Summary Report of Benefit-Risk Assessment

ENSPRYNG SOLUTION FOR INJECTION IN PREFILLED SYRINGE 120MG/1ML

NEW DRUG APPLICATION

Active Ingredient(s)	Satralizumab
Product Registrant	Roche Singapore Pte Ltd
Product Registration Number	SIN16348P
Application Route	Abridged evaluation
Date of Approval	19 Oct 2021

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A INTRODUCTION

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 adolescents who are anti-aquaporin 4 (AQP4) seropositive.

The active substance, satralizumab is a humanised anti-interleukin-6 receptor (IL-6R) monoclonal antibody that inhibits IL-6-stimulated production of AQP4-IgG. AQP4-IgG binds to aquaporin-4 water channels in the astrocytes of the brain, spinal cord, and optic nerve resulting in demyelination, axonal damage and neurological symptoms characteristic of NMOSD.

Enspryng is available as a solution for injection in a pre-filled syringe containing 120 mg / ml of satralizumab. Other ingredients in the prefilled syringe are L-arginine, L-aspartic acid, L-histidine, poloxamer 188 and water for injection.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, satralizumab, is manufactured at Chugai Pharma Manufacturing Co., Ltd, Tokyo, Japan. The drug product, Enspryng Solution for Injection in Prefilled Syringe 120 mg/1 ml, is manufactured at Chugai Pharma Manufacturing Co., Ltd, Tochigi, Japan and assembled at F. Hoffmann-La Roche Ltd, Kaiseraugst, Switzerland.

Drug substance:
Adequate controls have been presented for the starting materials, intermediates and cell banks. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP). The process parameter ranges and the critical process parameters were established from site and scale-independent process validation studies, and these parameters were demonstrated to be appropriate based on process validation studies performed using qualified scale-down models.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities, including size and charged variants are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6B and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data presented for Chugai Pharma Manufacturing Co., Ltd was adequate to support the approved storage condition and shelf life. The packaging is 2 L ethylene vinyl acetate (EVA) single-use bags. The drug substance is approved for storage at -50ºC with a shelf life of 42 months.

Drug product:
The manufacturing process utilises aseptic processing.

All manufacturing sites involved are compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6B and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted was adequate to support the approved shelf-life of 24 months when stored between 2ºC-8ºC, protected from light. The container closure system is a 1 ml colourless polymer syringe 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.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of satralizumab as monotherapy or in combination with IST for the treatment of NMOSD in adult and adolescents who are AQP4 seropositive was based on two pivotal Phase 3 studies (Studies BN40898 and BN40900) conducted in patients with NMOSD or neuromyelitis optica (NMO). Both the studies had a double-blind phase followed by an open-label extension (OLE) phase. The efficacy was based on the double-blind phase in both the studies and the OLE phases are ongoing.

Study BN40898

Study BN40898 was a multicentre, double-blind, randomised (1:1), placebo-controlled study to assess the efficacy and safety of satralizumab as an add-on to baseline IST in adult and adolescent (12 to 17-year-old) patients. The satralizumab arm received a loading dose of 120mg subcutaneous (SC) injection every two weeks (Q2W) at Weeks 0, 2 and 4 followed by maintenance dose of 120mg SC injection every 4 weeks (Q4W).

The main inclusion criteria were patients diagnosed as having either NMO (optic neuritis AND acute myelitis AND at least two of three supportive criteria [Contiguous spinal cord lesion identified on an MRI scan extending over 3 vertebral segments, Brain MRI not meeting diagnostic criteria for Multiple Sclerosis, AQP4-IgG seropositive status]), or NMOSD with AQP4-IgG seropositive status with either idiopathic single or recurrent events of longitudinally extensive myelitis (≥3 vertebral segment spinal cord MRI lesion) or optic neuritis (single, recurrent or simultaneous bilateral). Enrolment of AQP4-IgG seronegative patients was capped at 30%. The included subjects had clinical evidence of at least 2 documented relapses in the last 2 years, with at least one of which occurred in the last 12 months. Patients with protocol defined relapse (PDR) as well as those who experienced a clinical relapse that required rescue therapy were allowed to enter the OLE phase of the study. A PDR was defined as a clinical relapse confirmed as PDR by the clinical endpoint committee (CEC). Only those PDRs for which the Expanded Disability Status Scale (EDSS)/ Functional Systems Score (FSS) assessment was performed within seven days after the patient reported symptoms to the site were included in the primary analysis.

For a clinical relapse to be considered a PDR, new or worsening neurological symptoms attributable to NMO or NMOSD were required to persist for >24 hours and were not attributable to confounding clinical factors; reoccurrence of symptoms within 31 days was considered part of the same relapse. The reported date of onset of the first relapse was the 'onset date' for the analysis. The neurologic symptoms had to meet either of the following:
1. An increase of at least 1.0 point on the EDSS score, or a 2.0 point increase if the baseline EDSS was zero
2. An increase of at least 2.0 points on one of the appropriate FSS
3. An increase of at least 1.0 point on two or more of the appropriate FSS if the baseline score was one or more
4. An increase of at least 1.0 point in single eye FSS when the baseline score in that eye was one or more.

The basis of comparison for the increase was the score at the most recent EDSS/FSS assessment visit. An "appropriate FSS" change was one which affected at least one of the following functional systems: pyramidal, cerebellar, brainstem, sensory, bowel/bladder or visual (single eye). Sexual dysfunction and cerebral function did not suffice to establish a protocol-defined relapse.

The primary efficacy endpoint was the time to first central CEC adjudicated PDR during the double-blind period. Statistical hypotheses for treatment comparisons were tested at the 5% significance level using a two-sided log-rank test. The key secondary endpoints were the change from baseline at Week 24 in the Visual Analogue Scale (VAS) score for pain and in the Functional Assessment of Chronic Illness Therapy (FACIT) fatigue score. Other secondary endpoints included the change in EDSS and the change in the Modified Rankin Scale (mRS) from baseline at Week 24.

A total of 83 patients (41 in satralizumab arm and 42 in placebo arm) were randomised, of which 55 (66.3%) were AQP4-IgG seropositive. There were 76 adults and 7 adolescents enrolled in the study. The mean age of the adults was 42.1 years old, and the majority was females (92.8%). The mean age of the 7 adolescent patients was 15.4 (range: 13-17) years old. Baseline demographic and disease characteristics of the patients were generally balanced across the treatment groups. The adult patients were on stable doses of oral corticosteroids (OC), azathioprine (AZA), or mycophenolate mofetil (MMF), while the adolescent patients received a combination of AZA and OCs or MMF and OCs as baseline IST.

The clinical cut-off date (CCOD) for the primary analysis was the onset of the 26th required PDR. At Week 24, the results met the primary endpoint with satralizumab demonstrating a statistically significant reduction in the risk of PDR compared to placebo by 62% (HR of 0.38 [95% CI: 0.16, 0.88], p=0.0184). In adolescents,1 subject each had PDR in the satralizumab group (n=4) and the placebo group (n=3) respectively. The remaining two subjects in the placebo group had a clinical relapse. Sensitivity analyses of time to investigator assessed PDR was not statistically significant (HR of 0.48 [95% CI: 0.23, 1.00], p=0.05). Nevertheless, the HR was below 1 suggesting a numerical benefit favouring satralizumab arm. In AQP4-IgG-positive patients, satralizumab treatment was associated with a clinically meaningful and statistically significant reduction in the risk of PDR by 79% (HR of 0.21 [95% CI 0.06, 0.75], p=0.0086) while no statistically significant difference was observed in AQP4-IgG-negative patients.

No difference between satralizumab and placebo was observed for the secondary endpoints with respect to pain and fatigue at week 24 (difference in adjusted means for VAS and FACIT scores were 6.376 [p=0.0602] and -2.089 [p=0.1224]), as well as disability outcome measures based on mRS score and EDSS score.

Study BN40900

Study BN40900 was a multicentre, double-blind, randomised (2:1), placebo-controlled study to assess the efficacy and safety of satralizumab as monotherapy in adult patients. The dosing regimen of satralizumab was the same as Study BN40898. The key inclusion criteria were similar to Study BN40898 except that Study BN40900 included subjects with clinical evidence of at least 1 documented relapse in the last 12 months. In addition, only patients who experienced a PDR during the double-blind period or completed the double-blind period were eligible for entering the OLE phase.

A total of 95 patients (63 in satralizumab group and 32 in placebo group) were enrolled, of which 64 (67.4%) were AQP4-IgG seropositive. The mean age of the patients was 43.7 years old. The majority of patients were females, with a lower proportion in the satralizumab group (73%) compared to placebo group (97%). The other baseline demographic and disease characteristics of the patients were generally balanced across the treatment groups except for the mean bodyweight, which was higher in the satralizumab group (78.9 kg) compared to the placebo group (70.5 kg).

The CCOD was 1.5 years after the last patient was enrolled. At week 24, the results met the primary endpoint with satralizumab demonstrating a statistically significant reduction in the risk of PDR compared to placebo by 55% (HR of 0.45 [95% CI: 0.23, 0.89], p=0.0184). Sensitivity analyses of time to investigator's assessed PDR was not statistically significant (HR of 0.52 [95% CI: 0.27,1.00], p=0.05). In AQP4-IgG-positive patients, satralizumab treatment was associated with a clinically meaningful and statistically significant reduction in the risk of PDR by 74% (HR 0.26 [95% CI: 0.11, 0.63], p=0.0014), while no statistically significant differences were observed in AQP4-IgG-negative patients.

