22 April 2021
EMA/CHMP/265568/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Enspryng

International non-proprietary name: satralizumab

Procedure No. EMEA/H/C/004788/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Table of contents

List of abbreviations

ADAs	Anti-Drug Antibodies
ADCC	Antibody-Dependent Cell-mediated Cytotoxicity
AEs	Adverse Effects
AE-HPLC	Anion Exchange High Performance Liquid Chromatography
AEX	Anion Exchange
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AQP4-IgG	Aquaporin-4 Immunoglobulin G antibodies
ARR	Annualized Relapse Rate
AST	Aspartate Aminotransferase
AUC_{inf}	Area under the concentration-time curve from time zero to infinity
AUCR	Area under the concentration-time curve ratio
AUC_{τ}	Area under the concentration-time curve tau
$AUC_{0\text{-}7d}$	Area under the concentration-time curve from hour 0 to day 7
$AUC_{0\text{-}28,\ SS}$	Area under the concentration-time curve from hour 0 to day 28 at steady state
BIC	Bayesian information criterion
BLQ	Below the Limit of Quantitation
BMI	Body Mass Index
BOCF	Baseline Observation Carried Forward
BW	Body Weight
CCOD	Clinical Cut-Off Date
CDC	Complement-Dependent Cytotoxicity
CDR	Complementarity-determining region
CEC	Clinical Endpoint Committee
CFU	Colony-Forming Unit
CH50	Total complement activity
CHMP	Committee for Medical Products for Human Use
CHO	Chinese Hamster Ovary
CIs	Confidence Intervals
CL	Clearance
CL_{total}	Total Clearance
C_{max}	Maximum Concentration
CNS	Central Nervous System
CPH	Cox Proportional Hazard
CPPs	Critical Process Parameters
CRP	C-reactive protein
CQA	Critical Quality Attribute
CRS	Cytokine Release Syndrome
CSF	Cerebrospinal Fluid
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough Concentration
Ctr56	trough concentrations at Day 56
CV	Coefficient of Variation
ΔΔQTcF	placebo-adjusted change from baseline in Corrected QT interval by Fredericia
DALYs	Disability Adjusted Life Years
DB	Double-blind
DDI	Drug-Drug Interaction
DoEs	Design of experiments
EC_{50}	half maximal Effective Concentration
ECG	Electrocardiogram
ECL	Electrochemiluminescence
ECLIAs	Electrochemiluminescence immunoassays
EDSS	Expanded Disability Status Scale
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EPC	End-of-process Cells
ePPND	Enhanced Pre- and Postnatal Development
EQ-5D-3L	EuroQol-5D 3 Level Version
EVA	Ethylene Vinyl Acetate
FACIT	Functional Assessment of Chronic Illness Therapy

Fc	Fragment crystallizable effector portion of the immunoglobulin molecule
FcRn	neonatal Fc receptor
FcR	Fc receptors
FSS	Functional System Scores
F_{SC}	Subcutaneous bioavailability
K_a	First order absorption rate constant
K_D	Dissociation Constant
K_m	Michaelis-Menten constant
GCP	Good Clinical Practices
GEE	Generalized Estimating Equations
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practice
HDL	High Density Lipoprotein
HDPE	High-Density Polyethylene
HFLS-RA	Human Fibroblast-Like Synoviocytes from Rheumatoid Arthritis patients
HIC	Hydrophobic Interaction Chromatography
HMWS	High Molecular Weight Species
HR	Hazard Ratio
HRP	Horseradish peroxidase
IBP	International Birth Date
IC_{50}	Half maximal inhibitory concentration
IL-6	Interleukin 6
IL-6R	Anti-IL-6 receptor
IOV	Inter-occasion variability
IPCs	In-process controls
IRR	Injection Related Reactions
IST	Immunosuppressive therapy
ITT	Intent-To-Treat
IxRS	Interactive web/voice response system
IV	Intravenous
IVIG	IV immunoglobulin
LCSLC	Low-contrast Sloan Letter Chart
LETM	Longitudinally Extensive Transverse Myelitis
LDL	Low Density Lipoprotein
LMWS	Low-Molecular Weight Species
MCB	Master Cell Bank
MCP-1	Monocyte Chemoattractant Protein-1
MMRM	Mixed-effect Model Repeated Measures
MMV	Minute Virus of Mice
MOG	Myelin Oligodendrocyte Glycoprotein
mRS	Modified Rankin Scale
MRI	Magnetic Resonance Imaging
NAb	Neutralizing antibodies
NSD	Needle Safety Device
NMOSD	Neuromyelitis Optica Spectrum Disorder
NONMEM	Nonlinear Mixed Effects Modeling
OFV	Objective Function
OLE	Open Label Extension
OQ	Operational Qualification
PD	Pharmacodynamics
PDR	Protocol-defined relapse
PFS	Pre-Filled Syringe
PCB	Placebo
PK	Pharmacokinetics
PIP	Paediatric Investigation Plan
PND	Post-natal days
PBPK	Physiologically-based pharmacokinetic
PQ	Performance Qualification
PopPK	Population Pharmacokinetics
PPC	Post-Production Cells
PPS	Per-Protocol Set
PT	Preferred Terms
Q	Inter-compartmental clearance
Q4W	Every Four Weeks

QbD	Quality by Design
RA	Rheumatoid Arthritis
RO	Receptor Occupancy
RRF	Ranking and filtering
RSE	Relative Standard Error
SAEs	Serious Adverse Events
SAT	Satralizumab
SBP	Systolic Blood Pressure
SC	Subcutaneous
SD	Standard Deviation
SDMs	Scale-Down Models
SE-HPLC	Size Exclusion High Performance Liquid Chromatography
SF-36v2	Short Form Health Survey 36 Version 2
sIL-6R	Soluble IL-6R
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SPR	Surface Plasmon Resonance
TDAR	T-cell dependent antibody response
TFR	Time to First Relapse
TMDD	Target Mediated Drug Disposition
t_{max}	Time to maximum concentration
$t_{1/2}$	plasma elimination half-life
T25W	Timed 25-Foot Walk
TI	Tolerance Intervals
ULN	Upper Limit Normal
UF/DF	Ultra-/Diafiltration
VAS	Visual Analogue Scale
VEGF	Vascular Endothelial Growth Factor
V_C	Central volume of distribution
V_{max}	Maximum Michaelis-Menten elimination rate
V_P	Peripheral volume of distribution
V_{ss}	Volume of Distribution at Steady State
VP	Visible Particles
WBC	While Blood Cells
WCB	Working Cell Bank
ZBI	Zarit Burden Interview

1. Background information on the procedure

1.1. Submission of the dossier

The Applicant Roche Registration GmbH submitted on 20 August 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Enspryng, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 March 2017.

Enspryng, was designated as an orphan medicinal product EU/3/16/1680 on 27 June 2016 in the following condition: Treatment of neuromyelitis optica spectrum disorders.

The Applicant applied for the following indication: Enspryng is indicated as a 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).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0220/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0220/2019 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Enspryng as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/Enspryng

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the Applicant did submit a critical report addressing the possible similarity with an authorised orphan medicinal product.

Applicant's request(s) for consideration

Accelerated assessment

The Applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No

726/2004.

New active Substance status

The Applicant requested the active substance satralizumab contained in the above medicinal product to be considered as a new active substance, as the Applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
19 September 2013	EMEA/H/SA/2571/1/2013/III	*Jens Reinhardt, André Elferink*
22 October 2015	EMEA/H/SA/2571/2/2015/I	*Dieter Deforce, Mario Miguel Rosa*
21 April 2017	EMEA/H/SA/2571/2/FU/1/2017/PA/I	*André Elferink, Mario Miguel Rosa*
21 April 2017	EMEA/H/SA/2571/1/FU/1/2017/PA/III;	*André Elferink, Mario Miguel Rosa*
22 March 2018	EMEA/H/SA/2571/2/FU/2/2018/PA/II	*Elena Wolff-Holz, Kerstin Wickström*
18 October 2018	EMEA/H/SA/2571/2/FU/3/2018/PA/III	*David Brown, Andreas Kirisits*

The Protocol assistance pertained to the following *quality, non-clinical, and clinical* aspects:

- Quality
    - Analytical comparability assessment of drug substance produced via several manufacturing processes as part of the comparability strategy in support of clinical development and MAA, including stability study design for the drug product;
    - Adequacy of design verification data supporting home administration by patient/caregiver; use of a cell-based bioassay for potency testing; visible particle control strategy for stability testing
- Non-clinical - leveraging the toxicological information from other IL-6R targeting agents and data generated with a surrogate anti-murine IL-6Ra monoclonal antibody mAb to address reproductive toxicity risk
- Clinical
    - Study design elements, enrolment criteria (including the enrolment of 12-year-old patients as lower age cut-off limit), dosing strategy and sample size considerations for the planned clinical study(-ies) in support of the potential indication "for maintenance treatment of patients with NMO" – i.e. including both add-on and monotherapy indications.
    - Choice of time-to-first relapse as the primary endpoint for confirmatory trials and the definition of relapse. Follow-up advice was also sought on the statistical analysis plan, sensitivity analyses and handling of missing data related to the time to event analyses selected as primary EP.
    - Adequacy of the expected safety database and immunogenicity data to be accrued during clinical development

- QT Assessment and need for a thorough QT study, drug-drug interaction risk assessment, human factor studies to prove that the assembled PFS with NSD is safe and effective to administer the medicinal product and that the design verification safety data generated supports home administration by patient/caregiver.
- Use of clinical data generated with an initial drug substance manufacturing process and with a different administration device.

