ENSPRYNG®/TM

satralizumab

1. NAME OF THE MEDICINAL PRODUCT

Enspryng 120 mg/mL sterile solution for subcutaneous (SC) injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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.
Excipients: L-Histidine, L-Aspartic Acid, L-Arginine, Poloxamer 188, Water for Injection

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).

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 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 adolescent patients from 12 years of age who are anti-aquaporin-4 IgG (AQP4-IgG) seropositive

4.2 Posology and method of 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.

Enspryng can be used as a monotherapy or in combination with either oral corticosteroids (OCs), azathioprine (AZA) or mycophenolate mofetil (MMF) (*see section 5.1.2 Clinical / Efficacy Studies*). Please also refer to the full prescribing information for these products.

Loading Doses

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). 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 x109/L and confirmed by repeat testing, Enspryng should be interrupted until the neutrophil count is > 1.0 x109/L.

4.2.1 Special Dosage Instructions

Pediatric use

The safety and efficacy of Enspryng in pediatric population <12 years of age have not been studied (*see section Pediatric Use*).

Geriatric use

No dose adjustment is required in patients ≥ 65 years of age (*see sections Geriatric Use and 5.2.5 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 Renal Impairment and 5.2.5 Pharmacokinetics in special populations*).

Hepatic Impairment

The safety and efficacy of Enspryng have not been studied in patients with hepatic impairment (*see sections Hepatic Impairment and 5.2.5 Pharmacokinetics in special populations*).

Other Special Patient Populations

Not applicable

4.3 Contraindications

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

4.4 Special Warnings and Precautions for use

4.4.1 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 4.2 Posology and method of administration, Delayed and Missed Doses*).

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 4.8.1 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 4.1. Therapeutic Indication(s)*

4.4.2 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.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

The potential for treatment with Enspryng 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.

This indicates that suppression of IL-6 signalling by treatment with Enspryng from the low baseline levels seen in the phase III studies will have only a minor impact on exposure of a range of probe CYP450 substrates (≤15% decrease in AUC for all substrates of CYPs 1A2, 3A4, 2D6, 2C19). This indicates that the risk of drug interaction is low, however caution should be exercised when Enspryng is administered or discontinued in patients also receiving CYP450 substrates with a narrow therapeutic index.

4.6 Fertility, pregnancy and lactation

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 5.3.3 Impairment of Fertility*).

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 5.3.4 Reproductive toxicity*).

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

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 5.3.4 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.

Use In Special Populations

Pediatric Use

The safety and efficacy of Enspryng have been studied in a limited number of adolescent patients ≥12 years of age. Pharmacokinetic, efficacy and safety results were consistent with those in adults (*see sections 5.1.2 Clinical/ Efficacy Studies and 5.2.5 Pharmacokinetics in Special Populations*).

The safety and efficacy of Enspryng in pediatric patients <12 years of age has not yet been studied (*see section 4.2.1 Special Dosage Instructions).*

Geriatric Use

The safety and efficacy of Enspryng have been studied in geriatric patients up to 74 years of age (*see sections 4.2.1 Special Dosage Instructions and 5.2.5 Pharmacokinetics in special populations*).

The safety and efficacy of Enspryng in geriatric patients >74 years of age have not been studied (*see section 4.2.1 Special Dosage Instructions).*

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 4.2.1 Special Dosage Instructions and 5.2.5 Pharmacokinetics in Special Populations*).

Hepatic Impairment

The safety and efficacy of Enspryng in patients with hepatic impairment have not been studied (*see sections 4.2.1 Special Dosage Instructions and 5.2.5 Pharmacokinetics in Special Populations*).

4.7 Effects on ability to drive and use machine effects

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.

