first administration after the restart of treatment.

Dose modification advice for neutropenia

If the neutrophil count is below 1.0 x 10^9/L and confirmed by repeat testing, treatment should be interrupted until the neutrophil count is >1.0 x 10^9/L.

Dose modification advice for low platelet count

If the platelet count is below 75 x 10^9/L and confirmed by repeat testing, treatment should be interrupted until the platelet count is ≥75 x 10^9/L.

Special populations

Paediatric population

The posology in adolescent patients ≥12 years of age with body weight ≥ 40 kg and adult patients is the same (see sections 5.1 and 5.2). The safety and efficacy of satralizumab in children with body weight < 40 kg have not yet been established. No data are available.

Elderly

No dose adjustment is required in patients ≥65 years of age (see section 5.2).

Renal impairment

The safety and efficacy of satralizumab have not been formally studied in patients with renal impairment. No dose adjustment is recommended for patients with mild renal impairment (see section 5.2).

Hepatic impairment

The safety and efficacy of satralizumab have not been studied in patients with hepatic impairment. No data are available (see section 5.2).
Elevations of liver enzymes have been observed during treatment with satralizumab (see sections 4.4 and 4.8). For dose adjustment, see above section Dose modification advice for liver enzyme abnormalities.

Method of administration

Satralizumab 120 mg is administered by SC injection using a single-dose PFS. The total content (1 mL) of the PFS should be administered.

The recommended injection sites are the abdomen and thigh. Injection sites should be rotated and injections should never be given into moles, scars, or areas where the skin is tender, bruised, red, hard, or not intact.

Comprehensive instructions for the administration of satralizumab are given at the end of the package leaflet.

Administration by the patient and/or caregiver

The first injection must be performed under the supervision of a qualified Healthcare Professional (HCP).

After adequate training on how to prepare and perform the injection, an adult patient/caregiver may administer all other doses at home if the treating physician determines that it is appropriate and the adult patient/caregiver can perform the injection technique.

Patients/caregivers should seek immediate medical attention if the patient develops symptoms of serious allergic reactions and should check with their HCP to confirm whether treatment can be continued or not.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Infections

Administration of satralizumab should be delayed in patients with an active infection until the infection is controlled (see section 4.2).

Vigilance for the timely detection and diagnosis of infection is recommended for patients receiving treatment with satralizumab. Treatment should be delayed in case the patient develops any serious or opportunistic infection and appropriate therapy should be initiated under further monitoring. Patients should be instructed on seeking early medical attention in case of signs and symptoms of infections to facilitate timely diagnosis of infections. Patients should be provided with a patient alert card.

Vaccinations

Live and live-attenuated vaccines should not be given concurrently with satralizumab as clinical safety has not been established. The interval between live vaccinations and initiation of satralizumab treatment should be in accordance with current vaccination guidelines regarding immunomodulatory or immunosuppressive agents.

No data are available on the effects of vaccination in patients receiving satralizumab. It is recommended that all patients be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating satralizumab treatment.

Liver enzymes

Mild and moderate elevations of liver transaminases have been observed with satralizumab treatment, most elevations were below 5 x ULN (see section 4.8).

ALT and AST levels should be monitored every four weeks for the first three months of treatment, followed by every three months for one year, thereafter as clinically indicated.

Treatment with satralizumab should be discontinued in patients with ALT or AST >5 x ULN (see section 4.2).

Neutrophil count

Decreases in neutrophil counts have occurred following treatment with satralizumab (see section 4.8). Neutrophil counts should be monitored 4 to 8 weeks after start of treatment and thereafter as clinically indicated. For recommended dose interruption see section 4.2.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Population pharmacokinetic (PK) analyses did not detect any effect of azathioprine (AZA), oral corticosteroids (OCs) or mycophenolate mofetil (MMF) on the clearance of satralizumab.

Both *in vitro* and *in vivo* studies have shown that the expression of specific hepatic CYP450 enzymes (CYP1A2, CYP2C9, CYP2C19, and CYP3A4) is suppressed by cytokines such as IL-6.