- Adequacy of the overall development program for NMO/NMOSD patients (self- and caregiver-assisted administration) and risk mitigation actions related to unblinding for both pivotal studies SA-307JG and SA-309JG (and associated GCP compliance aspects), and amendment (early termination) of the SA-309JG CT protocol.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: Maria Concepcion Prieto Yerro

The application was received by the EMA on	20 August 2019
Accelerated Assessment procedure was agreed-upon by CHMP on	25 July 2019
The procedure started on	12 September 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	12 November 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	20 November 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	19 November 2019
In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days	
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 November 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on The CHMP also agreed to revert to standard timetable	10 December 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	28 March 2020
The following GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
- A GCP inspection at two investigator sites in Spain and Poland, at sponsor site in Japan and at a CRO site in USA between 4/11/2019 and 7/08/20. The outcome of the inspection carried out was issued on	21 December 2020

21/12/2020.	
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	5 May 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	5 May 2020
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	28 May 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	25 January 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	11 February 2021
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	25 February 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	02 March 2021
The outstanding issues were addressed by the Applicant during an oral explanation before the CHMP during the meeting on	23 March 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Enspryng on	22 April 2021
The CHMP adopted a report on similarity of Enspryng product with Soliris on (Appendix 1)	22 April 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

NMO/NMOSD are severe autoimmune inflammatory demyelinating disorders that are typically characterized by optic neuritis and transverse myelitis (Wingerchuk et al. 2015).

The applicant seeks approval for satralizumab (Enspryng) in the following indication: *as a 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).*

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

2.1.2. Epidemiology

Epidemiological studies of the uncommon disorder neuromyelitis optica spectrum disorder (NMOSD) may be difficult to interpret because of the evolving nature of diagnostic criteria, differences in the definition and accuracy of NMOSD diagnosis, the completeness of case ascertainment, and variability in assays for the disease-specific biomarker aquaporin-4 immunoglobulin G antibody (AQP4-IgG). A significant increase in yearly incidence rate has been reported over time. In recent European epidemiological studies on NMO(SD), the incidence rate was found to be 0.07-0.079 per 100 000 and the prevalence 1.04-1.09 per 100 000 (e.g. Jonsson *et al.* 2019; Asgari *et al.* 2019).

Standard treatment is based on the use of steroids and immunosuppressive drugs and aims to control the severity of acute attacks and to prevent relapses of the disease (Bruscolini et al. 2018). Disability and mortality are associated with the severity of these acute attacks and frequency of relapses. While NMO(SD) prognosis has improved over the last decades, it remains a severely debilitating disease with a significant proportion of patients suffering from neurological sequelae after the initial period of the disease and after relapses. A female predominance is observed in many published cohorts, with a female to male ratio ranging from 3:1 in France to 10:1 in Japan (Jacob et al. 2013). NMO(SD) occurs at all ages, with a mean age of onset around the age of 40, resulting in a high level of disability adjusted life years (DALYs). In a recently published study from Sweden, 49% and 75% of NMO(SD) patients had a relapse within 5 and 10 years respectively, and 2.4% died within the follow up (mean time of 8 years) (Jonsson et al. 2019).

2.1.3. Aetiology and pathogenesis

NMOSD is an inflammatory central nervous system (CNS) disease that is associated with serum AQP4-IgG. The major pathological mechanism of injury in AQP4-IgG seropositive NMOSD involves the AQP4-IgG binding to aquaporin-4 water channels in the astrocytes of brain, spinal cord, and optic nerve, followed by inflammation, disruption of blood–brain barrier, and complement-dependent cytotoxicity (CDC), with ensuing demyelination and axonal damage, and ultimately neurological symptoms characteristic of NMOSD. Thus, AQP4-IgG seropositive NMOSD could be viewed as an autoimmune astrocytopathy.

In 20–30% of patients, depending on the assay used, AQP4-IgG are not detectable (Melamed et al., 2015). AQP4-IgG seronegative NMOSD includes patients with a myelin oligodendrocyte glycoprotein (MOG)-antibody-seropositive disease and patients who are negative for both antibodies (double seronegative) (Fujihara et al. 2019). Whether AQP4-Ab positive and AQP4-Ab negative diseases are varieties of the same entity is a topic of ongoing research (Jarius et al., 2012, Jiao et al., 2013, Kiyat-Atamer et al., 2013).

A plasmablast B cell subset has been identified (Chihara et al., 2011), associated with production of AQP4-IgG and shown to be selectively increased in the blood of NMOSD patients. The survival of this plasmablast subpopulation is promoted by interleukin 6 (IL-6), which was shown to enhance their antibody production, whereas anti-IL-6 receptor (IL-6R) blockade selectively inhibited survival of AQP4-IgG producing plasmablasts. Consequently, this IL-6-dependent B-cell subpopulation may be assumed to play an important role in the pathophysiology of NMOSD.

2.1.4. Clinical presentation, diagnosis and prognosis

NMOSD is typified by recurrent attacks of severe optic neuritis and/or myelitis, often in form of an extensive transverse myelitis (LETM). In AQP4-IgG seropositive NMOSD, the reported frequency of optic neuritis is 37-54% and of LETM 30–47% (Jarius et al., 2012, Aboul-Enein et al, 2013, Zhang Bao et al,

2017). Also, other symptoms or syndromes occur, for instance brainstem and brain involvement. Persistent hiccup, nausea or vomiting (area postrema syndrome), narcolepsy, acute diencephalic syndrome or muscle affection are possible (Chen et al, 2017, Bab et al., 2009). The ensuing disability accumulates predominantly through relapses of the disease as recovery of the neurologic deficits is often incomplete. The most common and burdensome clinical symptoms are pain, especially neuropathic, fatigue, headache, depression, and sleep disorders (Kleiter et al., 2016, Mizuno et al, 2018, Asseyer et al, 2018, Song et al, 2015; Penner et al, 2017). Prognosis of the disease is worse and mortality rate higher without long-term IST (Mealy et al, 2018). Disease may appear at any age (given range 4-88 years), but the incidence is most common in early middle age (mean age of onset 39 years) (Pandit et al. 2015, Krumbholz et al., 2015). Female sex predominates, especially in AQP4-IgG seropositive NMOSD patients, female to male-ratios as high as 10:1 have been reported (Pandit et al, 2015; Borisow et al., 2017, Wingerchuk 2009). It is notable that comorbidity with other autoimmune disorders is fairly common.

A central component of diagnostics is the detection of antibodies in serum. Magnetic Resonance Imaging (MRI) is an essential part of diagnostics, helping to differentiate NMO/NMOSD from other CNS disorders. Clinical criteria have been revised in 2015, and they distinguish between NMOSD with AQP4-IgG and NMOSD without AQP4-IgG or with unknown antibody status. The core clinical symptoms are 1) optic neuritis, 2) acute myelitis, 3) area postrema syndrome, 4) acute brainstem syndrome, 5) symptomatic narcolepsy or acute diencephalic clinical syndrome with typical MRI, 6) symptomatic cerebral syndrome with typical brain lesions. In case of AQP4-IgG seropositivity, one core symptom is needed, but without this evidence, two core features are necessary, at least one being optic neuritis, LETM, or area postrema syndrome (Wingerchuk et al, 2015).

The prognosis is affected by the stepwise deterioration due to relapses which usually worsen over days to a nadir and recover over several weeks to months with sequelae. Predictors of a worse prognosis include the number of relapses during the first two years, the severity of the first attack, older age, and probably association with other autoimmune disorders. The high mortality rates are frequently caused by neurogenic respiratory failure occurring with brainstem or extended cervical lesions (Sellner et al., 2010). Reported mortality rate ranges (25-50%) may be biased towards the severe end.

2.1.5. Management

NMOSD attacks are treated with high-dose intravenous corticosteroids and apheresis therapies, in particular therapeutic plasma exchange. In cases of incomplete remission, escalation of attack treatment is recommended.

Preventive therapy is IST and should be commenced as early as possible. Apart from classical immunosuppressants such as azathioprine and mycophenolate mofetil, repurposed biologicals, particularly B-depleting agents (e.g. rituximab) are widely used. The preventive therapy has been regarded as beneficial, and the scarce published data provide an indication of a preventive effect to an extent; consensus treatment regimens have been published and are widely used throughout the world with an apparent clinical benefit. Nevertheless, an adequate evidence base of randomized controlled trials has been lacking to support these currently used treatment options. Thus, an unmet medical need has long been prevalent. In 2019, Eculizumab was authorised for the treatment of NMOSD AQP4-IgG seropositive adult patients with a relapsing course of the disease.

About the product

A treatment that blocks IL-6 signalling may inhibit key NMOSD pathophysiological processes and lead to reduction of relapses. Satralizumab (SA237) is a humanized IgG2 anti IL-6R monoclonal antibody. It

specifically targets the human IL-6R, blocks IL-6 from binding to membrane-bound and soluble IL-6R, and thereby inhibits IL-6 downstream signalling.

The claimed indication was the following:

> *As a 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) (see section 5.1).*

The approved indication is the following:

> *As a monotherapy or in combination with immunosuppressive therapy (IST) for the treatment of neuromyelitis optica spectrum disorders (NMOSD) in adult and adolescent patients from 12 years of age who are anti-aquaporin-4 IgG (AQP4-IgG) seropositive (see section 5.1).*
>
> At a body weight of at least 40 kg, the recommended loading dose is 120 mg subcutaneous (SC) injection every two weeks for the first three administrations (first dose at week 0, second dose at week 2 and third dose at week 4).
>
> The recommended maintenance dose is 120 mg SC injection every four weeks.

