Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Satralizumab

Proprietary Product Name: Enspryng

Sponsor: Roche Products Pty Ltd

July 2021

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse event
AQP4	Anti-aquaporin 4 antibody
ARGPM	Australian Regulatory Guidelines for Prescription Medicines
ARR	Annualised relapsed rate
ARTG	Australian Register of Therapeutic Goods
AUC	Area under the concentration versus time curve
AusPAR	Australian Public Assessment Report
AZA	Azathioprine
BBB	Blood brain barrier
BW	Body weight
CEC	Clinical endpoint committee
CHO	Chinese hamster ovary
CI	Confidence interval
C_{max}	Maximum concentration
CNS	Central nervous system
CPD	Certified Product Details
CSF	Cerebrospinal fluid
C_{trough}	Trough concentration
DBP	Double blind period
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency (European Union)
EU	European Union

Abbreviation	Meaning
FcRn	Neonatal Fc receptor
FDA	Food and Drug Administration (United States of Amerca)
FSS	Functional systems score
HR	Hazard ratio
IgG2	Immunoglobulin G2
IL-6	Interleukin-6
IL-6R	Interleukin-6 receptor
ILD	Interstitial lung disease
IRR	Injection related reaction
IST	Immunosuppressive therapy
ITT	Intent to treat
IV	Intravenous
IxRS	Interactive Web Response and Voice Response System
LLOQ	Lower limit of quantitation
mAb	Monoclonal antibody
MMF	Mycophenolate mofetil
MRI	Magnetic resonance imaging
NAb	Neutralising antibody
NMO	Neuromyelitis optica
NMOSD	Neuromyelitis optica spectrum disorders
OC	Oral corticosteroids
OLP	Open label period
ON	Optic neuritis
PD	Pharmacodynamic(s)
PDR	Protocol defined relapse
PFS	Pre-filled syringe

Abbreviation	Meaning
PI	Product Information
PIP	Per intent protocol
PK	Pharmacokinetic(s)
PopPK	Population pharmacokinetic(s)
PT	Preferred Term
PY	Patient-Year
RO	Receptor occupancy
SAE	Serious adverse event
SC	Subcutaneous
sIL-6R	Serum soluble interleukin-6 receptor
SJS	Stevens-Johnson syndrome
SOC	System Organ Class
TFR	Time to first relapse
TGA	Therapeutic Goods Administration
US(A)	United States (of America)
UTI	Urinary tract infection
VAS	Visual analogue score
WBC	White blood cell

I. Introduction to product submission

Submission details

Type of submission:	New biological entity
Product name:	Enspryng
Active ingredient:	Satralizumab
Decision:	Approved
Date of decision:	13 November 2020
Date of entry onto ARTG:	17 November 2020
ARTG number:	326047
, *Black Triangle Scheme:*[1]	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia
Sponsor's name and address:	Roche Products Pty Limited Level 8, 30 – 34 Hickson Road, Sydney, NSW, 2000
Dose form:	Solution for injection
Strength:	120 mg/mL
Container:	Pre-filled syringe
Pack size:	One
Approved therapeutic use:	*Enspryng is indicated as monotherapy or in combination with immunosuppressive therapy (IST) for the treatment of adults with neuromyelitis optica spectrum disorders (NMOSD) who have an anti-aquaporin 4 antibody (AQP4)-IgG (also termed NMO-IgG) positive status.*
Route of administration:	Subcutaneous injection
Dosage:	Treatment should be initiated under the supervision of a physician experienced in the treatment of neuromyelitis optica spectrum disorders. Enspryng (satralizumab) may be used as monotherapy or in combination with immunosuppressive therapy (IST) such as oral

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

corticosteroids (OCs), azathioprine (AZA), or mycophenolate mofetil (MMF).

Loading dose

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

Maintenance dose

The recommended maintenance dose is 120 mg SC every 4 weeks. For further information regarding dosage, refer to the Product Information.

Pregnancy category: C

Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

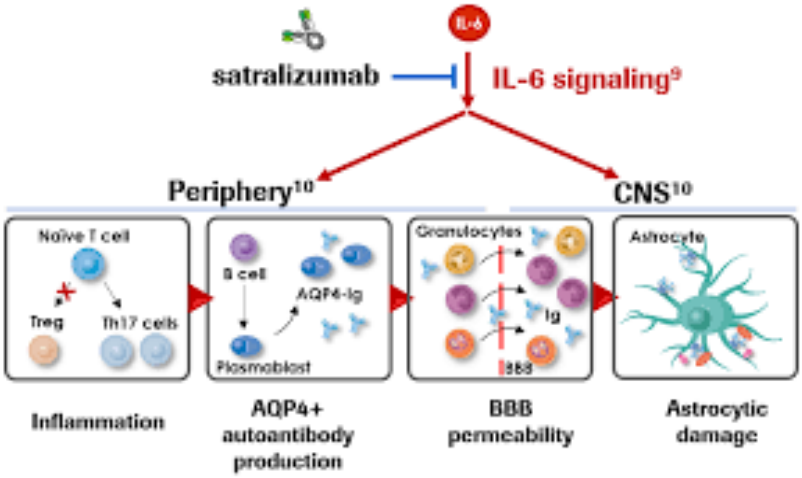
This AusPAR describes the application by Roche Products Pty Ltd (the sponsor) to register Enspryng (satralizumab) 120 mg/mL, solution for subcutaneous injection for the following proposed indication:

> *Enspryng is indicated as monotherapy or in combination with immunosuppressive therapy (IST) for the treatment of adult and adolescent patients from 12 years of age with neuromyelitis optica spectrum disorders (NMOSD).*

Satralizumab is a first in class recombinant humanised engineered immunoglobulin G2 (IgG2) monoclonal antibody (mAb), derived via genetic modification in a non-human species (Chinese hamster ovary cells). The IgG2 mAb targets the human interleukin-6 receptor (IL-6R) and blocks interleukin-6 (IL-6) from binding to both membrane-bound and serum-soluble IL-6R (sIL-6R) sites, thereby inhibiting IL-6 signalling pathways. Satralizumab is therefore a humanised anti-human IL-6R monoclonal antibody.

The mechanisms of the actions of satralizumab, and the downstream consequences, are summarised in Figure 1, below.

Figure 1: Mechanism of satralizumab



Satralizumab is a humanised anti-interleukin 6 receptor monoclonal recycling antibody. The inhibition of downstream IL-6 receptor signalling has effects on both the periphery, including reduced inflammation and reduced auto-anti-aquaporin 4+ (AQP4+) production; and in the central nervous system (CNS), the reduced inflammation is believed to lower blood-brain barrier permeability and subsequent astrocytic damage from inflammatory mediators.

Neuromyelitis optica (NMO) and neuromyelitis optica spectrum disorder (NMOSD, also sometimes known as Devic's disease) are rare, potentially life-threatening inflammatory disorders of the central nervous system (CNS). They are characterised by severe, immune-mediated demyelination and axonal damage that predominantly target the spinal cord and optic nerve.

IL-6 is a cytokine that plays a key role in the immuno-pathogenesis of both NMO and NMOSD. For a start, increased levels of IL-6 are found in both NMO and NMOSD patients' serum and cerebrospinal fluid (CSF) during episodes of disease severity and activity (that is, relapses). IL-6 also functions to increase blood-brain barrier (BBB) permeability, thereby facilitating CNS tissue penetration of white blood cells (such as neutrophils) and autoantibodies.

Aquaporin-4 (AQP4), is a water channel protein encoded by the AQP4 gene in humans. AQP4 belongs to the aquaporin family of integral membrane proteins (*AQP1, 3, 4, 5, 8, 9, and 11*) that conduct water through the cell membrane. In the CNS tissue, AQP4 is the most prevalent aquaporin channel, specifically located at the perimicrovessel astrocyte foot processes at the BBB, spinal cord and optic nerve. When activated, this channel commonly facilitates water movement near cerebrospinal fluid and vasculature and in some cases, small solutes across the membrane. AQP4 is involved in CNS tissue water balance, neuro-excitation, astrocyte migration and neuroinflammation stability. The presence of anti-AQP4 antibodies (anti-AQP4-IgG positive) in the systemic blood is associated with the main pathogenesis of NMO and NMOSD. Anti-AQP4-IgG can penetrate the BBB and react with AQP4 in astrocyte feet, along with the recruitment and activation of complement, to produce complement dependent cytotoxicity. In addition, effector cells, such as natural killer cells, are activated and induce antibody dependent cytotoxicity, which triggers astrocyte damage. Complement activation and astrocyte derived cytokines attract inflammatory cells including eosinophils, neutrophils, and macrophages, giving rise to further BBB damage and thus enhancing the entry of anti-AQP4-IgG into the CNS.

Furthermore, inflammatory cell degranulation and astrocyte damage induce secondary injury of oligodendrocytes, resulting in accelerated myelin sheath loss, axonal injury, and associated neurological deficits. Accordingly, anti-AQP4-IgG positive NMO and generally NMOSD are characterised by pathological changes which include loss of astrocytic AQP4 and the myelin sheath, axonal injury, perivascular deposition of anti-AQP4-IgG and

activated complement components, macrophage accumulation, and inflammatory infiltration with granulocytes.

A plasmablast B cell subset (phenotype: $CD19^{int}CD27^{high}CD38^{high}CD180^{-}$ and $CD20^{-}$) was identified to be associated with the production of anti-AQP4 antibodies.[2] The survival activity of this B cell subset was promoted by IL-6. This finding suggests a pivotal role for IL-6-dependent B-cell subpopulation in the pathogenesis of anti-AQP4-IgG positive NMO and generally NMOSD.

However, while some IL-6 functions can be directly linked to the presence of relevant autoantibodies production that is anti-AQP4-IgG, other IL-6 damaging functions could be autoantibodies production independent, as mentioned above. As previously alluded to, satralizumab was studied in both anti-AQP4-IgG seropositive and seronegative NMO patients and by inclusion criteria, in only anti-AQP4-IgG seropositive NMOSD patients.

A beneficial effect of IL-6R blockade in anti-AQP4-IgG positive NMO and generally NMOSD has been suggested in several small open label studies. Satralizumab specifically targets the human IL-6R sites and blocks IL-6 from binding to both membrane-bound and soluble IL-6R sites, thereby inhibiting IL-6 signalling.

Satralizumab has no current therapeutic indication on the Australian Register of Therapeutic Goods (ARTG) in Australia. There are currently no approved treatments for NMO and NMOSD, neither in Australia nor in the European Union (EU).

Acute relapses are typically treated with high dose corticosteroids, followed by gradual tapering or plasmapheresis.

Relapse prevention is the paramount treatment objective in both NMO and NMOSD, which are currently treated with off-label immuno-suppressive therapies (IST) such as azathioprine (AZA), mycophenolate mofetil (MMF) and rituximab, based on experience from small uncontrolled trials, case series or case reports. However, no randomised controlled trials have been reported that have established the efficacy and safety of these unapproved therapies in NMO and NMOSD.

Regulatory status

This product is considered a new biological entity for Australian regulatory purposes.

At the time the TGA considered this application, a similar application had been approved in United States of America (USA) on 14 August 2020, Switzerland on 13 July 2020, Canada on 1 June 2020 and Japan on 29 June 2020. Enspryng was under consideration in EU and Singapore.

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
European Union Centralised procedure via Rapporteur: Sweden Co-rapporteur: Spain	20 August 2019	Under consideration	Under consideration

[2] Chihara N, Aranami T, Oki S, et al. Plasmablasts as migratory IgG-producing cells in the pathogenesis of neuromyelitis optica. PLoS One. 2013;8(12):e83036. December 2013.

Region	Submission date	Status	Approved indications
United States of America	15 August 2019	Approved 14 August 2020	*Enspryng is indicated for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive*
Switzerland	25 October 2019	Approved 13 July 2020	*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 lgG antibodies are detected (that is who are AQP4 lgG seropositive).*
Canada	15 November 2019	Approved 1 June 2020	*Enspryng (satralizumab) is indicated as monotherapy or in combination with immunosuppressive therapy (IST) for the treatment of neuromyelitis optica spectrum disorders (NMOSD) in adult and adolescent patients who are anti-aquaporin 4 (AQP4) seropositive. Enspryng is not intended for acute treatment of an NMOSD relapse.*
Singapore	9 September 2020	Under consideration	Under consideration
Japan	8 November 2019	Approved 29 June 2020	*Enspryng is indicated in prevention of relapses of neuromyelitis optica spectrum disorders (NMOSD), including neuromyelitis optica (NMO) to patients who are positive for anti-AQP4 antibodies.*

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2019-04752-1-1

Description	Date
Submission dossier accepted and first round evaluation commenced	2 December 2019
First round evaluation completed	3 June 2020
Sponsor provides responses on questions raised in first round evaluation	26 June 2020
Second round evaluation completed	24 July 2020
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	1 September 2020
Sponsor's pre-Advisory Committee response	14 September 2020
Advisory Committee meeting	1 and 2 October 2020
Registration decision (Outcome)	13 November 2020
Completion of administrative activities and registration on the ARTG	17 November 2020
Number of working days from submission dossier acceptance to registration decision*	219

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

There are no objections on quality grounds to the approval of satralizumab (Enspryng).