4.8 Undesirable Effects

4.8.1 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 5.1.2 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

Adverse reactions (MedDRA)	**Events per 100 PY**		**Number of patients (%)**		**Frequency Category for Enspryng**
	Enspryng PY=193.74	**Placebo[1] PY=100.10**	**Enspryng n=104**	**Placebo[1] n=74**	
Nervous system disorders					
Headache	18.07	10.99	20 (19.2%)	8 (10.8%)	Very common
Migraine	2.06	0.00	4 (3.8%)	0	Common

Injury, poisoning and procedural complications					
Injection-related reactions	17.03	8.99	13 (12.5%)	7 (9.5%)	Very common
Musculoskeletal and connective tissue disorders					
Arthralgia	7.23	1.0	14 (13.5%)	1 (1.4%)	Very common
Musculoskeletal stiffness	2.58	0.00	5 (4.8%)	0	Common
Skin and subcutaneous tissue disorders					
Rash	7.23	4.00	9 (8.7%)	3 (4.1%)	Common
Pruritus	4.13	1.00	6 (5.8%)	1 (1.4%)	Common
Psychiatric disorders					
Insomnia	3.10	1.00	6 (5.8%)	1 (1.4%)	Common
General disorders and administration site conditions					
Oedema peripheral	2.58	0.00	5 (4.8%)	0	Common
Respiratory, thoracic and mediastinal disorders					
Rhinitis allergic	2.06	0.00	4 (3.8%)	0	Common
Blood and lymphatic system disorders					
Hypofibrinogenaemia	1.55	0.00	3 (2.9%)	0	Common
Investigations					
White blood cell count decreased	11.36	12.99	14 (13.5%)	4 (5.4%)	Very common
Blood bilirubin increased	5.16	0.00	2 (1.9%)	0	Common

[1] Placebo or placebo in combination with IST

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 Enspryng (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 Enspryng (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 Enspryng 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 Enspryng (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 Enspryng (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 Enspryng.

Elevations in ALT or AST >3x ULN occurred in 2.9% and 1.9% of patients treated with Enspryng (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 Enspryng in combination with IST, normalizing after discontinuation of Enspryng.

Lipid parameters

In the double-blinded treatment period, 10.6% of patients receiving Enspryng (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 Enspryng 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.

4.8.2 Postmarketing Experience

Not applicable

4.9 Overdose

There is no experience with overdose in patients with neuromyelitis optica (NMO) or NMOSD. A single dose of up to 240 mg Enspryng 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.

5. PHARMACOLOGICAL PROPERTIES AND EFFECTS

5.1 Pharmacodynamic Properties

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

5.1.1 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.

5.1.2 Clinical / Efficacy Studies

The efficacy and safety of Enspryng 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 Enspryng 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 Enspryng 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 Enspryng 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 Enspryng.

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: Enspryng 100 weeks, placebo 74 weeks*	
Treatment groups, in 1:1 randomization	Group A: Enspryng 120 mg SC Group B: placebo	
Baseline characteristics	Enspryng +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 Enspryng monotherapy compared to placebo. The study included 95 AQP4-IgG seropositive and seronegative adult patients. Patients received the first 3 single doses of Enspryng 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 Enspryng.

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: Enspryng 95.4 weeks, placebo 60.5 weeks*	
Treatment groups, in 2:1 randomization	Monotherapy: Group A: Enspryng 120 mg SC Group B: placebo	
Baseline characteristics	Enspryng (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 Enspryng 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 Enspryng-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 Enspryng-treated patients remained adjudicated relapse-free when used in combination with IST or as monotherapy, respectively. When data from the two studies were pooled, Enspryng 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).