Type of Application and aspects on development

The CHMP agreed to the Applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on the lack of evidence-based treatment options for NMO/NMOSD at the time of the request and the Applicant's presentation of the pivotal studies, indicating that satralizumab may constitute an efficacious treatment option for the prevention of relapses in patients with NMO/NMOSD in adults and adolescents, potentially with an acceptable safety profile. At the time of the Applicant's request, CHMP considered that the overall design of these studies and scope of the data may be sufficient to address the unmet medical need in patients with NMO(SD).

However, the CHMP concluded during assessment that it was no longer appropriate to pursue accelerated assessment. During the evaluation of this MAA, a new product was approved for market authorisation in the Treatment of adult patients with Neuromyelitis Optica Spectrum Disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody (Ab) positive. At the time of the Applicant's request for accelerated procedure, there was a lack of approved treatments and a high unmet medical need. The initially sought indication; 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) included patients who are anti-aquaporin-4 (AQP4) antibody (Ab) negative and adolescents, patient groups which are not covered by the approved product. However, the Applicant was unable to demonstrate efficacy in the AQP4-IgG seronegative NMOSD patients and proposed a revised indication excluding these patients. At that moment, there were major objections to the efficacy and safety regarding other subgroups including the one of age span 12-17 years.

As outlined in previous central advice procedures (EMEA/H/SA/2571/2/FU/2/2018/PA/II), prior concerns regarding the breached blinding of the studies (related to satralizumab's lowering effect on fibrinogen) were present, and this was also raised in the accelerated procedure assessment (Enspryng-478AA-Briefing Note). Following further assessment, major objections were raised regarding these GCP violations and possibly correlated protocol amendments for study BN40900, resulting in loss of study integrity and control of type 1 error, overall questioning the robustness of the results and trial integrity of this pivotal study. A routine inspection of the sponsor and of one investigator site was performed, prompting the need for triggered inspection. At that moment, the final inspection report from the routine

inspection was pending and the full impact of these and other critical issues raised in the preliminary report, could not be fully evaluated.

In light of above arguments questioning the strength of evidence to support fulfilment of unmet medical need, the CHMP agreed on 10 December 2019 that the accelerated process is to be reverted to standard timetable (Guideline on the procedure for accelerated assessment, EMEA/274268/2006).

2.2. Quality aspects

2.2.1. Introduction

Satralizumab, the active substance contained in Enspryng, is a recombinant humanised IgG2 monoclonal antibody that binds to soluble and membrane-bound IL-6R and thereby prevents IL-6 downstream signalling through these receptors.

The finished product is presented as a 1 mL solution for subcutaneous injection in a single-use PFS containing 120 mg of satralizumab formulated with commonly used compendial excipients: L-histidine, L-aspartic acid, L-arginine, poloxamer 188 and water for injections. The PFS is presented assembled with an automatic needle guard.

2.2.2. Active Substance

General Information

Satralizumab is a recombinant humanised IgG2 monoclonal antibody produced in Chinese hamster ovary (CHO) cells. Satralizumab was designed by amino acid substitutions to improve some functional properties such as reduction of effector functions, pH-dependent binding to its antigen (IL-6R) and binding to neonatal Fc receptor (FcRn).

Satralizumab consists of two heavy chains (443 amino acid residues each), and two light chains (214 amino acid residues each). The calculated molecular mass is approximately 143.4 kDa (peptide chains only).

The heavy chain has a single conserved glycosylation site at Asn295 in the Fc domain. The N-linked glycans of satralizumab are typical of those observed on other CHO-produced monoclonal antibodies. C-terminal processing cannot occur in satralizumab because the heavy chains of satralizumab lack the Gly-Lys sequence at the C-terminus.

Manufacture, process controls and characterisation

Description of the manufacturing process and process controls

Satralizumab active substance is manufactured at Chugai Pharma Manufacturing Co., Ltd. (CPMC), 5-1, Ukima 5-Chome, Kita-ku, Tokyo, 115-8543, Japan. The name, address, and responsibilities of each manufacturer involved in the manufacture, storage, and testing of the active substance is available in the dossier. The EU Good Manufacturing Practice (GMP) compliance status was confirmed. No concerns are raised.

A batch of active substance is defined as the material purified from one production bioreactor. One working cell bank (WCB) vial can be used for several cultivation batches during a cultivation campaign.

This approach is acceptable. All media used for the cell culture process are free of animal-derived substances. Recombinant human insulin is used in non-selective cultivation media.

The commercial manufacturing process of satralizumab active substance encompasses cell culture (fed-batch), harvest and primary capture, purification, concentration, formulation, conditioning and filtration to final fill. The purification encompasses four chromatography steps, low-pH virus inactivation, virus filtration and ultra-/diafiltration (UF/DF). The manufacturing process and process controls are summarised in flow charts and tables. The purpose of each step is clearly stated and a brief description is provided. Process parameters and in-process controls (IPCs) are listed, including criticality assignment, and criteria for collection of fractions are provided. Critical steps, critical process parameters (CPPs) and IPCs are presented in a condensed format. The impact of each process parameter to critical quality attributes (CQAs) is clearly described. Management of deviations to these limits is acceptably described.

Operating sequences, resin and filter materials, buffers, reuses (where applicable), and collection of fractions are provided for the chromatography steps and the filtration steps. Pre-harvest samples are tested for adventitious agents. The level of detail is considered sufficient.

For some steps, there are clearly indicated restriction relationships where certain process parameter setpoint combinations are not allowed.

In practice, the variation of one or more process parameter set points within the acceptable ranges is allowed. Process parameter changes within the acceptable ranges will be managed per the Applicant's Quality System. The definition used by the Applicant is similar to the definition of proven acceptable ranges as provided by ICH Q8. No design space is claimed.

IPCs are supported by the attribute criticality assessment. In-process pool hold times and hold conditions are appropriately described for each step.

Reprocessing is allowed for certain manufacturing steps. Protocols for concurrent validation at the manufacturing scale are provided. The overall approach for reprocessing is appropriate.

In summary, it can be concluded that the description of the proposed manufacturing process and process controls are acceptable.

Control of materials

Raw materials

Detailed descriptions of raw materials and consumables such as resins and filters are presented. Specifications are provided for non-compendial raw materials. The information provided is sufficient. Raw materials of animal origin are discussed and assessed in the section for adventitious agents.

Source, history, and generation of the cell substrate

The information regarding the host cell and the vector is sufficient. The source, history and generation of the production cell line is described and information on the plasmid sequence and cloning is provided. Genetic stability throughout the cell culture production process is demonstrated. Information on storage and stability testing of cell banks is provided.

Cell banking system, characterisation and testing

A safety assessment of the materials of animal origin that were used for the cell bank development and preparation has been provided with supplier information/certificates. The procedures for MCB and WCB preparation are described. The MCB and WCB were produced and tested according to ICH Q5A, Q5B and Q5D guidelines. Safety testing from parent seed stock to post-production cells (PPC) is described with viral and non-viral adventitious agents and screening for retroviruses.

The overall approach and result of the cell bank testing and the claimed limit of *in vitro* cell age is acceptable.

Control of critical steps and intermediates

The satralizumab CPPs are a subset of process parameters that have been determined to impact or potentially impact CQAs of the active substance.

CQAs were determined using a risk ranking and filtering (RRF) tool that assesses the possible impact of each quality attribute on bioactivity, pharmacokinetics, immunogenicity risk, and safety.

Process parameter criticality is based on an assessment of process validation data for the impact of each process parameter on the CQAs. A process parameter is critical if it has a practically significant impact on a CQA across the characterised range for that parameter.

Process validation

An extensive set of studies for process evaluation and process verification is presented, along with descriptions of methods and tools. The described process evaluation encompasses an enhanced approach with several elements of Quality by Design (QbD) (risk assessments, multivariate design of experiments (DoEs), statistical tools). Process parameter criticality evaluation is based on small-scale experiments and prior knowledge. In summary, a solid process understanding is demonstrated.

Experimental design and statistical tools are sufficiently described. The definitions of CPPs and CQAs are aligned with ICH Q8(R2). Key performance indicators are also used to evaluate process performance.

Overall, the set of CPPs defined for the active substance manufacturing process is as expected and considered acceptable. Predictions based on the DoE studies are used for risk assessment before changes and to justify the active substance specifications.

Process verification of the manufacturing steps (at manufacturing scale) for active substance is adequately described and reported. The process verification activity is based on an enhanced approach for process development and process characterisation but executed at setpoint within the acceptable ranges proposed in the process description. Process verification data support the conclusion that the manufacturing process for active substance can be considered validated.

In-process hold times are considered validated. Small-scale data support the proposed reuse of chromatography resins and UF/DF membranes. The approach to demonstrate clearance of raw materials is endorsed. Information provided regarding leachables and extractables (studies performed in accordance with ICH M7 and ICH Q3C) is considered sufficient.

The information provided regarding shipping validation is sufficient.

Manufacturing process development

Based on clinical experience and product characterisation, CQAs were identified and acceptable levels were defined to ensure safety and efficacy of the product. CPPs were identified and acceptable ranges were defined to ensure the process produces acceptable product quality.

A clear and structured description is given regarding the QbD elements included in the approach utilised for development of the satralizumab manufacture and control. The same approach has been used by the Applicant for other, already approved, products. However, a separate assessment was made for this application. No concerns are raised on the overall approach.

The manufacturing history and comparability exercises are described in sufficient detail. Comparability is demonstrated for the versions used throughout development.

Characterisation

Elucidation of structure and other characteristics

A comprehensive physicochemical and biological characterisation of satralizumab is presented. It is agreed that the results show that satralizumab has the covalent structure, post-translational modifications and other characteristics of a typical humanised monoclonal antibody derived from CHO cells. Studies of primary, secondary and higher order structures, various physicochemical properties, carbohydrate structure, heterogeneity pattern, biological functions, degradation pathways, and product variants were included.