Satralizumab is a recombinant humanized monoclonal antibody based on a human IgG2 framework containing heavy chain V_H and light chain V_κ subgroup sequences. Satralizumab was designed by humanization and further amino acid substitutions to

improve some functional properties such as pH-dependent binding to its antigen (IL-6R) and binding to neonatal Fc receptor (FcRn). The recombinant humanized monoclonal antibody is produced in Chinese hamster ovary (CHO) cells and consists of two heavy chains (443 amino acid residues each), and two light chains (214 amino acid residues each). The mouse-derived amino acid sequences that remained in the framework region have been replaced by human antibody amino acid sequences. The structure and amino acid sequence of the satralizumab are shown in, Figure 2 and Figure 3 respectively.

Figure 2: Amino sequence for light chain of satralizumab

DIQMTQSPSS LSASVGDSVT ITCQASTDIS SHLNWYQQKP GKAPELLIYY GSHLLSGVPS
RFSGSGSGTD FTFTISSLEA EDAATYYCGQ GNRLPYTFGQ GTKVEIERTV AAPSVFIFPP
SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT
LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC

The calculated molecular mass of the light chain is 23,185 Da (cysteine residues are in the reduced form).

Figure 3: Amino acid sequence for heavy chain of satralizumab

QVQLQESGPG LVKPSETLSL TCAVSGHSIS HDHAWSWVRQ PPGEGLEWIG FISYSGITNY
NPSLQGRVTI SRDNSKNTLY LQMNSLRAED TAVYYCARSL ARTTAMDYWG EGTLVTVSSA
STKGPSVFPL APSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG
LYSLSSVVTV PSSNFGTQTY TCNVDHKPSN TKVDKTVERK SCVECPPCPA PPVAGPSVFL
FPPKPKDTLM ISRTPEVTCV VVDVSQEDPE VQFNWYVDGV EVHNAKTKPR EEQFNSTFRV
VSVLTVVHQD WLNGKEYKCK VSNKGLPAPI EKTISKTKGQ PREPQVYTLP PSQEEMTKNQ
VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPMLDSDG SFFLYSKLTV DKSRWQEGNV
FSCSVMHEAL HAHYTQKSLS LSP

The calculated molecular mass of heavy chain with carbohydrate is 49,966 Da.

The glycosylation site at Asn295 is shown as N (position 297 according to generic Eu numbering system.[3]

Proposed conditions of registration

Laboratory testing and compliance with Certified Product Details:

All batches of Enspryng supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

When requested by the TGA, the sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index and periodically in testing reports on the TGA website.

Certified Product Details

The CPD, as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) [http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm], in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

[3] Edelman, et al. The covalent structure of an entire γG immunoglobulin molecule. *Proceedings of the National Academy of Sciences*.1969; 63 (1): 78-85.

Nonclinical

The overall quality of the nonclinical dossier was high. All pivotal safety-related studies were Good Laboratory Practice guidance compliant.

In vitro, satralizumab bound to human and cynomolgus monkey (but not rat or mouse) IL-6R with nanomolar affinity and inhibited both IL-6R classical (membrane-bound) signalling and trans-signalling (soluble IL-6R). Satralizumab also inhibited antibody production in human plasmablasts (potential mechanism contributing to NMOSD pathophysiology). *In vivo*, satralizumab inhibited IL-6-stimulated plasma C-reactive protein production and suppressed free sIL-6R levels. There was no direct *in vivo* evidence in the sponsor's submitted dossier to support the proposed indication.

No off-target sites were identified in a panel of human tissues. Satralizumab is not expected to induce complement-dependent cytotoxicity or antibody-dependent cellular cytotoxicity.

Examination of safety pharmacology (incorporated into general repeat-dose toxicity studies) revealed no effects of satralizumab on CNS or respiratory function, or on electrocardiogram parameters in monkeys. Thus, no adverse effects on the cardiovascular, respiratory and central nervous systems are predicted during clinical use.

The pharmacokinetics (PK) of satralizumab in monkeys and human subjects was generally consistent with the protein nature of the drug: long half-lives and limited distribution.

Repeat-dose toxicity studies by the SC route were conducted in cynomolgus monkeys (up to six months). The studies were adequately conducted, achieving high relative exposures. No target organs for toxicity were identified. Blood IL-6 levels were increased in treated animals.

No genotoxicity studies were conducted. Given the protein nature of the drug this is considered acceptable. No carcinogenicity studies were conducted. No proliferative lesions were seen in the repeat-dose toxicity study. However, a risk of malignancy secondary to the immunomodulatory functions of satralizumab cannot be discounted. This risk is expected to be similar to other IL-6R antibody based drugs.

No adverse effects on surrogate male or female fertility endpoints were seen at high satralizumab exposures in the pivotal repeat-dose toxicity study. The concentration of satralizumab in milk was very low in lactating monkeys. Satralizumab crosses the blood-placenta barrier and given the long half-life, infants will be exposed for part of the first year of life. However, in an enhanced pre/postnatal study in monkeys, no adverse embryofetal or postnatal effects were evident. The only notable effects were a significant increase in circulating IL-6 levels and a slight impairment of the T-cell dependent antibody responses in infants following maternal exposure. These effects are a pharmacological consequence of blocked IL-6R. A reversible effect on immunocompetence may be seen in infants exposed to satralizumab during the last stages of pregnancy.

There were no notable injection site reactions in monkeys following SC administration of satralizumab.

Satralizumab was immunogenic in cynomolgus monkeys and some anti-drug antibodies (ADA)-positive animals showed neutralising activity, with a consequential reduction in satralizumab exposures. Therefore, ADAs in patients may result in reduced satralizumab exposures and possibly reduced efficacy.

There was no effect on lymphocyte populations or cytokine levels, excluding IL-6 levels, or organs of the immune system in repeat-dose toxicity studies. Some impairment of T-cell dependent antibody responses was seen in infant monkeys following maternal exposure to satralizumab during gestation. Based on its mechanism of action, an effect on immunocompetence may be seen in patients.

There are no issues of concern with the excipients used in the proposed formulation as all of them are currently used in other registered injectable products.

The Pregnancy category should be revised from B1;[4] to C.[5]

There are no nonclinical objections to the registration of satralizumab

Clinical

The clinical dossier contains:

- Two Phase I clinical pharmacology studies, SA-001JP and SA-105JP
- Two population pharmacokinetics (PopPK) reports
- Two pivotal efficacy/safety Phase III studies, BN40898 and BN40900
- One paediatric investigation report
- One bias assessment report
- Eighty literature references

Pharmacology

Pharmacokinetics

Other than two Japanese Phase I studies (Studies SA-001JP and SA-105JP), which had been translated into English, much of the PK data in adults, and all the PK data in adolescents (aged 12 to 17 years old, inclusive), were derived from population pharmacokinetic (PopPK) analyses that used sparse PK data from two Phase III clinical trials (Studies BN40898 and BN40900).

[4] Category B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals have not shown evidence of an increased occurrence of fetal damage.
[5] Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

Table 2: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK Single ascending dose	SA-001JP	*
	Multi-dose	No studies	
PK in special populations	Target population	PopPK	
	Hepatic impairment	No studies	
	Renal impairment (mild)	PopPK	
	Adolescents (12 to 17 years old, inclusive)	PopPK	
	RA (multiple ascending dose)	SA-105JP	*
Gender/genetic related PK	Males versus females	PopPK	
	Effect of race (Japanese versus Caucasian)	SA-001JP	*
PK interactions		No studies	
Population PK analyses	Healthy subjects/target population (adults and adolescents aged 12-17)	1094498 1093049**	*

PK = pharmacokinetics; PopPK = population pharmacokinetics; RA = rheumatoid arthritis

* Indicates the primary PK aim of the study.

** A summary of report Study 1093049 is not included in the summary of PK studies, since this PopPK analyses section initially included subjects with rheumatoid arthritis from Study SA-105JP, which were later excluded due to differences in PK from subjects with NMO and NMOSD. In addition, subject data from Study BN40900 were not included in this PopPK analysis. In contrast, report from Study 1094498 included data from SA-001JP and sparse PK data from Studies BN40900 and BN40898.

There were no PK studies that had their results excluded from consideration.

Pharmacokinetics according to age

No Phase I studies were undertaken in the target population. The PopPK analyses included adult and adolescent subjects (aged 12 to 17 years old, inclusive) with NMO and NMOSD.

PK in adolescent subjects (aged 12 to 17 years old, inclusive) and PK in elderly subjects (aged 65 years and older) were evaluated in the PopPK analysis and were determined to be generally consistent with the PK in adults aged 18 to 64 years old, inclusive. Exposure for mean trough concentration (C_{trough}), maximum concentration (C_{max}) and area under concentration versus time curve (AUC) was lower in the adolescent population versus the adult population by 33.8%, 27.6% and 29.7%, respectively, in Study BN40898. These results were consistent with the difference in mean body weight (BW) between adolescents (79.3 kg) and adults (61.5 kg), in which there appears to be an inverse relationship between BW and exposure.

Pharmacokinetics according to anti-drug antibody status

In Study SA-001JP, 54.2% (n = 39) of healthy adults developed anti-satralizumab antibodies, irrespective of race status (Japanese or Caucasian), route of administration (SC or intravenous (IV)) or satralizumab dose (30 mg to 240 mg). No significant differences in the time course of serum satralizumab concentrations of subjects who tested negative or positive for ADAs were reported. In Study SA-105JP, ADAs were detected in 6.1% (n = 2; 1 tested immunoglobulin E (IgE) positive) of subjects. Serum satralizumab concentrations decreased below the lower limit of quantitation (LLOQ) after ADAs were detected in the extension period.

In the PopPK analysis, NMO and NMOSD subjects in the Phase III studies who had at least one available ADA sample result (39% (n = 25) in BN40898 and 56% (n = 45) in Study BN40900), demonstrated treatment induced persistent ADAs up to the clinical cutoff date. Similar incidence was noted in paediatric subjects in Study BN40898, with 71.4% (n = 5) adolescents being ADA positive at some time. Incidence of ADAs showed similar results for the vial and pre-filled syringe (PFS) formulations. ADAs were found with higher incidence in subjects with higher BW (that is lower exposure). ADAs led to lower (13%) SC bioavailability at all timepoints and an increase (approximately 20%) in total clearance.

Model predictions following 120 mg SC satralizumab four weekly dosing, at steady-state, indicated high median IL-6R occupancy (RO) in ADA-positive subjects, close to 100% at peak, and maintained at approximately 95% at trough versus ADA-negative subjects who maintained values close to 100% throughout the dose interval. These findings indicated that there was high saturation of the nonlinear elimination pathway during the whole dosing period.

Conclusions on pharmacokinetics

Model-estimated PK parameters, such as half-life, time to steady state and volume of distribution were generally consistent with the results from designated PK studies.

The key assumptions in the development of the final PopPK model appeared to be reasonable and the sponsor's conclusions appeared to be supported by the data. No dose-adjustment is necessary based on sex, race, mild renal impairment or formulation (vial versus PFS)

Correlations between higher body weight, lower exposure and higher probability of developing ADAs were observed in adults and adolescents. This may have implication for efficacy and safety. Also, a greater proportion of adolescents (71.4%) developed ADAs compared with all pooled adult (approximately 52%) subjects across the double blind and open label aspects of each Phase III study. However, this finding should be interpreted with caution, given the small number of adolescent subjects who participated in Study BN40898.

PK parameters were generally consistent with tocilizumab (an IL6 inhibitor) except for linear clearance, which was in the lower range (as designed through protein engineering).

Conditions of approval

The Delegate had recommended the following as condition of approval.

The sponsor undertaking to:

- have closer examination of the statistical power of the studies to elucidate the sub-group analyses for efficacy per weight; and
- to carry out exploration of the optimal receptor occupancy related to therapeutic efficacy, so as to inform whether exposures in certain weight groups is more than required for the chosen dosage regimen.

