Date: 27 August 2020
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Enspryng

International non-proprietary name: satralizumabum
Pharmaceutical form: Solution for injection
Dosage strength: 120 mg
Route(s) of administration: subcutaneous use
Marketing Authorisation Holder: Roche Pharma (Schweiz) AG
Marketing Authorisation No.: 67617
Decision and Decision date: approved on 13 July 2020

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AQP4	Anti-aquaporin-4
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
BBB	Blood-brain barrier
CNS	Central nervous system
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IL-6	Interleukin-6
IL-6R	Interleukin-6 receptor
INN	International Nonproprietary Name
IRR	Injection-related reaction
IST	Immunosuppressive therapy
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
N/A	Not applicable
NMO	Neuromyelitis optica
NMOSD	Neuromyelitis optica spectrum disorder
NO(A)EL	No Observed (Adverse) Effect Level
OLE	Open-label extension
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
Q2W	Every 2 weeks
Q4W	Every 4 weeks
RMP	Risk Management Plan
SC	Subcutaneous
sIL-6R	Soluble interleukin-6 receptor
SwissPAR	Swiss Public Assessment Report
FTPA	Federal Act of 15 December 2000 (Status as of 1 January 2020 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)
ULN	Upper limit of normal

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance satralizumab of the medicinal product mentioned above.

Fast-track authorisation procedure (FTP)
The applicant requested a fast-track authorisation procedure in accordance with Article 7 of the TPO.

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a^{decies} no. 1 or 2 of the TPA. The Orphan Status was granted on 10 October 2019.

2.2 Indication and Dosage

2.2.1 Requested Indication

Enspryng is indicated as monotherapy or in combination with immunosuppressive therapy (IST) for the treatment of adult and adolescent patients with neuromyelitis optica spectrum disorders (NMOSD).

2.2.2 Approved Indication

Enspryng is used as a monotherapy or in combination with immunosuppressive therapy (IST) for the treatment of neuromyelitis optica spectrum disorders (NMOSD) in adult and adolescents in whom aquaporin-4 IgG antibodies are detected (i.e. who are AQP4 IgG seropositive).

2.2.3 Requested Dosage

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

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	25 October 2019
Formal control completed	28 October 2019
List of Questions (LoQ)	19 December 2019
Answers to LoQ	31 March 2020
Predecision	20 May 2020
Answers to Predecision	16 June 2020
Labelling corrections	6 July 2020
Answers to Labelling corrections:	8 July 2020
Final Decision	13 July 2020
Decision	approval

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3 Medical Context

Neuromyelitis optica (NMO) and NMO spectrum disorders (NMOSD) are rare autoimmune inflammatory disorders of the central nervous system (CNS) characterised by demyelination and axonal damage, which mainly affect the spinal cord and the optic nerve.

The disease presents itself clinically as unilateral or bilateral optic neuritis and extensive transverse myelitis with a typically relapsing course. NMO and NMOSD can lead to various, and sometimes very severe, disabilities such as impairment of visual function (including blindness), impaired mobility (including paralysis), loss of sensory perception and bowel and bladder dysfunction. Fatigue and neuropathic pain are common in NMO and NMOSD, significantly impacting patients' quality of life (Wingerchuk et al. 2007, Jacob et al. 2013). Cervical myelitis can extend into the brainstem, resulting in nausea, hiccoughs or acute neurogenic respiratory failure, the main cause of death in NMO patients (Wingerchuk et al. 1999).

The relapses usually occur over a period of several days, the degree of recovery can vary over a period of weeks to months, but often only an incomplete remission occurs. With NMO and NMOSD, the accumulation of neurological deficits after several attacks is very often the main reason for the progressive disability.

NMO and NMOSD are considered rare diseases with a prevalence between 0.52 and 4.4 per 100,000 (Etamadifar et al. 2015). There are no precise data on the incidence and prevalence of NMO and NMOSD in Switzerland.

The onset of the disease is at an average age of 39 years. However, it can occur from early childhood to late adulthood (Lotze et al. 2008).
A female predominance is observed in many published cohorts, with a female to male ratio ranging from 3:1 in France to 10:1 in Japan (Jacob et al. 2013).

NMO was previously considered a subtype of multiple sclerosis (MS). However, following the discovery of NMO-IgG (anti-aquaporin-4 [AQP4]-IgG) (Lennon et al. 2004), a circulating antibody which targets the dominant water channel in the CNS, NMO became recognised as a separate entity. AQP4-IgG is detectable in 70-80% of patients with NMO (Lennon et al 2004), is highly specific for clinically diagnosed NMO, and has pathogenic potential (Hinson et al. 2007). Anti-AQP4 antibodies and inflammatory cells are believed to enter the CNS via a compromised blood-brain barrier (BBB), where they cause astrocyte dysfunction and local inflammation, leading to demyelination and axonal damage, and ultimately neurological symptoms characteristic of NMO.

NMO is diagnosed as patients with optic neuritis and acute myelitis and at least two of three supportive criteria (Wingerchuk et al. 2006): contiguous spinal cord lesion identified on a magnetic resonance imaging (MRI) scan extending over 3 vertebral segments, brain MRI not meeting diagnostic criteria for multiple sclerosis, or AQP4-IgG seropositive status. The clinical spectrum of NMO was subsequently broadened, with the term NMOSD being introduced to include seropositive patients with limited forms of NMO (e.g. isolated longitudinal extensive transverse myelitis [LETM] or optic neuritis [ON]) who are at high risk of future attacks (Wingerchuk et al. 2007).
The improved understanding of clinical features of AQP4-IgG seropositive NMOSD also permitted diagnostic criteria for AQP4-IgG seronegative NMOSD to be defined even if patients do not present with all of the classical clinical features of NMO (Wingerchuk et al. 2015). Overall, the group of AQP4-IgG seronegative patients is clinically very heterogeneous and includes patients with severe disease, but also patients with less severe, and in some cases very mild, disease courses (Jarius et al. 2012).

Distinguishing NMO and NMOSD from MS in the early stages of the disease is critical.
NMO and NMOSD are radiologically and prognostically distinct from MS and have a pathophysiology that can be unresponsive to, or even worsen with, typical MS treatment (Weinshenker 2007; Oh and Levy 2012). Other distinctive features of NMO and NMOSD include a stronger female predominance,

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longitudinally extensive spinal cord lesions, and commonly an absence of oligoclonal bands (OCB) in the cerebrospinal fluid (CSF).

Overall, NMO and NMOSD have a poor prognosis; over 50% of patients evaluated at the Mayo Clinic between 1950 and 1997 developed severe visual loss in at least one eye, or were unable to walk without assistance within 5 years of disease onset, with an estimated 5-year mortality rate in relapsing patients of 32% (Wingerchuk et al., 1999). More recent studies suggest an improved prognosis (Kitley et al., 2012), possibly due to increased awareness and earlier treatment, as well as the off-label use of immunosuppressive therapies.

IL-6 (interleukin-6) is a cytokine that appears to play a key role in the immune pathogenesis of NMO and NMOSD. Since increased levels of IL-6 have been described in NMOSD patients' serum and CSF during episodes of disease activity (i.e. relapses) (İçöz et al. 2010; Uzawa et al. 2009; Uzawa et al. 2010), the potential role of IL-6 in the immunopathogenesis of NMOSD has been further elucidated.
A beneficial effect of IL-6R blockade in NMO and NMOSD has been suggested in a few small open-label studies (Araki et al. 2014; Komai et al. 2013; Ringelstein et al. 2015; Ayzenberg et al. 2013).

Satralizumab specifically targets the human IL-6 receptor (IL-6R), blocks IL-6 from binding to membrane-bound and soluble IL-6R, and thereby prevents IL-6 signalling.

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4 Quality Aspects

4.1 Drug Substance

Satralizumab is an IgG2 monoclonal antibody that binds to the soluble and membrane-bound interleukin-6 receptor (IL-6R) and achieves its pharmacological effects by inhibiting IL-6 signalling. It is produced from a mammalian cell line (Chinese Hamster Ovary, CHO) using a fed-batch production process in a production bioreactor. The cell broth is harvested and subsequently purified by several chromatographic steps. The drug substance is finally stored frozen.