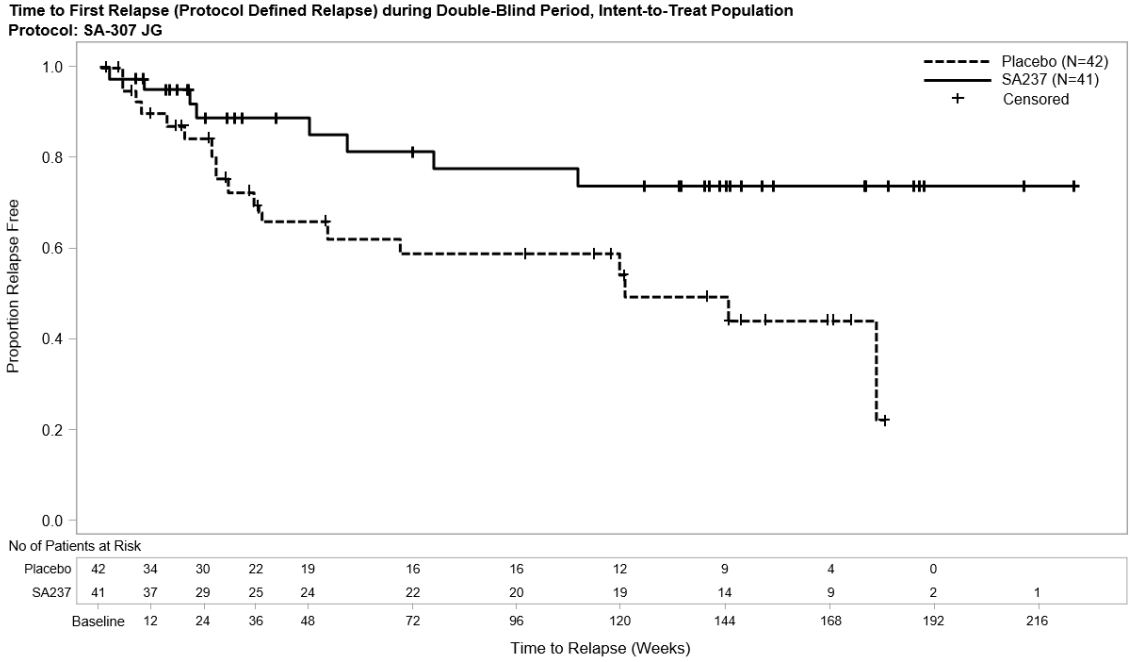
The strongest subgroup effect was observed in AQP4-IgG seropositive patients. In AQP4-IgG seropositive patients the relative risk of experiencing an adjudicated relapse in Study BN40898 was reduced by 79% (HR [95% CI]: 0.21 [0.06-0.75]), in Study BN40900 by 74% (HR [95% CI]: 0.26 [0.11-0.63]). At 48 weeks, 91.5% and 82.9% of Enspryng-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 Enspryng-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 Enspryng 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 Enspryng 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**	
	Enspryng + IST	Placebo + IST	Enspryng	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)



Protocol Defined Relapse: Adjudicated by the Clinical Endpoint Committee. EDSS assessment performed within 7 days of relapse reporting.
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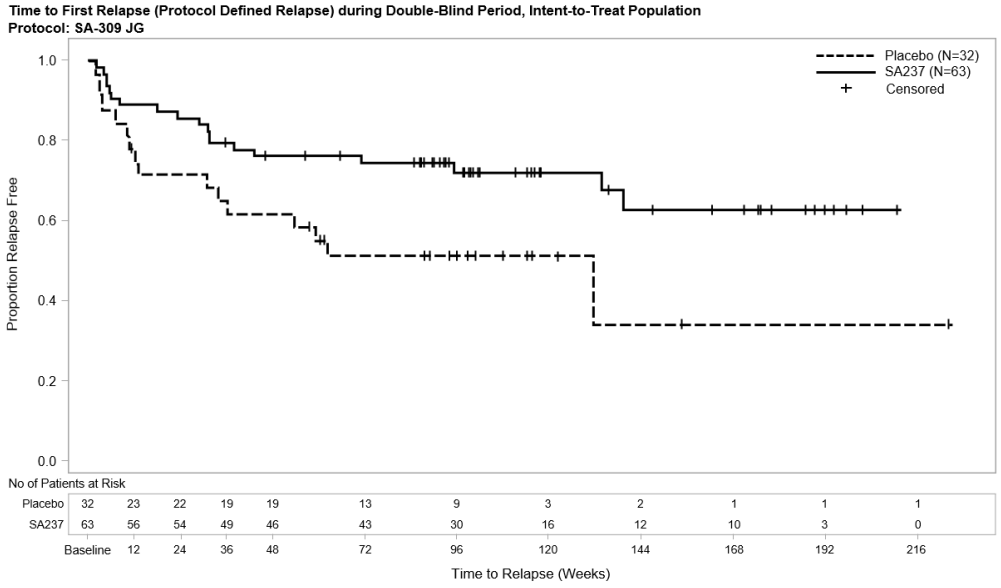
Figure 2 Study BN40900: Time to First Adjudicated Relapse during the Double-blind Period (ITT Population)