Pharmacodynamics

The submitted pharmacodynamic (PD) studies are summarised in Table 3. Since much PD data in this application were derived from the Phase III studies in NMO and NMOSD (Study BN40900 and BN40898).

Table 3: Studies providing pharmacodynamics information

PD Topic	Subtopic	Study ID	*
Primary Pharmacology	Effect on serum IL-6	SA-001JP SA-105JP	* *
	Effect on serum sIL-R6	SA-001JP SA-105JP	* *
Secondary Pharmacology	Effect on QT interval	Pop PD	
	Effect on serum CRP	SA-001JP SA-105JP	* *
	Effect on serum complement (CH50, C3, C4)	SA-001JP	*
	Effect on fibrinogen**		
Gender other genetic and Age-Related Differences in PD Response	Effect of gender	SA-105JP	
	Effect of race (Japanese versus Caucasian)	SA-001JP	*
	Effect of age (adolescence)	Pop PD	
PD Interactions		No studies	
Population PD analyses	Healthy subjects/target population (adults and adolescents aged 12-17)	Report 1094498	*

IL-6 = interleukin 6; sIL-R6 = soluble interleukin 6 receptor; CRP = C-reactive protein; PD = pharmacodynamics.

* Indicates the primary PD aim of the study.

**Fibrinogen data were provided to the study sites throughout the DBP for safety reasons.

Conclusions on pharmacodynamics:

- Generally, PD data provided in the clinical dossier were sufficiently comprehensive to support the proposed indication of satralizumab in adults and adolescents with NMO and NMOSD
- There is no universally accepted PD biomarker for NMOSD and extrapolation of PD results from adults to adolescents, is regarded as supportive of efficacy and safety. In that regard, the PD responses were generally consistent between adult and adolescent subjects

- Plasma concentration-effect relationships were defined for many important secondary PD effects, including effects on QT interval;[6] and dose-related effects on soluble IL-6R, IL-6R, IL-6, high-sensitivity C-reactive protein (hsCRP) and complement components (CH50, C3 and C4). Notwithstanding the fact that PK of satralizumab are nonlinear, the secondary PD effects were generally consistent with C_{max} and total exposure (AUC).
- The predicted results from exposure-response *post hoc* analyses of the Phase III studies, did not reveal clinically meaningful effects of satralizumab treatment on QT prolongation. QT analyses outcome should be interpreted with caution, since correction for circadian variation could not be performed properly.
- Major anticipated clinical safety concerns, based on the claimed mechanism of action, relate to immune-related events. The following immune-related events are evaluated in
  - Enhanced risk of development of serious and opportunistic infections, especially in combination with ISTs
  - Enhanced risk of development of malignancies, especially in long-term combination with ISTs
  - Enhanced risk of hypersensitivity reactions, including anaphylaxis, from the development of anti-satralizumab antibodies.

Dosage selection

Data from healthy adults (Study SA-001JP) showed that the mean increase in sIL-6R stabilisation level (reflected target engagement) and the mean decrease in serum CRP level (an inflammatory biomarker, to below the LLOQ < 50 ng/mL) within the first 28 days, were similar between the 120 mg and 240 mg subcutaneous SC satralizumab doses. Lower treatment effects were observed with the 60 mg dose regimen.

These findings were confirmed in subjects with rheumatoid arthritis (Study SA-105JP), which demonstrated that a dose of 120 mg SC satralizumab administered as a loading dose (that is 120 mg x 3 doses at two week intervals), followed by a maintenance dose of 120 mg every four weeks, resulted in sustained and stable sIL-6R concentrations for the duration of treatment. Also, since rheumatoid arthritis subjects generally had higher circulating IL-6 levels and larger differences in baseline PD biomarkers relative to the normal range, as compared with NMO and NMOSD subjects, a dose-regimen that achieved sustained blockade in IL-6 signalling in rheumatoid arthritis might be expected to achieve adequate suppression of IL-6 signalling in a NMO/NMOSD population.

Furthermore, the median predicted occupancy at the IL-6R in NMO and NMOSD subjects was maintained at > 95% throughout the dose-interval at the proposed dose at steady-state, which is achieved by the end of the loading phase. Robust and sustained sIL-6R stabilisation and increases in IL-6 were seen to parallel the satralizumab concentration-time course, which were maintained for the study duration. At median steady-state concentrations achieved in the Phase III studies, the effective satralizumab half-life was approximately 30 days, based on pooled Phase III data, which supported the proposed maintenance dose interval of every four weeks.

However, the Delegate is of the view that finding from Study SA-105JP can only have an assumptive interpretation given then variations in PK data for RA and NMO/NMOSD patients.

[6] The **QT interval** is the time from the start of the QRS wave complex to the end of the corresponding T wave. It approximates to the time taken for ventricular depolarisation and repolarisation, that is to say, the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation.

Conclusion on dosage selection

The proposed dose regimen in NMO and NMOSD is 120 mg SC satralizumab at Weeks 0, 2, and 4 as loading doses, and every four weeks thereafter. The dose regimen selected for the Phase III trials was based on the results from the Phase I studies (Studies SA-001JP and SA-105JP) and not from traditional proof-of-concept dose-finding studies. Furthermore, the Phase I studies did not include data from subjects with NMO and/or NMOSD. Instead, the sponsor confirmed the adequacy of the proposed dose-regimen in NMO and NMOSD based on results from the Phase III clinical studies, Studies BN40898 and BN40900. This approach is considered reasonable given the non-linear PK of satralizumab and the difficult in recruiting subjects with NMOSD into clinical trials, since it is a rare disease.

Efficacy

Pivotal efficacy studies

- Study BN40900 (satralizumab as monotherapy; adults only); and
- Study BN40898 (satralizumab as 'add-on' therapy; adults and adolescents).

Efficacy data from the Phase I astudy (Study SA-105JP) in patients with rheumatoid arthritis, were not evaluated since the results have limited application to NMO and NMOSD, due to differences in study design, study population and efficacy endpoints. However, safety data from Study SA-105JP were evaluated in Safety section.

Studies BN40900 and BN40898

The two pivotal studies were evaluated together due to the similarities in study design, efficacy endpoints and satralizumab dose regimens used. Notable differences in design, conduct and/or analysis are discussed under relevant subheadings.

- Study BN40900: A multicentre, randomised, double-blind, placebo-controlled, Phase III study to evaluate the efficacy and safety of satralizumab as monotherapy in patients with NMO and NMOSD study
- Study BN40898: A multicenter, randomised, addition to baseline treatment, double-blind, placebo-controlled, Phase III study to evaluate the efficacy and safety of satralizumab in patients with NMO and NMOSD study

Study design

Each study comprised a placebo controlled double blind period (DBP), which provided data for the primary analysis, followed by an open label period (OLP), to further characterise long-term satralizumab safety and efficacy

In Study BN40898, subjects who experienced a relapse, which was treated with rescue therapy and/or had a clinical endpoint committee (CEC) adjudicated protocol-defined relapse (PDR) or who completed the DBP, could enter the OLP.

In Study BN40900, only subjects who completed the DBP or experienced a CEC adjudicated PDR in the DBP could enter the OLP.

Primary objective

To assess efficacy and safety of satralizumab compared with placebo in subjects with NMO and NMOSD.

Key inclusion criteria

- Adult subjects aged ≥ 18 years with NMO or NMOSD in both studies. Study BN40898 also included adolescent subjects, aged 12 to 17 years old
- Expanded Disability Status Scale (EDSS) score from 0 to 6.5 (inclusive) at screening

- Ability and willingness to provide written informed consent and to comply with the requirement of the protocol

NMO subjects were enrolled in both studies according to the criteria.[7] Diagnosis required:

- optic neuritis (ON);
- myelitis/inflammation of the spinal cord (transverse);

plus at least two out of the listed three supportive criteria;

- contiguous spinal cord lesion identified on an magnetic resonance imaging (MRI) scan, extending over three vertebral segments;
- brain MRI not meeting diagnostic criteria for multiple sclerosis;
- NMO-IgG (anti-AQP4 antibody) seropositive status.

NMOSD subjects were enrolled in both studies according to the criteria.[8]

- Anti-AQP4-IgG seropositive subjects who met NMO criteria only partially;
  - And having either single or recurrent events of longitudinally extensive myelitis
  - or recurrent or simultaneous bilateral ON events

Subjects in Study BN40900 required clinical evidence of at least one documented attack (inclusive of first episode or relapse) in the last 12 months prior to screening, but were not allowed to have any clinical relapse within 30 days prior to Baseline.

Subjects in Study BN40898 required clinical evidence of at least two documented attacks (inclusive of first episode or relapse) in the last 2 years prior to screening, at least one of which had occurred in the 12 months prior to screening.

The Delegate noted that the percentage of enrolled (adult) subjects who were seronegative for anti-AQP4-IgG antibodies was capped at approximately 30% of the total subjects enrolled, based on epidemiologic data. By inference, it means that anti-AQP4-IgG seronegative subjects can still otherwise meet the criteria;[7] for NMO inclusion in StudiesBN40898 and BN40900.

In Study BN40898, in accordance with the per intent protocol (PIP) analysis, a minimum of six adolescent subjects had to be evaluable for the primary analysis, including at least four with anti-AQP4-IgG antibody seropositive status at screening.

Key exclusion criteria

- clinical relapse onset (including first attack) < 30 days prior to Baseline (Study BN40900);
- evidence of a demyelinating disease or progressive multifocal leukoencephalopathy
- previous treatment of tocilizumab within six months prior to baseline
- subjects at potential risk for gastrointestinal perforation for example diverticulitis
- subjects with history of Stevens-Johnson syndrome (SJS)
- active or recent suicidal ideation
- known active infection
- active interstitial lung disease (ILD)

[7] Wingerchuk DM, et al. Revised diagnostic criteria for neuromyelitis optica. *Neurology*. 2006; 66(10):1485-9.
[8] Wingerchuk DM et al: The spectrum of neuromyelitis optica. *Lancet Neurol* 2007; 6: 805-815.

- history of malignancy (excluding excised cutaneous basal cell carcinoma or squamous cell carcinoma) within the last five years
- history of severe allergic reactions to biologic agents; and
- abnormal baseline white blood cell counts, platelets or liver function tests

Study treatments

The same satralizumab dose-regimen was used in both studies: 120 mg SC at Weeks 0, 2 and 4 (loading phase) and 120 mg SC every four week (maintenance phase) thereafter. For the complete duration of each DBP, satralizumab or matching placebo were administered using a glass vial. In the OLP, subjects were switched to the PFS with needle safety device, either at entry to, or at a later time point in the OLP (for subjects already receiving satralizumab from vials). In Study BN40898, satralizumab (or placebo) treatment was administered in combination with pre-specified baseline ISTs (as in add-on trial).

Permitted rescue therapy for clinical relapse in both studies included IV corticosteroids, OCs for tapering, IV immunoglobulin and/or apheresis (that is plasma exchange, also known as plasmapheresis).

Across studies, stable doses of medicines for pain treatment were permitted, with dose increase or change of pain medication permitted. However, no dose increases were permitted in IST or change in IST for Study BN40898.

Dose reduction and temporary treatment suspension of permitted medicines (including pre-specified ISTs for Study BN40898) were allowed across studies, for safety reasons only.

Randomisation and blinding methods

In Study BN40900, eligible subjects were randomised 2:1 to satralizumab and placebo via a centralised Interactive Web Response and Voice Response System (IxRS).

Randomisation was stratified by:

- baseline therapy for prevention of NMO or NMOSD relapse (B-cell lymphocyte depleting therapy, IST or others);
- the most recent attack in the last year prior to screening (first attack or relapse).

In contrast for Study BN40898, eligible subjects were randomised 1:1 to satralizumab and placebo via an IxRS.