Several changes were implemented during the development of the satralizumab drug substance process, including changes to production scale, media adaptions, and drug substance concentration. However, all processes used the same cell line, and the analytical comparability studies, which included batch release data, extended characterisation (including functional assays), and stability data, demonstrated comparability between process changes.

The physicochemical and biological properties of the drug substance and its impurities were characterised using state-of-the-art methods.
The specifications for release include relevant tests and limits, e.g. for appearance, identity, pH, several purity tests (e.g. SE-HPLC, CE-SDS), assay of protein, and a cell-based potency assay. Specifications are based on clinical experience, batch analysis data (release and stability data) and are in conformance with current compendial or regulatory guidelines.

Batch analysis data of non-clinical batches, clinical batches, and commercial batches were provided. All specific analytical methods are described and were fully validated.

During storage, no changes were observed under the proposed storage conditions. A shelf life of 42 months has been accepted.

4.2 Drug Product

Satralizumab drug product is a prefilled 1 mL polymer syringe containing a sterile, solution for subcutaneous injection with no preservatives. Each single-dose, 1 mL prefilled syringe, contains 120 mg (nominal) of satralizumab. All excipients used comply with the European Pharmacopoeia.

During process development of the drug product, a few changes were implemented. However, these changes were minimal, and the corresponding studies demonstrated comparability with respect to quantitative and qualitative critical quality attributes (CQAs).

The finished product manufacturing process consists of thawing of formulated drug substance, pooling of drug substance bags, pre-filtration, sterile filtration, filling/stoppering, visual inspection and assembly.

The validation was executed by manufacturing and testing four process performance qualification batches.

The release and stability specifications include relevant tests and limits, e.g. for appearance, identity, pH, extractable volume, purity tests (e.g. SE-HPLC, CE-SDS), assay of protein, a cell-based potency assay, visible and subvisible particles, sterility, bacterial endotoxins, and functional performance tests. All specific methods were validated.

Batch analysis data of several batches (clinical phase 1 and 3 batches, technical and supportive batches) were provided. All batch release data comply with the drug product specifications, which were valid at the time of batch release.

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The primary packaging consists of a 1 mL colourless USP/Ph. Eur./JP compliant polymer syringe with a staked-in, stainless steel needle, fitted with a rigid needle shield and sealed with a rubber plunger stopper.

The drug product is stored at 2 – 8°C, protected from light. Purity decreases slightly under the proposed storage conditions. However, all shelf-life acceptance criteria are fulfilled at the end of shelf life. A shelf life of 24 months has been accepted.

4.3 Quality Conclusions

The manufacturing processes (drug substance and drug product) are well described and demonstrate a consistent quality of drug substance and drug product. The shelf lives of the drug substance and drug product are supported by data from recommended storage conditions, as well as accelerated and stress studies. Safety concerns with regard to viral and non-viral contaminants were satisfactorily addressed. The risk for adventitious agents is minimised.

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5 Nonclinical Aspects

5.1 Pharmacology

Satralizumab demonstrated *in vitro* high affinity to soluble interleukin-6 receptor (sIL-6R) and membrane-bound IL-6R (mIL-6R) from humans and cynomolgus monkeys. The affinity to human IL-6R was pH-dependent and decreased significantly between pH 7.4 and pH 6.0 (K_D values for binding to human sIL-6R increased from 1.9 x 10^{-9} mol/L to 33.6 x 10^{-9} mol/L), which supports the proposed mechanism of antibody recycling following uptake in endosomes.
The neutralising activity of satralizumab against signalling via human or monkey sIL-6R and mIL-6R was shown *in vitro* in Ba/F3 cells. Satralizumab also inhibited the IL-6-dependent proliferation of activated human peripheral blood T-cells at low concentrations (IC_{50} 2.6 to 8.0 µg/mL), but not the IL-6-dependent growth of murine 7TD1 cells or activated rat splenic T-cells. This indicates that the antibody is not cross-reactive with mouse or rat IL-6R.
In an *in vitro* study, satralizumab only slightly reduced the IL-6-dependent IgG1 production by human plasmablasts. This raised concerns with regard to the propagated mode of action; however, clinical efficacy data superseded the results of this nonclinical study. Similarly, the lack of preclinical studies to support the proposed additional effects of blockage of IL-6 signalling in NMOSD patients (e.g. inhibition of Th17-T-cell formation) is accepted, since efficacy was evaluated in the clinical studies.
In vivo, a single subcutaneous (SC) administration of 2 mg/kg satralizumab to cynomolgus monkeys led to significant inhibition of IL-6-dependent production of C-reactive protein (CRP) for 28 days. The duration of the pharmacological effect correlated well with the longer plasma residence time of satralizumab compared to similar products. This is probably related to the proposed antibody recycling mechanism.
As expected for a monoclonal antibody, satralizumab showed *in vitro* highly targeted binding. It was not cross-reactive with gp130-family cytokine receptors other than IL-6R. In a tissue cross-reactivity study, the satralizumab-related staining was generally consistent with published reports of IL-6R expression and was comparable in tissues from humans and cynomolgus monkeys.
Based on the results of *in vitro* studies, the potential of satralizumab to induce antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) is considered low.
Dedicated safety pharmacology studies were not conducted. Cardiovascular and respiratory parameters were evaluated in the toxicity studies, and no effects were observed. No satralizumab-related abnormalities in behaviour and appearance were observed during the routine examinations up to exposure levels significantly above the clinical exposure. Notably, healthy monkeys (with intact blood-brain barrier, BBB) were used in the toxicity studies, whereas the BBB in NMO patients is impaired.

5.2 Pharmacokinetics

In studies with single intravenous (IV) or SC administration to cynomolgus monkeys, satralizumab displayed non-linear pharmacokinetics (PK) between 0.4 and 50 mg/kg. The mean plasma half-lives following SC administration ranged from 2.2 days to 22.7 days. Peak concentrations were reached after 3-4 days, and apparent bioavailability was between 62 and 78%, indicating slow but good absorption from the injection site. The PK in monkeys was similar to that in humans.
In monkey studies with weekly SC administration of 2 to 50 mg/kg, exposure increased approximately proportional to dose, and no sex-related differences in exposure were observed. As expected, there was accumulation of exposure with this treatment of 2.7-fold to 11.6-fold.
Satralizumab was immunogenic in monkeys. In general, the anti-drug antibodies (ADAs) formed under treatment had neutralising properties and led to a decreased exposure. Due to the low occurrence of ADA-positive animals in the high-dose groups, the validity of the toxicity studies was not affected by the immunogenic properties of satralizumab.
The applicant did not submit dedicated studies on the distribution, metabolism, and excretion of satralizumab, which is acceptable considering ICH S6(R1). The volume of distribution in monkeys (44.9 to 70.8 mL/kg) is close to the plasma volume, indicating limited tissue distribution potential. In

the enhanced pre- and postnatal development (ePPND) study, satralizumab crossed the placental barrier and was excreted in milk. This has implications for the recommendations for use during pregnancy and lactation.
Nonclinical studies on the PK drug interaction potential of satralizumab were not conducted, which is acceptable. Under disease conditions of increased IL-6, it is possible that the treatment leads to changes in CYP enzyme expression, as observed for similar products that affect IL-6 signalling. This is addressed in the information for healthcare professionals.