Protocol Defined Relapse: Adjudicated by the Clinical Endpoint Committee. EDSS assessment performed within 7 days of relapse reporting.
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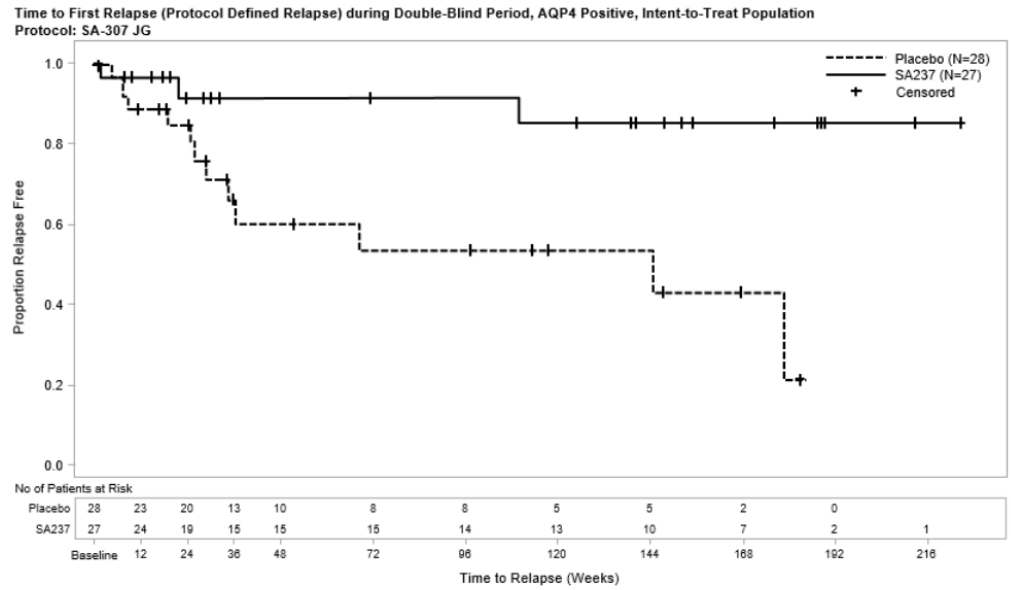
Figure 3 Study BN40898: Time to First Adjudicated Relapse during the Double-blind Period in AQP4-IgG seropositive Patients