Therefore caution should be exercised when starting or discontinuing satralizumab treatment in patients also receiving substrates of CYP450 3A4, 1A2, 2C9 or 2C19, particularly those with a narrow therapeutic index (such as warfarin, carbamazepine, phenytoin and theophylline), and doses adjusted if needed.

Given the prolonged terminal half-life of satralizumab, the effect of satralizumab may persist for several weeks after stopping treatment.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of satralizumab in pregnant women. Studies in monkeys do not indicate harmful effects with respect to reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of Enspryng during pregnancy.

Breast-feeding

It is unknown whether satralizumab is excreted in human breast milk. Human IgG is known to be excreted in breast milk during the first days after birth, which is decreasing to low concentrations soon afterwards; consequently, a risk to breast-fed infants cannot be excluded during this short period. Afterwards, use of Enspryng could be considered during breast-feeding only if clinically needed.

Fertility

No clinical data are available on the effect of satralizumab on human fertility. Animal studies showed no impairment of male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Enspryng has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions observed were: headache (19.2%), arthralgia (13.5%), white blood cell count decreased (13.5%), hyperlipidaemia (13.5%), and injection-related reactions (12.5%).

Tabulated list of adverse reactions

Table 3 summarises the adverse reactions that have been reported in association with the use of satralizumab as a monotherapy or in combination with IST in clinical trials.

Adverse reactions from clinical trials (Table 3) are listed by MedDRA system organ class. Adverse reactions are presented using number of adverse events per 100 patient years and by frequency figures. The corresponding frequency category for each adverse reaction is based on frequency figures and the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).

Table 3: Adverse reactions

System Organ Class	Frequency	
	Very common	**Common**
Blood and lymphatic system disorders		Hypofibrinogenaemia
Metabolism and nutrition disorders	Hyperlipidaemia	
Psychiatric disorders		Insomnia
Nervous system disorders	Headache	Migraine
Cardiac disorders		Bradycardia
Vascular disorders		Hypertension
Respiratory, thoracic and mediastinal disorders		Allergic rhinitis
Gastrointestinal disorders		Gastritis
Skin and subcutaneous tissue disorders		Rash, pruritus
Musculoskeletal and connective tissue disorders	Arthralgia	Musculoskeletal stiffness
General disorders and administration site conditions	Injection-related reactions	Peripheral oedema
Investigations	White blood cell count decreased	Neutrophil count decreased platelet count decreased, transaminases increased, blood bilirubin increased, weight increased

Description of selected adverse reactions

Injection-related reactions (IRRs)

IRRs reported in patients treated with satralizumab were predominantly mild to moderate, and most occurred within 24 hours after injections. The most commonly reported systemic symptoms were diarrhoea and headache. The most commonly reported local injection site reactions were flushing, erythema, pruritus, rash and pain.

Body weight

In the double-blinded treatment period, body weight increase ≥15% from baseline were observed in 3.8% of patients treated with satralizumab (monotherapy or in combination with IST) as compared with 2.7% of patients receiving placebo (or plus IST).

Laboratory abnormalities

Neutrophils
In the double-blinded treatment period, decreased neutrophils were observed in 31.7% of patients treated with satralizumab (monotherapy or in combination with IST) as compared with 21.6% of patients receiving placebo (or placebo plus IST). The majority of neutrophil decreases were transient or intermittent.
9.6% of patients receiving satralizumab had neutrophils below 1 x 10^9/L, compared with 5.4% receiving placebo (or placebo plus IST).

Platelets
In the double-blinded treatment period, decreases in platelet count (below 150 × 10^9/l) occurred in 24.0% of patients on satralizumab (monotherapy or in combination with IST) as compared with 9.5% of patients receiving placebo or placebo plus IST. The decreased platelet count was not associated with bleeding events.
The majority of the decreased platelets were transient and not below 75 × 10^9/l.