5.3 Toxicology

The cynomolgus monkey was selected for nonclinical safety assessment since it is a pharmacologically relevant species. The intended clinical route of administration was used in the pivotal toxicity studies, and the treatment frequency was once weekly.
The repeated dose toxicity studies included a 4-week IV study (non-GLP; 8, 40, or 200 mg/kg/week) as well as GLP-compliant 4-week and 26-week SC studies with doses of 2, 10, or 50 mg/kg/week. No local or systemic adverse effects were observed up to the highest dose levels (NOAELs). No parameter, except for an increase in plasma IL-6 levels (due to IL-6R blockage), was consistently changed in the studies. In satralizumab-treated males, a transient decrease in neutrophil count was seen in the 26-week study. Neutropenia also occurred in the clinical studies with satralizumab and is a common finding with anti-IL-6R antibodies. The exposure (AUC) of animals treated with 50 mg/kg per week at the end of the 26-week study was about 21-fold the estimated clinical exposure.
In line with ICH S6(R1), no genotoxicity studies were conducted with satralizumab. The applicant provided an adequate carcinogenicity risk assessment based on the available nonclinical and clinical data for satralizumab, published data on the role of IL-6 in malignancies, and clinical experience from other anti-IL6R antibodies. There is no particular concern with respect to a carcinogenic potential of satralizumab.
The assessment of fertility parameters in the 26-week toxicity study with sexually mature monkeys, including histopathology of reproductive organs, sperm analysis, and evaluation of menstrual cycling, did not reveal any satralizumab-related changes.
In the ePPND study (0, 2, or 50 mg/kg/week from gestation day 20 until delivery), no satralizumab-related effects were observed in the maternal animals except for increased IL-6 plasma levels. Increases in plasma IL-6 levels and systemic exposure to satralizumab were also measured in infants from satralizumab-treated animals up to Day 178 *post partum*. The incidences of pre- and postnatal losses in satralizumab-treated groups were similar to, or lower than, those in the control group, and no adverse effects on the development of foetuses or infants were observed. The mean T-cell-dependent antigen response (TDAR) was slightly lower, but this was considered non-adverse. The death of one infant in the high-dose group due to septicaemia was considered unlikely related to satralizumab due to lack of adverse effects on immune response in infants from satralizumab-treated animals and since the laboratory also reported a case of spontaneous septicaemia.
Additional toxicity studies included an *in vitro* blood compatibility study and an *in vitro* study to assess the cytokine release potential of satralizumab. Based on the results of these studies, the risk for serious reactions following administration of satralizumab is low. This is consistent with the lack of respective findings in the clinical trials.
Due to the protein structure of satralizumab, the risk for the environment is negligible.

5.4 Nonclinical Conclusions

Overall, the pharmacological properties of satralizumab as an anti-human IL-6R antibody were sufficiently characterised in the nonclinical studies. The toxicity studies in a pharmacologically responsive species did not reveal any adverse changes up to exposures significantly above the clinical exposure, which is consistent with the low spectrum of adverse reactions in the clinical trials. All safety-relevant preclinical data are mentioned in the information for healthcare professionals.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

The pharmacokinetics of satralizumab in patients with NMO/NMOSD and healthy subjects were analysed using a population pharmacokinetic approach.

ADME
The pharmacokinetics of satralizumab were described by a two-compartment model with parallel linear and Michaelis-Menten elimination. The subcutaneous bioavailability of satralizumab was 85.4%. The central (3.46 L) and peripheral (2.07 L) volumes of distribution were in the range typically observed for monoclonal antibodies. The linear clearance was 0.060 L/day, and the associated terminal half-life was approximately 30 days.

Special Populations / Intrinsic Factors
Body weight and presence of anti-drug antibodies, were found to affect the pharmacokinetics of satralizumab. However, based on the efficacy results, dose adjustments based on these factors are not required.
Effects of renal and hepatic impairment on the pharmacokinetics of satralizumab were not studied. Limited pharmacokinetic data from 8 paediatric patients (≥12 years) indicated that the pharmacokinetics of satralizumab in this age group is comparable to the pharmacokinetics in adults.

Interactions
No clinical interaction studies were conducted, as no direct interactions with enzymes or transporters involved in elimination of xenobiotics are expected for an antibody. However, an inhibitory effect of cytokine signalling on CYP expression is known from other antibodies that target signalling of IL-6 or IL-6R. This effect is expected for satralizumab as well and is appropriately labelled.

Pharmacodynamics - Mechanism of Action
Satralizumab is a recombinant humanised monoclonal antibody against soluble and membrane-bound human IL-6R. Satralizumab binding to IL-6Rs inhibits downstream signalling through these receptors.

6.2 Dose Finding and Dose Recommendation

Dose Finding
The dosing regimen selected for the phase III trials was based on the results of two clinical phase I studies:
In the single ascending dose study (SAD) SA-001JP, 60 healthy volunteers (both Japanese and Caucasian) were treated with 30, 60, 120 and 240 mg satralizumab as a subcutaneous (SC) injection. In the multiple ascending dose study SA-105JP, 33 patients with rheumatoid arthritis (RA) were treated with 30, 60 and 120 mg SC every 4 weeks (Q4W) after a loading dose with 120 mg SC every 2 weeks (Q2W) in the first month for up to 11 months. A dedicated dose finding in patients with NMOSD was not carried out.

The dose of 120 mg SC Q4W was chosen for the phase III studies BN40898 and BN40900 with NMO and NMOSD patients because this dose was the lowest dose that contributed to a "stable concentration" and a stable effect on the "pharmacodynamic markers" in patients with RA. In these two pivotal studies, a ≥ 95% blocking of soluble interleukin-6 receptor (sIL-6R) and cell-bound receptor (mIL-6R) could be calculated using popPK analysis for both ADA-positive and ADA-negative patients throughout the dose interval at the recommended dose at steady state, which is achieved by the end of the loading dose.

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Dose Recommendation
The recommended loading dose is 120 mg by SC injection at weeks 0, 2, and 4 for the first three administrations, followed by a maintenance dose of 120 mg every 4 weeks.
Satralizumab is intended for long-term treatment.

6.3 Efficacy

Trial Design and Study Demographics
Satralizumab was evaluated in two phase III, multicentre, randomised, placebo-controlled, double-blind studies (BN40898 and BN40900) that examined the efficacy and safety of satralizumab in patients with a diagnosis of AQP4-IgG seropositive or AQP4-IgG seronegative NMO (criteria in Wingerchuk 2006), or with a diagnosis of AQP4-IgG seropositive NMOSD (criteria in Wingerchuk 2007). In retrospect, these patients also met the latest criteria proposed by the international committee for the diagnosis of NMO (Wingerchuk et al. 2015).

A total of 178 patients were included in both studies. Study BN40898 enrolled 56.6% European, 2.4% North American and 41.0% Asian patients, whereas study BN40900 included 61.1% patients from North America, 28.4% from Europe and 10.5% from Asia.

Patients received the first 3 single doses of satralizumab 120 mg or matching placebo by SC injection in the abdominal or femoral region every 2 weeks for the first 4 weeks and once every 4 weeks thereafter.

Both studies were event-driven with a primary endpoint of time to first protocol-defined relapse (PDR) during the double-blind study period.

Study BN40898 (also known as SA-307JG or SAkuraSky)
Study BN40898 evaluated the effect of satralizumab in combination with stable IST (oral corticosteroids [OCs] up to 15 mg/day [prednisolone equivalent], azathioprine [AZA] up to 3 mg/kg/day or mycophenolate mofetil [MMF] up to 3,000 mg/day; adolescents received a combination of AZA and OCs or MMF and OCs). The study included 83 patients between the ages of 12 and 74 (including 7 adolescents: N=4 satralizumab, N=3 placebo), of whom 55 (66.3%) were AQP4-IgG seropositive.

A total of 41 patients were randomised to receive satralizumab and 42 were randomised to receive matching placebo (1:1 ratio).

Study BN40900 (also known as SA-309JG or SAkuraStar)
Study BN40900 evaluated the effect of satralizumab monotherapy compared to placebo. The study included 95 adult patients, of whom 64 (67.4%) were AQP4-IgG seropositive.

A total of 63 patients were randomised to receive satralizumab and 32 were randomised to receive matching placebo (2:1 ratio).

The double-blind phases of the pivotal studies were completed at the time of submission.

Patients treated with satralizumab had a median exposure of 115.1 weeks (placebo 42.5 weeks) in the double-blind phase of study BN40898 and a median exposure of 95.4 weeks (placebo 60.5 weeks) in study BN40900, before transfer to the open-label extension phase (OLE).