Randomisation was stratified by:

- baseline annualised relapsed rate (ARR) that is ARR = 1 or ARR > 1;
- geographical region (Asia, Europe/other)

Table 4: Summary of subject disposition and analysis populations at clinical cut-off in Phase III studies in NMO/NMOSD

	BN40900		BN40898	
	PLB	SAT	PLB	SAT
Number of subjects, n (%)				
Randomised	32 (100.0)	63 (100.0)	42 (100.0)	41 (100.0)
ITT population	32 (100.0)	63 (100.0)	42 (100.0)	41 (100.0)
PP population	30 (93.8)	56 (88.9)	39 (92.9)	35 (85.4)
Safety population	32 (100.0)	63 (100.0)	42 (100.0)	41 (100.0)
Adolescent population	n/a	n/a	3 (7.1)	4 (9.8)
Completed DBP, n (%)	17 (53.1)	18 (28.6)	24 (57.1)	18 (43.9)
Discontinued study drug, n (%)	4 (12.5)	7 (11.1)	10 (23.8)	3 (7.3)
Primary reason for study drug discontinuation, n (%)				
Adverse event	1 (3.1)	1 (1.6)	5 (11.9)	3 (7.3)
Lack of efficacy	0	0	0	0
Lost to follow-up	0	0	0	0
Subject died	0	0	0	0
Voluntarily withdrew	2 (6.3)	2 (3.2)	2 (4.8)	0
Other	1 (3.1)	4 (6.4)	3 (7.2)	0

ITT = intention to treat; PP = per protocol; DBP = double blind period; PLB = placebo; SAT = satralizumab

In Study BN40900, 168 subjects were screened, 73 subjects fail to meet the eligibility criteria and 95 subjects were enrolled. Of the 95 subjects, 63 person were randomised to satralizumab and 32 subjects to placebo up to the clinical cutoff date. Regarding withdrawals, a similar % of subjects discontinued from the study in both treatment groups (n = 7 that is 7/63, or 11.1% and n =4 that is 4/32, or 12.5% respectively for satralizumab and placebo) for the DBP, if the 2 satralizumab: 1 placebo randomisation is taken into account. Few (< 2) subjects per treatment group withdrew due to AEs. In the OLP, 17.1% (n = 6) of subjects withdrew.

The Delegate noted that given the similar % of subjects who completed the DBP in both satralizumab (n = 18 that is 18/63 = 28.6 %) and placebo (n = 17 that is 17/32 = 53.1%) for Study BN40900 and the satralizumab 2: 1 placebo randomisation in the latter. The Delegate noted that there is suggestion for more drift out of satralizumab than placebo in the DBP before the scheduled study duration. The Delegate has request the sponsor to clarify if this observation is related to efficacy sequelae or some other rationale, in section 'Questions to sponsor' below.

In Study BN40898, 96 subjects were screened, 12 subjects failed to meet the eligibility criteria and 83 subjects were enrolled. Of the 83 subjects, 41 subjects were randomised to satralizumab, while 42 subjects to placebo up to the clinical cutoff date. Study BN40898 included seven adolescents at the clinical cutoff date.

Similarly, the Delegate noted that the number of subjects who completed the DBP were n = 18 (43.9%) for satralizumab and n = 24 (57.1%) for placebo in Study BN40898. The Delegate noted that there is suggestion for more drift out of satralizumab than placebo in the DBP before the scheduled study duration. The Delegate has request the sponsor to clarify if the observation is related to efficacy sequelae or some other rationale, in section 'Questions to sponsor' below.

Endpoint

Primary endpoint: Time to the first clinical endpoint committee –adjudicated protocol defined relapse during the double blinded treatment period (followed with an EDSS/Functional Systems Score (FSS)) assessment, performed within seven days of those relapse symptoms).

Key secondary endpoint: Change from Baseline in visual analogue score (VAS) score for pain at Week 24.

Minor secondary endpoints included: assessed every 24 weeks from Baseline:

- Change in Short Form Health Survey 36 Version 2 scores consists of 36 items: eigth domain scores and two component (physical and mental) summary scores
- Change in EuroQol-5D 3 Level Version consists of a questionnaire assesses five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with three possible responses: 1) no problems; 2) some problems; 3) severe problems. The response from each dimension is converted into a single index value
- Change in modified Rankin Scale score is a seven point disability scale that assesses the degree of disability in persons with neurological impairment. Possible scores range from 0 (no symptom at all) up to 6 (death)
- Change in Zarit Burden Interview score assesses caregiver burden. The 22 items ask for the strain caregivers perceive from 0 (never) to 4 (nearly always). Maximum score of 88. The higher the total score, the heavier the perceived burden
- Change in EDSS score
- Change in visual acuity (Snellen Chart), subjects were assessed monocularly, with their habitual distance glasses or contact lenses.
- ARR is total number of relapses experienced / person-years at risk for each year of the study period;
- Proportion of relapse-free patients (during the DBP, OLP and entire study);
- Study BN40900 only: Change in low-contrast sloan letter chart evaluates visual function and assesses the minimum size at which individuals can recognise letters of a particular contrast level;
- Study BN40900 only: Change in timed 25-foot walk assesses walking ability. The time (in seconds) it takes to walk 25 feet is measured.

Sample size and statistical methods

The sample sizes (70 in Study BN40898 for 26 CEC-confirmed PDRs and 90 in Study BN40900 for 44 CEC-confirmed PDRs) were predicted to provide 80% power, to maintain the Type I error rate of 0.05, which assumed a 2-year drop-out rate of approximately 10%.

In BN40900, the time to first-relapse (TFR) hazard ratio (HR) of satralizumab over placebo was assumed to be 1 for the initial two months from randomisation and 0.25 thereafter. The distribution of TFR in the placebo group was assumed to follow an annual HR of 1.1295. In Study BN40898, the TFR HR of satralizumab over placebo was assumed to be 0.335, which was expected to result in 66.5% reduction in the risk of relapse. The distribution of TFR in the placebo group was assumed to follow an annual HR of 0.4184.

Statistical hypotheses for treatment comparisons were tested at the 5% significance level ($\alpha = 0.05$), against 2-sided alternatives, for the intent to treat (ITT) populations.

For the primary efficacy endpoint, the comparison of TFR between satralizumab and placebo was performed using a stratified two sided log rank test. The US Food and Drug Administration (FDA) agreed with the choice of analysis method.

For the primary and key secondary efficacy endpoints, to control for multiplicity, a serial gatekeeping methodology that is a hierarchical approach was employed to control the overall significance level at 0.05:

- TFR based on PDR (primary endpoint);
- VAS for pain (first key secondary endpoint);

- FACIT fatigue score (second key secondary endpoint).[9]

For the ITT populations across both studies, the baseline demographic characteristics of the ITT populations were generally well balanced between placebo and satralizumab treatment groups. ITT populations were predominantly female (86.5%) and White race (58.4%).

For the ITT populations across both studies, the baseline disease characteristics were generally well balanced between placebo and satralizumab treatment groups. There were predominantly NMO subjects (74.2%) and the majority were anti-AQP4-IgG positive (66.9%; as per the entry requirement).

The Delegate noted that by inference, 25.8% subjects were NMOSD and all of whom, will be expected to be anti-AQP4-IgG positive, as per the definition of NMOSD. 33.1% of NMO subjects were anti-AQP4-IgG negative. 92.7% of the combined NMO and NMOSD subjects would therefore be expected to be anti-AQP4-IgG positive. The breakdown from Table 5 in terms of treatment received anti-AQP4-IgG status, NMO and NMOSD classification. For Studies BN40900 and BN40898, there were 51 and 68 anti-AQP4-anti IgG positive adults, respectively in placebo and satralizumab. Adults with NMO were 73 and those with NMOSD were 46. There are 23 and 36 anti-AQP4-anti IgG negative adults, respectively in in placebo and satralizumab. Adults with NMO will be 59 while those with NMOSD will be zero (based on their definitions).

Table 5: Disease characteristics in the Phase III clinical studies (intent to treat population)

Parameter	BN40900		BN40898	
	PLB (n = 32), n (%)	SAT (n = 63), n (%)	PLB (n = 42), n (%)	SAT (n = 41), n (%)
Baseline ARR				
Mean (SD)	n/a	n/a	1.50 (0.60)	1.48 (0.63)
Range:	n/a	n/a	1.0-3.0	1.0-3.5
Median	n/a	n/a	1.5	1.5
Baseline ARR category				
< 1	9 (28.1)	27 (42.9)	0 (0.0)	0 (0.0)
1	15 (46.9)	20 (31.7)	20 (47.6)	20 (48.8)
> 1	8 (25.0)	16 (25.4)	22 (52.4)	21 (51.2)
Diagnosis				
NMO	24 (75.0)	47 (74.6)	28 (66.7)	33 (80.5)
NMOSD	8 (25.0)	16 (25.4)	14 (33.3)	8 (19.5
Anti-AQP4-IgG status				
Positive	23 (71.9)	41 (65.1)	28 (66.7)	27 (65.9)
Negative	9 (28.1)	22 (34.9)	14 (33.3)	14 (34.1)
Baseline EDSS				
Mean (SD)	3.66 (1.61)	3.92 (1.50)	3.63 (1.32)	3.83 (1.57)
Range:	1.0-6.5	1.5-6.5	1.5-6.5	1.0-6.5
Median	3.5	4	3.5	3.5
Baseline treatment				
Adults				
AZA	n/a	n/a	13 (31.0)	16 (39.0)
MMF	n/a	n/a	8 (19.0)*	4 (9.8)
OC	n/a	n/a	20 (47.6)	17 (41.5)
Adolescents				
AZA + OC	n/a	n/a	0 (0.0)	3 (7.3)
MMF + OC	n/a	n/a	1 (2.4)	1 (2.4)
Most recent attack				
First attack	4 (12.5)	7 (11.1)	n/a	n/a
Relapse	28 (87.5)	56 (88.9)	42 (100.0)	41 (100.0)
Prior therapy				
B-cell depletors	4 (12.5)	8 (12.7)	n/a	n/a
IST/others	28 (87.5)	55 (87.3)	n/a	n/a

***Includes 2 adolescent subjects**

PLB = placebo; SAT = satralizumab; ARR =annualised relapsed rate; AQP4-IgG = anti-aquaporin 4 immunoglobulin (antibodies); SD = standard deviation; AZA = azathioprine; MMF =mycophenolate mofetil; OC = oral corticosteroids; IST = immunosuppressive therapy.

[9] The Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) is a 40-item measure that assesses self-reported fatigue and its impact upon daily activities and function. It is a subset of the longer (47-item).

A total of seven adolescent subjects were included in Study BN40898 (mean age 15.4 years, range: 13 to 17years, four were anti-AQP4-IgG negative and three were anti-AQP4-IgG positive (NMOSD = 2 and NMO = 1)) and mean bodyweight 79.3 kg (range: 47.5 to 140 kg). The latter was higher than the mean bodyweight in adults (61.5 kg (range: 40.3 to 103 kg)) in Study BN40898 (see Table 6).

The Baseline disease characteristics were similar between the adolescent and adult populations in Study BN40898 for baseline ARR, EDSS score and diagnosis. However, no adolescent subjects with NMOSD received satralizumab treatment (only two subjects and, were assigned to the placebo group, see Table 6)

Table 6: The baseline disease characteristics in the adolescent subjects

Treatment Group	Age (years) / Sex	Race	AQP4-IgG status	Baseline treatment	Treatment Duration (days)	Clinical Relapse Study Day	PDR
placebo	16/F	Black or African American	Positive	mycophenolate mofetil	174 (DB) 533 (O)	170	No
placebo	14/F	Black or African American	Positive	mycophenolate mofetil + oral corticosteroids	253 (DB) 167 (O)	259	Yes
placebo	17/F	Asian	Negative	mycophenolate mofetil	28 (DB) 695 (O)	44	No
satralizumab	13/F	White	Positive	mycophenolate mofetil + oral corticosteroids	503 (DB) 503 (O)	-	-
satralizumab	15/F	White	Negative	azathioprine + oral corticosteroids	57 (DB) 302 (O)	72	Yes
satralizumab	17/F	White	Negative	azathioprine + oral corticosteroids	283 (DB) 283 (O)	-	-
satralizumab	16/F	White	Negative	azathioprine + oral corticosteroids	113 (DB) 113 (O)	-	-

The Delegate noted that there is no adolescent with anti-AQP4-IgG positive in NMOSD received satralizumab. There were proportionately more adolescents (57.1%; n = 4) with anti-AQP4-IgG negative status compared with adults (31.6%; n = 24). The adult % age was in accordance with the agreed per intent protocol analysis. Most (75.0%; n = 3) adolescents who were anti-AQP4-IgG negative received satralizumab treatment compared to the one adolescent who received placebo treatment (25.0%; n = 1). In contrast, most (66.7%; n = 2) anti-AQP4-IgG positive adolescents received placebo treatment compared to the one adolescent (33.3%; n = 1) who received satralizumab.

The Delegate noted that out of the four adolescents in the satralizumab group, three were anti-AQP4-IgG negative with NMO and one was anti- AQP4-IgG positive with NMO compared to the placebo group, where out of the three adolescents, two were anti-AQP4-IgG positive with NMOSD and one was anti-AQP4-IgG negative with NMO.