Liver enzymes
In the double-blinded treatment period, elevations in ALT or AST occurred in 27.9% and 18.3% of patients treated with satralizumab (monotherapy or in combination with IST) respectively, compared with 12.2% and 13.5% of patients receiving placebo or placebo plus IST. The majority of the elevations were below 3 x ULN, were transient and resolved without interruption of satralizumab.
Elevations in ALT or AST >3 x ULN occurred in 2.9% and 1.9% of patients treated with satralizumab (monotherapy or in combination with IST) respectively. These elevations were not associated with increases in total bilirubin.
Elevations of ALT above 5 x ULN were observed 4 weeks after initiation of therapy in one (1%) patient receiving satralizumab in combination with IST; normalising after discontinuation of treatment, and satralizumab was not reintroduced in this patient (see sections 4.2 and 4.4).

Lipid parameters

In the double-blinded treatment period, 10.6% of patients receiving satralizumab (monotherapy or in combination with IST) experienced elevations in total cholesterol above 7.75 mmol/l as compared with 1.4% of patients receiving placebo (or placebo plus IST); 20.2% of patients receiving satralizumab experienced elevations in triglycerides above 3.42 mmol/l as compared with 10.8% of patients receiving placebo.

Paediatric population

The safety and efficacy of satralizumab have been studied in 9 children ≥12 years of age. Frequency, type and severity of adverse reactions in children from 12 years of age are expected to be the same as in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the national regulation by using the form https://sideeffects.health.gov.il.

4.9 Overdose

In the event of an overdose, the patient should be closely supervised, treated symptomatically, and supportive measures instituted as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immunosuppressants, interleukin inhibitors, ATC code: L04AC19

Mechanism of action

Satralizumab is a recombinant humanised immunoglobuline G2 (IgG2) monoclonal antibody (mAb) that binds to soluble and membrane-bound human IL-6 receptor (IL-6R) and thereby prevents IL-6 downstream signalling through these receptors.

IL-6 levels are increased in cerebrospinal fluid and serum of patients with NMO and NMOSD during periods of disease activity. IL-6 functions have been implicated in the pathogenesis of NMO and NMOSD, including B-cell activation, differentiation of B-cells to plasmablasts and production of pathological autoantibodies, e.g. against AQP4, a water channel protein mainly expressed by astrocytes in the CNS, Th17-cell activation and differentiation, T-regulatory cell inhibition, and changes in blood-brain-barrier permeability.

Pharmacodynamic effects

In clinical studies with satralizumab in NMO and NMOSD, decreases in C-reactive protein (CRP), fibrinogen and complement (C3, C4 and CH50) were observed.

Clinical efficacy and safety

The efficacy and safety of satralizumab were evaluated in two pivotal phase III clinical trials in patients with NMOSD (diagnosed as AQP4-IgG seropositive or seronegative NMO [Wingerchuck 2006 criteria], or as AQP4-IgG seropositive NMOSD [Wingerchuk 2007 criteria]).
Study BN40898 included adult and adolescent NMOSD patients aged 12-74 years treated with stable IST, with at least 2 relapses in the last 2 years prior screening (with at least one relapse within the 12 months prior to screening) and expanded disability status scale (EDSS) of 0 to 6.5, whereas study BN40900 included adult patients aged 18-74 years on no background IST, with at least 1 relapse or first attack within the last 12 months prior to screening and EDSS of 0 to 6.5.
Both studies included approximately 30% AQP4-IgG seronegative NMO patients.

Efficacy in both studies was evaluated based on time to first relapse as adjudicated by an independent Clinical Endpoint Committee (CEC), with relapse defined by pre-specified worsening in the EDSS and functional system score (FSS) criteria, evaluated within 7 days after the patient reported symptoms (adjudicated relapse).

Study BN40898 (also known as SA-307JG or SAkuraSky)

Study BN40898 was a randomised, multicentre, double-blind, placebo-controlled clinical trial to evaluate the effect of satralizumab in combination with stable IST (OCs up to 15 mg/day [prednisolone equivalent], AZA up to 3 mg/kg/day or MMF up to 3000 mg/day, adolescents received a combination of AZA and OCs or MMF and OCs). The double blind period of the study included 83 AQP4-IgG seropositive and seronegative patients (76 adults and 7 adolescents). Patients received the first 3 single doses of satralizumab 120 mg or matching placebo by SC injection in the abdominal or femoral region every 2 weeks for the first 4 weeks and once every 4 weeks thereafter.
Study design and baseline characteristics of the study population are presented in table 4.