The OLE, during which all patients receive satralizumab, is ongoing at the time of approval. The final clinical study report is expected in 2023.

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After the first year of OLE there was an adjusted annualised relapse rate (aARR) of 0.40 (95% CI 0.28 - 0.56, n = 104), 0.20 (95% CI 0.12 - 0.34, n = 95) after the second year, 0.15 (95% CI 0.06 - 0.35, n = 64) after the third year, and 0.08 (95% CI 0.02 - 0.34, n = 38) after the fourth year.

Study Results
Treatment with satralizumab resulted in a statistically significant reduction in the risk of experiencing an adjudicated relapse as compared to placebo (hazard ratio [HR] [95% CI]: 0.38 [0.16-0.88]; p [log rank] = 0.0184) when administered in combination with stable IST.

When used as monotherapy, satralizumab resulted in a statistically significant reduction in the risk of experiencing an adjudicated relapse when compared to placebo (HR [95% CI]: 0.45 [0.23-0.89]; p [log rank] = 0.0184).

No statistically significant differences between satralizumab and placebo were demonstrated in either of the pivotal studies for the secondary endpoints “change in pain” and “change in fatigue” from baseline to week 24.

No statistically significant effect of satralizumab was observed in AQP4-IgG seronegative patients in either of the clinical studies.

Immunogenicity
Anti-drug-antibodies (ADAs) were observed in 41% (study BN40898) and 71% (study BN40900) of patients receiving satralizumab. The ability of these ADAs to neutralise satralizumab binding is unknown.
Although exposure was lower in ADA-positive patients, there was no evident impact of ADAs on safety and no clear impact on efficacy or pharmacodynamic markers indicative of target engagement.

6.4 Safety

The evaluation of safety for satralizumab is based on the primary analysis of the two pivotal phase III studies BN40898 and BN40900 in patients with NMO and NMOSD, which collectively provide safety data from 145 patients treated with satralizumab and 328 patient-years of exposure.

The mean / median duration of treatment with satralizumab was 92.3 and 93.7 weeks, respectively (placebo 64.0 / 42.6 weeks). Taking into account the open-label phase, during which all enrolled patients received satralizumab, the total treatment duration available for assessment was 114.3 / 110.9 weeks. In addition, supportive safety data is available from 72 healthy volunteers (study SA-001JP) and 33 RA patients (study SA-105JP).

No deaths have been reported in any of the clinical studies.

Adverse events (AEs) occurred in 86.5% of patients in the placebo group and 91.3% of patients treated with satralizumab.

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

3.8% of patients treated with satralizumab were withdrawn from trials due to adverse events, and 22.1% experienced dose interruptions due to adverse events (e.g. infections). These rates were comparable to rates seen in placebo-treated patients.

In 18.9% (placebo) and 18.3% (satralizumab) of patients, these were classified as “serious”, and in 5.4% (placebo) and 1.0% (satralizumab) the study was discontinued because of “serious AEs”.

For the "severe AEs" there was a percentage overhang in the satralizumab group (placebo 9.5% versus satralizumab 21.2%).

Serious drug-related adverse events, including infections, were reported in 2.9% of patients that received satralizumab treatment in the placebo-controlled portion of the clinical trials.

More frequently occurring AEs (≥ 5%) included headache (placebo / satralizumab 10.8% / 19.2%), nasopharyngitis (10.8% / 18.3%), arthralgia (1.4% / 13.5%), fatigue (4.1% / 8.7 %), rash (4.1% / 8.7%), depression (2.7% / 6.7%), pruritus (1.4% / 5.8%), hypoaesthesia (0% / 5.8%), leucocytopenia (0% / 5.8%) %) and IRRs (9.5% / 12.5%).

Description of Selected Adverse Drug Reactions from Clinical Trials

Infections
Infections occurred as AEs in 54.1% of patients in the placebo group and 59.6% of patients in the satralizumab group. The incidence of infections classified as “serious” or “severe” were comparable between the treatment groups (placebo versus satralizumab: “serious”: 8.1% versus 7.7%; “severe”: 4.1% versus 5.8%). Opportunistic infections were less common in the satralizumab group versus placebo (13.5% versus 6.7%). There was no evident increase of infection rates over time.

Anaphylaxis
Injection-related reactions (IRRs) occurred more often in patients receiving satralizumab as compared to placebo (13.5% versus 9.5%, respectively). None of the events was classified as “serious” and / or led to study discontinuation. In most cases, IRRs occurred after the first application of the drug.

Changes in blood count
9.6% of patients treated with satralizumab had grade 3 or 4 neutropenia as compared to 5.4% of patients receiving placebo. 5.8% in the satralizumab group and 4.1% of patients in the placebo group had grade 3 leucopenia. A grade 2 thrombocytopenia was documented in 1.9% of the patients treated with satralizumab.

Liver Enzymes
Elevations in ALT or AST occurred in 27.9% and 18.3%, respectively, of patients treated with satralizumab (monotherapy or in combination with IST), compared to 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 treatment interruption.
Elevations in ALT or AST >3x ULN (without concomitant increase in bilirubin) occurred in 2.9% (monotherapy) and 1.9% (combination with IST) of patients treated with satralizumab. One case of ALT-elevation above 5x ULN was observed 4 weeks after initiation of therapy in a patient receiving satralizumab in combination with IST, leading to drug discontinuation. After discontinuation, ALT values returned to normal.
No case of Hy`s law was documented.

Lipid Parameters
In 10.6% of patients receiving satralizumab there was a grade 1 increase in cholesterol (placebo 1.4%). There were no grade 3 or 4 increases in cholesterol.

Body weight increase
An increase in body weight ≥ 15% from baseline was observed in 4.8% of patients treated with satralizumab, compared to 2.7% of patients receiving placebo.

Suicidality
At baseline examination, suicidal ideation or suicidal behaviour were documented in a higher proportion of patients included in the satralizumab group (placebo 6.8%, satralizumab 20.2%). During

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the double-blind phase, suicidal ideation and suicidal behaviour occurred with equal frequency in both treatment groups (placebo 4.1%, satralizumab 4.8%).

Fibrinogen
A decrease in fibrinogen levels is a known effect of satralizumab related to its mechanism of action. 71.2% of satralizumab-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 satralizumab related to its mechanism of action. Decreases in C3, C4 and CH50 occurred in 66.7%, 56.9% and 89.6%, respectively, of satralizumab-treated patients, compared to 18.2%, 4.1% and 44.4% of patients receiving placebo.

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

The data from the two pivotal studies BN40898 (administration of satralizumab in combination with another IST) and BN40900 (satralizumab as monotherapy) provide strong evidence of the efficacy of satralizumab with regard to relapse prevention in patients with NMO and NMOSD who are AQP4-IgG seropositive.

In the pooled analyses of both studies, a 58% risk reduction of relapse occurence was observed under therapy with satralizumab versus placebo ($p = 0.0008$). For AQP4-IgG seropositive patients, the effect was even more pronounced, with a 75% risk reduction of relapse occurence ($p < 0.0001$). Meanwhile, no positive effect was found for AQP4-IgG seronegative patients.
Available data thus support the positive therapeutic effect of satralizumab in NMOSD patients with AQP4-IgG antibodies.
Consequently, the indication is limited to AQP4-IgG seropositive patients.
While the treatment effect has been demonstrated for a treatment period of 2 years, the longer-term efficacy of satralizumab cannot be finally assessed as long as the OLE study is still ongoing.

Seven adolescents between 12 and 17 years of age were included in study BN40898 (satralizumab: 4 patients; placebo: 3 patients). One patient in the satralizumab group and all three patients in the placebo group experienced a relapse during the double-blind phase. Due to the small number of cases, no reliable conclusion can be made about the efficacy of satralizumab in this age group.
Based on the following clinical considerations, however, it seems acceptable to grant treatment of patients aged ≥ 12 years:
i) In adolescent and adult patients with AQP4-positive NMOSD, the same pathomechanism is most likely.
ii) No age -specific safety signals were identified.
iii) Due to the rarity of NMOSD in adolescents, the conduction of an independent study in this age group might be difficult to be realised.