No difference between satralizumab and placebo was observed for the secondary endpoints with respect to pain and fatigue at week 24 (difference in adjusted means for VAS and FACIT scores were 3.215 [p=0.4436] and 2.107 [p=0.1824]), as well as disability outcome measures based on mRS score and EDSS score.

Data from the two pivotal studies were pooled in a supportive analysis which demonstrated that satralizumab treatment reduced the risk of PDR by 58% (HR 0.42 [95% CI: 0.25, 0.71], p=0.0008). Exploratory post-hoc analyses suggested that there was a lower proportion of patients who experienced a severe relapse in the satralizumab group (18.5%) compared to the placebo group (35.3%). Body weight was shown to be a negative prognostic factor, but it did not seem to have an impact on treatment effect as higher weight patients benefited from treatment as much as lower weight patients. No clear impact of anti-drug antibodies (ADAs) was observed on efficacy in the studies.

Time to First Protocol Defined Relapse during the Double-blind Period in Studies BN40898 and BN40900

	Study BN40898		**Study BN40900**		**Pooled (Studies BN40898 and BN40900)**	
	Placebo	SAT	Placebo	SAT	Placebo	SAT
Overall population	n = 42	n = 41	n = 32	n = 63	n = 74	n = 104
Patients with an event	18 (42.9%)	8 (19.5%)	16 (50.0%)	19 (30.2%)	34 (45.9%)	27 (26.0%)
Hazard ratio (95% CI)	0.38 (0.16, 0.88)		0.45 (0.23, 0.89)		0.42 (0.25, 0.71)	
p value (log-rank)	0.0184		0.0184		0.0008	
AQP4-IgG positive	n=28	n=27	n=23	n=41	n=51	n=68
Patients with an event	12 (42.9%)	3 (11.1%)	13 (56.5%)	9 (22.0%)	25 (49.0%)	12 (17.6%)
Hazard ratio (95% CI)	0.21(0.06, 0.75)		0.26 (0.11, 0.63)		0.25 (0.12, 0.50)	

p value (log-rank)	0.0086		0.0014		<0.0001	
AQP4-IgG negative	n=14	n=14	n=9	n=22	n=23	n=36
Patients with an event	6 (42.9%)	5 (35.7%)	3 (33.3%)	10 (45.5%)	9 (39.1%)	15 (41.7%)
Hazard ratio (95% CI)	0.66 (0.20, 2.23)		1.19 (0.30, 4.78)		0.97 (0.41, 2.33)	
p value (log-rank)	0.5047		0.8036		0.9540	

Overall, satralizumab demonstrated substantial improvement in CEC adjudicated PDR and showed a clear benefit for the subgroup of patients with AQP4 seropositive NMOSD. There was no clinical benefit observed in AQP4 seronegative NMOSD subjects. While Study BN40898 included only few adolescents (n=7), based on the consideration that the clinical presentation and underlying pathophysiology of the disease are similar between adults and adolescents, the treatment effect of the therapy based on the IL-6 blockade mechanism of action is expected to be the same between adults and adolescents. In addition, pharmacokinetic data has shown that satralizumab exposures were comparable between adults and adolescents. Taken together, extrapolation of efficacy from adult to adolescent patients ≥12 years of age with body weight ≥ 40 kg was considered acceptable.

D ASSESSMENT OF CLINICAL SAFETY

The safety of satralizumab was based on a total of 145 satralizumab treated patients with 328 patient-years of exposure (mean duration: 114 weeks), and 90 NMO and NMOSD patients followed for more than 96 weeks in Studies BN40898 and BN40900. In both the studies the combined patient years of safety observation in the double-blind period were longer for patients in the satralizumab group than the placebo group (Study BN40898 satralizumab group: 78.52PY, PLB group: 59.50PY; Study BN40900 satralizumab group 115.21PY, PLB group 40.59PY).

Summary of Safety Findings during the Double-blind Period in Studies BN40898 and BN40900

	Study BN40898 (add-on to ISTs)						**Study BN40900 (monotherapy study)**					
	Placebo (N=42, PY=59.50)			SAT(N=41, PY=78.52)			Placebo (N=32, PY=40.59)			SAT (N=63, PY=115.21)		
	No. of events	Events/ 100PY (95% CI)	No. of patients (%)	No. of events	Events/ 100PY (95% CI)	No. of patients (%)	No. of events	Events/ 100PY (95% CI)	No. of patients (%)	No. of events	Events/ 100PY (95% CI)	No. of patients (%)
All events	306	514.25 (458.24, 575.21)	40 (95.2)	381	485.22 (437,71, 536.47)	37 (90.2)	201	495.18 (429.09, 568.57)	24 (75.0)	546	473.90 (434.98, 515.37)	58 (92.1)
Number of patients withdrawn from study due to an AE	-	-	5 (11.9)	-	-	3 (7.3)	-	-	1 (3.1)	-	-	1 (1.6)
Fatal AE	0	0.00 (NE, 6.20)	0	0	0.00 (NE, 4.70)	0	0	0.00 (NE, 9.09)	0	0	0.00 (NE, 3.20)	0
Serious AE	12	20.17 (10.42, 35.23)	9 (21.4)	9	11.46 (5.24, 21.76)	12 (17.1)	6	14.78 (5.42, 32.17)	5 (15.6)	20	17.36 (10.60, 26.81)	12 (19.0)
Related AEs	82	137.80 (109.60, 171.05)	20 (47.6)	59	75.14 (57.20, 96.92)	17 (41.5)	45	110.86 (80.86, 148.34)	11 (34.4)	102	88.53 (72.19, 107.47)	22 (34.9)
Severe AE	7	11.76 (4.73, 24.24)	5 (11.9)	5	6.37 (2.07, 14.86)	5 (12.2)	4	9.85 (2.68, 25.23)	2 (6.3)	37	32.11 (22.61, 44.27)	17 (27)
Infection AE	89	149.57 (120.12, 184.06)	26 (61.9)	104	132.45 (108.22, 160.48)	28 (68.3)	66	162.60 (125.75, 206.86)	14 (43.8)	115	99.81 (82.41, 119.81)	34 (54)
Serious Infectious AE	3	5.04 (1.04, 14.73)	3 (7.1)	2	2.55 (0.31, 9.20)	2 (4.9)	4	9.85 (2.68, 25.23)	3 (9.4)	6	5.21 (1.91, 11.33)	6 (9.5)
Injection Related Reactions	2	3.36 (0.41, 12.14)	2 (4.8)	17	21.65 (12.61, 34.66)	5 (12.2)	7	17.25 (6.93, 35.53)	5 (15.6)	16	13.89 (7.94, 22.55)	9 (14.3)

The overall incidences of AEs per 100PY were comparable between the treatment groups (PLB: 506.51 events/100PY and satralizumab: 478.49 events/100PY) and were similar across the studies. Most AEs were mild to moderate in intensity. In the Study BN40898, the rate of Grade 3 or 4 AEs was lower in the satralizumab group (6.37 events/100PY) compared to the placebo group (11.76 events/100PY); while in the monotherapy study BN40900, the rate was higher in the satralizumab group (32.11 events/100PY) compared to the placebo group (9.85 events/100PY). In both studies, the most commonly reported AEs were infections in both satralizumab (113.04 events/100PY) and placebo (154.85 events/100PY) groups. Other AEs which were of higher incidences in satralizumab group compared to placebo were headache (18.07 events/100PY vs 10.99 events/100PY), injection-related reactions (IRRs, 17.03 events/100PY vs 8.99 events/100PY), and arthralgia (7.23 events/100PY vs 1 event/100PY). Decreased fibrinogen, a known effect of satralizumab, was more common in satralizumab group (71.2% vs 20.3% in placebo group) and of moderate severity. There were no bleeding events reported in the patients who had low fibrinogen in the studies.

The rate of serious AEs (SAEs) in Study BN40898 was lower in the satralizumab group (11.46 events/100PY) compared to placebo group (20.17 events/100PY), while it was similar between the two groups in Study BN40900 (17.36 events/100PY vs 14.78 events/100PY). In both the studies, the most commonly reported SAEs were infections which occurred at a lower incidence in satralizumab group (4.13 events/100PY) compared to the placebo group (6.99 events/100PY). There were no deaths reported in both the studies.

Infections and IRRs are selected events in the studies, elevated liver enzymes in combination with either an elevated bilirubin or clinical jaundice were identified as adverse events of special interest (AESIs). The rate of infections per 100PY in the satralizumab group was lower than in the placebo group in both studies, especially in the monotherapy Study BN40900. The incidence of urinary tract infections was lower in satralizumab group (22.71 events/100PY) compared to the placebo group (31.97 events/100PY). The rates of upper respiratory tract infection were similar across treatment groups (23.74 events/100PY vs 25.98 events/100PY). The rates of serious infections were below 2 events/100PY for all predefined baskets in both treatment groups except urinary tract infections, which were reported at a higher rate in the placebo group (4.00 event/100PY) compared to satralizumab group (1.55 events/100PY). Majority of infections (75.3%) resolved within 14 days, while 9.3% resolved in > 28 days.

The rate of IRRs was higher in the satralizumab group compared to the placebo group in the add-on study BN40898 but were similar between the treatment and placebo groups in the monotherapy study BN40900. Symptom associated with systemic IRRs were headache, nausea, diarrhoea, vertigo, and single event of chills, hypertension, pyrexia, micturition urgency, vision blurred, and diastolic hypotension. Most IRR events were mild to moderate in intensity. A total of 3 Grade 3 or 4 events were reported in 2 patients treated with satralizumab (2 events of vertigo in 1 patient and 1 event of hypertension in 1 patient). No IRRs were considered as SAE and none led to interruption or discontinuation of study drug. All events resolved, except 1 mild systemic IRR of vision blurred which was ongoing at the time of CCOD. There were no anaphylactic reactions reported in the satralizumab group in either study. Similar rates of IRRs occurred during the ADA-negative period compared to the ADA-positive period, suggesting a lack of relationship between the presence of ADAs and risk of IRRs.