Table 4: Study design and baseline characteristics in AQP4-IgG seropositive patients for study BN40898

Study name	**Study BN40898 (AQP4-IgG seropositive: N=55; ITT*: N=83)**	
Study design		
Study population	Adolescent and adult patients with NMO or NMOSD, treated with stable IST Age 12-74 years, ≥ 2 relapses in the last 2 years prior screening (with at least one relapse in the 12 months prior to screening), EDSS of 0 to 6.5	
Study duration for efficacy evaluation	Event-driven** (26 adjudicated relapses) Median follow-up time: satralizumab 139.4 weeks, placebo 40.2 weeks (in ITT: 115.1 weeks and 42.5 weeks, respectively)	
Treatment groups, in 1:1 randomisation	Group A: satralizumab 120 mg SC Group B: placebo	
Baseline characteristics of AQP4-IgG seropositive patients	Satralizumab + IST (n=27)	Placebo + IST (n=28)
Diagnosis, n (%): NMO NMOSD	 19 (70.4) 8 (29.6)	 14 (50.0) 14 (50.0)
Mean age in years (SD) (Min-Max)	44.4 (15.7) (13 – 73)	43.4 (12.9) (14 – 65)
Elderly (≥65 years), n (%)	3 (11.1)	1 (3.6)
Adolescents (≥12 to <18 years), n (%)	1 (3.7)	2 (7.1)
Gender distribution, n (%) male/ n (%) female	 0 / 27 (100)	 0 / 28 (100)
Immunosuppressive therapy (IST), n (%): Oral corticosteroids (OCs) Azathioprine (AZA) Mycophenolate mofetil (MMF) AZA + OCs*** MMF + OCs***	 14 (51.9) 11 (40.7) 1 (3.7) 0 1 (3.7)	 13 (46.4) 11 (39.3) 3 (10.7) 0 1 (3.6)

* Intention-To-Treat (ITT)
** Patients treated with rescue therapy with no adjudicated relapse were allowed to enter the OLE period of the study and were censored from the primary efficacy analysis
*** Combination allowed for adolescent patients

Study BN40900 (also known as SA-309JG or SAkuraStar)

Study BN40900 was a randomised, multicentre, double-blind, placebo-controlled clinical trial to evaluate the effect of satralizumab monotherapy compared to placebo. The study included 95 AQP4-IgG seropositive and seronegative adult patients. Patients received the first 3 single doses of satralizumab 120 mg or matching placebo by SC injection in the abdominal or femoral region every 2 weeks for the first 4 weeks and once every 4 weeks thereafter.
Study design and baseline characteristics of the study population are presented in table 5.

Table 5: Study design and baseline characteristics in AQP4-IgG seropositive patients for study BN40900

Study name	**Study BN40900 (AQP4-IgG seropositive: N=64; ITT*: N=95)**	
Study design		
Study population	Adult patients with NMO or NMOSD Age 18-74 years, ≥ 1 relapse or first attack in the last 12 months prior to screening, EDSS of 0 to 6.5. Patients either received prior relapse prevention treatment for NMOSD or were treatment naïve	
Study duration for efficacy evaluation	Event-driven (44 adjudicated relapses, or 1.5 years after the date of randomisation of the last patient enrolled, whichever comes first) Median follow-up time: satralizumab 96.7 weeks, placebo 60.1 weeks(in ITT: 95.4 weeks and 60.5 weeks, respectively)	
Treatment groups, in 2:1 randomisation	Monotherapy: Group A: satralizumab 120 mg SC Group B: placebo	
Baseline characteristics of AQP4-IgG seropositive patients	Satralizumab (n=41)	Placebo (n=23)
Diagnosis, n (%): NMO NMOSD	 26 (63.4) 15 (36.6)	 15 (65.2) 8 (34.8)
Mean age in years (SD) (Min-Max)	46.0 (12.0) (22 – 70)	40.1 (11.5) (20 – 56)
Elderly (≥65 years), n (%)	1 (2.4)	0
Gender distribution, n (%) male/ n (%) female	 10 (24.4) / 31 (75.6)	 1 (4.3) / 22 (95.7)