Safety data are limited with regard to the total number of patients exposed so far and the total length of exposure. It is thus possible that rare and possibly serious ADRs have remained undetected in the clinical study programme. To date and based on the available data, no prohibitive safety signals were observed.

In conclusion, in view of the high clinical need, the rarity of the disease and the established efficacy of satralizumab documented for at least 2 years, the overall benefit-risk is positive for the treatment (monotherapy or in combination with IST) of adult and adolescent patients with NMOSD who are AQP4-IgG seropositive.
However, as long as the final data from the OLE study are not available, the limitation of data concerning longer-term effects has to be acknowledged in the drug information.

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6.6 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Enspryng was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The MAH is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Enspryng®

Composition

Active substances

*S*atralizumabum (genetically produced in CHO [Chinese Hamster Ovary] cells).

Excipients

L-histidinum; acidum L-asparticum; L-arginini hydrocloridum; poloxamera 188; aqua ad iniectabilia q.s. ad solutionem pro 1,0 ml.

Pharmaceutical form and active substance quantity per unit

Solution for injection in pre-filled syringe.

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

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.

Indications/Uses

Enspryng is used as a monotherapy or in combination with immunosuppressive therapy (IST) for the treatment of neuromyelitis optica spectrumdisorders (NMOSD) in adult and adolescents in whom aquaporin-4 IgG antibodies are detected (i. e. who are AQP4 IgG seropositive).

Dosage/Administration

General

To ensure the traceability of biological medicinal products, it is recommended that the trade name and batch number be documented with every treatment.

Recommended dosage

Enspryng must be administered as subcutaneous injection.

Initiation of treatment / 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 therapy

The recommended maintenance dose is 120 mg SC injection every 4 weeks (from week 8).

Duration of treatment

Enspryng is intended for long-term treatment.

Dose adjustment following undesirable effects/interactions

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 permanently discontinued.

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 permanently discontinued.

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.

Combination therapy

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

Special dosage instructions

Patients with impaired hepatic function

The safety and efficacy of Enspryng have not been studied in patients with hepatic impairment (see section *"*Pharmacokinetics*,* Kinetics in specific patient groups").

Patients with impaired renal function

The safety and efficacy of Enspryng have not been formally studied in patients with renal impairment; however, 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 (*see*

section "Pharmacokinetics, Kinetics in specific patient groups". Patients with mild renal impairment were included in clinical trials, the pharmacokinetics of satralizumab in these patients was not impacted (*See section "Pharmacokinetics, Kinetics in specific patient groups").*

Elderly patients

The safety and efficacy of Enspryng have been studied in geriatric patients up to 74 years of age. No dose adjustment is required in patients ≥65 years of age (*see sections "Pharmacokinetics, Kinetics in specific patient groups").*

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

Children and adolescents

The safety and efficacy of Enspryng have been studied in a limited number (N=4) of adolescent patients ≥12 years of age. Pharmacokinetic, efficacy and safety results were consistent with those in adults (*see section "Properties/Effects, Clinical efficacy and section "Pharmakokinetics, Kinetics in specific patient groups"*).
The safety and efficacy of Enspryng in pediatric population <12 years of age have not been studied.

Delayed or missed administration

If an injection is missed, it should be administered as soon as possible; do not wait until the next planned dose. After the delayed or missed dose is administered, the treatment interval of 2 weeks (loading period) or 4 weeks (maintenance period) should be maintained between doses.

Administration schedule

The first injection must be performed under the supervision of a qualified healthcare professional (HCP). An adult patient/caregiver may administer subsequent injections of 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.

Mode of administration

Subcutaneous (SC) injection.
Enspryng must be administered as a subcutaneous injection
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".

Contraindications

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

Warnings and precautions

Infections

Delay Enspryng administration in patients with an active infection until the infection is resolved (*see section "Dosage/Administration, Delayed and Missed Doses"*). Patients with recurrent infections or patients suffering from underlying diseases that predispose to infections (e.g. diverticulitis, diabetes, and interstitial lung disease) should be treated with caution.

Immunosuppression
Under Enspryng the humoral immune response may be impaired.

Tuberculosis

As recommended for other immunomodulatory therapies, all patients should be examined for the presence of a latent tuberculosis infection before starting treatment with Enspryng. Patients with latent tuberculosis should be treated with standard antimycobacterial therapy before starting treatment with Enspryng.

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 5 xULN 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 “Dosage/Administration, Dose adjustment following undesirable effects”.

Hepatitis B reactivation

Hepatitis B reactivation has been reported with biologic therapies. In clinical studies with Enspryng, patients who screened positive for hepatitis were excluded.

Neutrophil count

As a result of treatment with Enspryng, there has been a decrease in neutrophil counts. Grade 3 and 4 neutrophil count decrease occurred in 9.6% of patients on Enspryng and in 5.4% of patients on placebo (see "Undesirable effects" section).
The neutrophil count should be monitored 4 to 8 weeks after the start of treatment and, depending on the clinical indication, also afterwards. Recommendations regarding the interruption of therapy: see section "Dosage/Administration".

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.

Caution is indicated when switching the treatment to a different pharmaceutical form and/or a different medicinal product with the same active substance. The patient should be monitored appropriately.

Malignancies

Immunomodulating drugs can increase the risk of malignancies.
The impact of treatment with Enspryng on the development of malignancies is not known.

Hypersensitivity reactions
Hypersensitivity reactions can occur in patients treated with biologics. Patients must be informed about possible symptoms of a hypersensitivity reaction before starting treatment.
The first injection must be administered under the supervision of a qualified healthcare professional.
If hypersensitivity reactions occur, patients must inform their doctor immediately and, if necessary, seek emergency medical attention.

Cardiovascular events

IL-6 receptor inhibitors can increase the risk of cardiovascular disease. Particularly patients with risk factors such as arterial hypertension, dyslipidemia and diabetes mellitus should therefore be monitored regularly (ECG, blood pressure measurement).

Lipid parameters
Increases in triglycerides and cholesterol (lipid parameters) have been observed in patients treated with Enspryng (see "Undesirable effects"). Patients with elevated lipid parameters should be treated according to current clinical guidelines for the treatment of hyperlipidaemia.

Activation of the complement system

Treatment with IL-6 receptor inhibitors may result in activation of the complement system. Based on the previous clinical data, no such effect has been observed under Enspryng. However, due to the limited data available, the risk for Enspryng in this respect cannot be assessed with certainty.

Demyelinating CNS diseases

During treatment with IL-6 receptor inhibitors, the occurrence of other inflammatory CNS diseases has been observed. Attention should be paid to symptoms that indicate an emerging demyelinating disease of the CNS. However, due to the limited data available, the risk for Enspryng in this respect cannot be assessed with certainty.

Diverticular/intestinal perforation
During treatment with IL-6 receptor inhibitors in rheumatoid arthritis (RA) patients, the occurrence of diverticular and intestinal perforation has been observed. In the pivotal studies with Enspryng, patients with a history of known diverticulitis were excluded. An increased risk of diverticular/intestinal perforation, as occurs with other inhibitors of the IL-6 receptor, cannot be ruled out under treatment with Enspryng. Enspryng should be used with caution in patients with a history of intestinal ulceration or diverticulitis. If acute abdominal pain occurs, patients should be examined immediately so that a gastrointestinal perforation can be detected early on.

Interactions

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

Pharmacokinetic interactions

The expression of hepatic CYP450 enzymes is suppressed by cytokines such as IL-6, for example, which stimulate chronic inflammations. Therefore, the expression of CYP450 could change when cytokine inhibition is initiated with Enspryng.
For this reason, patients taking drugs in individually adjusted doses that are metabolized by CYP450 3A4, 1A2 or 2C9 (e.g. atorvastatin, calcium channel blockers, theophylline, warfarin, phenytoin, cyclosporine or benzodiazepines), at the start and end of Enspryng therapy should be monitored and the dose of these substances adjusted if necessary. In view of its long elimination half-life, the efficacy of Enspryng on the activity of CYP450 enzymes can remain for several weeks after the treatment has ended.
Population PK analyses did not detect any effect of AZA, corticosteroids or MMF on the clearance of Enspryng.