Result

Table 7: Studies BN40900 and BN40898 Time to the first clinical efficacy committee adjudicated protocol defined relapse (intent to treat population)

Variable	Study BN40900		Study BN40898	
	PLB (n = 32)	SAT (n = 63)	PLB (n = 42)	SAT (n = 41)
Time to first PDR during the DBP				
Subjects with an event, n (%)	16 (50.0)	19 (30.2)	18 (42.9)	8 (19.5)
Hazard ratio (95% CI)	0.45 (0.23, 0.89)		0.38 (0.16, 0.88)	
P-value (log-rank)	0.0184		0.0184	
Proportion of relapse-free subjects (%)				
Week 48 (95% CI)	61.9 (42.66, 76.26)	76.1 (63.55, 84.86)	66.0 (47.65, 79.25)	88.9 (72.81, 95.70)
Week 96 (95% CI)	51.2 (32.36, 67.23)	72.1 (58.91, 81.75)	58.7 (39.85, 73.43)	77.6 (58.08, 88.82)

PLB = placebo; SAT = satralizumab; PDR = protocol defined relapse

Primary efficacy outcome:

- For satralizumab administered as monotherapy (Study BN40900), the % of subjects with an event relative to time to first PDR during the DBP was 50% in placebo and 30.2% in satralizumab. For satralizumab administered as add on therapy (Study BN40898), the % of subjects with an event relative to time to first PDR during the DBP was 42.9% in placebo and 19.5% in satralizumab;
- For satralizumab administered as monotherapy (Study BN40900) and add on therapy (Study BN40898), the satralizumab/placebo HRs in terms of time to first PDR during the DBP, were respectively 0.45 and 0.38 that is 55% and 62% of subjects are less likely to experience a relapse event respectively in Studies BN40900 and BN40898 throughout the treatment period. The latter suggests a positive trend towards 'add-on therapy' as being slightly better than 'monotherapy';
- Statistical separations, which favoured satralizumab treatment over that of placebo were demonstrated in both studies (p = 0.0184 in each comparison).
- The proportion of relapse-free subjects at Weeks 48 and 96 favoured satralizumab treatment over placebo treatment, across studies. The latter demonstrated maintenance effect of satralizumab treatment for up to 96 weeks.

Table 8: Study BN40900 and BN40898 Sensitivity analysis (intent to treat population)

Sensitivity Analysis	Study BN40900				Study BN40898			
	Subjects with events (n)	Proportion of relapse-free subjects at Week 48 (%)	Hazard Ratio (95% CI)	P-value (2-sided log rank test)	Subjects with events (n)	Proportion of relapse-free subjects at Week 48 (%)	Hazard Ratio (95% CI)	P-value (2-sided log rank test)
ITT population								
PDR regardless of 7-day EDSS assessment limit	PLB: 16 SAT: 21	PLB: 61.85 SAT: 76.13	0.49 (0.25, 0.95)	0.0301	PLB: 19 SAT: 9	PLB: 64.02 SAT: 85.97	0.41 (0.19, 0.92)	0.0256
Clinical relapse	PLB: 17 SAT: 31	PLB: 56.25 SAT: 64.94	0.74 (0.41, 1.35)	0.3212	PLB: 27 SAT:18	PLB: 50.57 SAT: 69.23	0.59 (0.33, 1.08)	0.0859
Treated clinical relapse	PLB: 17 SAT: 21	PLB: 56.25 SAT: 74.24	0.46 (0.24, 0.88)	0.0158	PLB: 26 SAT: 18	PLB: 52.49 SAT: 69.23	0.62 (0.34, 1.14)	0.1236
PDR censored by affecting medications*	PLB: 16 SAT: 19	PLB: 61.57 SAT: 75.72	0.45 (0.23, 0.89)	0.0194	n/a	n/a	n/a	n/a
Treated clinical relapse: optic neuritis	PLB: 7 SAT: 8	PLB: 74.65 SAT: 91.70	0.43 (0.15, 1.20)	0.0975	PLB: 11 SAT: 7	PLB: 75.47 SAT: 81.34	0.59 (0.23, 1.52)	0.2665
TFR based on PDR during DBP using weighted log-rank test	PLB: 16 SAT: 19	n/a	n/a	0.0252	n/a	n/a	n/a	n/a
PDR based on EDSS/FSS increase relative to baseline	n/a	n/a	n/a	n/a	PLB: 19 SAT: 11	PLB: 61.83 SAT: 82.90	0.52 (0.25, 1.09)	0.0794
Per-protocol population								
PDR	PLB: 16 SAT: 16	PLB: 59.24 SAT: 76.79	0.4 (0.20, 0.81)	0.0082	PLB: 18 SAT: 8	PLB: 63.69 SAT: 86.87	0.4 (0.17, 0.93)	0.0286

ITT = intent to treat (population); PDR = protocol defined relapse; EDSS = Expanded Disability Status Scale; TFR = time to first replapse; protocol defined relapse.

*Censored at the first start date of the following medications: relapse prevention therapy and systemic administration of steroid for other indication for more than 5 days

Comparisons of the HRs for the pre-specified ITT/PP sensitivity parameters tended to favour satralizumab treatment compared to placebo treatment, although few of those demonstrated statistical separation over placebo.

Some results were also inconsistent between studies for example treated clinical relapse in the satralizumab group demonstrated a statistically significant and clinically meaningful difference in treatment effect compared to the placebo group in Study BN40900 (HR 0.46: 95% confidence interval (CI): 0.24, 0.88: p = 0.0158), but not in BN40898 (HR 0.62: 95% CI: 0.34, 1.14: p = 0.1236).

Primary efficacy endpoint as per the subgroup analyses

The pre-specified subgroup analyses of the primary efficacy endpoint in each of the Phase III studies were generally consistent with the results of the primary efficacy analysis.

In Study BN40900, there was a tendency to favour satralizumab treatment over placebo treatment in all subgroups.

- for anti-AQP4-IgG positive subjects: HR 0.26: 95% CIs: 0.11, 0.63; p = 0.0014
  - In NMO anti-AQP4-IgG positive/NMOSD (by definition, all NMOSD subjects must be anti-AQP4-IgG positive) subjects at Weeks 48 and 96 respectively, 82.9% and 76.5% on satralizumab were relapse free compared to 55.4% and 41.1% on placebo;

In contrast for anti-AQP4-IgG negative subjects, there was a tendency to no satralizumab treatment effect (HR 0.995)

  - anti-AQP4-IgG negative subjects (anti-AQP4 –IgG negative combined with NMOSD subjects, HR 1.192; or NMO anti-AQP4-IgG negative status, HR 1.250)

In Study BN40898, there was a tendency to favour satralizumab treatment in all subgroups, except for time to relapse in adolescent subjects (one satralizumab group versus one placebo group), in which there were too few subjects to draw meaningful conclusions.

In adults, HR was 0.362 (95% CI: 0.149, 0.878: p = 0.0192), which was consistent with the pooled Study BN40898 results, as previously accounted for

- Similar to Study BN40900, the strongest subgroup effect was observed for anti-AQP4-IgG positive subjects. The risk of experiencing a PDR was reduced by 79% in satralizumab treated anti-AQP4-IgG positive subjects, HR 0.21; 95% CIs: 0.06, 0.75; p = 0.0086;
- At Weeks 48 and 96 respectively, 91.5% of anti-AQP4-IgG positive subjects on satralizumab were relapse free versus 59.9% and 53.3% of placebo treated anti-AQP4-IgG positive subjects with NMO/NMOSD.

The Delegate is of view that there is insufficient efficacy data to support approval for satralizumab in anti-AQP4-IgG positive or negative adolescents based on sponsor submitted dossier. There is insufficient adolescent number (n = 7) to draw any conclusion. In addition, there is only three adolescents with NMO anti-AQP4-IgG negative that received satralizumab and one adolescent with NMO anti-AQP4-IgG positive received satralizumab. Concurrently, the available data do not robustly support the use of satralizumab in adults with NMO anti-AQP4-IgG negative status. The latter is hardly surprising given, the pharmacological basis for the clinical action/benefit of satralizumab in NMO/NMOSD.

Secondary efficacy outcomes

The key secondary efficacy endpoints assessed using the VAS score for pain and the FACIT score for fatigue, (see Table 9). Measures include change from Baseline in a) VAS score and b) FACIT score, to Week 24, in the Phase III studies.

Table 9: Studies BN40900 and BN40898 secondary efficacy outcome (double blinded period, intent to treat population)

Variable	Study BN40900		Study BN40898	
	PLB (n = 32)	SAT (n = 63)	PLB (n = 42)	SAT (n = 41)
Change in VAS for pain from baseline to Week 24				
Adjusted mean change (SE)	(-)5.949 (4.832)	(-)2.735 (4.260)	(-)3.505 (2.357)	2.871 (2.391)
95% CI for adjusted mean	(1-)15.550, 3.652	(-)11.199, 5.730	(-)8.198, 1.188	(-)1.890, 7.632
Difference in adjusted means (SE)	3.215 (4.178)		6.376 (3.344)	
95% CI for difference in adjusted means	(-)5.086, 11.515		(-)0.280, 13.03	
P-value	0.4436		0.0602	
Change in FACIT fatigue scale score from baseline to Week 24				
Adjusted mean change (SE)	3.602 (1.820)	5.709 (1.610)	2.234 (0.943)	0.145 (0.963)
95% CI for adjusted mean	(-)0.013, 7.218	2.510, 8.907	0.356, 4.112	(-)1.772, 2.061
Difference in adjusted means (SE)	2.107 (1.567)		(-)2.089 (1.338)	
95% CI for difference in adjusted means	(-)1.008, 5.221		(-)4.752, 0.574	
P-value	0.1824		0.1224	

SE = standard error; CI = confidence interval.

There were no clinically meaningful differences between the satralizumab and placebo groups in change from Baseline in mRS score, ZBI score or EDSS score at each 24 week interval of the DBP, in both Phase III studies. Similarly, there were no clinically meaningful differences between the two groups in utilities derived from the EQ-5D-3L scores at any time point. There were no consistent differences between the satralizumab and placebo groups in the physical component summary or the domain scores in each study. In Study

BN40900, there was a consistent trend towards greater increase in the mental health component summary score in the satralizumab group compared to the placebo group at all visits up to Week 120. In contrast, this trend was not observed at each 24 week interval of the DBP in Study BN40898. Across studies, changes in adjusted ARRs nominally favoured satralizumab treatment. In Study BN40900, the observed reduction in adjusted ARR (0.551) was 73% in the satralizumab group versus the placebo group (2.005) and in Study BN40898, the observed reduction in adjusted ARR (0.141) was 74% in the satralizumab group versus the placebo group (0.538). These results generally supported the primary end point efficacy analyses.

Regarding rescue therapy, the proportion of subjects who received relapse rescue therapy was higher in the placebo groups (53.1% in Study BN40900 and 59.5% in Study BN40898, respectively) compared to the satralizumab groups (33.3% in Study BN40900 and 43.9% in Study BN40898, respectively). These results were consistent with the general primary end point efficacy analysis results.

Analyses performed across trials: pooled and meta-analyses

- Pooled results for the primary efficacy endpoint were consistent with the individual study results: HR 0.42 (95% CI: 0.25, 0.71: p = 0.0008).
- The proportion of pooled relapse-free subjects at Week 48 (80.5% satralizumab group versus 64.4% placebo group) and Week 96 (74.2% satralizumab versus 55.3% placebo) were consistent with the primary efficacy analysis, and demonstrated maintenance of effect over 96 weeks satralizumab treatment.
- The treatment benefit of satralizumab was generally similar in the individual and pooled BW and BMI subgroup analyses of the primary efficacy endpoint.
- Pooled and individual study results for the primary efficacy endpoint by anti-AQP4-IgG status favoured satralizumab treatment in anti-AQP4-IgG postive subjects versus anti-AQP4-IgG negative subjects (HR 0.25 (95% CI: 0.12, 0.50: p < 0.0001)). In comparison, HR was 0.97 (95% CI: 0.41, 2.33: p = 0.9540) for placebo treated anti-AQP4 -IgG positive subjects versus anti-AQP4-IgG negative subjects.

The subgroup results of the primary efficacy endpoint by ADA status (positive or negative) were inconsistent between individual studies. However, pooled results indicated there was a favourable treatment effect of satralizumab treatment versus placebo treatment, irrespective of ADA status, albeit less favourable for ADA-positive subjects (HR 0.50) versus ADA-negative subjects (HR 0.32).