* Intention-To-Treat (ITT)

Primary efficacy

In AQP4-IgG seropositive patients the relative risk of experiencing an adjudicated relapse in study BN40898 was reduced by 79% (Hazard Ratio, HR [95% CI]: 0.21 [0.06-0.75]), in study BN40900 by 74% (HR [95% CI]: 0.26 [0.11-0.63]) (see Figures 1 and 2). When data across studies BN40898 and BN40900 were pooled, treatment with satralizumab with or without IST led to an overall risk reduction of 75% (HR [95% CI]; 0.25 (0.12-0.50]) in AQP4-IgG seropositive patients. At 48 weeks, 85.7% of satralizumab-treated AQP4-IgG seropositive patients remained adjudicated relapse-free when used in combination with IST or as monotherapy compared to 58.7% in the placebo group. At 96 weeks, 81.4% of satralizumab-treated AQP4-IgG seropositive patients remained adjudicated relapse-free when used in combination with IST or as monotherapy compared to 47.2% in the placebo group. Efficacy was not significant in AQP4-IgG seronegative patients.

Figure 1: Study BN40898 - time to first adjudicated relapse during the double-blind period in AQP4-IgG seropositive patients

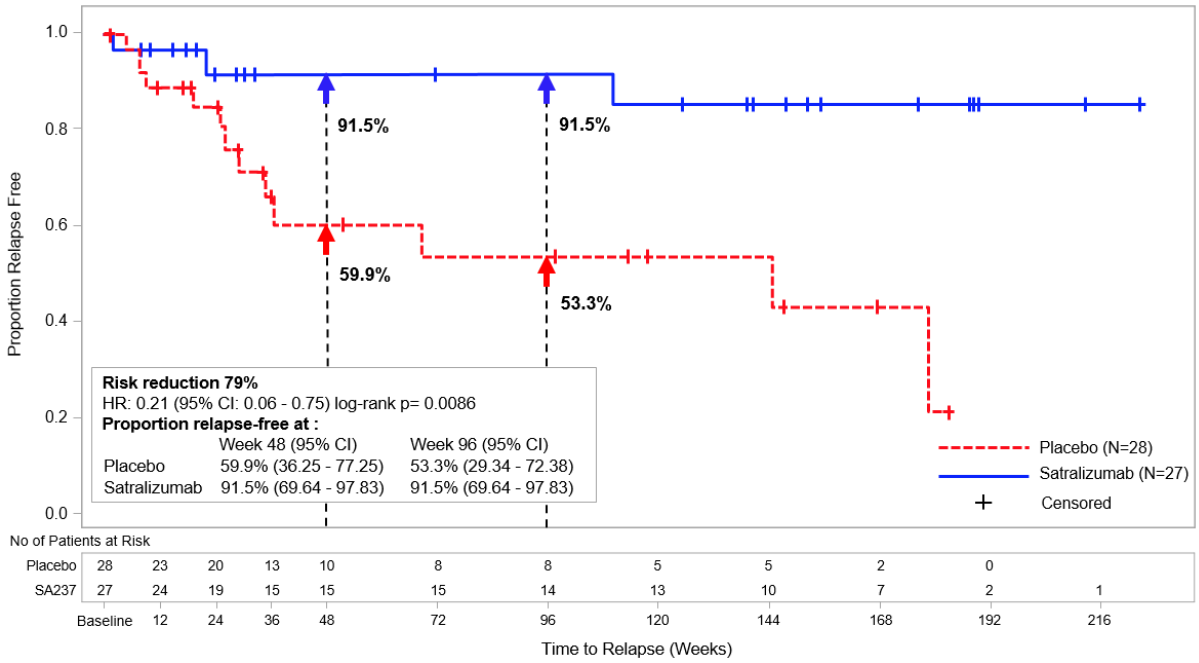
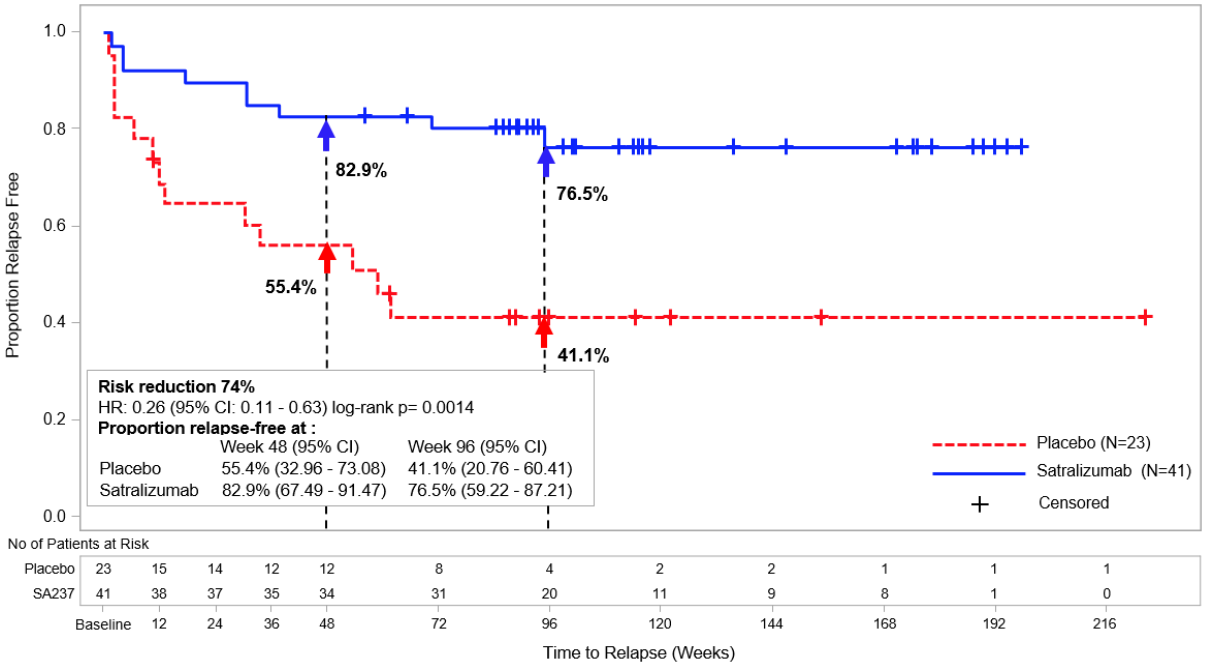


Figure 2: Study BN40900 - time to first adjudicated relapse during the double-blind period in AQP4-IgG seropositive patients



Treatment with satralizumab in AQP4-IgG seropositive patients reduced the annualized rate of adjudicated relapses (ARR) by 88% (rate ratio [RR]=0.122, 95% CI: 0.027 - 0.546; p=0.0039) in study BN40898 and 90% (RR=0.096, 95% CI: 0.020 - 0.473; p= 0.0086) in study BN40900 compared to treatment with placebo.

As compared to placebo-treated patients, the need for rescue therapy (e.g., corticosteroids, intravenous immunoglobulin, and/or apheresis [including plasmapheresis or plasma exchange]) was reduced in satralizumab-treated AQP4-IgG seropositive patients by 61% (odds ratio [OR]= 0.3930, 95% CI:

0.1343 -1.1502; p=0.0883) in study BN40898 and by 74% (OR = 0.2617, 95% CI: 0.0862 - 0.7943; p=0.0180) in study BN40900.