Elevations in ALT and AST occurred in 27.9% and 18.3% of patients in the satralizumab group respectively, compared with 12.2% and 13.5% in the placebo group. Majority of the elevations were below 3x ULN, transient and resolved with ongoing treatment. Elevations in ALT and AST >3x ULN occurred in 2.9% and 1.9% of patients in the satralizumab group and normalised with

either ongoing treatment or discontinuation. There were 10.6% and 20.2% of patients in the satralizumab group that experienced elevations in total cholesterol (>7.75 mmol/L) and triglycerides (>3.42 mmol/L) respectively, compared with 1.4% and 10.8% of patients in the placebo group. The elevations in lipid parameters did not require dose interruption.

Overall, satralizumab was generally well-tolerated. The safety profile in the two studies was similar, indicating no marked increased risk associated with the concomitant use of ISTs. Safety information and warnings on the potential risks associated with satralizumab including infections, hypersensitivity and liver enzyme elevations have been included in the label.

E ASSESSMENT OF BENEFIT-RISK PROFILE

NMOSD and NMO are inflammatory disorders of the CNS associated with severe, immune-mediated demyelination and axonal damage, which predominantly target the spinal cord and optic nerve, and present as neurological disability over time. A full recovery from NMOSD relapses is rare. In this regard, preventing and reducing the frequency of relapses remain the mainstay of clinical management for patients with NMOSD, which typically rely on the use of immunosuppressants such as high dose corticosteroids. Given the role of IL-6 in the immune-pathogenesis of NMO and NMOSD, targeting IL-6 signalling presents a therapeutic strategy for the treatment of NMO and NMOSD.

Both the pivotal studies BN40898 and BN40900 showed that treatment with satralizumab statistically significantly reduced the frequency of relapses compared to placebo by 62% (HR of 0.38 [95% CI: 0.16, 0.88], p=0.0184]) and 55% (HR of 0.45 [95% CI: 0.23, 0.89], p=0.0184) respectively. The results were further supported by the high efficacy observed in the subgroup of AQP4-IgG seropositive patients with risk reductions of 79% (HR [95% CI]: 0.21 [0.058-0.750], p=0.0086) and 74% (HR [95% CI]: 0.26 [0.108-0.627], p=0.0014) respectively.

Satralizumab was generally well-tolerated in the clinical studies and the safety profile was consistent with the known safety profile of the anti-IL-6 receptor antagonist drug class. The AESIs included infections, IRRs and elevated liver enzymes which are adequately addressed in the local package insert with relevant warnings and precautions. The incidences of SAEs were generally higher in the placebo group compared to the satralizumab group. No deaths were reported in the pivotal studies. Overall, the AEs were considered manageable. The warning and precautions include infections, elevated liver enzymes, and decreased neutrophil count; recommendations for monitoring these adverse events (or laboratory parameter changes) and for dosing during such events are adequately addressed in the local package insert.

Taken together, the benefits of Enspryng outweighed the risks associated with the treatment as a monotherapy or in combination with IST for the treatment of NMOSD in adult and adolescents who are AQP4 seropositive.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Enspryng for use as monotherapy or in combination with IST for the treatment of NMOSD in adult and adolescents who are anti-aquaporin 4 seropositive was deemed favourable and approval of the product registration was granted on 19 October 2021.

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ENSPRYNG®

Satralizumab

1. DESCRIPTION

1.1 THERAPEUTIC / PHARMACOLOGIC CLASS OF DRUG

Enspryng is a recombinant humanized immunoglobulin G2 (IgG2) monoclonal antibody against the human interleukin-6 receptor (IL-6R), produced in Chinese hamster ovary cells by recombinant DNA technology (including a pH-dependent binding technology).
ATC code: L04AC19

1.2 TYPE OF DOSAGE FORM

Ready-to-use sterile solution for subcutaneous (SC) injection in a single-dose, prefilled syringe (PFS) with needle safety device (NSD).

1.3 ROUTE OF ADMINISTRATION

Subcutaneous (SC) injection

1.4 STERILE / RADIOACTIVE STATEMENT

Sterile product

1.5 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: satralizumab
Excipients: L-histidine, L-aspartic acid, L-arginine, poloxamer 188 and water for injection
Enspryng solution for SC injection is a colorless to slightly yellow liquid supplied in a PFS filled with 1 mL of solution. Each PFS contains 120 mg of satralizumab.

2. CLINICAL PARTICULARS

2.1 THERAPEUTIC INDICATION(S)

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 adolescents who are anti-aquaporin 4 (AQP4) seropositive.

2.2 DOSAGE AND ADMINISTRATION

General
Substitution by any other biological medicinal product requires the consent of the prescribing physician.

The safety and efficacy of alternating or switching between Enspryng and products that are biosimilar but not deemed interchangeable have not been established. Therefore, the benefit-risk of alternating or switching needs to be carefully considered.

In order to prevent medication errors, it is important to check the prefilled syringe label to ensure that the drug being administered is Enspryng.

Recommended Dosage
Enspryng must be administered as a subcutaneous injection.

Advise patients to consult with their healthcare professional (HCP) if they suspect an active infection (including localized infections) before administration or the next dose of Enspryng. In case of active infection, delay use of Enspryng until the infection is controlled (see section 2.4 Warnings and Precautions).

Enspryng can be used as a monotherapy or in combination with either oral corticosteroids (OCs), azathioprine (AZA) or mycophenolate mofetil (MMF) (*see section 3.1.2 Clinical / Efficacy Studies*). Please also refer to the full prescribing information for these products.

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

Maintenance Dose
The recommended maintenance dose is 120 mg SC injection every 4 weeks.

Method of administration
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 Enspryng are given in the Instructions for Use (IFU)

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 Enspryng 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 with Enspryng can be continued or not.

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
Less than 8 weeks during the maintenance period or missed a loading dose	Administer 120 mg by subcutaneous injection as soon as possible, and do not wait until the next planned dose. Maintenance period After the delayed or missed dose is administered, reset the dose schedule to every 4 weeks. Loading period If the second loading dose is delayed or missed, administer as soon as possible and administer the third and final loading dose 2 weeks later. If the third loading dose is delayed or missed, administer as soon as possible and administer the 1st maintenance dose 4 weeks later.
8 weeks to less than 12 weeks	120 mg by subcutaneous injection at 0* and 2 weeks, followed by 120 mg every 4 weeks.
12 weeks or longer	120 mg by subcutaneous injection at 0*, 2, and 4 weeks followed by 120 mg every 4 weeks.

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

Dose Modifications
Liver Enzyme Abnormalities
If the alanine aminotransferase (ALT) or aspartate transaminase (AST) elevation is >5x Upper Limit of Normal (ULN) and associated with any bilirubin elevation, treatment with Enspryng must be discontinued, and reinitiation is not recommended.

If the ALT or AST elevation is >5x ULN and not associated with any bilirubin elevation, treatment with Enspryng should be discontinued; it can be restarted (120 mg SC injection every 4 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, the liver parameters must be closely monitored, and if any subsequent increase in ALT/AST and/or bilirubin is observed the drug must be discontinued, and reinitiation is not recommended.

Table 2 Recommended Dosage for Restart of Treatment After Liver Transaminase Elevation

Last Dose Administered	Recommended Dosage for Restart of Treatment
Less than 12 weeks	Restart at a dosage of 120 mg by subcutaneous injection every 4 weeks.
12 weeks or longer	Restart at a dose of 120 mg by subcutaneous injection at Weeks 0*, 2, and 4, followed by a dosage of 120 mg every 4 weeks.

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

Neutropenia
If the neutrophil count is below 1.0 x10^9/L and confirmed by repeat testing, Enspryng should be interrupted until the neutrophil count is > 1.0 x10^9/L.

2.2.1 Special Dosage Instructions

Pediatric use
The posology in adolescent patients ≥12 years of age with body weight ≥ 40 kg and adult patients is the same. The safety and efficacy of Enspryng in pediatric population <12 years of age have not been studied (*see section 2.5.4 Pediatric Use*).

Geriatric use
No dose adjustment is required in patients ≥65 years of age (*see sections 2.5.5 Geriatric Use and 3.2.5 Pharmacokinetics in special populations*).

Renal Impairment
The safety and efficacy of Enspryng have not been formally studied in patients with renal impairment; however a dose adjustment is not expected to be required for patients with renal impairment (*see sections 2.5.6 Renal Impairment and 3.2.5 Pharmacokinetics in special populations*).

Hepatic Impairment
The safety and efficacy of Enspryng have not been studied in patients with hepatic impairment (*see sections 2.5.7 Hepatic Impairment and 3.2.5 Pharmacokinetics in special populations*).

Other Special Patient Populations
Not applicable

2.3 CONTRAINDICATIONS

Enspryng is contraindicated in patients with a known hypersensitivity to satralizumab or any of the excipients.

2.4 WARNINGS AND PRECAUTIONS

2.4.1 General

In order to improve traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

Infections
Delay Enspryng administration in patients with an active infection until the infection is controlled (*see section 2.2 Dosage and Administration, Delayed and Missed Doses*).