An extensive panel of state-of-the-art and orthogonal tests were applied. Characterisation methods and preparations of variants for characterisation studies are sufficiently described. All peaks are characterised and defined and relevant chromatograms are provided.

Satralizumab contains N-linked glycosylation at position Asn295 of each heavy chain. Satralizumab is an engineered IgG2 monoclonal antibody.

Impurities

Product-related substances and product-related impurities are all considered "product-related variants". These variants are assessed by a risk-based approach for impact to bioactivity, pharmacokinetics, immunogenicity and safety to identify the CQAs. The approach is considered scientifically sound and the list of identified CQAs is acceptable.

Product-related variants and process-related impurity CQAs were identified using a RRF tool that evaluates the impact of each product quality attribute on patient safety and product efficacy. The definition of a CQA is in line with ICH Q8.

The submitted information is acceptable and demonstrates a solid product understanding.

Specification

The release and shelf life specifications for the active substance were provided. The test panel is acceptable and in line with the requirements of ICH Q6B. The test panel includes control of identity, purity and impurities, potency and other general tests. The proposed limits are acceptable.

The proposed specifications for active substance and finished product were developed as part of a quality attribute-based control strategy, using the concepts of ICH guidelines. Prior knowledge was also used and acceptably justified (throughout the sections). The approach used for setting the specifications is considered appropriate.

Analytical procedures

Pharmacopoeia-based and satralizumab-specific analytical procedures are used to test the commercial batches of the active substance for release and/or stability. The development history of analytical procedures was provided.

Appropriate validation of non-compendial methods was performed confirming suitability for their intended use.

Batch analysis

Batch genealogies and batch release results for active substance lots are provided.

Each batch was tested to the specification in place at the time of manufacture, and the PPQ batches were also tested to the proposed commercial specification. All limits were met. The release data provided from the commercial process support a consistent manufacture of active substance. No concerns are raised.

Reference standards

The same reference material is used for active substance and finished product testing. Reference is made to the finished product section.

Container closure

The active substance container closure consists of a single-use bag.

The approach described for assessment of extractables and leachables from the active substance container closure system is found adequate. The Applicant concludes that the single-use bags are safe and suitable for storage of the active substance ≤ -50 °C. This conclusion is supported.

In conclusion, the container closure system is considered sufficiently described.

Stability

The description of the stability studies, stability data and post-approval stability protocol are appropriate, in compliance with ICH Q1A(R2) and Q5C, and the chosen analytical methods are stability indicating. The container closure material is representative of the active substance container closure, except for the volume.

The Applicant proposed a commercial shelf life for satralizumab active substance of 42 months at the recommended long-term storage condition of -50°C. The proposed shelf life of 42 months at -50°C is considered approvable.

It is acknowledged that one batch per year will be placed into the stability program. The Applicant is reminded that the stability protocol may need to be revised for post-approval process changes, depending on the nature of the change.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Description of the finished product

The proposed presentation is a 1 mL single-use PFS containing 120 mg satralizumab formulated with histidine (buffer), aspartic acid (pH-adjusting agent, pH 6.0), arginine (tonicity agent), poloxamer 188 (surfactant) and water for injections (solvent) (Table 1). These excipients are commonly used for formulating monoclonal antibodies. The formulation does not contain a preservative.

The solution is colourless to slightly yellow

Table1: Composition of satralizumab finished product

Ingredients	Nominal Amount per Syringe	Concentration	Function	Specification
Satralizumab	120 mg	120 mg/mL	Active ingredient	Section S.4.1 *Specification*
L-Histidine	3.1 mg	20 mmol/L[a]	Buffering agent	USP-NF/ Ph. Eur/JP
L-Aspartic Acid	q.s. to pH 6.0	q.s.to pH 6.0	pH-adjusting agent	USP-NF/ Ph. Eur/JP
L-Arginine	26.1 mg	150 mmol/L	Tonicity agent	USP-NF/ Ph. Eur/JP
Poloxamer 188[b]	0.5 mg	0.5 mg/mL	Surfactant	USP-NF/ Ph. Eur/JPE
Water for Injection	q.s. to 1 mL	NA	Solvent	USP-NF/ Ph. Eur/JP

Abbreviations: NA = not applicable; q.s. = quantum satis (as much as may suffice).

[a] Buffer concentration to obtain a pH of 6.0.

[b] Poloxamer 188 = polyoxyethylene (160) polyoxypropylene (30) glycol.

The primary packaging components consist of a 1 mL colourless Ph. Eur. compliant polymer syringe with a staked-in, stainless steel needle, fitted with a chlorinated butyl rubber-polypropylene rigid needle shield and sealed with a chlorinated butyl rubber plunger stopper. The PFS is labelled and assembled with an automatic needle safety guard, plunger rod, and extended finger flanges. The secondary packaging consists of a folding box made of fully coated folding boxboard. A pack size of 1 PFS is proposed.

Compliance with Ph. Eur. 3.1.3 (Polyolefins) has been confirmed for the polymer syringe and sufficient information has been provided. Information in relation to sterilisation of the syringe components is included in the dossier.

Pharmaceutical development

Formulation development

An acceptable overview of the formulation development is provided, including satisfactory data supporting the proposed composition of the commercial finished product. The rationale used to select the final composition/formulation has been described in the dossier. A formulation robustness DoE study was performed identifying the solution pH to significantly impact the Sum of HMW Forms, Acidic Region 1, and Basic Region 2. Based on these results the pH acceptance criterion was tightened to 5.8-6.2 to improve control of stability of the commercial formulation.

A low number of translucent to white visible particles (VP) has been observed during stability studies. Extended characterisation studies were performed to identify the observed particles. The results show that the particles are composed of protein and/or silicone oil and do not dissolve at room temperature, i.e. the particle formation is irreversible. VPs are routinely controlled at release and shelf life. This is acceptable.

Manufacturing process development

Several manufacturing processes have been used for finished product. Comparability between finished product from the different processes has been confirmed. Long-term stability studies demonstrated the presence of VPs during storage of finished product manufactured from the commercial process (see above).

Container closure

The development of the primary container closure system is sufficiently described. The barrel of the PFS is made from a polymer (see above). The safety of the materials of construction was established.

Compatibility between the finished product and the components of the PFS has been demonstrated through stability, leachables and temperature excursion studies, and is found appropriate.

The assembled PFS complies with the essential requirements of the Medical Device Directive. Design verification was performed as per relevant ISO standards.

Manufacture of the product and process controls

Manufacture

Roche Diagnostics GmbH, Mannheim, Germany is responsible for batch release testing for EU.

The manufacturing process description involves six unit operations: thawing of active substance, pooling and mixing, bioburden reduction filtration, in-line sterile filtration, aseptic filling and stoppering, and 100% visual inspection.

The PFS assembly involves labelling and assembly, secondary packaging and final packaging. Reprocessing (refiltration) has been described. Refiltration may be permitted when the finished product solution is at risk, e.g. due to technical issues. This is found acceptable.

Limits for process parameters and process controls have been presented. The bioburden limit before sterile filtration is defined as ≤10 CFU/100 mL in line with guideline requirements. Hold times have been defined and are supported by the process validation data.

The information provided in the dossier on the manufacturing process and controls is sufficiently detailed.

Process validation

Process validation studies comprise process verification, process design studies, microbial control and media fills, environmental monitoring, assembly process and shipping qualification. Results from the process design studies demonstrate that the finished product manufacturing process parameters proposed for the commercial process deliver acceptable product quality.

Filter validation was performed, and data has been included in accordance with guideline requirements.

The defined hold times prior to sterile filtration were demonstrated to be acceptable from a microbial perspective.

Shipping conditions for the finished product are considered qualified.

In conclusion, process validation is considered satisfactory.

Product specification

The release and shelf life specifications for the finished product includes control identity, purity and impurities, potency and other general tests. The test panel is acceptable and in line with the requirements of ICH Q6B. The proposed limits are acceptable.

The proposed acceptance criteria for the finished product specific parameters sub-visible particles, extractable volume, sterility, container closure integrity, break loose force and average injection force are found approvable.

A risk evaluation regarding the potential presence of elemental impurities in the active substance and finished product was conducted in accordance with ICH Q3D. It can be concluded that the risk and the

impact on patient safety associated with the presence of elemental impurities is negligible. Specific control on elemental impurities are considered not needed. This is agreed.

A risk evaluation concerning the potential presence of nitrosamines in the finished product was provided. The risk evaluation found that there is no risk for the presence and/or introduction of nitrosamines and/or their formation during the active substance manufacturing, in raw materials, in excipients, during the finished product manufacturing process, or in the packaging materials. This is acceptable.

Analytical procedures

The following tests are performed in accordance with Ph. Eur.: extractable volume, visible and sub-visible particles, sterility, colour, clarity/opalescence, pH, osmolality and bacterial endotoxins. The non-compendial analytical procedures are described with a sufficient level of detail.

The non-compendial procedures as well as procedures specific to the control of finished product have been appropriately validated. The validations were performed in accordance with the requirements in ICH Q2(R1). Compendial procedures have been appropriately verified for their intended use.

Batch analysis

Batch analyses data has been provided. All data complies with the proposed finished product specifications. In conclusion, the batch analyses data demonstrates acceptable batch-to-batch consistency and reproducibility of the manufacturing process proposed for satralizumab finished product.

Reference standards

A two-tiered reference standard system, consisting of a primary and a secondary reference material, both derived from the same active substance batch, was established for commercial use. This batch was produced using the manufacturing and formulation representative of the commercial process

The primary reference material will be used to qualify subsequent reference materials. The secondary reference material is used as working standard for testing the active substance and finished product in all assays requiring a reference material.