Treatment with satralizumab in AQP4-IgG seropositive patients reduced the risk of experiencing a severe relapse defined as an EDSS increase ≥ 2 points from the previous EDSS assessment by 85% (time to severe adjudicated relapse during the double blind period; HR=0.15, 95% CI: 0.02 -1.25; p=0.0441) in study BN40898 and by 79% (HR=0.21, 95% CI: 0.05 - 0.91; p=0.0231) in study BN40900 compared to treatment with placebo.

Key secondary endpoints

Change from baseline to week 24 in pain or fatigue were not met in studies BN40898 and BN40900.

Open-label extension

Analyses of longer term data including the OLE period (based on relapse treated with rescue therapy) showed that 58% and 73% of AQP4-IgG seropositive patients treated with satralizumab remained relapse-free after 120 weeks of treatment, when satralizumab was administered as add-on therapy or as monotherapy, respectively.

Immunogenicity

In phase III study BN40898 (in combination with IST) and in phase III study BN40900 (in monotherapy), anti-drug-antibodies (ADAs) were observed in 41% and 71% of patients receiving satralizumab in the double-blind period, respectively. The ability of ADAs to neutralise satralizumab binding is unknown.

Exposure was lower in ADA positive patients, however there was no impact of ADAs on safety and no clear impact on efficacy nor pharmacodynamic markers indicative of target engagement.

Treatment with satralizumab led to a similar reduction in the risk of experiencing an adjudicated relapse in patients in the phase III studies despite different ADA rates between those studies.

Paediatric population

In study BN40898, there were 7 adolescent patients enrolled during the double blind period. Their mean age was 15.4 years and the median body weight was 79.6 kg. The majority were female (n=6). Four patients were White, 2 were Black/African American, and 1 was Asian. Three (42.9%) adolescent patients were AQP4-IgG seropositive at screening (2 in the placebo group and 1 in the satralizumab group). During the double-blind period, 1 of 3 adolescents in the placebo group and 1 of 4 adolescents in the satralizumab group experienced an adjudicated relapse. Due to the small sample size, the hazard ratio for the primary endpoint of time to first adjudicated relapse in this subgroup was not calculated. Two additional adolescent patients were enrolled in the open-label period of the study.

5.2 Pharmacokinetic properties

The pharmacokinetics of satralizumab have been characterised both in Japanese and Caucasian healthy volunteers, and in NMO and NMOSD patients. The pharmacokinetics in NMO and NMOSD patients using the recommended dose were characterised using population PK analysis methods based on a database of 154 patients.

The concentration-time course of satralizumab in patients with NMO or NMOSD was accurately described by a two-compartment population PK model with parallel linear and target-mediated (Michaelis-Menten) elimination and first-order SC absorption. Satralizumab clearance and volume parameters allometrically scaled by body weight (through power function with the fixed power

coefficient of 0.75 and 1 for clearance and volume parameters, respectively). Bodyweight was shown to be a significant covariate, with clearance and Vc for patients weighing 123 kg (97.5th percentile of the weight distribution) increased by 71.3% and 105%, respectively, compared to a 60 kg patient.

Steady state pharmacokinetics were achieved after the loading period (8 weeks) for C_{min}, C_{max} and AUC as follows (mean (±SD): C_{min}: 19.7 (12.2) mcg/mL, C_{max}: 31.5 (14.9) mcg/mL and AUC: 737 (386) mcg. mL/day.

Absorption

The absorption rate constant of satralizumab was 0.0104/h equating to an absorption half-life of around 3 days (66 hours) at the recommended dose (see section 4.2). The bioavailability was high (85.4%).

Distribution

Satralizumab undergoes biphasic distribution. The central volume of distribution was 3.46 L, the peripheral volume of distribution was 2.07 L. The inter-compartmental clearance was 14 mL/h.

Biotransformation

The metabolism of satralizumab has not been directly studied, as monoclonal antibodies are principally cleared by catabolism.

Elimination

The total clearance of satralizumab is concentration-dependent. Linear clearance (accounting for approximately half of the total clearance at steady state using the recommended dose in NMO and NMOSD patients) is estimated to be 2.50 mL/h. The associated terminal $t_{1/2}$ is approximately 30 days (range 22-37 days) based on data pooled from the phase 3 studies.