Pregnancy, lactation

Pregnancy

There are no data from the use of Enspryng in pregnant women.
Studies in monkeys did not show any direct toxicity that affected pregnancy, foetal development and postnatal development. In animals, satralizumab passed the placental barrier. In animal descendants that had been treated with satralizumab some findings were possibly associated with the pharmacological effect on IL-6 (see section “Preclinical Data”, Reproductive toxicity). The clinical impact of these findings is unknown.
Enspryng must not be used during pregnancy unless the potential benefit for the mother outweighs the potential risk to the foetus.
Since satralizumab crosses the placental barrier, children of women treated with Enspryng may have an increased risk of infection; caution should be exercised when administering live vaccines to these children.
In women of childbearing age, consideration should be given to the use of an appropriate method of contraception during treatment and up to 5 months after the last Enspryng dose.

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 “Preclinical data”), women being treated with Enspryng should not breastfeed. In this case, the breastfeeding benefit for the child and the therapeutic benefit for the mother should be weighed against one another.

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 “Preclinical data”).

Effects on 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.

Undesirable effects

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 (BN40898 and BN40900), which includes 63 patients exposed to Enspryng monotherapy and 41 patients exposed to Enspryng in combination with IST (see section “Properties/Effects, Clinical efficacy”).

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

The available safety data are limited with regard to the number of patients exposed to Enspryng and the length of exposure. Potential relatively rare and possibly serious ADRs may not be detected in the study programme. Possible class effects with other IL-6 receptor inhibitors, such as intestinal perforations, opportunistic infections including tuberculosis, hepatitis B reactivation, increased cardiovascular risk, activation of the complement system, demyelinating diseases and malignancies cannot be excluded (see section "Warnings and precautions").

Tabulated summary of adverse drug reactions from clinical trials

Table 1 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 from clinical trials (Table 1) 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 <1/1’000), very rare (<1/10’000).

Table 1: Summary of ADRs occurring in patients treated with Enspryng as monotherapy or in combination with immunosuppressive therapy in clinical trials

Adverse reactions (MedDRA)	Number of patients (%)		Frequency Category for Enspryng
	Enspryng n=104	Placebo[1] n=74	
Infections and Infestations			
Urinary tract infections	18 (17,3%)	15 (20,3%)	very common
Upper respiratory tract infections	20 (19,2%)	12 (16,2%)	very common
Nasopharyngitis	19 (18,3%)	8 (10,8%)	very common
Influenza	5 (4,8%)	6 (8,1%)	common
Nervous system disorders			
Headache	20 (19.2%)	8 (10.8%)	Very common
Migraine	4 (3.8%)	0	Common
Injury, poisoning and procedural complications			
Injection-related reactions	13 (12.5%)	7 (9.5%)	Very common
Musculoskeletal and connective tissue disorders			
Arthralgia	14 (13.5%)	1 (1.4%)	Very common
Musculoskeletal stiffness	5 (4.8%)	0	Common
Skin and subcutaneous tissue disorders			
Rash	9 (8.7%)	3 (4.1%)	Common
Pruritus	6 (5.8%)	1 (1.4%)	Common
Psychiatric disorders			
Insomnia	6 (5.8%)	1 (1.4%)	Common
General disorders and administration site conditions			
Oedema peripheral	5 (4.8%)	0	Common
Blood and lymphatic system disorders			
Hypofibrinogenaemia	3 (2.9%)	0	Common
Respiratory, thoracic and mediastinal disorders			
Rhinitis allergic	4 (3.8%)	0	Common
Metabolism and nutrition disorders			

Hyperlipidaemia	14 (13.5%)	09 (12.2%	Very common
Blood and lymphatic system disorders			
Hypofibrinogenaemia	3 (2.9%)	0	Common
Investigations			
White blood cell count decreased	14 (13.5%)	4 (5.4%)	Very common
Blood bilirubin increased	2 (1.9%)	0	Common
Weight Increased	5 (4.8%)	2 (2.7%)	Common
Platelet count decreased	4 (3.8%)	2 (2.7%)	Common
Transaminases increased	7 (6.7%)	6 (8.1%)	Common

[1] placebo or placebo in combination with IST

Description of selected undesirable effects

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 injections. 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 order to adjust for the longer treatment duration in the satralizumab than in the placebo group the information on infections is presented in events per 100 PY (events occurring in 100 patients after one year of treatment) in addition to percentages.
In the Enspryng monotherapy study, frequencies of infections in patients treated with Enspryng were 99.8 events/100 PY (95% CI: 82.4, 119.8) or 34/63 patients [54.0% (95% CI: 40.94%, 66.61)] compared with patients receiving placebo [162.6 events/100 PY (95% CI: 125.8, 206.9)] or 14/32 patients [43.8% (95% CI: 26.36%, 62.34%)]. Frequencies of serious infections were 5.2 events/100 PY (95% CI: 1.9, 11.3) or 6/63 patients [9.5% (95% CI: 3.58%, 19.59%)] in patients treated with Enspryng compared with 9.9 events/100 PY (95% CI: 2.7, 25.2) or 3/32 patients [9.4% (95% CI: 1.98%, 25.02%)] in patients receiving placebo.

In patients treated with Enspryng in combination with IST, frequencies of infections were 132.5 events/100 PY (95% CI: 108.2, 160.5) or 28/41 patients [68.3% (95% CI: 51.91%, 81.92%)] compared with 149.6 events/100 PY (95% CI: 120.1, 184.1) or 26/42 patients [61.9% (95% CI: 45.64%,

76.43%)] in patients receiving placebo in combination with IST; frequencies of serious infections were 2.6 events/100 PY (95% CI: 0.3, 9.2) or 2/41 patients [4.9% (95% CI: 0.60%, 16.53%)] compared with 5.0 events/100 PY (95% CI: 1.0, 14.7) or 3/42 patients [7.1% (95% CI: 1.50%, 19.48%)] 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 4.8% 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 3 x ULN, were transient, and resolved without interruption of Enspryng.

Elevations in ALT or AST >3 x 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 5 x 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; 18.3% of patients receiving Enspryng experienced elevations in triglycerides above 3.42 mmol/L as compared with 6.8% of patients receiving placebo. The elevations in lipid parameters did not require dose interruption.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

No cases of overdose in patients with NMO or NMOSD have been reported.
There is no experience with overdose in patients with NMO or NMOSD.

Signs and symptoms

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.

Treatment

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

Properties/Effects

ATC code

L04AC19

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.

Pharmacodynamics

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

Clinical efficacy

The efficacy and safety of Enspryng was 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 (Ref: Wingerchuk et al 2015). The effect of Enspryng was studied in adult (studies BN40898 and BN40900) and adolescent (aged ≥12 to <18 years, total N=7 (N=4 Enspryng, N=3 placebo) 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 2.

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 2: 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 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 3.