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.

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

No data are available on the effects of vaccination in patients receiving Enspryng. It is recommended that all patients be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating Enspryng therapy.

Liver enzymes
Mild and moderate elevations of liver transaminases have been observed with Enspryng treatment, most elevations were below 5x ULN and not treatment-limiting and resolved while Enspryng was given.

ALT and AST levels should be monitored every 4 weeks for the first 3 months of treatment, followed by every 3 months for 1 year, thereafter as clinically indicated. For treatment discontinuation recommendations please refer to section 2.2 Dosage and Administration, Dose Modifications.

Neutrophil count
Decreases in neutrophil counts have occurred following treatment with Enspryng (*see section 2.6.1 Clinical Trials*).

Neutrophil counts should be monitored 4 to 8 weeks after start of therapy and thereafter as clinically indicated. For recommended dose interruption see section 2.1 Therapeutic Indications.

2.4.2 Drug Abuse and Dependence

No studies on drug abuse and dependence have been conducted. However, there is no evidence from the available data that Enspryng treatment results in dependence.

2.4.3 Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed. However, there is no evidence from the available data that Enspryng treatment affects the ability to drive and use machines.

2.5 USE IN SPECIAL POPULATIONS

2.5.1 Females and Males of Reproductive Potential

Fertility
No clinical data are available on the effect of Enspryng on human fertility. Animal studies showed no impairment of male or female fertility (*see section 3.3.3 Impairment of Fertility*).

2.5.2 Pregnancy

There are no data from the use of Enspryng in pregnant women.

Studies in monkeys do not indicate harmful effects with respect to reproductive toxicity (*see section 3.3.4 Reproductive toxicity*).

Enspryng is not recommended during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus.

2.5.3 Lactation

It is unknown whether Enspryng is excreted in human breast milk or absorbed systemically after ingestion. However, because IgGs are excreted in human milk and there is preclinical evidence of excretion in milk (*see section 3.3.4 Reproductive toxicity*), a decision should be made whether to discontinue breastfeeding or to discontinue Enspryng therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the mother.

2.5.4 Pediatric Use

The safety and efficacy of Enspryng have been studied in a limited number of adolescent patients ≥12 years of age with body weight ≥ 40 kg (n=8). Pharmacokinetic, efficacy and safety results were consistent with those in adults (*see sections 3.1.2 Clinical/ Efficacy Studies and 3.2.5 Pharmacokinetics in Special Populations*).

The safety and efficacy of Enspryng in pediatric patients <12 years of age has not yet been studied (*see section 2.2.1 Special Dosage Instructions*).

2.5.5 Geriatric Use

The safety and efficacy of Enspryng have been studied in a limited number of geriatric patients up to 74 years of age (n=4 aged 65-74). Although there were no apparent age-related differences observed in studies, the number of patients aged 65 and over is not sufficient to determine whether they respond similarly to younger patients (*see sections 2.2.1 Special Dosage Instructions and 3.2.5 Pharmacokinetics in special populations*).

The safety and efficacy of Enspryng in geriatric patients >74 years of age have not been studied (*see section 2.2.1 Special Dosage Instructions*).

2.5.6 Renal Impairment

The safety and efficacy of Enspryng in patients with renal impairment have not been formally studied, but given that Enspryng is a monoclonal antibody and cleared via catabolism (rather than renal excretion), a dose adjustment is not expected to be required for patients with renal impairment. Patients with mild renal impairment were included in clinical trials, the pharmacokinetics of satralizumab in these patients was not impacted (*see sections 2.2.1 Special Dosage Instructions and 3.2.5 Pharmacokinetics in Special Populations*).

2.5.7 Hepatic Impairment

The safety and efficacy of Enspryng in patients with hepatic impairment have not been studied (*see sections 2.2.1 Special Dosage Instructions and 3.2.5 Pharmacokinetics in Special Populations*).

2.6 UNDESIRABLE EFFECTS

2.6.1 Clinical Trials

Summary of the safety profile
The safety of Enspryng as monotherapy or in combination with IST was evaluated based on data from two phase III randomized, multicenter, double-blind, placebo-controlled clinical trials (BN40900 and BN40898), which include 63 patients exposed to Enspryng monotherapy and 41 patients exposed to Enspryng in combination with IST (*see section 3.1.2 Clinical / Efficacy Studies*). In the double-blind controlled period, patient median exposure to satralizumab was approximately 2 years in both studies BN40900 and BN40898 each. The median exposure to placebo was approximately 1 year.

The most frequently reported adverse drug reactions (ADRs) were headache, arthralgia and injection related reactions.

Tabulated summary of adverse drug reactions from clinical trials
Table 3 summarizes the ADRs that have been reported in association with the use of Enspryng as monotherapy or in combination with IST in clinical trials. Patients in the Enspryng groups in both clinical studies had longer treatment period than those in the placebo (or placebo in combination with IST) groups, ADRs were evaluated during 194 patient-years (PY) in the Enspryng groups and 100 PY in the placebo groups. ADRs from clinical trials (Table 3) are listed by MedDRA system organ class. The corresponding frequency category for each adverse drug reaction is based on 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 <1/1000), very rare (<1/10,000).

Table 3 Summary of ADRs occurring in patients treated with Enspryng as monotherapy or in combination with immunosuppressive therapy in clinical trials

ADR	BN40898 (in combination with IST)				BN40900 (monotherapy)			
	Number of Patients n (%)		Rate of AE /100PY		Number of Patients n (%)		Rate of AE/100PY	
	Placebo n=42	ENSPRYNG n=41	Placebo (PY= 59.5)	ENSPRYNG (PY=78.5)	Placebo n=32	ENSPRYNG n=63	Placebo (PY= 40.6)	ENSPRYNG (PY=115.21)
Blood and lymphatic system disorders								
Hypofibrinogenemia	0	1 (2.4%)	0	1.3	0	2 (3.2%)	0	1.7
General disorders and administration site conditions								
Peripheral Edema	0	1 (2.4%)	0	1.3	0	4 (6.3%)	0	3.5
Injury, poisoning and procedural complications								
Injection-Related Reactions	2 (4.8%)	5 (12.2%)	3.4	21.7	5 (15.6%)	8 (12.7%)	17.3	13.9
Investigations								
White blood cell count decreased	4 (9.5%)	7 (17.1%)	21.85	14.01	0	7 (11.1%)	0	9.55
Blood bilirubin increased	0	1 (2.4%)	0	11.46	0	1 (1.6%)	0	0.87
Musculoskeletal and connective tissue disorders								
Arthralgia	0	4 (9.8%)	0	5.1	1 (3.1%)	10 (15.9%)	2.5	8.7
Musculoskeletal stiffness	0	1 (2.4%)	0	1.3	0	4 (6.3%)	0	3.5
Nervous system disorders								
Headache	4 (9.5%)	10 (24.4%)	10.1	28.0	4 (12.5%)	10 (15.9%)	12.3	11.3
Migraine	0	0	0	0	0	4 (6.3%)	0	3.5
Psychiatric disorders								
Insomnia	0	1 (2.4%)	0	1.3	1 (3.1%)	5 (7.9%)	2.5	4.3
Respiratory, thoracic and mediastinal disorders								
Rhinitis allergic	0	2 (4.9%)	0	2.6	0	2 (3.2%)	0	1.7
Skin and subcutaneous tissue disorders								
Rash	2 (4.8%)	0	3.4	0	1 (3.1%)	9 (14.3%)	4.9	12.2
Pruritus	1 (2.4%)	0	1.7	0	0	6 (9.5%)	0	6.9

ADRs=Adverse Drug Reactions
IST=Immunosuppressive Therapy
AE=Adverse Events
PY= Patient Years

Description of selected adverse drug reactions from clinical trials
Injection-Related Reactions (IRRs)
IRRs reported in patients treated with Enspryng as monotherapy or in combination with IST were predominantly mild to moderate, most occurred within 24 hours after injection. The most commonly reported systemic symptoms were diarrhea and headache. The most commonly reported local injection site reactions were flushing, erythema, pruritus, rash and pain. None of the injection related reactions required dose interruption or discontinuation.

Infections
In the Enspryng monotherapy study, the rate of infections was lower in patients treated with Enspryng [99.8 events/100 PY (95% CI: 82.4, 119.8)] compared with patients receiving placebo [162.6 events/100 PY (95% CI: 125.8, 206.9)]. The rate of serious infections was 5.2 events/100 PY (95% CI: 1.9, 11.3) in patients treated with Enspryng compared with 9.9 events/100 PY (95% CI: 2.7, 25.2) in patients receiving placebo.

In patients treated with Enspryng in combination with IST, the rate of infections was 132.5 events/100 PY (95% CI: 108.2, 160.5) compared with 149.6 events/100 PY (95% CI: 120.1, 184.1) in patients receiving placebo in combination with IST; the rate of serious infections was 2.6 events/100 PY (95% CI: 0.3, 9.2) compared with 5.0 events/100 PY (95% CI: 1.0, 14.7) in patients receiving placebo in combination with IST.

Body weight increase

In the double-blinded treatment period, body weight increase ≥ 15% from baseline were observed in 3.8% of patients treated with Ensprynq (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 Ensprynq (monotherapy or in combination with IST) as compared with 21.6% of patients receiving placebo (or plus IST). The majority of neutrophil decreases were transient or intermittent.

Of the patients in the Ensprynq group, 9.6% had neutrophils below 1 x 10^9/L as compared with 5.4% in placebo or placebo plus IST, which was not temporally associated with any serious infections.