Protocol Defined Relapse: Adjudicated by the Clinical Endpoint Committee. EDSS assessment performed within 7 days of relapse reporting.
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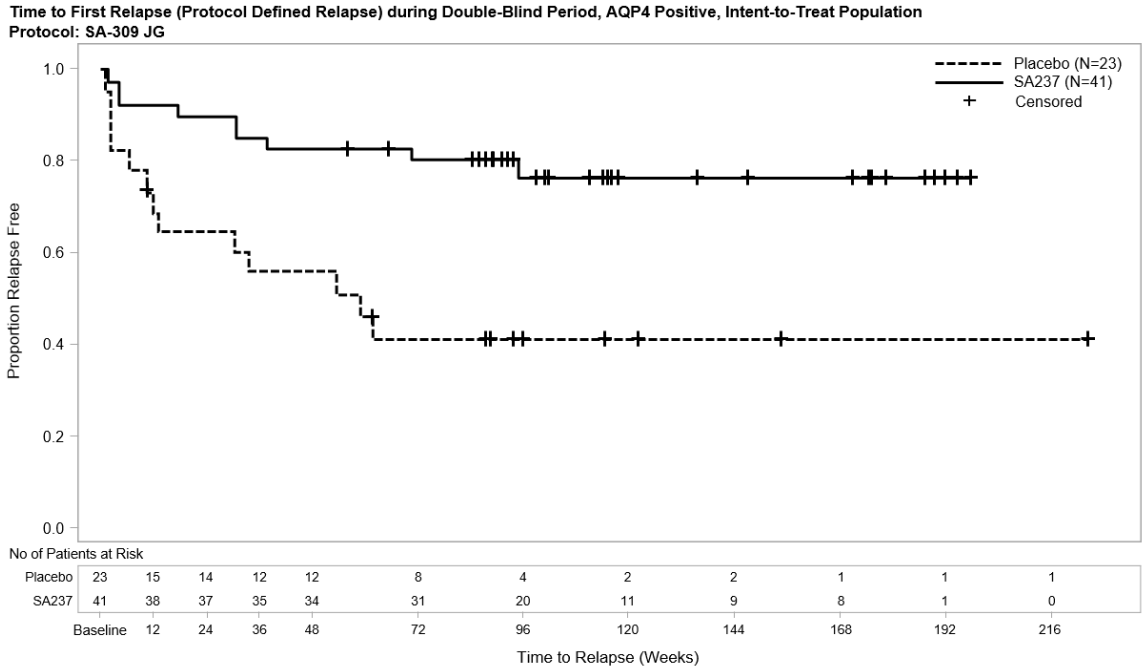
Figure 4 Study BN40900: Time to First Adjudicated Relapse during the Double-blind Period in AQP4-IgG seropositive Patients



AQP4=Aquaporin-4
Protocol Defined Relapse: Adjudicated by the Clinical Endpoint Committee. EDSS assessment performed within 7 days of relapse reporting.
Program: root/clinical_studies/RO5333787/CDP70210/BN40900/data_analysis/CSRPrimary/prod/program/g_tte_km.ah.sas
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Treatment with Enspryng 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	**Enspryng**	**Placebo**	**Enspryng**	**Placebo**	**Enspryng**
ITT	**N = 42**	**N = 41**	**N = 32**	**N = 63**	**N = 74**	**N = 104**
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

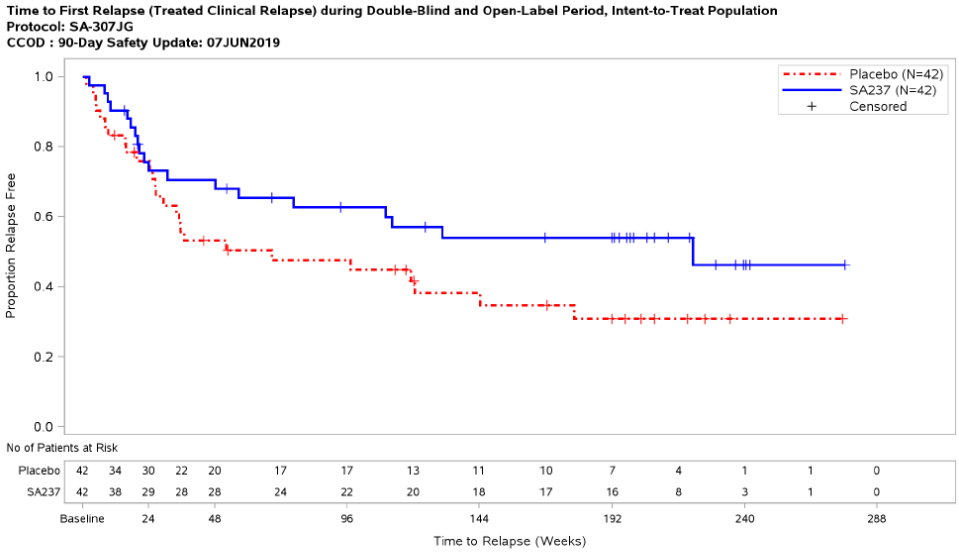
	BN40898		**BN40900**		**Pooled**	
	Placebo	**Enspryng**	**Placebo**	**Enspryng**	**Placebo**	**Enspryng**
ITT	**N=41**	**N=41**	**N=32**	**N=63**	**N=73**	**N=104**
Patients with an event	6 (14.6%)	1 (2.4%)	6 (18.8%)	4 (6.3%)	12 (16.4%)	5 (4.8%)
Risk reduction	84% (HR: 0.16; 95% CI : 0.02, 1.33; p=0.0522)		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)	

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



Treated Clinical Relapse: Relapse treated with rescue therapy during DB and OLE period.
For 307, Patients were censored at the earliest day of end of Overall SA237 exposure period or at the Clinical Cut off Date (CCOD).