Special populations

Population pharmacokinetic analyses in adult patients with NMO or NMOSD showed that age, gender, and race did not meaningfully influence the pharmacokinetics of satralizumab. Although body weight influenced the pharmacokinetics of satralizumab, no dose adjustments are recommended for any of these demographics.

Paediatric population

Data obtained in 8 adolescent patients [13-17 years of age] who received the adult dosing regimen show that population PK parameters for satralizumab are not significantly different from those in the adult population. Therefore, no dose adjustment is necessary.

Elderly

No dedicated studies have been conducted to investigate the PK of satralizumab in patients ≥65 years of age, however patients with NMO or NMOSD between 65 and 74 years of age were included in the BN40898 and BN40900 clinical studies.

Renal impairment

No formal study of the effect of renal impairment on the PK of satralizumab has been conducted. However, patients with mild renal impairment (creatinine clearance ≥50 mL/min and <80 mL/min) were included in the phase III studies. Based on population PK analysis there is no impact of renal impairment on the PK of satralizumab which is in line with the known mechanisms of clearance for satralizumab. Therefore no dose adjustment is required.

Hepatic impairment

No formal study of the effect of hepatic impairment on the PK of satralizumab has been conducted (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and toxicity to reproduction and development.

Carcinogenicity

No rodent carcinogenicity studies have been performed to establish the carcinogenic potential of satralizumab. Proliferative lesions have not been observed in a chronic cynomolgus monkey 6-month toxicity study.

Genotoxicity

No studies have been performed to establish the mutagenic potential of satralizumab. Antibodies are not expected to cause effects on DNA.

Reproductive toxicity

Prenatal treatment and postnatal exposure with satralizumab in pregnant monkeys and their offspring did not elicit any adverse effects on maternal animals, foetal development, pregnancy outcome or infant survival and development including learning ability.

The concentrations of satralizumab in breast milk were very low (<0.9% of the corresponding maternal plasma levels).

Fertility

No effects on male or female reproductive organs were seen with chronic treatment of satralizumab in monkeys.

Cytokine release syndrome

Based on *in vitro* studies with human blood, the risk of the release of pro-inflammatory cytokines with satralizumab is considered low in terms of incidence and increase in cytokines.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-Arginine
L-Histidine
Poloxamer 188
L-Aspartic Acid

Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze. Do not use the syringe if it has been frozen.
Always keep the syringe dry.

Keep the PFS in the outer carton in order to protect from light and moisture.

If unopened and kept in the outer carton, the syringe may be left out of the refrigerator below 30°C for a single period up to 8 days. After storage at room temperature the product should not be returned to the refrigerator and should be either used or discarded.

6.5 Nature and contents of container

1 mL solution in a PFS (polymer) with a staked-in, stainless steel needle, fitted with a chlorinated butyl rubber-polypropylene rigid needle shield and sealed with a chlorinated butyl rubber plunger stopper. The PFS is labelled and assembled with an automatic needle guard, plunger rod, and extended finger flanges (EFF).

Pack size of 1 PFS.

6.6 Special precautions for disposal and other handling

After removing the carton from the refrigerator, the sealed carton should be open and the PFS carefully lifted out of the carton by holding the barrel. It is important to let the PFS reach room temperature by waiting for 30 minutes before initiating the administration process.

The medicinal product should not be used if the liquid is cloudy, discoloured, has visible particles in it or if any part of the PFS appears to be damaged.

The injection must be performed right after removing the cap and no later than 5 minutes, to prevent the medicinal product from drying out and blocking the needle. If the pre-filled syringe is not used within 5 minutes of removing the cap, you must dispose of it in a puncture resistant container and use a new pre-filled syringe.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Roche Pharmaceuticals (Israel) Ltd., P.O. Box 6391, Hod Hasharon, 4524079

8. MARKETING AUTHORISATION NUMBER

169-11-36563-00

9. MANUFACTURER

F. Hoffmann-La Roche Ltd., Basel, Switzerland

Approved on February 2022