Platelets

In the double-blinded treatment period, decreases in platelet counts occurred in 24.0% of patients on Ensprynq (monotherapy or in combination with IST) as compared with 9.5% of patients receiving placebo or placebo plus IST. The decreased platelet counts were not associated with bleeding events.

The majority of the decreased platelets were transient and not below 75 × 10^9/L. None of the patients had a decrease in platelet count to ≤ 50 × 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 Ensprynq (monotherapy or as 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 3x ULN, were transient, and resolved without interruption of Ensprynq.

Elevations in ALT or AST >3x ULN occurred in 2.9% and 1.9% of patients treated with Ensprynq (monotherapy or in combination with IST) respectively, which were not associated with increases in total bilirubin. Elevations of ALT above 5x ULN were observed 4 weeks after initiation of therapy in one patient receiving Ensprynq in combination with IST, normalizing after discontinuation of Ensprynq.

Lipid parameters

In the double-blinded treatment period, 10.6% of patients receiving Ensprynq (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 plus IST; 20.2% of patients receiving Ensprynq experienced elevations in triglycerides above 3.42 mmol/L as compared with 10.8% of patients receiving placebo. The elevations in lipid parameters did not require dose interruption.

Fibrinogen

Decreased fibrinogen is a known effect of ENSPRYNG related to its mechanism of action. In the double-blinded treatment period of clinical trials, 71.2% of ENSPRYNG-treated patients and 20.3% of patients receiving placebo had downward shifts from baseline fibrinogen levels. There were no bleeding events among patients with decreased fibrinogen levels.

Complement Factors

Decreases in C3, C4, and CH50 are known effects of ENSPRYNG related to its mechanism of action. In the double-blinded treatment period of clinical trials, decreases in C3, C4 and CH50 occurred in 66.7%, 56.9% and 89.6% of ENSPRYNG-treated patients, respectively, compared with that in 18.2%, 4.1% and 44.4% of patients receiving placebo.

2.6.2 Postmarketing Experience

Not applicable

2.7 OVERDOSE

There is no experience with overdose in patients with neuromyelitis optica (NMO) or NMOSD. A single dose of up to 240 mg Ensprynq was administered subcutaneously to healthy adult volunteers in a phase I study and no serious or severe adverse events were observed in the study.

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

2.8 INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

No formal drug-drug interaction studies have been performed with Ensprynq.

Population pharmacokinetic (PK) analyses did not detect any effect of AZA, corticosteroids or MMF on the clearance of Ensprynq.

The potential for treatment with Ensprynq to reduce exposure to concomitant medications metabolized by CYP450 isozymes via blockade of IL-6 signalling has been explored using physiologically based pharmacokinetic (PBPK) modelling approaches.

Since the expression of specific hepatic CYP450 enzymes (CYP1A2, CYP2C9, CYP2C19, and CYP3A4) is suppressed by cytokines such as IL-6 in vitro and in vivo, caution should be exercised when starting or discontinuing Ensprynq 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 & theophylline), and doses adjusted if needed.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 PHARMACODYNAMIC PROPERTIES

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

3.1.1 Mechanism of Action

Satralizumab is a humanized IgG2 monoclonal antibody (mAb) that binds to soluble and membrane-bound human IL-6 receptor (IL-6R), and thereby prevents IL-6 downstream signaling through these receptors.

IL-6 is a pleiotropic cytokine produced by a variety of cell types and is involved in diverse inflammatory processes including B-cell activation, differentiation of B-cells to plasmablasts and production of autoantibodies, Th17-cell activation and differentiation, T-regulatory cell inhibition, and changes in blood-brain-barrier permeability. IL-6 levels are increased in cerebrospinal fluid and serum of patients with NMO and NMOSD during periods of disease activity. Some IL-6 functions have been implicated in the pathogenesis of NMO and NMOSD, including production of pathological autoantibodies against Aquaporin-4 (AQP4), a water channel protein mainly expressed by astrocytes in the CNS.

3.1.2 Clinical / Efficacy Studies

The efficacy and safety of Ensprynq were evaluated in two pivotal phase III clinical trials (BN40898 and BN40900) in patients with a diagnosis of AQP4-IgG seropositive or seronegative NMO (Wingerchuck 2006 criteria), or with a diagnosis of AQP4-IgG seropositive NMOSD (Wingerchuk 2007 criteria). In retrospect, these patients also met the latest criteria proposed by the international panel for NMO diagnosis (Wingerchuk et al 2015). The effect of Ensprynq was studied in adult (studies BN40898 and BN40900) and adolescent (aged ≥12 to <18 years) patients (study BN40898). The inclusion of AQP4-IgG seronegative adult NMO patients was limited to approximately 30% in both studies in order for the study population to reflect the real-world NMO patient population.

The primary efficacy measure in both studies was protocol-defined relapses (PDR) based on a pre-specified worsening in the Expanded Disability Status Scale (EDSS) and Functional System Scores (FSS) and confirmed by an independent Clinical Endpoint Committee (CEC). The primary endpoint analysis was time to first CEC-confirmed PDR with EDSS/FSS assessment performed within 7 days after symptoms were reported by the patient (adjudicated relapse).

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

Study BN40898 was a randomized, multicenter, double-blind, placebo-controlled clinical trial to evaluate the effect of Ensprynq 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 study included 83 AQP4-IgG seropositive and seronegative patients (including 7 adolescents). Patients received the first 3 single doses of Ensprynq 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.

The study was event-driven and the double-blind study period for efficacy evaluation ended when a total of 26 adjudicated relapses were observed. Patients who experienced a CEC-confirmed PDR or received rescue therapy for a relapse during the double-blind (DB) period or completed the DB period could enter the open-label extension period (OLE) where all patients received open-label treatment with Ensprynq.

Table 4 Study Design and Baseline Characteristics for Study BN40898

Study Name	Study BN40898 (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 CEC confirmed protocol-defined relapses)* *Median follow-up time: Ensprynq 115.1 weeks, placebo 42.5 weeks*	
Treatment groups, in 1:1 randomization	Group A: Ensprynq 120 mg SC Group B: placebo	
Baseline characteristics	Ensprynq +IST (n=41)	Placebo +IST (n=42)
Diagnosis, n (%): NMO NMOSD	 33 (80.5) 8 (19.5)	 28 (66.7) 14 (33.3)
AQP4-IgG seropositive status, n (%)	27 (65.9)	28 (66.7)
Mean Age in years (SD) (Min-Max)	40.8 (16.1) (13 – 73)	43.4 (12.0) (14 – 65)
Adolescents (≥12 to <18 years), n (%)	4 (9.8)	3 (7.1)
Gender distribution, n (%) male/ n (%) female	4 (9.8) / 37 (90.2)	2 (4.8) / 40 (95.2)
Immunosuppressive therapy (IST), n (%): Oral corticosteroids (OCs) Azathioprine (AZA) Mycophenolate mofetil (MMF) AZA + OCs* MMF + OCs*	 17 (41.5) 16 (39.0) 4 (9.8) 3 (7.3) 1 (2.4)	 20 (47.6) 13 (31.0) 8 (19.0) 0 1 (2.4)

* Combination allowed for adolescent patients

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

Study BN40900 was a randomized, multicenter, double-blind, placebo-controlled clinical trial to evaluate the effect of Ensprynq monotherapy compared to placebo. The study included 95 AQP4-IgG seropositive and seronegative adult patients. Patients received the first 3 single doses of Ensprynq 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.

The double-blind study period for efficacy evaluation ended 1.5 years after the date of randomization of the last enrolled patient. Patients who experienced a CEC-confirmed PDR during the DB period or completed the DB period could enter the OLE period where all patients received open-label treatment with Ensprynq.

Table 5 Study Design and Baseline Characteristics for Study BN40900

Study Name	Study BN40900 (N=95)	
Study design		
Study population	Adult patients with NMO or NMOSD *Age 18-74 years, ≥1 relapse or first attack in 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 CEC confirmed protocol-defined relapses, or 1.5 years after the date of randomization of the last enrolled patient, whichever comes first)* *Median follow-up time: Ensprynq 95.4 weeks, placebo 60.5 weeks*	
Treatment groups, in 2:1 randomization	Monotherapy: Group A: Ensprynq 120 mg SC Group B: placebo	
Baseline characteristics	Ensprynq (n=63)	Placebo (n=32)
Diagnosis, n (%): NMO NMOSD	 47 (74.6) 16 (25.4)	 24 (75.0) 8 (25.0)
AQP4-IgG seropositive status, n (%)	41 (65.1)	23 (71.9)
Mean Age in years (SD) (Min-Max)	45.3 (12.0) (21 – 70)	40.5 (10.5) (20 – 56)
Gender distribution, n (%) male/ n (%) female	17 (27.0) / 46 (73.0)	1 (3.1) / 31 (96.9)

Primary Efficacy – Double-Blind Period

Treatment with Ensprynq resulted in a statistically significant 62% reduction in the risk of experiencing an adjudicated relapse (Hazard ratio [HR] [95% CI]: 0.38 [0.16-0.88]; p [log rank]=0.0184) when administered in combination with stable IST (Study BN40898) and 55% reduction in the risk of adjudicated relapse (HR [95% CI]: 0.45 [0.23-0.89]; p [log rank]=0.0184) when used as monotherapy (Study BN40900) when compared to placebo. At 48 weeks, 88.9% and 76.1% of Ensprynq-treated patients remained adjudicated relapse-free when used in combination with IST or as monotherapy, respectively. At 96 weeks 77.6% and 72.1% of Ensprynq-treated patients remained adjudicated relapse-free when used in combination with IST or as monotherapy, respectively. When data from the two studies were pooled, Ensprynq treatment resulted in a 58% reduction in risk of adjudicated relapse compared to placebo (HR [95% CI]: 0.42 [0.25-0.71]; p [log rank]=0.0008) (see Table 6, Figure 1, Figure 2).