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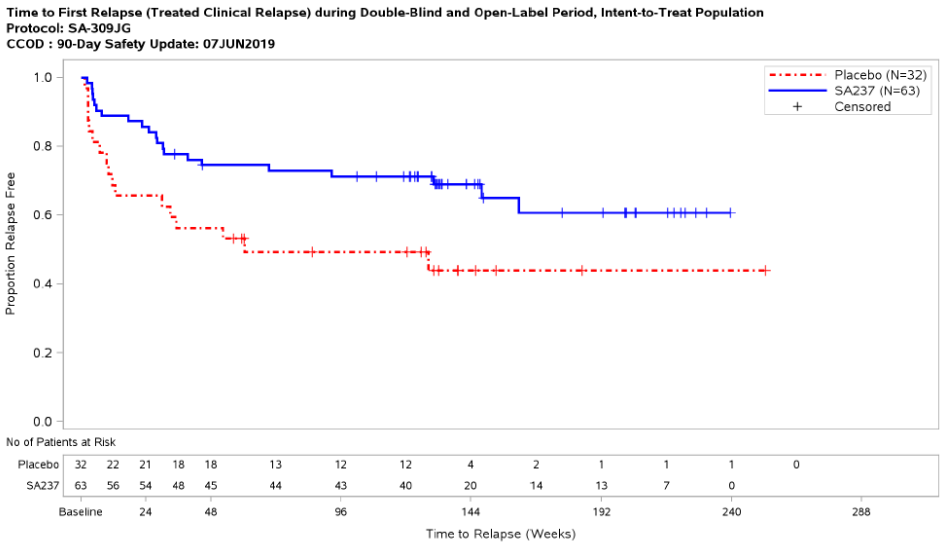
Figure 6 Study BN40900: Time to First Relapse (Treated Clinical Relapse) during Double-Blind and Open-Label Period



Treated Clinical Relapse: Relapse treated with rescue therapy during DB and OLE period.
For 309, Patients were censored at the earliest day of end of Overall SA237 exposure period or at the Clinical Cut off Date (CCOD).

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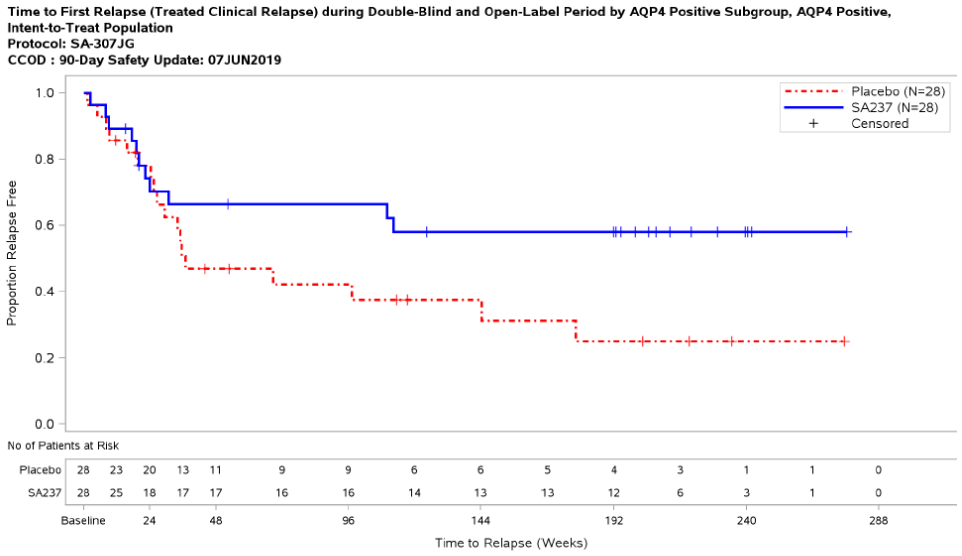
Figure 7 Study BN40898: Time to First Relapse (Treated Clinical Relapse) during Double-Blind and Open-Label Period in AQP4-IgG seropositive Patients