Conclusion and summary

The study design, conduct and analyses used in the pivotal Phase III placebo controlled studies were generally acceptable and consistent with advice provided by the FDA and European Medicines Agency (EMA). There was no Australian or TGA adopted Guideline for NMO and NMOSD.

The indication for satralizumab in subjects with NMO and NMOSD is based on efficacy data from two placebo controlled pivotal Phase III clinical studies (Studies BN40900 and BN40898).

Satralizumab administered as monotherapy in Study BN40900 is likely to provide a more informative clinical baseline for efficacy (and safety) assessment than the add on study, since concomitant ISTs have potential to confound the effects of satralizumab. This is reflected, in part, by inclusion of more subjects with satralizumab treatment in Study BN40900, to allow for absence of baseline therapies. Notwithstanding the differences in design, the magnitude and duration of the treatment effects in each study were comparable.

There were no validated endpoints to evaluate efficacy for the treatment of NMO or NMOSD at the time of the application. However, given that substantial disability can result from any relapse, and in order to reduce the potential risk associated with the use of placebo, a time-to-event outcome (that is TFR), instead of ARR, was chosen as the primary efficacy measure in both Studies BN40898 and BN40900. This was acceptable to both the FDA and EMA. Although during scientific advice, the EMA stated that the analysis should be based on physician reported relapses (or 'clinical relapses'). The sponsor considered the primary analysis of CEC-adjudicated relapses ensured more consistent and independent assessment of relapses than clinical relapses. Hence, clinical relapses (and treated clinical relapses) were included as sensitivity analyses of protocol defined CEC-adjudicated relapses. Both the Delegate and evaluator find this approach acceptable, since the PDR analysis provided a more stringent measure of treatment effect than clinical relapse.

Notwithstanding some notable differences in the design and population in both studies, and the relatively small numbers of subjects with NMOSD in each study, there was general agreement between studies for the primary efficacy endpoint. Statistical superiority and clinically meaningful reductions were demonstrated in the time to first relapse for satralizumab treatments compared to placebo treatment, sustained over 96 weeks, in a broad population of NMO (mostly) and NMOSD subjects, as monotherapy (Study BN40900) and as adjunctive treatment with ISTs (Study BN40898). These findings were generally supported by the results from the sensitivity analyses of the primary efficacy endpoint. However, key secondary efficacy endpoints were not met in each Phase III study. Also, there were generally no clinically meaningful differences between satralizumab and placebo treatments in the minor efficacy analyses.

Randomisation was stratified by first episode (first attack or relapse) within 12 months before screening in Study BN40900, to follow treatment with satralizumab at an earlier stage of disease than in Study BN40898 without such stratification. However, this subgroup of subjects did not appear to obtain a clinically meaningful beneficial effect from satralizumab treatment.

The Delegate agrees with evaluator that this result outcome needs to be interpreted with caution, since the number of subjects in this subgroup category was small. It may reflect a problem with diagnosis of NMO and/or NMOSD, since there was no international consensus on diagnosis and management of NMOSD at the time of the application. It revealed furthermore, that when the sample size was increased in Study BN40900, with proportionately more subjects who had had a first attack being enrolled, a *post hoc* analysis did not find a clinically meaningful difference in estimation of the HRs, before and after protocol amendment, in Study BN40900.

Study entry criteria, randomisation and the blinding methods used, sample size calculations and SAPs were generally acceptable. However, the selection of adolescents into either adjunctive treatment Study BN40898 or monotherapy treatment Study BN40900 or inclusion in a variety of paediatric investigational plan trial designs, is unclear from the paediatric investigational plan report. The clinical evaluator has request clarification from sponsor with regards to why adolescent subjects (aged 12 to 17 years, inclusive) were a) only recruited into the add-on Phase III Study BN40898, and not into the monotherapy Study BN40900; and b) should be approved to receive satralizumab as monotherapy. The sponsor has submitted their response (not in scope of this AusPAR) and the clinical evaluator agrees that sponsor response is acceptable. The sponsor provided detailed justification to support the use of satralizumab as monotherapy (and add on therapy) in adolescents aged 12 to 17 years, inclusive, with NMOSD, based on similar efficacy and safety profiles between adults and adolescents. In addition, the PK profiles between these age groups were similar. The justification provided is generally acceptable. There were insufficient numbers of study participants to fully assess efficacy and safety by

Anti-AQP4-IgG status in adolescents. However, from the evidence provided in the clinical dossier for adults it appears reasonable to assume that adolescent patients who are Anti-AQP4-IgG seropositive are also likely to benefit from satralizumab treatment.

The clinical evaluator has request further clarification from sponsor with regards to comparative efficacy results between elderly subjects (aged 65 years and older) and younger adults (aged between 18 and 64 years, inclusive) for the primary efficacy endpoint in the Phase III clinical studies. The sponsor submitted further information and data (not in scope of this AusPAR) and agrees that the sponsor's response was generally acceptable. The data provided generally supported the use of satralizumab for an elderly population (aged 65 to 74 years old) for the revised proposed indication, albeit the number of elderly subjects was too small to draw meaningful conclusions.

Results for the primary efficacy analysis in the individual and pooled Phase III studies consistently demonstrated a statistically significant and clinically meaningful difference in treatment effect, which favoured satralizumab treatment over placebo treatment, for adult subjects who were anti-AQP4-IgG positive. No clinically meaningful treatment effect was apparent in subjects treated with satralizumab over placebo in either Phase III study who were anti-AQP4-IgG negative.

A higher proportion of pooled ADA-positive subjects had a relapse event (30.6%) versus pooled ADA-negative subjects (19.0%), respectively. Satralizumab treated ADA-positive subjects experienced a 50% reduction in time to relapse (HR 0.50) compared with placebo treatment, while satralizumab treated ADA-negative subjects experienced a 32% reduction in time to relapse (HR 0.32) compared with placebo treatment. The latter indicated a reduction of 18% percentage points of relapse in ADA-negative subjects compared with ADA-positive subjects in reference to placebo treated patients. The Delegate commented that the plausibility exists that the presence of ADA alone may be sufficient to account for the observed relapse rate difference in ADA-positive subjects compared to ADA-negative subjects without the need, to postulate the presence of neutralising antibody (NAb) in ADA-positive subjects. Furthermore, based on pharmacologic principle, any NAb will be expected to equally affect both ADA-positive and ADA-negative subjects.

Safety

Adverse events

Integrated safety analysis

The System Organ Classes (SOC) with the highest proportions of subjects reporting adverse events (AEs) in the Phase III studies were Infections and Infestations, Musculoskeletal and Connective Tissue Disorders and Gastrointestinal Disorders (Table 10). Overall AE incidence in the pooled analysis in the phase III studies was similar between the satralizumab and placebo treatment groups.

AEs reported with 5% or greater incidence with satralizumab treatment compared with placebo treatment were: Arthralgia, headache, nasopharyngitis, nausea, white blood cell (WBC) count decreased and hypoaesthesia. AEs reported with 5% or greater incidence with placebo treatment compared with satralizumab treatment were: constipation and pyrexia.

Table 10: Studies BN40900 and BN40898 Treatment-emergent adverse events irrespective of treatment with incidence ≥ 5% (pooled data; double blinded period; safety population)

System Organ Class Preferred Term	Placebo (N = 74) n (%)	Satralizumab (N = 104) n (%)
Subjects with at least 1 TEAE	**64 (86.5)**	**95 (91.3)**
Infections and infestations	**40 (54.1)**	**62 (59.6)**
Urinary tract infection	15 (20.3)	18 (17.3)
Upper respiratory tract infection	12 (16.2)	20 (19.2)
Nasopharyngitis	8 (10.8)	19 (18.3)
Influenza	6 (8.1)	5 (4.8)
Cystitis	5 (6.8)	5 (4.8)
Oral herpes	4 (5.4)	3 (2.9)
Musculoskeletal and connective tissue disorders	**16 (21.6)**	**45 (43.3)**
Arthralgia	1 (1.4)	14 (13.5)
Back pain	8 (10.8)	8 (7.7)
Pain in extremity	6 (8.1)	10 (9.6)
Gastrointestinal disorders	**28 (37.8)**	**39 (37.5)**
Nausea	5 (6.8)	14 (13.5)
Constipation	9 (12.2)	5 (4.8)
Nervous system disorders	**21 (28.4)**	**32 (30.8)**
Headache	8 (10.8)	20 (19.2)
Hypoaesthesia	0 (0.0)	6 (5.8)
Injury, poisoning and procedural complications	**20 (27.0)**	**32 (30.8)**
Injection-related reactions	7 (9.5)	13 (12.5)
Fall	4 (5.4)	4 (3.8)
Blood and lymphatic system disorders	**13 (17.6)**	**31 (29.8)**
Leukopenia	4 (5.4)	8 (7.7)
Anaemia	5 (6.8)	5 (4.8)
Neutropenia	3 (4.1)	6 (5.8)
Lymphopenia	4 (5.4)	5 (4.8)
Skin and subcutaneous tissue disorders	**10 (13.5)**	**30 (28.8)**
Rash	3 (4.1)	9 (8.7)
Pruritis	1 (1.4)	6 (5.8)
Investigations	**21 (28.4)**	**30 (28.8)**
White blood cell count decreased	0 (0.0)	6 (5.8)
General disorders and administration site conditions	**14 (18.9)**	**24 (23.1)**
Fatigue	3 (4.1)	9 (8.7)
Pyrexia	5 (6.8)	1 (1.0)
Respiratory, thoracic and mediastinal disorders	**10 (13.5)**	**23 (22.1)**
Oropharnygeal pain	4 (5.4)	5 (5.8)
Psychiatric disorders	**6 (8.1)**	**18 (17.3)**
Depression	2 (2.7)	7 (6.7)
Insomnia	1 (1.4)	6 (5.8)
Metabolism and nutrition disorders	**12 (16.2)**	**15 (14.4)**
Hypercholesterolaemia	5 (6.8)	6 (5.8)

TEAE = treatment emergent adverse effect.

Pivotal and/or main efficacy studies

Study BN40900: SOCs with the highest proportions of subjects reporting AEs were generally consistent with Table 10. In contrast, subjects in the satralizumab group (92.1%; n = 58) had higher overall AE incidence compared with the placebo group (75.0%; n = 24).

AEs reported with 5% or greater incidence with satralizumab treatment compared with placebo treatment were generally consistent with the individual Preferred Terms (PTs) in Table 10: arthralgia, nasopharyngitis, rash and nausea, pruritis, headache and WBC count decreased, depression, bronchitis, constipation, migraine, oedema peripheral, alanine aminotransferase increased, musculoskeletal pain and musculoskeletal stiffness.

AEs reported with 5% or greater incidence with placebo treatment compared with satralizumab treatment were: urinary tract infection (UTI), oral candidiasis, vision blurred and tooth abscess. These AEs were not generally consistent with those in Table 10. However, the number of AEs were too few to draw a meaningful comparison with Table 10.

Study BN40898: While infections and infestations SOC had the highest proportion of AEs (68.3%), which was higher than in Study BN40900 (54.0%) and Table 10, investigations and blood and lymphatic systems disorders SOCs had higher proportions of AEs (both 36.6%) than in Study BN40900 (23.8% and 25.4%, respectively) and Table 10. These differences may, in part, be attributed by differences in study design, including add on IST medicines in Study BN40898. Overall AE incidence was similar between treatment groups in Study BN40898 consistent with Table 10.

AEs reported with 5% or greater incidence with satralizumab treatment compared with placebo treatment were generally consistent with the PTs in Table 10: urticaria, hypertension, upper respiratory tract infection, rhinitis, nasopharyngitis, sinusitis, gastritis, leukopenia, arthralgia, headache and injection related reaction (IRR).

AEs reported with 5% or greater incidence with placebo treatment compared with satralizumab treatment were generally consistent with Table 10: pyrexia, influenza and constipation.

Treatment related adverse events

In the Phase III studies, SOCs with the highest proportions of subjects reporting adverse drug reactions (ADRs) were Infections and Infestations, blood and lymphatic system disorders and investigations (Table 11).

In the Phase III studies, ADRs reported with ≥ 2% incidence with satralizumab treatment compared with placebo treatment: hypofibrinogenaemia, WBC count decreased, IRRs and diarrhoea. ADRs reported with ≥ 2% incidence with placebo treatment compared with satralizumab treatment: UTI, cystitis, herpes simplex, anaemia, blood triglycerides increased, hypercholesterolaemia, hypertransaminasaemia and pyrexia.