The strongest subgroup effect was observed in AQP4-IgG seropositive patients. In AQP4-IgG seropositive patients the relative risk of experiencing an adjudicated relapse in Study BN40898 was reduced by 79% (HR [95% CI]: 0.21 [0.06-0.75]), in Study BN40900 by 74% (HR [95% CI]: 0.26 [0.11-0.63]). At 48 weeks, 91.5% and 82.9% of Ensprynq-treated AQP4-IgG seropositive patients remained adjudicated relapse-free when used in combination with IST or as monotherapy, respectively. At 96 weeks 91.5% and 76.5% of Ensprynq-treated AQP4-IgG seropositive patients remained adjudicated relapse-free when used in combination with IST or as monotherapy, respectively. When data across studies BN40898 and BN40900 were pooled, treatment with Ensprynq 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 (see Table 6, Figure 3, Figure 4). No significant differences in the time to first adjudicated relapse in AQP4-IgG seronegative patients between those patients receiving Ensprynq with or without IST and those receiving placebo with or without IST were observed (BN40898 and BN40900 pooled: HR [95% CI]: 0.97 [0.41-2.33]).

Table 6 Key Efficacy Endpoints from Study BN40898 and BN40900

	BN40898		BN40900	
	Ensprynq + IST	Placebo + IST	Ensprynq	Placebo
	(n=41)	(n=42)	(n=63)	(n=32)
Primary Endpoint				
Risk Reduction (Individual Studies)	62% (HR: 0.38; 95% CI: 0.16, 0.88; p=0.0184)		55% (HR:0.45; 95% CI: 0.23, 0.89; p=0.0184)	
Risk Reduction (Pooled Analysis)	58% (HR: 0.42 ;95% CI: 0.25, 0.71; p=0.0008)			
Proportion of adjudicated relapse-free patients at 48 weeks	88.9% (95% CI: 72.81, 95.70)	66.0% (95% CI: 47.65, 79.25)	76.1% (95% CI: 63.55, 84.86)	61.9% (95% CI: 42.66, 76.26)
Proportion of adjudicated relapse-free patients at 96 weeks	77.6% (95% CI: 58.08, 88.82)	58.7% (95% CI: 39.85, 73.43)	72.1% (95% CI: 58.91, 81.75)	51.2% (95% CI: 32.36, 67.23)
Subgroup Analysis of Primary Endpoint (AQP4-IgG seropositive patients)				
Number of AQP4-IgG seropositive patients (n)	27	28	41	23
Risk Reduction (Individual Studies)	79% (HR: 0.21; 95% CI: 0.06, 0.75; p= 0.0086)		74% (HR: 0.26; 95% CI: 0.11, 0.63; p=0.0014)	
Risk Reduction (Pooled Analysis)	75% (HR: 0.25; 95% CI: 0.12, 0.50; p: <0.0001)			
Proportion of adjudicated relapse-free patients at 48 weeks	91.5% (95% CI: 69.64, 97.83)	59.9% (95% CI: 36.25, 77.25)	82.9% (95% CI: 67.49, 91.47)	55.4% (95% CI: 32.96, 73.08)
Proportion of adjudicated relapse-free patients at 96 weeks	91.5% (95% CI: 69.64, 97.83)	53.3% (95% CI: 29.34, 72.38)	76.5% (95% CI: 59.22, 87.21)	41.1% (95% CI: 20.76, 60.41)

Figure 1 Study BN40898:Time to First Adjudicated Relapse during the Double-blind Period (ITT Population)

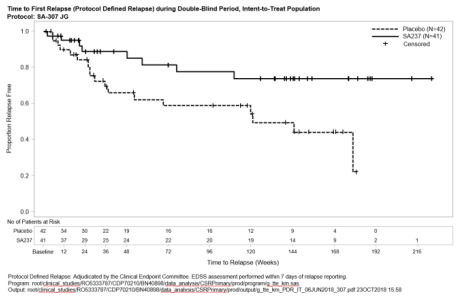


Figure 2 Study BN40900: Time to First Adjudicated Relapse during the Double-blind Period (ITT Population)

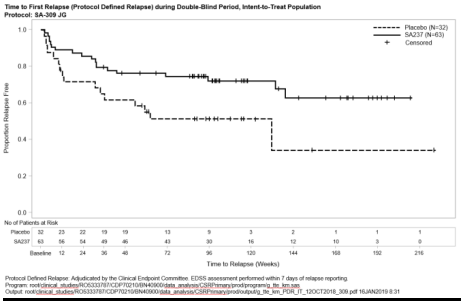


Figure 3 Study BN40898: Time to First Adjudicated Relapse during the Double-blind Period in AQP4-IgG seropositive Patients

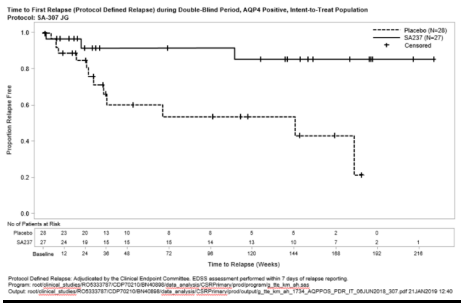
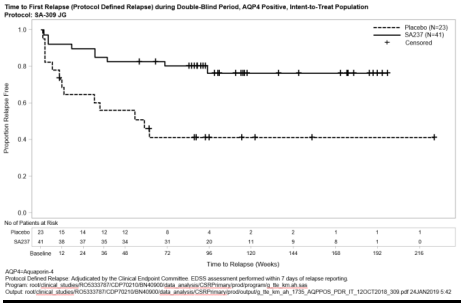


Figure 4 Study BN40900: Time to First Adjudicated Relapse during the Double-blind Period in AQP4-IgG seropositive Patients



Treatment with Ensprynq reduced the annualized rate of adjudicated relapses (ARR) by 74% in Study BN40898 and 73% in Study BN40900 compared to treatment with placebo (Table 7). The relative reduction in ARR in the AQP4-IgG seropositive subgroup was 88% and 90% in Studies BN40898 and BN40900 respectively.

Table 7 Annualized Adjudicated Relapse Rate during the Double-Blind Period Using Negative Binomial Regression Model

	BN40898		BN40900		Pooled	
	Placebo	Ensprynq	Placebo	Ensprynq	Placebo	Ensprynq
ITT	N = 42	N = 41	N = 32	N = 63	N = 74	N = 104

	BN40898		BN40900		Pooled	
	Placebo	Enspryng	Placebo	Enspryng	Placebo	Enspryng
Number of patients with relapse	18	8	16	19	34	27
Adjusted annualized relapse rate	0.538	0.141	2.005	0.551	1.090	0.294
Relative ARR reduction (Rate ratio)	74% (RR: 0.261, 95% CI: 0.087,0.787; p=0.0175)		73% (RR: 0.275; (95% CI: 0.071,1.069; p=0.0668)		73% (RR: 0.270; 95% CI: 0.112,0.653; p=0.0050)	
Subgroup: AQP4-IgG Seropositive	**N = 28**	**N = 27**	**N = 23**	**N = 41**	**N = 51**	**N = 68**
Number of patients with relapse	12	3	13	9	25	12
Adjusted annualized relapse rate	0.520	0.063	2.853	0.275	1.339	0.136
Relative ARR reduction (Rate ratio)	88% (RR: 0.122, 95% CI: 0.027,0.546; p=0.0039)		90% (RR: 0.096, 95% CI: 0.020,0.473; p= 0.0086)		90% (RR: 0.102; 95% CI: 0.034,0.301; p=0.0002)	

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 Enspryng-treated patients by 51% in Study BN40898 and by 55% in Study BN40900 (ITT population). In the AQP4-IgG seropositive subgroup, ENSPRYNG treatment reduced the need for rescue therapy by 61% and 74% in Studies BN40898 and BN40900 respectively (Table 8).

Table 8 Use of Rescue Therapy in Patients with any Relapse during the Double-Blind Period

	BN40898		BN40900		Pooled	
	Placebo	Enspryng	Placebo	Enspryng	Placebo	Enspryng
ITT	**N = 42**	**N = 41**	**N = 32**	**N = 63**	**N = 74**	**N = 104**
Patients with rescue therapy	26 (61.90%)	18 (43.90%)	17 (53.13%)	21 (33.33%)	43 (58.11%)	39 (37.50%)
Risk reduction (Odds Ratio)	51% (OR: 0.4915; 95% CI: 0.2065, 1.1698, p=0.1084)		55% (OR: 0.4509; 95% CI: 0.1916, 1.0612; p=0.0682)		54% (OR:0.4649; 95% CI: 0.2517, 0.8589; p=0.0145)	
Subgroup: AQP4-IgG seropositive	**N = 28**	**N = 27**	**N = 23**	**N = 41**	**N = 51**	**N = 68**
Patients with rescue therapy	18 (64.29%)	11 (40.74%)	14 (60.87%)	13 (31.71%)	32 (62.75%)	24 (35.29%)
Risk Reduction (Odds Ratio)	61% (OR: 0.3930; 95% CI: 0.1343, 1.1502; p=0.0883)		74% (OR:0.2617; 95% CI: 0.0862, 0.7943; p=0.0180)		66% (OR:0.3430; 95% CI: 0.1614, 0.7289; p=0.0054)	

Treatment with Enspryng reduced the risk of experiencing a severe relapse defined as an EDSS increase ≥ 2 points from the previous EDSS assessment by 84% in study BN40898 and by 74% in study BN40900 compared to treatment with placebo (Table 9). The relative reduction in severe relapses in AQP4-IgG seropositive patients was 85% and 79% in studies BN40898 and BN40900, respectively.