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 3: 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

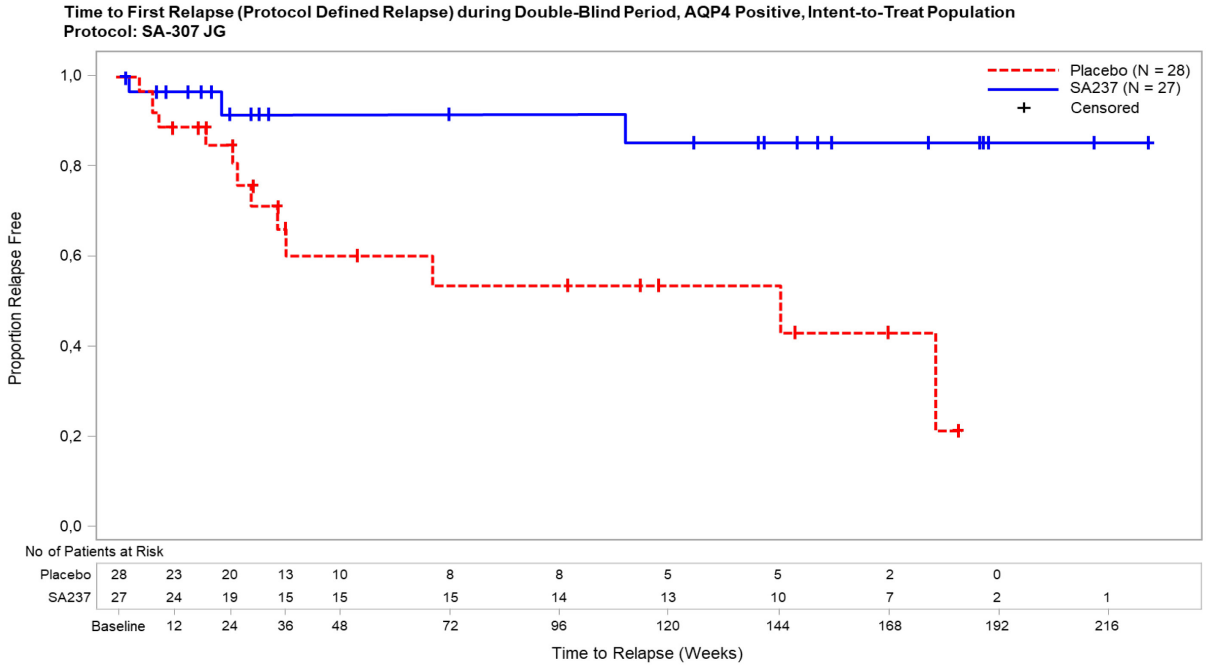
In the ITT population treatment with Enspryng resulted in a statistically significant 62% reduction in the risk of experiencing an adjudicated relapse (Hazard ratio [HR] [95% CI]: 0.38 [0.16-0.88]; p [log rank]=0.0184) when administered in combination with stable IST (Study BN40898) and 55% reduction 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.

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. (see table 4, Figures 1, Figure 2). 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. 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 not significant (BN40898 and BN40900 pooled: HR [95% CI]: 0.97 [0.41-2.33]).

Table 4: Key Efficacy Endpoints in Study BN40898 and BN40900 in AQP4-IgG-+seropositive patients

	BN40898		**BN40900**	
	Enspryng + IST	Placebo + IST	Enspryng	Placebo
Primary endpoint Analysis in 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 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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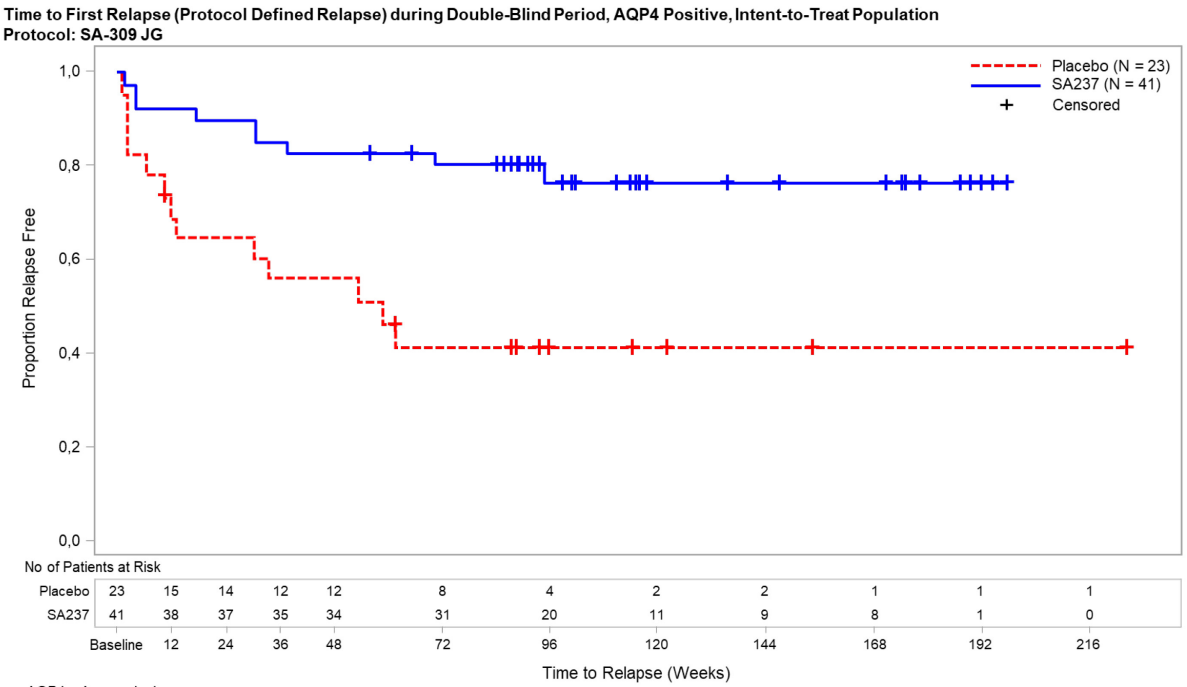
Figure 2: Study BN40900: Time to First Adjudicated Relapse during the Double-blind Period in AQP4-IgG seropositive Patients



AQP4 = Aquaporin-4
Protocol Defined Relapse: Adjudicated by the Clinical Endpoint Committee. EDSS assessment performed within 7 days of relapse reporting.
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Treatment with Enspryng in AQP4-IgG seropositive patients reduced the annualized rate of adjudicated relapses (ARR) by 88% in Study BN40898 and 90% in Study BN40900 compared to treatment with placebo (Table 5).

Table 5: Annualized adjudicated relapse rate during the double-blind period using negative binomial regression model

	BN40898		BN40900		Pooled	
	Placebo	**Enspryng**	**Placebo**	**Enspryng**	**Placebo**	**Enspryng**
AQP4-IgG seropositive patients	**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 AQP4-IgG seropositive patients by 61% in Study BN40898 and by 74% in Study BN40900.

Table 6: Use of rescue therapy in patients with any relapse during the double-blind period

	BN40898		BN40900		Pooled	
	Placebo	**Enspryng**	**Placebo**	**Enspryng**	**Placebo**	**Enspryng**
AQP4-IgG seropositive patients	**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 in AQP4-IgG seropositive patients reduced the risk of experiencing a severe relapse defined as an EDSS increase ≥ 2 points from the previous EDSS assessment by 85% in Study BN40898 and by 79% in Study BN40900 compared to treatment with placebo (Table 7).

Table 7: Time to first severe adjudicated relapse during the double-blind period

	BN40898		BN40900		Pooled	
	Placebo	**Enspryng**	**Placebo**	**Enspryng**	**Placebo**	**Enspryng**
AQP4-IgG seropositive patients	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)	

Treatment with Enspryng in AQP4-IgG seropositive patients reduced the risk of EDSS worsening from baseline by 65% in Study BN40898 and by 66% in Study BN40900 compared to treatment with placebo (Table 8).