Sufficient information was provided for the reference standard, including preparation and qualification of future reference materials according to defined protocols.

Stability of the product

The proposed shelf life is 2 years at 2°C-8°C, protected from light.

The stability studies are performed in accordance with ICH guidelines.

Data from an excursion/patient convenience study demonstrate that temperature excursions do not impact the stability of the finished product when put back into the refrigerator and stored for up to 24 months. The possibility of storage out of the refrigerator (below 30°C) for a single period of 8 days has been added to the dossier, including also the statement that the product must be either used or discarded after such storage. The Summary of Product Characteristics (SmPC) was revised accordingly.

The briefly described results from photostability studies indicate that the finished product is sensitive to light. However, the secondary packaging provides sufficient light protection. An appropriate warning has been included in the product information.

Long-term stability data demonstrate that satralizumab finished product is stable at long-term storage conditions and the claimed self-life of 2 years (2°C-8°C), protected from light is approvable.

After removing the cap, the injection must be started within 5 minutes to prevent the medicinal product from drying out and blocking the needle. If not used within 5 minutes of removing the cap, the PFS must be disposed of.

Adventitious agents

The cell banks have been tested for bacteria, fungi and mycoplasma. No material of human origin is used in the manufacturing process of satralizumab. All animal-derived ingredients are discussed, and risk mitigated following EMA/410/01 guideline. Certificates of origin have been supplied. Control measures for non-viral adventitious agents and TSE for raw materials are acceptable.

Testing for adventitious agents on MCB, WCB and PPCs has been performed in accordance with ICH Q5A (R1). Original reports are provided.

The quantitative virus risk assessment demonstrates an acceptable safety margin for the studied viruses in the manufacturing process including the retroviral clearance.

The information presented supports adequate control of starting and raw materials including cell banks, IPCs for viral contamination in pre-harvest cell culture fluid and virus clearance by the manufacturing process.

In conclusion, an acceptable safety level with regards to adventitious agents is demonstrated.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The Enspryng dossier is of good quality.

An enhanced science- and risk-based approach with QbD elements was used for process development and process evaluation, supporting the proposed manufacturing process control strategy and demonstrating a solid process understanding. The active substance and finished product manufacturing processes and process controls are described in sufficient detail. CPPs are identified and the processes are appropriately validated. Comparability was demonstrated for the material from three active substance process versions used during non-clinical and clinical development. Characterisation of satralizumab was performed using an extensive panel of appropriate methods. The overall control strategy for the active substance and finished product is supported.

The risk of nitrosating conditions or the presence of nitrosamines in the finished product was assessed in a risk evaluation, concluding the risk of nitrosamine impurities in the finished product is negligible. The outcome of the nitrosamine risk evaluation is considered acceptable.

The information provided for the PFS with needle safety guard is comprehensive and confirms the suitability of the chosen device.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The manufacturing process of the active substance is adequately described, controlled and validated. The active substance is well characterised and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications. Adventitious agents safety including TSE have been sufficiently assured.

The overall quality of Enspryng is considered acceptable when used in accordance with the conditions

defined in the SmPC. The application for marketing authorisation is recommended for approval from a quality point of view.

2.2.6. Recommendation(s) for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Pharmacology

Satralizumab has been constructed by modifying the amino acid sequence of tocilizumab (another anti-human IL-6R licensed in the EU under the tradename RoActemra for the treatment of moderate to severe rheumatoid arthritis (RA)) to introduce some functional properties such as a pH-dependent binding to IL-6R. This property prolongs the antibody half-life by recycling the previously bound antibody via the endosome instead of lysosomal degradation. Moreover, satralizumab is an IgG2 isotype, which reduces Fc receptor effector functions compared with tocilizumab (which is an IgG1 antibody). The isoelectric point has been lowered by amino acid modifications with the aim of reducing non-specific elimination in the body. Finally, satralizumab has been modified to promote a stronger binding to neonatal Fc receptor in order to increase the antibody stability.

Primary pharmacodynamic studies

Mechanism of action

The proposed mechanism of action for the humanized IgG2 anti-human IL-6R monoclonal antibody satralizumab in the treatment of NMOSD includes binding to IL-6R (both soluble and membrane bound receptors on the surface of plasmablasts), inhibition of the IL-6 promoted survival of plasmablasts and their IL-6-stimulated production of AQP4-IgG. The major pathological mechanism of injury in AQP4-IgG seropositive NMOSD involves the AQP4-IgG binding to aquaporin-4 water channels in the astrocytes of brain, spinal cord, and optic nerve, followed by inflammation, disruption of blood–brain barrier, and CDC, with ensuing demyelination and axonal damage, and ultimately neurological symptoms characteristic of NMOSD. Markedly increased IL-6 levels have been observed in the serum and the cerebrospinal fluid (CSF) of NMOSD patients, and CSF IL-6 levels are correlated with disease severity of NMOSD patients.

In vitro studies

Satralizumab showed cross-reactivity in cynomolgus monkey but not in mice or rats. Based on these data, monkey was selected as the relevant species for nonclinical testing of satralizumab. A number of studies were conducted to characterize the nonclinical pharmacology of satralizumab, including its binding and selectivity to human and cynomolgus IL-6R (membrane-bound and soluble), binding to human and cynomolgus Fc receptors, induction of ADCC and CDC activities, and its functional and selective inhibition of IL-6 activity via IL-6R.

Binding affinity of satralizumab to human and cynomolgus monkey soluble IL-6R determined using a surface plasmon resonance (SPR) assay was similar with dissociation constant ($K_{D)}$ values of 1.5 nmol/L (0.22 µg/mL) and 2.0 nmol/L, respectively, at pH 7.4. Binding of satralizumab to human and cynomolgus membrane bound IL-6R expressed in Chinese hamster ovarian cells was determined by flow cytometry and resulted in a geometric mean EC_{50} of 0.019 µg/mL calculated for both species. The binding affinity to human soluble and membrane bound IL-6R in terms of K_D and EC_{50} indicates that sufficient amounts of satralizumab will be available for binding to IL-6R in NMOSD patients following SC administration every 4th week with a median trough concentration (C_{trough}) of 18.3 µg/mL at steady state.

The K_D-values for binding to the human soluble IL-6R were increased up to ten-fold when the pH was decreased from 7.4 to 6.0 indicating that the binding affinity of satralizumab to human soluble IL-6R is pH-dependent and that the dissociation is more rapid at a pH relevant for the intra-cellular endosomal compartment involved in the transport to lysosomes. Binding affinity of satralizumab to human and cynomolgus FcRn at acidic quasi-intra-endosomal conditions and to human and cynomolgus receptors for IgG (FcγR) at physiological conditions was determined by SPR. A higher binding to human and cynomolgus FcRn for satralizumab (K_D; 0.68 and 0.64 µM respectively) than for tocilizumab (K_D; 2.76 and 2.46 µM, respectively) or a conventional immunoglobulin G2 (IgG2; K_D was 2.1 and 1.9 µM, respectively) was shown, which is expected to result in a prolongation of the plasma elimination half-life ($t_{1/2}$). The binding of satralizumab to 8 types of human FcγR (Ia, IIa, IIb, IIIa, and IIIb) and 7 types of cynomolgus FcγR (Ia, IIa, IIb and IIIa), was either comparable to or weaker than that of the IgG2 control antibody, indicating a low potential for ADCC and CDC. Satralizumab was shown not to induce ADCC or CDC against U266 cells (human B-cells lymphoma) indicating that ADCC and CDC do not contribute to the mode of action of satralizumab.

Satralizumab was shown to inhibit both classical IL-6 signalling (via membrane-bound IL-6R) and IL-6 trans-signalling (via soluble IL-6R) in a concentration dependent manner when IL-6-induced proliferation of cells engineered to express both human gp130 and either human or cynomolgus monkey soluble and membrane bound IL-6R, were studied. On the contrary, no effect of satralizumab on signal transduction (classical signalling) via the receptors of other human gp130-family cytokines (including ciliary neurotrophic factor, leukaemia inhibitory factor, oncostatin M, interleukin 11), measured by effects on proliferation of cells engineered to express these gp130 receptors, were observed.

Satralizumab inhibited IL-6-stimulated proliferation of PHA-L-activated human peripheral blood T cells (half maximal inhibitory concentration [IC_{50}]; 4.4 µg/mL) and production of monocyte chemoattractant protein-1 (MCP-1, IC_{50}; 0.17 µg/mL) and vascular endothelial growth factor (VEGF, IC_{50}; 0.44 µg/mL) in human fibroblast-like synoviocytes from rheumatoid arthritis patients (HFLS-RA) stimulated by IL-6 and soluble IL-6R, in a dose-dependent manner. Furthermore, satralizumab inhibited IL-6-dependent IgG1 production, i.e. antibody production, from human plasmablasts shown by measuring the levels of IgG1 in supernatants of plasmablasts cultured in the presence of IL-6**.**

No data on the effect of satralizumab on production of plasmablast AQP4-IgG, which are thought to be involved in the pathophysiology of a large part of NMOSD patients and the inhibition of therefore would constitute a likely mode of action for satralizumab in the treatment of NMOSD, were however provided. Furthermore, the results indicating an inhibitory effect of satralizumab on IL-6-induced antibody production in plasmablasts from healthy donors are weak, for a major part of the 12 donors there was either a very small or no decrease in IgG1 production.