Table 9 Time to First Severe Adjudicated Relapse during the Double-Blind Period

	BN40898		BN40900		Pooled	
	Placebo	Enspryng	Placebo	Enspryng	Placebo	Enspryng
ITT	**N=41**	**N=41**	**N=32**	**N=63**	**N=73**	**N=104**
Patients with an event	6 (14.6%)	1 (2.4%)	6 (18.8%)	4 (6.3%)	12 (16.4%)	5 (4.8%)
Risk reduction	84% (HR: 0.16; 95% CI : 0.02, 1.33; p=0.0522)		74% (HR: 0.26; 95% CI:0.07, 0.93, p=0.0265)		79% (HR: 0.21, 95% CI: 0.07, 0.61, p=0.0018)	
Subgroup: AQP4-IgG seropositive	**N=27**	**N=27**	**N=23**	**N=41**	**N=50**	**N=68**
Patients with an event	6 (22.2%)	1 (3.7%)	5 (21.7%)	3 (7.3%)	11 (22.0%)	4 (5.9%)
Risk reduction	85% (HR: 0.15; 95% CI: 0.02, 1.25; p=0.0441)		79% (HR: 0.21; 95% CI: 0.05, 0.91; p=0.0231)		82% (HR: 0.18; 95% CI: 0.06, 0.58; p=0.0015)	

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 57% and 71% of patients treated with Enspryng remained relapse-free after 120 weeks of treatment, when Enspryng was administered as add-on therapy or as monotherapy, respectively.

In the AQP4-IgG seropositive population, 58% and 73% of patients remained relapse free after 120 weeks of treatment with Enspryng administered as add-on therapy or as monotherapy, respectively.

Figure 5 Study BN40898: Time to First Relapse (Treated Clinical Relapse) during Double-Blind and Open-Label Period

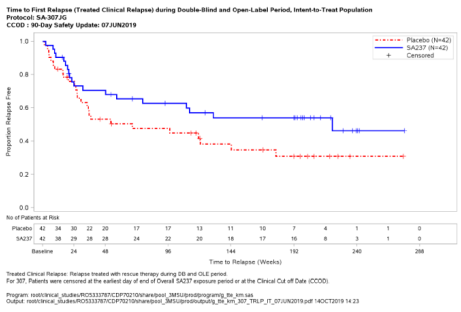


Figure 6 Study BN40900: Time to First Relapse (Treated Clinical Relapse) during Double-Blind and Open-Label Period

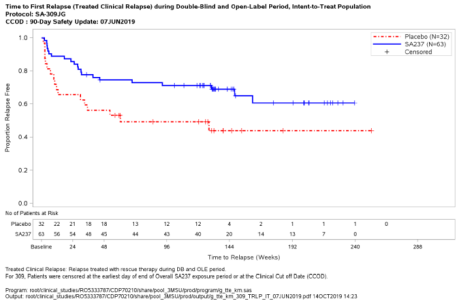


Figure 7 Study BN40898: Time to First Relapse (Treated Clinical Relapse) during Double-Blind and Open-Label Period in AQP4-IgG seropositive Patients

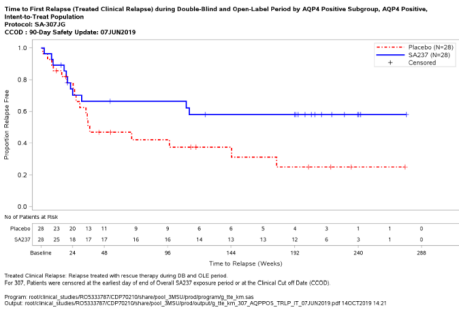
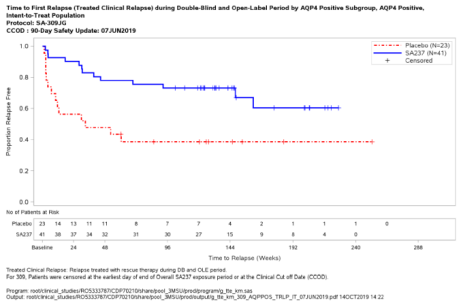


Figure 8 Study BN40900: Time to First Relapse (Treated Clinical Relapse) during Double-Blind and Open-Label Period in AQP4-IgG seropositive Patients



Baseline Characteristics and Efficacy in Adolescent Patients (Study BN40898)
The mean age of the 7 adolescent patients enrolled during the double-blind period of study BN40898 was 15.4 years and the median body weight was 79.6 kg. The majority of the adolescent patients were females (n=6). Four patients were White, 2 patients were Black/African American, and 1 patient was Asian. Three out of 7 (42.9%) adolescent patients were AQP4-IgG seropositive at screening (2 in the placebo group and 1 in the Enspryng group). During the DB period, 1 of 3 adolescents in the placebo group and 1 of 4 adolescents in the Enspryng 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.

3.1.3 Immunogenicity
In phase III Study BN40898 (combination with IST) and in phase III study BN40900 (monotherapy), anti-drug-antibodies (ADAs) were observed in 41% and 71% of patients receiving Enspryng in the double-blind period, respectively. The ability of these ADAs to neutralize Enspryng 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. Patients with higher bodyweight and lower exposure were more likely to develop ADAs (irrespective of background treatment with IST), however treatment effect was comparable in all bodyweight groups when used either in combination with IST, or as monotherapy. The recommended dose is appropriate for all patients, and neither dose interruption nor modification is warranted in patients who develop ADAs.

3.2 PHARMACOKINETIC PROPERTIES
The pharmacokinetics of Enspryng have been characterized 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 characterized using population pharmacokinetic analysis methods based on a database of 154 patients.

The concentration-time course of Enspryng 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. Enspryng 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. Pharmacokinetics were not impacted by background immunotherapy (*see section 2.8 Interractions with other medicinal products and other forms of interaction*).

3.2.1 Absorption
The absorption rate constant of Enspryng was 0.251 1/day (95% CI: 0.216-0.285) equating to an absorption half-life of around 3 days at the recommended dose (*see section 2.2 Dosage and Administration*). The bioavailability was high (85.4%, 95% CI: 79.5-95.3%).

3.2.2 Distribution
Enspryng undergoes biphasic distribution. The central volume of distribution was 3.46 L (95% CI: 3.21-3.97), the peripheral volume of distribution was 2.07 L (95% CI: 1.78-2.59). The inter-compartmental clearance was 0.336 L/day (95% CI: 0.261-0.443).

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

3.2.4 Elimination
The total clearance of Enspryng 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 0.0601 L/day (95% CI: 0.0524-0.0695). The associated terminal $t_{1/2}$ is approximately 30 days (range 22-37 days) based on data pooled from the phase 3 studies.

3.2.5 Pharmacokinetics in 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.

Pediatric Population
Data obtained in 8 adolescent patients [13-17 years] who received the adult dosing regimen show that population PK parameters for satralizumab are not significantly different from those in the adult population.

No dose adjustment is therefore necessary.

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

Population PK analyses based on data from in these patients showed that age did not affect the PK of satralizumab.

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 <80 mL/min and ≥50 mL/min) were included in the BN40898 and BN40900 clinical studies. As anticipated based on the known mechanisms of clearance for satralizumab, the PK in these patients was not impacted and 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.

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

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

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

3.3.4 Reproductive toxicity
Pre-natal treatment until delivery with up to 50 mg/kg/week satralizumab in pregnant monkeys and postnatal exposure in their offspring did not elicit any adverse effects on maternal animals, fetal 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).

3.3.5 Other
Repeat dose toxicity
Nonclinical studies with monkeys, a responder species with cross-reactivity to satralizumab did not reveal special hazards for humans based on safety pharmacology, acute and repeated dose toxicity endpoints. When up to 50 mg/kg satralizumab was administered to cynomolgus monkeys once a week in 4- and 26-week repeated-dose SC toxicity studies, no toxicity changes considered to be caused by drug administration were observed. The only relevant change in these studies was increase in blood IL-6 level, which was considered to be the result of the pharmacological action (IL-6R neutralizing action) of satralizumab, and not associated with any adverse findings. Treatment with satralizumab elicited an immune response with anti-drug antibodies in most of the treated animals, which was, however, not affecting the pharmacological response and did not result in any adverse events.

Local tolerance
The SC injection of the clinical formulation of satralizumab did not elicit any adverse reaction at the administration site in monkeys.

Tissue cross-reactivity
Tissue cross-reactivity detected with satralizumab in monkey and human tissues reflects the sites of IL-6R expression. No relevant tissue cross-reactivity was detected in other tissues.

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

4. PHARMACEUTICAL PARTICULARS
4.1 STORAGE
Storage
As registered locally.
Store at 2°C - 8°C until ready to use.

Enspryng, if unopened, can be removed from and returned to the refrigerator, if necessary. If stored at room temperature, the total combined time out of refrigeration should not exceed 8 days at a temperature that does not exceed 30°C.

Keep PFS in the outer carton in order to protect from light.
Do not freeze. Do not shake.

Shelf life
As registered locally.
This medicine should not be used after the expiry date (EXP) shown on the pack.