Table 11: Studies BN40900 and BN40898 Treatment-related adverse events with incidence ≥ 2% (pooled data; double blinded period; safety population)

System Organ Class Preferred Term	Placebo (N = 74) n (%)	Satralizumab (N = 104) n (%)
Subjects with at least 1 ADR	**31 (41.9)**	**39 (37.5)**
Infections and infestations	**13 (17.6)**	**10 (9.6)**
Urinary tract infection	4 (5.4)	1 (1.0)
Cystitis	3 (4.1)	0 (0.0)
Upper respiratory tract infection	1 (1.4)	3 (2.9)
Herpes simplex	2 (2.7)	0 (0.0)
Blood and lymphatic system disorders	**8 (10.8)**	**17 (16.3)**
Leukopenia	3 (4.1)	6 (5.8)
Lymphopenia	3 (4.1)	5 (4.8)
Anaemia	3 (4.1)	1 (1.0)
Hypofibrinogenaemia	0 (0.0)	3 (2.9)
Neutropenia	2 (2.7)	2 (1.9)
Investigations	**8 (10.8)**	**10 (9.6)**
White blood cell count decreased	0 (0.0)	3 (2.9)
Blood trigylerides increased	2 (2.7)	0 (0.0)
Injury, poisoning and procedural complications	**6 (8.1)**	**11 (10.6)**
Injection-related reactions	6 (8.1)	11 (10.6)
Metabolism and nutrition disorders	**6 (8.1)**	**5 (4.8)**
Hypercholesterolaemia	3 (4.1)	2 (1.9)
Gastrointestinal disorders	**3 (4.1)**	**7 (6.7)**
Diarrhoea	0 (0.0)	4 (3.8)
General disorders and administration site conditions	**4 (5.4)**	**5 (4.8)**
Fatigue	2 (2.7)	1 (1.0)
Pyrexia	2 (2.7)	0 (0.0)
Hepatobiliary disorders	**2 (2.7)**	**2 (1.9)**
Hypertransaminasaemia	2 (2.7)	0 (0.0)

ADR = adverse drug reaction.

Subjects in the satralizumab group had similar overall ADR incidence compared with the placebo group. SOCs with the highest proportions of subjects reporting ADRs were generally consistent with Table 11, except in Study BN40900, the highest proportion of ADRs (15.6%) were reported in the injury, poisoning and procedural complications category. There were some differences between studies in regards to type and frequency of ADRs:

- In Study BN40900, ADRs reported in ≥ 2 subjects with satralizumab treatment compared with placebo treatment: sinusitis, hypofibrinogenaemia, lymphocyte count decreased, WBC count decreased, influenza-like illness and lymphopenia and diarrhoea. ADRs reported in ≥ 2 subjects with placebo treatment compared with satralizumab treatment: IRRs (6.1%) and UTI (4.7%); and
- In Study BN40838, ADRs reported in ≥ 2 subjects with satralizumab treatment compared with placebo treatment: IRRs (9.8%), leukopenia (5.1%), neutrophil count decreased and oropharyngeal pain (each 4.9%). ADRs reported in ≥ 2 subjects with placebo treatment compared with satralizumab treatment: cystitis (7.1%), herpes zoster, blood triglycerides increased, pyrexia and hypertransaminasaemia (each 4.8%; n = 2); anaemia (4.7%) and hypercholesterolaemia (2.2%).

Deaths and other serious adverse events

No deaths were reported across the satralizumab clinical development program for NMO/NMOSD (or in the RA study). In the Phase I and Phase III studies, incidence of ≥ 1 serious adverse events (SAE) was generally low and similar across treatments.

Discontinuations due to adverse events

In both Phase III studies, few subjects discontinued from study treatment due to AEs (< 5 subjects in any treatment group). The incidence of AEs that led to study drug discontinuation were generally similar between placebo and satralizumab treatments, with higher numbers of subjects in both treatment groups in the add-on study (Study BN40898: 11.9% versus 7.3%, respectively) compared to the monotherapy study (Study BN40900: 3.1% versus 1.6%, respectively). This difference may be due, in part, to the additional IST medicines received in the add on study. Caution should be exercised in the interpretation of this finding, since the numbers of subjects with AEs that led to study drug discontinuation are too few to draw meaningful conclusions. No more than one subject, in any treatment group, discontinued the study due an AE, in either Phase III study.

Conclusion and safety

The safety profile of satralizumab has been reasonably well established in a subject population of more than 200 NMO or NMOSD subjects, with total cumulative exposure of 327.93 patient-years (PY).

No deaths were reported in the satralizumab studies at data cutoff. Overall incidence of other SAEs, severe AEs and AE frequencies by SOC category and PT, following satralizumab treatment, were generally low and similar to, or less than, placebo. Similarly, there were few study withdrawals due to AEs. ADRs associated with satralizumab treatment were diarrhoea, IRRs, decreased WBC, leukopenia and hypofibrinogenaemia.

The safety profiles in adults and adolescents were generally comparable. The safety of subjects aged 65 years and older were generally consistent with younger adults. The safety profiles of the satralizumab vial and the PFS formulations were also comparable.

Most alanine aminotransferase, aspartate transaminase and bilirubin elevations were mild or moderate in intensity, transient and resolved whilst on study treatment. No time-dependent elevations in liver function tests (LFT) were observed across all phases and studies in the satralizumab clinical program. There were no cases of severe drug induced liver injury identified across the clinical development program for satralizumab and no cases met the full criteria for Hy's law.

Across the entire satralizumab clinical development program, after up to four years of satralizumab exposure, no cases of disseminated or serious opportunistic infections were reported. Isolated, non-serious, infrequent cases of herpes zoster, oral herpes and herpes simplex were reported following satralizumab exposure, with no time dependency observed. Non-serious satralizumab related infections for example upper respiratory tract infection (URTI), occurred. satralizumab treatment was also associated with reductions in neutrophil and leukocyte counts, across clinical studies, although there were no clear correlations between reduced values and development of serious or opportunistic infections. Incidences of AEs of infections and serious infections that led to study discontinuation were low and similar across treatments. Risk associated with satralizumab withdrawal and rebound were not assessed. Given the long half-life of satralizumab, there is a risk, albeit perhaps low, of the development of serious or opportunistic infections later on following satralizumab treatment, even after its cessation, as well as the risk of NMO/NMOSD relapse.

The incidence of malignancies reported with satralizumab was low and similar across treatments. The malignancies reported did not demonstrate any particular pattern, and are not typical of an immunosuppressed population for example no lymphoma cases were reported. Risk of malignancy in long-term satralizumab exposure and risk in immunocompromised patients are unknown.

The evidence provided in the clinical dossier indicated that prolonged satralizumab exposure is not generally associated with cumulative toxicity. However, risk associated

with occurrence of rare events such as autoimmune disorders, disseminated cryptococcal infections or events associated with a long-lag time, such as lymphoma and other malignancies, cannot be fully characterised until much longer periods of satralizumab exposure have occurred that is in the post-market setting.

No clinically meaningful differences were observed in the AE profile of satralizumab as a function of BW, age, race, baseline ARR, anti-AQP4-IgG serostatus and ADA status.

There were no clinically meaningful differences between satralizumab and placebo treatments in regards to electrocardiogram abnormalities. There was no evidence of QT prolongation or pro-arrhythmicity following satralizumab treatment. There were some transient, non-time dependent elevations in total cholesterol and triglycerides, as well as transient elevations in systolic blood pressure (> 140 mmHg) in subjects who received satralizumab as monotherapy, none of which required intervention. Long term cardiovascular risk will become more apparent in the post market setting.

Higher rates of IRRs were reported in the satralizumab group compared with the placebo group, but none of the reactions appeared to be indicative of hypersensitivity and immune responses secondary to immune complex and complement-mediated reactions. No anaphylaxis reactions were reported in any Phase I or Phase III clinical study. However, since data on neutralising antibodies were not available, any effect of these neutralising antibodies on safety, including possible hypersensitivity reactions, cannot be assessed.

Reductions in fibrinogen levels were observed across all the Phase I and Phase III studies. This is an expected pharmacological effect of mAbs (that is inhibition of IL-6 signalling leading to a reduction in fibrinogen production) and since there is a real risk of occurrence of bleeding events, the Phase III clinical studies allowed study site investigators access to subject's fibrinogen results during the DBP of each study. In conjunction with reduced fibrinogen levels, reduced platelet counts were also observed across the Phase I and Phase III studies. Although a few cases of thrombocytopenia were reported in the satralizumab group and no bleeding events per se reported across the clinical program, bleeding events may be reasonably expected given the above.

Since fibrinogen levels and predicted satralizumab exposure were highly correlated, potential bias was introduced into the studies, which could adversely impact both internal and external validity of the study results. The sponsor undertook extensive review of study data, in conjunction with FDA input, including *post hoc* sensitivity analyses, and concluded that bias was not introduced into the Phase III studies. There did not appear to be changes in the numbers of study withdrawals, particularly in the placebo group;

Across the satralizumab program, the incidences of depression and suicidal behaviours were infrequent and balanced across treatments. No signal of concern was identified, and this was corroborated by Columbia-Suicide Severity Rating Scale data.

Subjects with ILD were excluded from Phase III studies. One severe (and serious) case of ILD was reported in Study SA-105JP in rheumatoid arthritis after 120 mg SC satralizumab dosing. ILD has also been reported with tocilizumab exposure. Since satralizumab was genetically engineered like tocilizumab, potential development of ILD cannot be ruled out.

No important identified risks were associated with satralizumab exposure in NMO/NMOSD subjects and, also no new safety signals were identified.

Clinical evaluator's recommendation

The benefit-risk balance of satralizumab is generally positive for use as first line monotherapy treatment, and adjunctive treatment with ISTs, in adults with NMO who are anti-AQP4-IgG positive and NMOSD.

Risk management plan

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 12.[10]

- Roche Products Pty Ltd submitted EU-RMP version 1.0 (dated 30 July 2019; DLP 18 July 2019) and ASA version 1.0 (dated October 2019) in support of the initial application.
- In response to recommendation in the second round of RMP evaluation report, sponsor has provided ASA version 1.1 (dated August 2020).
- In response to negotiations with the Delegate, ACM recommendations and recommendations from the RMP evaluator, sponsor provided ASA version 1.2 (dated August 2020).
- In response to recommendations in the fourth round of RMP evaluation report, sponsor has provided ASA version 1.3 (dated November 2020).
- Sponsor has provided ASA version 1.4 (dated December 2020) with the response to the fifth round of RMP evaluation report.

Table 12: Summary of safety concerns and their associated risk monitoring and mitigation strategies

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	None	_	_	_	_
Important potential risks	Serious and opportunistic infections	ü	_	ü	ü[1]
	Bleeding events	ü	_	ü	ü[1]
	Malignancies: incidence of skin cancers (melanoma and non-melanoma)	ü	_	_	ü[1]
	Hepatotoxicity	ü	_	ü	ü[1]
	Neutropenia	ü	_	ü	ü[1]

[10] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
	Immunogenicity	ü	_	ü	ü[1]
Missing information	Other demyelinating disorders	ü	_	_	_
	Pregnancy and lactation	ü[2]	_	ü	_

1 HCP brochure and Patient Alert Card (PAC)

2 Pregnancy form

The initial summary of safety concerns is considered inadequate from an RMP perspective. The sponsor was requested to update the summary of safety concerns in the first round of RMP evaluation report. The sponsor had not done so and had not provided adequate justifications for this. It was considered an outstanding recommendation and was referred to the Delegate for consideration. After the negotiations with the Delegate and recommendations from the ACM and the RMP evaluator, sponsor has updated the safety specification but has not included some of the safety concerns included in the EU-RMP as this is still under evaluation in the EU. The sponsor has provided assurance that the ASA will be updated to include any additional safety concerns included in the EU after the approval of the EU-RMP. This approach is acceptable.

Sponsor has proposed only routine pharmacovigilance activities. In response to the clinical evaluator questions, the sponsor stated that a pregnancy form will be used to follow up pregnancy reports and was recommended to update the ASA with this information. In response to second round of RMP evaluation, the sponsor provided the pregnancy follow up form appended to the ASA. This approach is acceptable. In response to the fourth round of RMP evaluation report, sponsor stated that in post-market setting all safety concerns except immunogenicity will be monitored through routine pharmacovigilance activities and that PSUR will not include data on this risk. This was deem unacceptable by the RMP evaluator. In response, in ASA version 1.4, sponsor has committed to monitor all safety concerns through routine pharmacovigilance activities. The pharmacovigilance plan is acceptable.