In vivo studies

As satralizumab showed cross-reactivity in cynomolgus monkey but not in mice or rats, *in vivo* pharmacology of satralizumab was studied in cynomolgus monkeys. The efficacy of satralizumab in NMOSD models *in vivo* have not been investigated since no NMOSD model has been established in monkeys. The pharmacology of satralizumab and tocilizumab was studied in terms of inhibitory effects on IL-6-stimulated C-reactive protein (CRP) production (i.e. on classical signaling), free and total (both free IL-6R and receptor bound to satralizumab) soluble IL-6R concentration (i.e. on trans-signaling).

Following a single subcutaneous dose of 0.5, 1 and 2 mg/kg satralizumab and 1 and 2 mg/kg tocilizumab, preliminary PK data showed that the maximum concentrations (C_{max}) in plasma of satralizumab and tocilizumab were similar, whereas the residence time was higher for satralizumab. Satralizumab were maintained at a high concentration in plasma for a longer time compared with tocilizumab.

The maximum effect in reduction of CRP protein production was achieved at a plasma concentration of 10 µg/ml of satralizumab. Satralizumab inhibited IL-6-induced CRP production at a level of plasma

concentration comparable to that of tocilizumab, indicating that the potency to inhibit CRP production in vivo was similar for both antibodies. However, given that satralizumab concentration was maintained longer than tocilizumab concentration, the effect of satralizumab had a longer duration, as it was expected after satralizumab structural modifications.

The decrease in free soluble IL-6R after satralizumab and tocilizumab administration indicated that both antibodies were able to bind to soluble IL-6R with similar potency. However, when antibody concentration fell below the limit of quantification (BLQ), an increase of free soluble IL-6R above basal levels was found. Accordingly, presence of satralizumab or tocilizumab increased total soluble IL-6R levels. The binding of soluble antigen to satralizumab is reported to reduce the clearance of antigen as satralizumab, with a long half-life, serves as a carrier for the antigen (Igawa 2010).

However, given that CRP and free soluble IL-6R are both general inflammatory biomarkers not specific for NMOSD and that satralizumab has not been studied in any disease model *in vivo*, additional clarification regarding the mechanism of action of satralizumab and the role of classical signalling and trans-signalling in NMO was required by the Applicant. In the response, the Applicant clarified that satralizumab affects both the classical and the trans-signalling pathways of IL-6 and that experimental models of the human NMOSD disease are very limited why the signalling effects via the IL-6 pathway in the disease setting need to be studied in the human disease context. Further, while blockage of IL-6R seems to be a rather non-specific interventional approach to NMOSD, it is similar to the likewise non-specific approach taken to RA which is based on the overall benefit of blockage of the pleiotropic actions of IL-6 in inflammatory diseases. This was agreed, and no further clarification was considered required for the mechanism of action of satralizumab.

Secondary pharmacodynamic studies

No specific secondary pharmacodynamic (PD) studies were provided. Studies showing antigenic specificity for IL-6R compared to receptors of other hgpg130-family cytokine and lack of ADCC or CDC activity in B cell lymphoma cells, indicating low potential for such activities, are provided. Furthermore, studies of *in vitro* tissue cross-reactivity of satralizumab showing comparable staining patterns between human and cynomolgus monkey tissues matching tissues reported as sites of IL-6R expression and studies not indicating a high risk of cytokine release in human blood were provided. As IL-6R are widely spread and binding to these receptors in tissues and organs may exert effects on other biological functions than the intended effects in plasmablasts, a discussion of potential risks theoretically related to blockade of IL-6R in NMOSD patients would have been valuable. Overall, the provided data, i.e. the non-clinical *in vitro* data referred to above together with the lack of toxicological target organs or tissues identified in the toxicological studies in cynomolgus monkey, a pharmacologically relevant species, were however considered sufficient and no further discussions were requested.

Safety pharmacology programme

With reference to applicable guidelines, effects on the central nervous, respiratory, and cardiovascular systems were evaluated in a repeat-dose toxicity study in young adult cynomolgus monkeys. No significant effects on cardiovascular (electrocardiogram (ECG), blood pressure), respiratory, or central nervous system functions were shown following subcutaneous administration of 2, 10 and 50 mg/kg satralizumab once weekly for 4 or 26 weeks with exposure levels providing acceptable margins to the clinical exposure.

Pharmacodynamic drug interactions

No PDs drug interaction studies have been conducted.

2.3.2. Pharmacokinetics

Satralizumab showed cross-reactivity in cynomolgus monkey but not in mice or rats. The non-clinical pharmacokinetics of satralizumab was evaluated in the toxicological species cynomolgus monkeys after single SC and IV administration (PK) and after multiple SC administration in the repeated-dose toxicity studies (TK).

Analytical methods

The method used for analyses of satralizumab in plasma in non-clinical GLP studies was an enzyme-linked immunosorbent assay (ELISA) using human soluble IL-6R as the capture reagent, biotinylated rabbit anti-satralizumab antibody that recognizes the complementarity-determining region (CDR) of satralizumab, and streptavidin-peroxidase conjugate as detection reagents for spectrophotometrically quantification of immobilised biotinylated satralizumab. It is not clear if the validation of the method was performed in accordance with GLP. The applicant was therefore asked to clarify this and if GLP was not confirmed the applicant should describe on which aspects the method deviates from GLP and potential impact on the results of the analyses. In the response, the Applicant declared that the validation study was conducted in accordance with Japanese law "Enforcement Regulations of the Pharmaceutical Affairs Law, Article 43 (Reliability Criteria of Application Data)" as stated in the report -ensuring reliability criteria such as accuracy, completeness/integrity, and preservation/retention, in a manner largely consistent with GLP principles. In addition, this validation study was inspected by the Quality Assurance Unit in the laboratory, and the QA statement is attached to the study report.

It is therefore concluded by the Assessor that although the method validation study for determination of satralizumab in monkey plasma was conducted under non-GLP conditions it was performed in a manner largely consistent with GLP principles. Acceptance criteria for e.g. specificity, dilution, stability, robustness, the calibration curve, precision and accuracy were met and documented. In addition, the validation study was audited and accepted by the Quality Assurance Unit in the laboratory which is documented in a QA statement attached to the study report.

Absorption

PK parameters of satralizumab were calculated using plasma concentration versus time data after excluding the time points with detected anti-drug antibodies (ADAs).

Single dose

The PK of satralizumab following SC single dose administration of 0.4 to 50 mg/kg to male cynomolgus monkeys was non-linear with a higher than dose proportional increase in exposure in terms of Area under the concentration-time curve from time zero to infinity (AUC_{inf}) (but not C_{max} and Area under the concentration-time curve from hour 0 to day 7 (AUC_{0-7d})) between the 2 lowest doses, 0.4 and 2.0 mg/kg. This was possibly due to target mediated drug distribution and saturation of binding to the target (membrane-bound IL-6R expressed in tissues).

Absorption of satralizumab from SC tissue was slow, mean Time to maximum concentration (T_{max}) ranged from 3.3 to 4.0 days. Elimination of satralizumab was slow with mean plasma $t_{1/2}$ values of 2.2 to 4.0 days at 0.4 and 2.0 mg/kg, which increased to 22.7 and 18.4 days at 10 and 50 mg/kg, respectively.

Apparent bioavailability calculated by comparison AUC_{inf} following SC administration with AUC_{inf} following IV administration was 78.2, 62.3 and 71.4% following doses of 0.4, 10 and 50 mg/kg, respectively, indicating good absorption from SC tissues.

As for SC administration, the PK of Intravenous (IV) administered satralizumab was non-linear, probably due to target mediated drug distribution.

When the dose was increased from 0.4 mg/kg to above 2 mg/kg total clearance (CL_{total}) decreased (mean CL_{total} decreased from 12.3 mL/day/kg at 0.4 mg/kg to 2.29-2.40 at 10-50 mg/kg, respectively) and the $t_{1/2}$ increased (mean $t_{1/2}$ increased from 1.9 day at 0.4 mg/kg to 22.6-25.8 days at 10-50 mg/kg). This resulted in a higher than dose proportional increase in exposure (AUC_{inf}) between the lowest dose of 0.4 and above 2.0 mg/kg. The volume of distribution at steady state (V_{ss}) ranged from 44.9 mL/kg at 0.4 mg/kg to 68.2-70.8 mL/kg at 10-50 mg/kg, which is close to the cynomolgus monkey plasma volume (45 mL/kg), suggesting limited tissue distribution of satralizumab.

Repeated dose

Toxicokinetics of satralizumab were determined in male and female cynomolgus monkeys following repeated SC administration of 2, 10 and 50 mg/kg once weekly for 4 and 26-weeks.

Based on C_{max} and AUC_{0-7d} steady state appears to have been reached after the 13^{th} dose (i.e. 12 weeks) for the 2 and 10 mg/kg dose levels, which is in line with the $t_{1/2}$ of up to 18 to 23 estimated for the 10 and 50 mg/kg dose levels following single SC administration. For the 50 mg/kg dose level the exposure was increased up to the last 26^{th} dose.

Due to the long $t_{1/2}$ the dosing once weekly is expected to result in accumulation during treatment. The accumulation (AUC_{0-7d} ratio relative to 1st dosing) ranged from 2.7 to 11.6 after the 26th weekly administration.

The AUC_{inf} following single dose treatment and AUC_{0-7d} after the 13^{th} dose were approximately similar for the 10 and 50 mg/kg dose level indicating time-independent PK at these dose levels.

There was an approximately dose proportional exposure in terms of C_{max} and AUC_{0-7d} after the 13^{th} dose.

No obvious sex differences in PK were found, except for single dose data calculated for Day 1 which resulted in higher accumulation in females than in males.