Table 8 Time to Expanded Disability Status Scale (EDSS) Scores Worsening* during the Double-Blind Period (AQP4-IgG Seropositive Patients)

	BN40898		BN40900		Pooled	
	Placebo	**Enspryng**	**Placebo**	**Enspryng**	**Placebo**	**Enspryng**
AQP4-IgG seropositive patients	N=27	N=28	N=23	N=41	N=50	N=69
Patients with an event	12 (44.4%)	5 (17.9%)	11 (47.8%)	11 (26.8%)	23 (46.0%)	16 (23.2%)
Risk reduction	65% (HR: 0.35; 95% CI: 0.12, 1.00; p=0.0407)		66% (HR: 0.34; 95% CI:0.14, 0.82; p=0.0124)		69% (HR: 0.31; 95% CI: 0.16, 0.59; p=0.0002)	

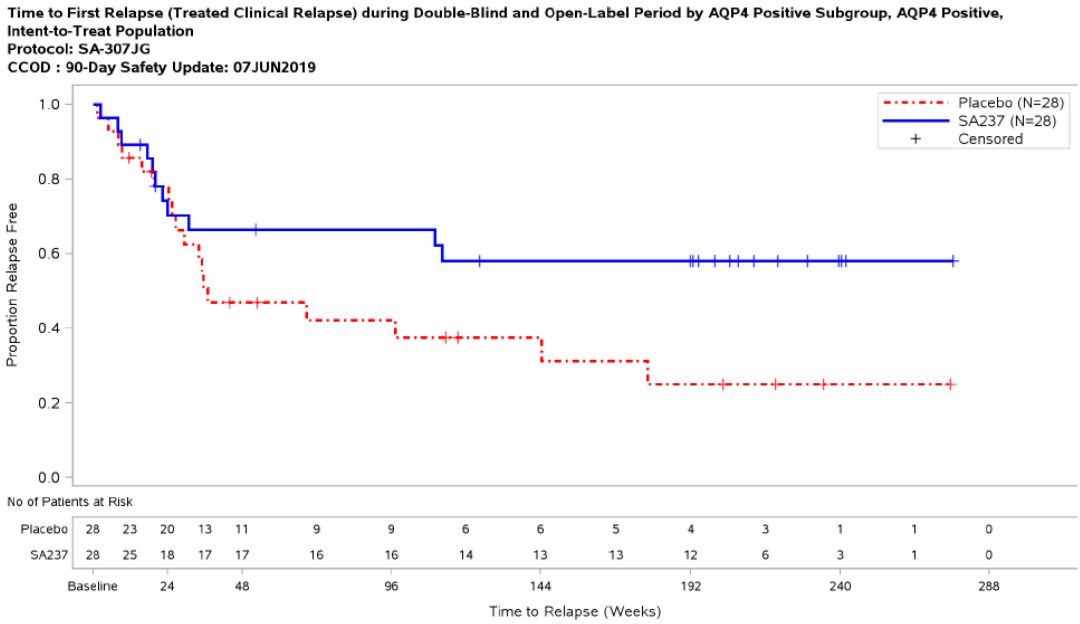
* EDSS worsening from baseline was defined based on the baseline EDSS as: a) worsening of ≥ 2 points in EDSS score for patients with baseline score of 0, b) worsening of ≥ 1 points in EDSS score for patients with baseline score of 1 to 5, c) worsening of ≥ 0.5 points in EDSS score for patients with baseline score of ≥ 5.5.

Open-Label Extension

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

Overall, only limited efficacy and safety data are available for treatment with Enspryng beyond 2 years.

Figure 3: 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).

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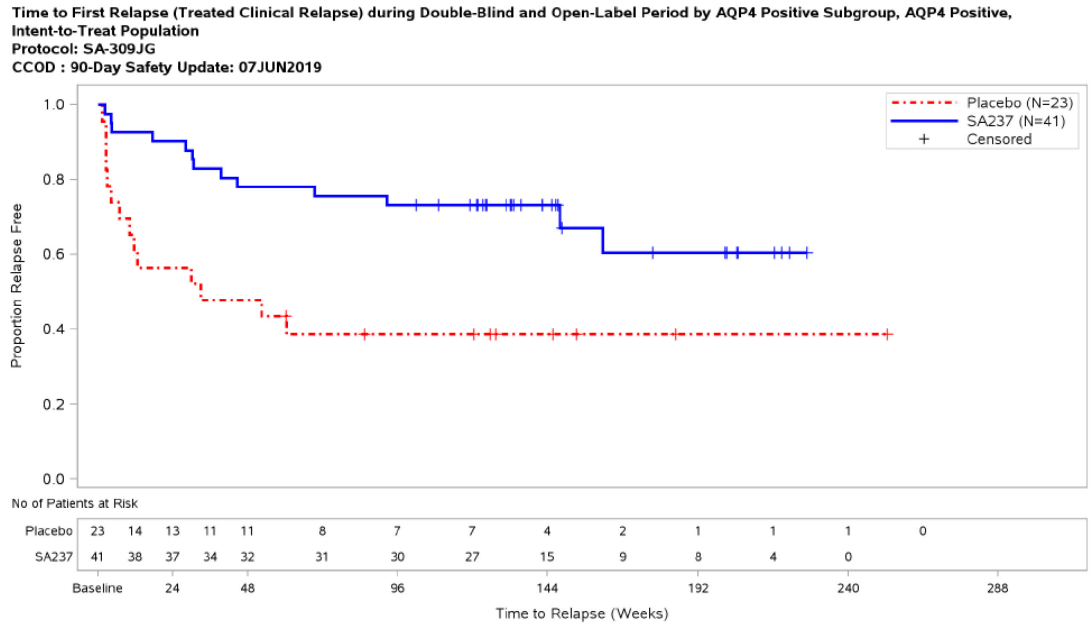
Figure 4: Study BN40900: time to first relapse (treated clinical relapse) during double-blind and open-label period in AQP4-IgG seropositive patients



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.

Further information

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 those patients who develop ADAs.

Pharmacokinetics

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.

The concentration-time course of Enspryng in patients with NMO or NMOSD could be 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}: 28.5 (10.2) mcg/mL, C_{max}: 42.7 (11.9) mcg/mL and AUC: 1020 (313) mcg.mL/day. Pharmacokinetics were not impacted by background immunotherapy (see section “Interactions”).

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 “Dosage/Administration). The bioavailability was high (85.4%, 95% CI: 0.795-0.953).

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).

Metabolism

The metabolism of Enspryng has not been directly studied. It is assumed that Enspryng is catabolically eliminated.

Elimination

The clearance of Enspryng is concentration-dependent. Linear clearance is estimated to be 0.0601 L/day (95% CI: 0.0524-0.0695) and accounts for approximately half of the total clearance at steady state using the recommended dose in NMO and NMOSD patients. The associated terminal $t_{1/2}$ is approximately 30 days (range 22-37 days) based on data pooled from the phase 3 studies.
Kinetics in specific patient groups

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

Hepatic impairment

No formal study of the effect of hepatic impairment on the PK of satralizumab has been conducted.

Renal impairment

No formal study of the effect of renal impairment on the PK of satralizumab has been conducted. however, 22 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.

Elderly patients

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.

Children and adolescents

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.

Preclinical data

Safety pharmacology / Long-term toxicity (or 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, 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 adverse effects 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 (blockage of IL-6R) of satralizumab. 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.

Genotoxicity

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

Antibodies are not expected to cause effects on the DNA.

Carcinogenicity

No carcinogenicity studies with satralizumab have been performed. Proliferate lesions have not been observed in a chronic cynomolgus monkey 6-month toxicity study.

Reproductive toxicity

Treatment of pregnant cynomolgus monkeys with up to 50 mg satralizumab per kg per week until birth did not cause any adverse effects on the dams, foetal development, the outcome of pregnancy or the survival and development of the young animals, including learning ability.

The antibody response to a T-cell dependent antigen was lower in offspring of satralizumab-treated animals than in offspring of control animals, which is probably related to the pharmacological effect on IL-6.

The offspring of satralizumab-treated dams had systemic exposure and showed increased plasma IL-6 levels up to 6 months after birth.

Satralizumab was detected in milk (< 0.9% of the respective plasma levels of the mother).

Other information

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the container.

Special precautions for storage

Store in a refrigerator at 2-8 °C.

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.

Do not shake. Do not freeze.

Keep the container in the outer carton in order to protect the contents from light

Keep out of the reach of children.

Instructions for handling

Enspryng is for single-dose only.
Keep the pre-filled syringe outside the folding box at room temperature for 30 minutes before use
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.

Authorisation number

67617 (Swissmedic).

Packs

Enspryng 120 mg/1 ml, solution for injectin in pre-filled syringes: 1 [A]

Marketing authorisation holder

Roche Pharma (Switzerland) Ltd., Basel.

Date of revision of the text

July 2020.