The sponsor has proposed only routine risk minimisation activities, through the draft PI, CMI and 'Instructions For Use' (included in the CMI). The sponsor updated the draft PI and CMI as recommended in the first round of RMP evaluation report and agreed to include the CMI as package insert. This approach was acceptable if the sponsor strengthens the advice in the draft PI and CMI pending outcome of the negotiations with the Delegate on the safety specification. In response to the negotiations with the Delegate and recommendations from the ACM and the RMP evaluator, sponsor has agreed to include a prescriber education brochure and a patient alert card for all important potential risks except immunogenicity. The non-inclusion of immunogenicity in the Prescriber education brochure was not acceptable. As such, sponsor was recommended to include information on immunogenicity in the Prescriber education brochure for now and to update the education materials for prescribers and patients once the safety specification is updated to include any additional risks approved in the EU. In response to fifth round of RMP evaluation report, in ASA version 1.4, sponsor has updated the RMP to include immunogenicity as one of the risks to be mitigated through the prescriber education brochure as requested. The risk minimisation plan is acceptable.

Sponsor has committed to the following in the post approval RMP negotiations:

- To update the ASA to align to the version of the EU-RMP approved by the EMA to ensure safety concerns approved by the EMA are captured in the ASA and to provide these to the TGA when available.
- To include prescriber education brochure and patient alert card.
- To update the Healthcare Professional (HCP) education brochure and post-acute care (PAC) to include any safety concerns added to the ASA.
- To provide additional risk minimisation materials to the TGA six weeks prior to the launch of Enspryng in Australia.

Proposed wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

> *The Enspryng European Union (EU)-Risk Management Plan (RMP) (version 1.0, dated 30 July 2019; data lock point 18 July 2019), with Australian Specific Annex (ASA)(version 1.2, dated August 2020), included with submission PM-2019-04752-1-1, to be revised to the satisfaction of the TGA, will be implemented in Australia.*

The following wording is recommended for the PSUR requirement:

> *An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).*
>
> *Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.*
>
> *If the product is approved in the EU during the three years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter.*
>
> *The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.*

As Enspryng is a new biological entity it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

> *Enspryng (satralizumab) is to be included in the Black Triangle Scheme. The PI and CMI for Enspryng must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.*

Risk-benefit analysis

Delegate's considerations

The sponsor proposed the following indication:

> *Satralizumab (Enspryng) is indicated as monotherapy or in combination with immunosuppressive therapy (IST), for the treatment of adult and adolescent patients from 12 years of age, with neuromyelitis optica spectrum disorder (NMOSD)*

However, the Delegate is of view that there is a lack of adequate efficacy data to support satralizumab usage currently, either as monotherapy or in combination with IST in adolescents (12 to 17 years old). There were only seven adolescents enrolled in the pivotal Phase III studies. Of the seven adolescents enrolled, four (three were anti-AQP4-IgG negative, one was anti-AQP4-IgG positive) were treated with satralizumab and three (one anti-AQP4-IgG negative, 2 anti-AQP4-IgG positive) were treated with placebo. The risk - benefit analysis in adolescents aged 12 to 17 years old, who are most likely to use satralizumab long term, has not been fully documented. Given the potential for the immune-modifier satralizumab to cause serious infections, such as, herpes zoster, tuberculosis, opportunistic infections (cryptococcal meningitis), and malignancies and to turn live attenuated vaccines into threatening diseases, especially on chronic use basis. The Delegate do not recommend use of satralizumab in adolescents.

With regards to anti-AQP4-IgG negative NMO patients, the Delegate noted that the percentage of adults who were anti-AQP4-IgG negative in the recruited NMO patients, was capped at approximately 30% of the total subjects enrolled, based on epidemiological data. The Delegate was of view that notwithstanding the above introduced bias, the statistically significant and clinically meaning outcome for SAT was in the anti-AQP4 IgG positive NMO rather than anti-AQP4-IgG negative cases.

The Delegate also noted that the variational difference in the inclusion criteria for NMO and NMOSD conditions specifies for NMOSD patients to be anti- AQP4-IgG positive at inclusion, while permitting the inclusion of NMO patients without anti-AQP4-IgG positive status.

The Delegate's recommended indication for approval is as follow:

> *Satralizumab (Enspryng) is indicated as monotherapy or in combination with immunosuppressive therapy (IST) for the treatment of adults aged ≥18 years with anti-AQP4-IgG positive Neuromyelitis Optica (NMO) and Neuromyelitis Optica Spectrum Disorder (NMOSD).*

The sponsor has amended the proposed indication post Delegate's recommendation to the following:[11]

[11] Sponsor clarification: In 2015, the International Panel for NMO Diagnosis (IPND) developed revised diagnostic criteria for the proposed condition. Importantly, the new nomenclature defines the unifying term Neuromyelitis optica spectrum disorders (NMOSD), which includes patients meeting the initial diagnostic

Enspryng is indicated as monotherapy or in combination with immunosuppressive therapy (IST) for the treatment of adults aged ≥ 18 years with Neuromyelitis Optica Spectrum Disorder (NMOSD) who are anti- aquaporin 4 (AQP4)-IgG positive.

Proposed conditions of registration

The Delegate proposed the following conditions of registration:

- Standard pharmacovigilance activity, watching for significant safety signals as per the Delegate and clinical evaluator's recommendations, in regard of:
  - Serious and opportunistic infections;
  - Bleeding events;
  - Malignancies: incidence of skin cancers (melanoma and non-melanoma);
  - Hepatotoxicity.
- Sponsor's undertaking, as per the PopPK evaluator's recommendations, to:
  - Have closer examination of the statistical power of the studies to elucidate the sub-group analyses for efficacy per weight.
  - Carry out exploration of the optimal receptor occupancy related to therapeutic efficacy, so as to inform whether exposures in certain weight groups is more than required for the chosen dosage regimen;
  - Aside from the cumbersome simulation compilations /statistical analyses provided by the sponsor, the Delegate's requirement is for the sponsor to undertake the relevant post marketing surveillance as it applies to:
    - § Weight and ADA Status in respect of receptor occupancy and with regard, to the probable dosing adjustments that will inevitably take place in contemporary clinical practice, so as to maintain efficacy and prevent relapse.

Proposed action

There is adequate evidence that the action of satralizumab (in blocking out the signalling effect of IL-6 yields both statistically significant and clinically meaningful outcomes, either as monotherapy or in combination with IST, for the treatment of adults aged ≥ 18 years with anti- AQP4-IgG positive NMO (excluding anti AQP4-IgG negative) and NMOSD. There is currently inadequate data to support an overall benefit of satralizumab, either as monotherapy or in combination with IST, in the younger adolescents aged 12 to 17 years old, when the potential serious adverse risks associated with their probable chronic long term use of satralizumab are considered.

Questions for the sponsor

The sponsor provided the following response to questions from the Delegate.

1. ***Given the similar percentage of subjects who completed the double blind period in both satralizumab (n = 18 that is 18/63→28.6 %) and placebo (n = 17 that is 17/32→53.1%) for Study BN40900 and the satralizumab 2:1 placebo randomisation in the latter. The Delegate noted that there is suggestion for more***

criteria for NMO and those that may not present with the full clinical picture of NMO but are seropositive for NMO-IgG (AQP4-IgG). Accordingly, all patients enrolled into the Phase III studies with a diagnosis of NMOSD according to the protocol inclusion criteria would have also met the 2015 IPND criteria. Because NMO has been incorporated into the definition of NMOSD, the sponsor proposes to only use NMOSD in the indication statement.

drift out of satralizumab than placebo in the double blind period before the scheduled study duration. The Delegate has request the sponsor to clarify if this observation is related to efficacy sequelae or some other rationale.

The sponsor would like to clarify that there was no fixed treatment period as BN40900 was an event driven trial where patients could exit the DBP and enter the open label extension period (OLE) after experiencing the pre-defined event that is a protocol-defined relapse (PDR). The numbers provided in the Delegate's comment reflect the numbers of PDRs that occurred in both treatment arms and not the number of patients that remained in the trial at the clinical cut-off date (CCOD). Therefore, the fact that the numbers are lower for the satralizumab arm is a direct reflection of the efficacy of satralizumab.

2. The number of subjects who completed the DBP were n = 18 (43.9%) for satralizumab and n = 24 (57.1%) for placebo in Study BN40898. The Delegate noted that there is suggestion for more drift out of satralizumab than placebo in the double blind period before the scheduled study duration. The Delegate has request the sponsor to clarify if the observation is related to efficacy sequelae or some other rationale.

As per the previous comment, the sponsor would like to clarify that there was no fixed treatment period and that Study BN40898, like BN40900, was an event driven trial where patients could exit the DBP and enter the open label extension period (OLE) after experiencing the pre-defined event. In the case of BN40898 patients could exit the DBP after experiencing a PDR or a relapse that was treated with rescue therapy (treated clinical relapse, TCR). The numbers provided in the Delegate's comment reflect the number of PDRs or TCRs that occurred in both treatment arms and not the number of patients that remained in the trial at the clinical cut-off date (CCOD). Therefore, the fact that the numbers are lower for the satralizumab arm is a direct reflection of the efficacy of satralizumab.

Advisory Committee considerations[12]

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

1. The approvability or not of the submission, based on the gamut of the available evidence

The ACM were satisfied with the efficacy and safety data provided in support of this application, agreeing that the clinical efficacy data generally supported satralizumab as a treatment as monotherapy, or as adjunctive treatment with ISTs, for an anti-AQP4-IgG-positive adult population with NMOSD.

The ACM discussed the significance of the anti-AQP4-IgG status on the efficacy of satralizumab, highlighting that both the SAkuraStar and SAkuraSky trials demonstrated

[12] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

efficacy for patients with an anti-AQP4-IgG positive status. It was considered appropriate to have the indication limited to this seropositive status.

With regard to dosing, the ACM advised that a loading dose regimen of 120 mg at Weeks 0, 2 and 4 followed by 120 mg maintenance doses every four weeks is appropriate. Given the non-linear pharmacokinetics and slow subcutaneous absorption of the drug, this regimen is expected to reduce the timeframe to reach steady state thereby providing faster therapeutic effect. However, the ACM emphasised that further clarification is required in relation to the impact of weight and anti-drug antibodies, as well as the expected receptor occupancy and outcome. Such clarification may be unmasked during the standard post marketing surveillance.

The ACM discussed the appropriateness of using satralizumab as a monotherapy, as clinical experience has demonstrated that some patients do relapse whilst on monotherapy, and may therefore require multiple agents such as immunosuppressants and corticosteroids to achieve and maintain remission.

2. The delegate's recommended indication as per the evidence based rationales

The ACM discussed the inclusion of adolescents within the indication and noted that this population was not well represented in the studies, citing only seven adolescents were included with the SAkuraSky trial and no adolescents in the SAkuraStar trial. Noting that the sponsor's pre-ACM proposed indication does not include the adolescent population, the ACM advised that off-label use may occur with these patients.

The ACM discussed available antibody biomarker testing options. They noted the importance of anti-AQP4 for determining treatment plans and acknowledged the availability of the older NMO IgG test.

The ACM recommended including both the disease and the antibody status within the indication wording.

Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for:

> *Satralizumab is indicated either as monotherapy or in combination with other immunosuppressive therapy (IST), for the treatment of adults with neuromyelitis optica spectrum disorders (NMOSD) who have anti-AQP4-IgG positive status, or a positive NMO IgG test as an alternative to AQP4 ab testing, if the latter is unavailable for testing.*

All issues pertaining to the draft Product Information and Registration must be resolved to the satisfaction of the TGA**.**

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Enspryng (satralizumab) 120 mg/mL, solution for injection, pre-filled syringe, indicated for:

> *Enspryng is indicated as monotherapy or in combination with immunosuppressive therapy (IST) for the treatment of adults with neuromyelitis optica spectrum disorders (NMOSD) who have an anti-aquaporin 4 antibody (AQP4)-IgG (also termed NMO-IgG) positive status.*

Specific conditions of registration applying to these goods

- Enspryng (satralizumab) is to be included in the black triangle scheme. The Product Information (PI) and Consumer Medicines Information (CMI) for Enspryng must

include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

- The Enspryng European Union (EU)-risk management plan (RMP) (version 1.0, dated 30 July 2019; data lock point 18 July 2019), with Australian specific annex (version 1.2, dated August 2020), included with submission PM-2019-04752-1-1, to be revised to the satisfaction of the TGA, will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

  If the product is approved in the EU during the three years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

- All batches of Enspryng supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

  When requested by the TGA, the sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the Product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index and periodically in testing reports on the TGA website.

- For all injectable products the Product Information must be included with the product as a package insert.

Attachment 1. Product Information

The PI for Enspryng approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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