Distribution

No dedicated distribution studies of satralizumab were provided. The Applicant refers to an *in vitro* tissue cross reactivity study which showed a staining pattern which was largely consistent with what is known regarding IL-6R expression and which was similar in human and cynomolgus monkey tissue. A justification why no standard tissue distribution study, which might have revealed valuable information (e.g. potential for passage over the blood-brain-barrier to CNS), have been performed was not provided. It was however acknowledged that interpretation of distribution studies with radiolabelled biologics would have been expected to be confounded by *in vivo* metabolism, release of label from the protein following degradation, and potential reincorporation of radiolabelled amino acids into the endogenous protein pool. Furthermore, the available data and information, i.e. a volume of distribution that indicates limited tissue distribution together with that no toxicological target organs or tissues were identified in the toxicological studies in cynomolgus monkey, did not raise any concerns. Overall, the data provided were therefore considered sufficient.

The results of the enhanced Pre- and Postnatal Development (ePPND) study with exposure levels during the postnatal period which were almost analogous between dams and their infants and very low concentrations in the milk suggested that satralizumab passed the blood-placenta barrier and that the infants were exposed to satralizumab during their dams' pregnant period.

Metabolism and excretion

The expected consequence of metabolism of biotechnology-derived pharmaceuticals is the degradation to small peptides and individual amino acids and small peptides and amino acids produced by catabolism are expected to be excreted in urine or added to the endogenous amino acid pool.

2.3.3. Toxicology

The toxicity profile of satralizumab has been evaluated in a toxicology programme consistent with ICH S6. The pivotal toxicology studies were conducted in accordance with GLP standards and regulations. Cynomolgus monkey was used as toxicology species based on that Cynomolgus monkey has shown pharmacological effects comparable to those in humans in IL-6R binding assays and also the satralizumab mediated neutralization of IL-6 via soluble IL-6R. Since there was no cross-reactivity with satralizumab in mouse or rat, the cynomolgus monkey was selected as an appropriate animal species for nonclinical safety evaluation. In a tissue cross-reactivity study, similar staining patterns were seen in cynomolgus and human tissues, and the results matched the information already reported as IL-6R-expressing sites. Collectively, the monkey is considered a relevant species and the only reasonable species for these investigations.

The pivotal toxicology studies were performed with SC injection as this is the route of administration that will be used clinically. Evaluation of general toxicity was performed by weekly administration of satralizumab to cynomolgus monkeys for up to 4 weeks by the IV route (up to 200mg/kg/week) and up to 26 weeks by the SC route (up to 50mg/kg/week).

No genotoxicity studies have been performed in the programme since satralizumab is an IgG class antibody and therefore unlikely to directly interact with DNA or other chromosomal components. Further, no standard carcinogenicity studies have been undertaken with the substance, as standard carcinogenicity assays are considered inappropriate for several reasons.

Evaluation of the effects on pre- and postnatal development was performed in an ePPND study in cynomolgus monkeys. This study was also intended to support dosing of satralizumab in the pediatric population of NMOSD patients. The ePPND study did not identify major causes for concern. An infant from a dam exposed to the highest dose died from multiple inflammations. While it could not be ruled out that the immune-modulatory effect of IL-6 could have an impact on the ability to mount an immune response to an infection leading to septicaemia in this case, it is agreed that a causative relation between the effects on IL-6 levels and the infant death was not apparent. The clinical relevance of the effects on IL-6 remained elusive but will become apparent with further clinical development.

The toxicokinetics of satralizumab has been characterized in all the preclinical toxicity studies including the reproductive and developmental toxicity study. The toxicokinetic profile of satralizumab with low clearance and a long $t_{1/2}$ is expected as satralizumab was constructed by modifying the amino acid sequence of tocilizumab with the aim of prolonging its plasma residence time by decreasing both nonspecific IgG clearance and antigen-dependent IgG clearance. Satralizumab exposure was generally similar in males and females across all studies.

ADAs development was commonly seen in the studies in monkey (overall incidence of 12-22%), and some animals showed neutralization activity. These animals often showed reduced exposure to satralizumab and were excluded in the TK calculations. However, given the relatively low incidence of ADAs, the overall validity of the studies was retained. While the immunogenicity of a product in animals (including monkeys) is usually a poor predictor of the immunogenicity in humans, neutralizing ADAs for satralizumab have been noted also in the clinical studies.

Satralizumab was considered well tolerated in monkeys up to doses of 50mg/kg/week, as the toxicities seen in the programme are few and non-adverse.

Single dose toxicity

Acute toxicity assessment was conducted by observation and tests after the first administration to cynomolgus monkeys in three repeat-dose studies. As results, no noteworthy toxicity changes were observed.

Repeat dose toxicity

Three repeat-dose toxicity studies have been submitted in support of the MAA for satralizumab: One non-GLP 4-week study using once-weekly IV administration, one GLP 4-week study using once-weekly SC administration and one GLP 26-week study (with 13-week recovery) using once-weekly SC administration. No mortalities were evident in the studies, and no obvious target organ of toxicity was identified. The small (1monkey/sex/group) non-GLP study using IV-administration up to 200mg/kg/week showed that satralizumab is well-tolerated in the Cynomolgus monkey. No toxicological effects were reported, and the only noteworthy finding was ADA-development which resulted in lower plasma satralizumab exposure.

In the 4-week SC study, higher IL-6-levels were noted in the treated groups, especially early after satralizumab administration. This is likely a reflection of the Ab blockade of the IL-6R. Safety-pharmacology parameters (ECG and blood-pressure) were included in the study, but no effects were reported. ADAs development was more prominent in the SC study compared to the IV study. 11 animals were positive for ADAs and neutralizing characterization was also confirmed in 4 animals of them. The observation that SC administration can pose a higher immunogenicity risk than IV administration for a given protein is not unexpected as it has been noted previously for other similar products.

26 weeks of satralizumab treatment using SC dosing was well tolerated, and no adverse toxicities were noted. As in the shorter 4-week study, the most apparent treatment related effects noted were pharmacological increases of IL-6 with weak dose-relation. This increase did apparently not translate to down-stream toxicities. Several animals were positive for ADAs. While some also showed neutralizing activity, the mean TK analyses were only marginally affected such that the exposure at the two highest doses and for the majority at the lower dose, was maximized throughout dosing.

Seminology and testicular assessments was undertaken throughout the study, including histopathology of the reproductive tract tissues at study termination. While no clear treatment relations were noted, the overall background of testicular lesions was increased. According to the Applicant, the underlying reason was that animals used in this study were of Chinese origin which according to the Applicant have shown a tendency towards slightly higher incidence of testicular lesions compared with those from Vietnam. One male in the 2mg/kg/week group had bilateral atrophy (marked) in the seminiferous tubules which apparently exceeded the normal background histopathology findings. The Applicant (the CRO) presented a plausible sequence of explanations, including the fact that the batch from which this animal was taken (432) had an approximately 3-fold higher incidence (57%) of tubular atrophy when compared to animals of the other batches (388 and 417) used for this study. Further, this animal was clearly shown to have neutralizing ADAs titers which reduced exposure. Finally, the animal was lowest in rank among his cage mates, which was also evident from lower weight and fights that required veterinary treatment. While the causative relation of some of the explanations to the study findings could be questioned, it is overall agreed that the atrophy of the seminiferous tubules (including findings of reduced ejaculate weight and sperm count) in this animal may be incidental.

However, a major reason leading up to this conclusion is the fact that the background findings are substantial and scattered across groups why it is difficult to identify a treatment relation. Thus, given the low number of animals per group (because it is a monkey study), the fact that it is a male-only mediated effect (which reduces the n even more), and the high background of similar but less severe

findings, it is possible that a real treatment effect may be masked. In addition, the membrane bound IL-6R was shown to be present on sperm surface from head to the end of flagellum (Lachance and Leclerc 2011). Furthermore, the IL6ST (IL6R heterodimerization with the signal transducer protein GP130) was detected in both the peritubular space and seminiferous tubules of human testes. This could serve as the molecular link to seminiferous tubular atrophy and head defects in the sperm morphology and/or impaired capacitation observed in the monkeys. Therefore, as the product is intended for chronic treatment of patients from the age of 12 years old, the Applicant was asked to discuss the clinical relevance of these findings and if appropriate modify the wording in section 5.3 of the SmPC accordingly. In the response provided, the Applicant pointed out that although there is experimental evidence that IL-6 affects sperm development, there is no experimental evidence that inhibition of IL-6R signalling may result in the particular findings observed in the repeat-dose toxicity study in monkeys with satralizumab. In addition, supportive evidence from the monkey toxicity studies conducted with tocilizumab, another IL-6R antibody, did not evidence the testis as a target organ of toxicity upon IL-6R inhibition. Collectively, based on the information and reasoning provided by the Applicant, the testicular findings observed in monkeys were not considered to be related to the treatment with satralizumab. Further, no clinical or non-clinical fertility or reproductive toxicity findings were included in the SmPCs of other anti-IL-6R antibodies tocilizumab or sarilumab.

As previously noted, satralizumab was generated as a result of amendments of the tocilizumab molecule. Based on the tocilizumab European Public Assessment Report (EPAR), no effects on organs of the reproductive system were seen in a chronic primate toxicity study. The EPAR further notes that there is also no preclinical evidence that IL-6 signalling is involved in processes of reproduction. While it is unclear if the chronic toxicity study referred to included histopathology of the reproductive organs enabling identification of the seminiferous tubule atrophy, the overall conclusions from the studies do not signify effects on the reproductive organs. Therefore, collectively, the effects noted in the reproductive tract after satralizumab exposure is likely indirect effects of background findings in the particular breed of monkeys. Further, the increased findings in one male from the 2mg/kg/week group are not likely a consequence of satralizumab exposure.