4.2 SPECIAL INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL
Enspryng is for single-dose only.
Do not inject the medicine if the liquid is cloudy, discolored, or has particles in it.
Check the PFS + NSD for any damage. Do not use if it is cracked or broken.

Disposal of PFS + NSD
The following points should be strictly adhered to regarding the use and disposal of the PFS + NSD:
- PFS should never be reused.
- Put your used syringe in a sharps disposal container immediately after use.
- Throw away (dispose of) the PFS+NSD in accordance with local requirements or as directed by your healthcare professional.
- Keep the PFS+NSD and all medicines out of the reach of children.

Disposal of unused/expired medicines
The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater, and disposal through household waste should be avoided. Use established 'collection systems' if available in your location.

4.3 PACKS
Pre-filled syringe 120 mg/1 ml

Medicine: keep out of reach of children

Current at October 2021

F. Hoffmann-La Roche Ltd, Basel, Switzerland

Instructions for Use

ENSPRYNG®

Satralizumab

What do I need to know to use the Enspryng pre-filled syringe safely?

Read this Instructions for Use:
- **Before you start using your pre-filled syringe**
- **Each time you get a prescription refill.**

This is because it may contain new information.
- This information does not take the place of talking to your healthcare provider about your medical condition or treatment.
- Your healthcare provider will decide if you or a caregiver can give you injections of Enspryng at home. They will also show you or a caregiver the correct and safe way to use the syringe before you use it for the first time.
- Talk to your healthcare provider if you have any questions.

Important Information
- Each syringe is pre-filled with a medicine called Enspryng.
- Each carton of Enspryng contains only 1 pre-filled syringe.
- Each pre-filled syringe can be used only once.

Do not:
- Share your syringes with other people - you may give them a serious infection or get a serious infection from them.

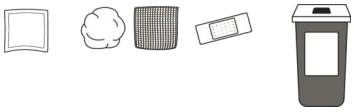
Do not:
- Take the needle cap off until you are ready to inject Enspryng.
- Use the syringe if it has been dropped or damaged.
- Try to take the syringe apart at any time.
- Leave the syringe unattended.
- Re-use the same syringe.

How should I store the Enspryng pre-filled syringe?
- Keep the unused syringe in the refrigerator between 2°C to 8°C until ready to use.
- Keep the syringe and all medicines out of the sight and reach of children.
- Keep the syringe in its original carton away from direct sunlight.
- Always keep the syringe dry.

Do not:
- Freeze the syringe.
- Use the syringe if it has been frozen.
- Shake

Supplies needed to give your injection
Each Enspryng carton contains:
- 1 pre-filled syringe for one-time use only.

Not included in the carton:



- 1 alcohol pad
- 1 sterile cotton ball or gauze
- 1 small bandage
- 1 puncture-resistant sharps container for safe disposal of the needle cap and used syringe. See Step 21 "Disposing of Enspryng" at the end of these Instructions for Use.

Enspryng pre-filled syringe
(See Figure A and Figure B)
Before use:

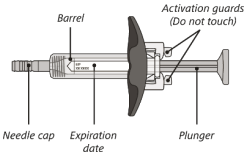


Figure A

After use:

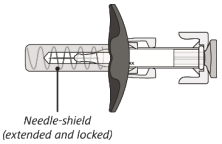


Figure B

The syringe has a needle-shield that automatically covers the needle when the injection is complete.

Prepare to use Enspryng
1. Take the carton containing the syringe out of the refrigerator and place it on a clean, flat work surface (like a table).
2. Check the expiration date on the back of the carton **(See Figure C)**. **Do not** use if the carton has expired.
3. Check that the front of the carton is sealed **(Figure C)**. **Do not** use if the seal has been broken.

If the expiration date has passed or the seal is broken, do not use. Then go to Step 21 "Disposing of Enspryng" and contact your healthcare provider.

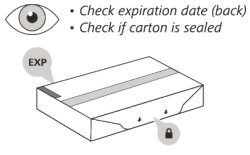


Figure C

4. Open the sealed carton **(See Figure D)**.

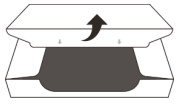


Figure D

5. Carefully lift the syringe out of the carton by holding the barrel **(See Figure E)**.
   Do not:
   - turn the carton upside down to remove the syringe.
   - touch the activation guards - this may damage the syringe.
   - hold the plunger or needle cap.

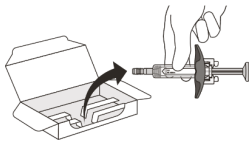


Figure E

Check the syringe
(See Figure F)
6. Check the expiration date on the syringe. **Do not** use the syringe if it has expired.
7. Check the syringe for any damage. **Do not** use if it is cracked or broken.
8. Check that the liquid through the viewing window is clear and colourless to slightly yellow. **Do not** inject the medicine if the liquid is cloudy, discoloured, or has particles in it.
   - There may be some small air bubbles in the syringe. This is normal and you should not try to remove them.

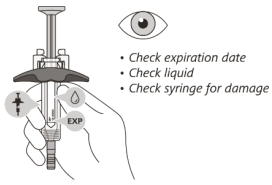


Figure F

If the expiry date has passed, the syringe is damaged or the liquid is cloudy, discoloured or has particles in it, do not use. Then go to Step 21 "Disposing of Enspryng" and contact your healthcare provider.

Let your syringe warm up
9. Once you have checked the syringe, place it on a clean, flat work surface (like a table) for **30 minutes** - this will allow it to reach room temperature **(See Figure G)**.
   It is important to let the syringe gently warm up as injecting cold medicine may feel uncomfortable and make it harder to push.
   Do not:
   - speed up the warming process in any way, such as using a microwave or placing the syringe in warm water.
   - remove the needle cover while the syringe is reaching room temperature.

Figure G

Wash your hands
10. Wash your hands with soap and water **(See Figure H)**.

Figure H

Choose the injection site
11. Choose your injection site in either:
    - the lower part of your stomach (abdomen) or
    - the front and middle of your thighs **(See Figure I)**.

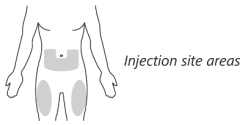


Figure I

Do not:
- inject into the 5 cm area around your belly button.
- inject into moles, scars, bruises, or areas where the skin is tender, red, hard or broken.

Choose a different injection site for **each new injection - choose a different place to inject which is at least 2.5 cm away from the place where you last injected.**

Clean the injection site
12. Wipe the injection site with an alcohol pad and let it air dry.
    Do not:
    - fan or blow on the area which you have cleaned.
    - touch the injection site again before you give the injection.

Figure J

Inject Enspryng
13. Hold the barrel of the syringe between your thumb and index finger. With your other hand, pull the needle cap straight off. You may see a drop of liquid at the end of the needle - this is normal and will not affect your dose **(See Figure K)**.
    - **Use the syringe within 5 minutes of removing the cap or the needle may clog.**

    Do not:
    - take the needle cap off until you are ready to inject Enspryng.
    - put the needle cap back on once it has been removed as this may damage the needle.
    - touch the needle or let it touch any surfaces after removing the needle cap.

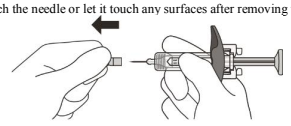


Figure K

14. Throw away the needle cap in a puncture-resistant sharps container immediately. See Step 21 "Disposing of Enspryng".
15. Hold the barrel of the syringe using your thumb and index finger. With your other hand, pinch the area of skin you have cleaned **(See Figure L)**.
16. Use a quick, dart-like motion to insert the needle at an angle between 45° to 90° **(See Figure L)**.

    Do not:
    - insert the needle through clothing.
    - change the angle of the injection.
    - insert the needle again.

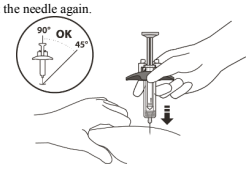


Figure L

17. After the needle is inserted, let go of the pinched skin.
18. Slowly inject all of the medicine by gently pushing the plunger all the way down until it touches the activation guards **(See Figure M)**.

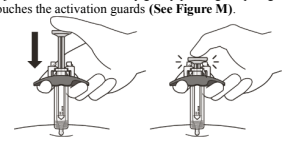


Figure M

19. Gently release the plunger and allow the needle to come out of the skin at the same angle it was inserted **(See Figure N)**.

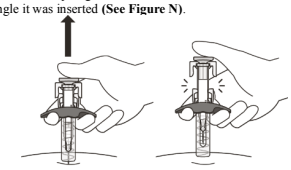


Figure N

- **The needle will now be covered by the needle-shield.** If the needle is not covered, carefully place the syringe into a puncture-resistant sharps container to avoid injury. See Step 21 "Disposing of Enspryng".

Taking care of the injection site
20. There may be a little bleeding at the injection site. You can press a cotton ball or gauze over the injection site but **do not** rub it. If needed, you may also cover the area you injected with a small bandage. If the medicine gets into contact with your skin, wash the area with water.

Disposing of Enspryng
21. Do not try to re-cap your syringe. Put your used syringe in a sharps disposal container immediately after use **(See Figure O)**. **Do not** throw away (dispose of) the syringe in your household waste and do not recycle them.

Figure O

- Ask your healthcare provider or pharmacist for information about where you can get a "sharps" container or what other types of puncture-resistant containers you can use to safely dispose of your used syringes and needle caps, if you do not have one.
- Dispose of the used sharps disposal container as instructed by your healthcare provider or pharmacist
- **Do not** dispose of your used sharps disposal container in your household waste
- **Do not** recycle your used sharps disposal container.