Treated Clinical Relapse: Relapse treated with rescue therapy during DB and OLE period.
For 307, Patients were censored at the earliest day of end of Overall SA237 exposure period or at the Clinical Cut off Date (CCOD).

Program: root/clinical_studies/RO5333787/CDP70210/share/pool_3MSU/prod/program/g_tte_km.sas
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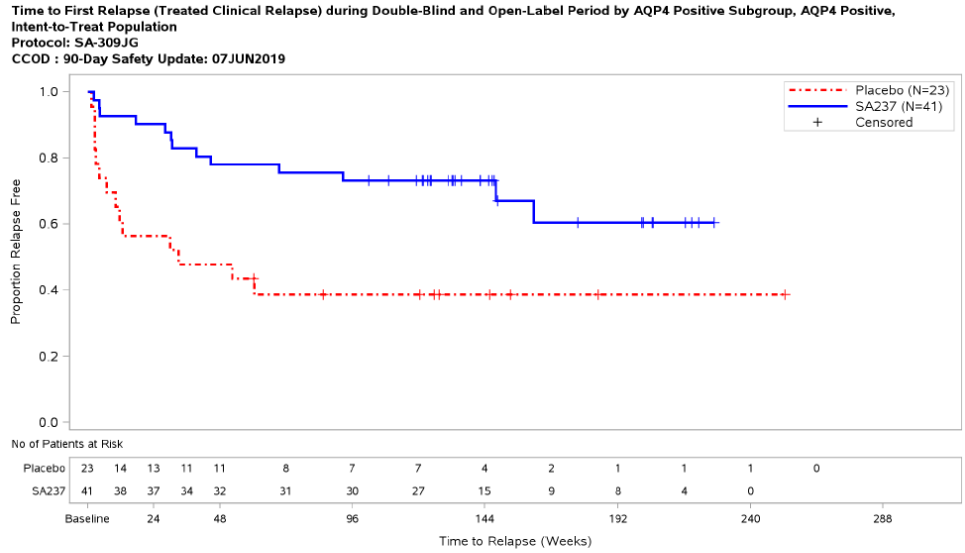
Figure 8 Study BN40900: Time to First Relapse (Treated Clinical Relapse) during Double-Blind and Open-Label Period in AQP4-IgG seropositive Patients



Treated Clinical Relapse: Relapse treated with rescue therapy during DB and OLE period.
For 309, Patients were censored at the earliest day of end of Overall SA237 exposure period or at the Clinical Cut off Date (CCOD).

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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.

5.1.3 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.

5.2 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 4.5 Interaction with other medicinal products and other forms of interaction*).

5.2.1 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 4.2 Posology and method of administration*). The bioavailability was high (85.4%, 95% CI: 79.5-95.3%).

5.2.2 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).

5.2.3 Metabolism

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

5.2.4 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.

5.2.5 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.

5.3 Preclinical safety data

5.3.1 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.

5.3.2 Genotoxicity

No studies have been performed to establish the mutagenic potential of satralizumab.

Antibodies are not expected to cause effects on the DNA.

5.3.3 Impairment of Fertility

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

5.3.4 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).

5.3.5 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipents

Excipients: L-Histidine, L-Aspartic Acid, L-Arginine, Poloxamer 188b, Water for Injection

6.2 Incompatibilities

N/A

6.3 Shelf life

2 years

6.4 Special precautions for storage

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.

This medicine should not be used after the expiry date (EXP) shown on the pack.

6.5 Nature and contents of container

Pre-filled syringe 120 mg/mL

6.6 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.

Medicine: keep out of reach of children

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