Genotoxicity

No genotoxicity studies have been undertaken, since satralizumab is a biotechnology-derived substance not expected to interact with DNA. The lack of genotoxicity testing for satralizumab was considered acceptable.

Carcinogenicity

No carcinogenicity studies have been performed. Standard carcinogenicity assays are generally inappropriate for biotechnology-derived products for several reasons. Further, no appropriate species commonly used for such assays can be identified for satralizumab, why no carcinogenicity studies can (or should) be performed.

Reproduction Toxicity

No stand-alone fertility and early embryonic study or embryofoetal development studies have been performed. Detailed evaluation of male and female reproductive organs was performed in the 4- and 26-week SC repeat-dose toxicology studies. No adverse effects on fertility parameters were found which were related to satralizumab.

The only reproductive and developmental study performed with satralizumab is an ePPND study designed to evaluate the potential effects of satralizumab on pregnancy loss, embryo-fetal development, parturition, survival and postnatal development of the offspring. Only two dose-levels plus control were used in this study. The highest dose in the study was 50 mg/kg/week. The same high-dose level was used in the 4- and 26-week studies. The dose was not associated with satralizumab induced toxicity in these studies but provided margins of exposure around 20-30 why it is considered an appropriate high-dose in this study.

IgG is transferred through the placenta mainly via the neonatal Fc receptor in later pregnancy, and the infant exposure was very similar to the maternal exposure from post-natal days (PND) 14 (the earliest measurement in the infants) supporting that satralizumab can pass the placenta. Overall the concentrations of satralizumab in breast milk were low (<0.9% of the corresponding maternal plasma levels) and the C_{max} in milk was around 1ug/ml in high-dosed mothers. This information was included in section 5.3 of the SmPC (reproductive toxicity). Upon request, the Applicant agreed to include in section 4.6 of the SmPC (subsection on breast-feeding) the standard formulation for monoclonal antibodies as requested by the Safety Working Party " *It is unknown whether Enspryng is excreted in human milk. Human IgG is known to be excreted in breast milk during the first days after birth, which is decreasing to low concentrations soon afterwards; consequently, a risk to breast-fed infants cannot be excluded during this short period. Afterwards, use of Enspryng could be considered during breast-feeding only if clinically needed"*

Satralizumab did not induce adverse effects (AEs) in maternal animals or on pregnancy outcome or fetal development until PND 293. In addition, no effects were found in a learning ability test (Wisconsin General Testing Apparatus) which was started at the age of 6 months and was fully completed at PND293. However, one infant in the 50mg/kg/week group had had multiple inflammations (pulmonary, cardiac, splenic, cerebral, renal) and died from septicaemia. This death could possibly be related to the treatment. An association could not be ruled out given the immunomodulatory effect of the treatment.

Reticulocytes and while blood cells (WBC) counts were clearly reduced in the drug treated groups. According to the Applicant, the effects were not test-item related. While the levels in the treated groups were within the reference values given by the Applicant and not adverse, the *changes* were clearly treatment related. Later time-points showed a regression to control values, perhaps suggesting homeostatic mechanisms. The platelet counts were also clearly reduced at PND 28, and while the control value was high, the changes in the treated groups were considered related to treatment.

IL-6 levels were significantly increased in the pups administered the highest dose throughout postnatal maturation, and effects were noted at earlier time-points in the lower dose group. IL-6 levels correlated with disease severity, why this is problematic. Further potential long-term effects of this lengthy IL-6 increase was unclear.

T-cell dependent antibody response (TDAR) response in the PND 147 infants was evaluated using keyhole limpet hemocyanin, which is a recognized T-cell dependent antigen that gives a robust antibody response. From the data presented on antigenic challenge, there was no apparent treatment-related effect on the overall ability to generate a T-cell dependent antibody response. In addition, the kinetics for the IgM and IgG responses were similar for all groups. However, there was a treatment effect on the IgG and IgM titers generated. According to the Applicant, statistically significant effects had not been reached due to high inter-animal variability. This variability is common for this assay and may well be due to individual differences in the kinetics of the response. For such situations, a more informative presentation can be to express the data as the sum of the antibody response over several collection dates (AUC-values). According to the Applicant, the reduction in IgG in the 50mg/kg/week group could be considered to be related to satralizumab exposure. However, the basis for not considering the effects in the 2 mg/kg/week group as treatment related were unclear.

Thus collectively, there were treatment related changes on several parameters (i.e. WBC counts, CD20+ B-cells, TDAR) considered important for a fully functional immune system for which the collective significance is uncertain. Further, IL-6 levels were increased in the infants post-partum reflecting that the foetus is exposed to increased IL-6 levels during pregnancy. In addition, an infant died on PND 40 with multiple inflammations which may be treatment related. Therefore, the Applicant was asked to further discuss the findings mentioned and elaborate on the relations to treatment and clinical relevance. In the response, the Applicant agreed that the IL-6 levels were increased in the infants postpartum, and that this was likely a consequence of satralizumab exposure during late pregnancy. This is expected, as it is generally held that foetal human exposure to monoclonal antibodies occur during the third trimester in humans and that a similar trend is seen in non-human primates. Further, since the reduction in TDAR was considered minor in the analysed infants, it was the Applicant's view that it was unlikely that the death of an infant in the 50mg/kg group was related to a pro-inflammatory effect of IL-6.

However, it could not be ruled out that the immune-modulatory effect of IL-6 could have an impact on the ability to mount an immune response to an infection leading to septicaemia as was seen in the infant which died. Overall, it was agreed that a causative relation between the effects on IL-6 levels and the infant death is not apparent. The clinical relevance of the effects on IL-6 remained elusive but will become apparent with further clinical development.

Juvenile toxicity

No stand-alone juvenile toxicity studies have been performed. According to the Applicant the provided ePPND study is sufficient for an evaluation of potential effects of the substance in the juvenile setting. It is agreed that the exposure levels seen in the juveniles from PND 14 and forward were similar to the exposure levels in the dams, but the relevance of the actual exposure for the juvenile clinical situation was questionable.

The exposure obtained in the juvenile period in this study was constantly declining, as it reflected clearance of the drug which is remaining in the animals from birth. Further, from PND 119 or 200 (in the 2mg/kg/week and 50mg/kg/week group respectively) the drug level was not measurable.

In the clinical situation, the children and adolescents will be administered satralizumab SC with a weekly administration regimen. While replicating the clinical dosing is not critical, obtaining adequate systemic exposure is considered paramount. Because of confounding effects on maternal care of offspring, dosing of the mother post-partum is generally not recommended. A possibility to increase exposure not discussed by the Applicant was direct exposure of the juveniles. This would have ensured a relevant dosing of the infants throughout the study period and enable a more clinically relevant setting. However, the ePPND study performed was conducted in compliance with the agreed PIP, why no further studies were considered needed.

Toxicokinetic data

In all in vivo-studies, the exposure increased in a roughly dose-proportionate manner and with no or minor sex differences in exposure. Accumulation was noted after repeated dosing throughout the studies. In the ePPND study, exposure in infants were similar to the exposure in the dams on PND 14, suggesting placental transport in later pregnancy.

Local Tolerance

No study has been provided by the Applicant.

Other toxicity studies

Tissue cross-reactivity

A cross-reactivity study was performed to evaluate the potential cross-reactivity of fluorescein-conjugated satralizumab (with cryosections of normal human and cynomolgus monkey tissues). The staining pattern produced was consistent with what is known regarding IL-6R expression in e.g. adrenal cells, liver, macrophages, and lymphocytes, and the staining pattern was similar in human and Cynomolgus monkey tissue. Additional staining was either cross-reactivity or previously non-reported IL-6 expression sites.

Blood compatibility

Based on a blood compatibility study where the haemolytic and precipitation potential of satralizumab was evaluated in human blood and plasma respectively, it could be concluded that satralizumab did not show any haemolytic or precipitation potential.

In vitro estimation of the risk of cytokine release syndrome

Based on a human *in vitro* blood cytokine assay, the potential of satralizumab to induce a cytokine release syndrome (CRS) is considered to be low in terms of incidence and increase in cytokines. This information was included in section 5.3 of the SmPC.

2.3.4. Ecotoxicity/environmental risk assessment

The Applicant has provided a justification for not performing ERA studies. The drug product is composed of naturally occurring amino acids, why satralizumab is not expected to pose a risk to the environment. The rationale is agreed by the CHMP.

2.3.5. Discussion on non-clinical aspects

Pharmacodynamics

The proposed mechanism of action for satralizumab in the treatment of NMOSD includes binding to IL-6R (both soluble and membrane-bound), inhibition of the IL-6 promoted survival of plasmablasts and their IL-6-stimulated production of AQP4-IgG, a major pathological mechanism in AQP4-IgG seropositive NMOSD patients.

Satralizumab showed cross-reactivity in cynomolgus monkey but not in mice or rats. Based on these data, monkey was selected as the relevant species for nonclinical testing of satralizumab.

Findings from *in vitro* studies indicated that sufficient amounts of satralizumab will be available for binding to IL-6R in NMOSD patients following SC administration every 4th week with a median Ctrough of 18.3 µg/mL at steady state. Furthermore *in vitro* results supported that satralizumab inhibits both classical IL-6 signalling (via membrane-bound IL-6R) and IL-6 trans-signalling (via soluble IL-6R) preventing IL-6 downstream signalling through these two pathways. *In vitro* results indicated that ADCC and CDC do not contribute to the mode of action of satralizumab.

The efficacy of satralizumab in NMOSD models *in vivo* have not been investigated since no NMOSD model has been established in monkeys. Instead, the pharmacology of satralizumab and tocilizumab was studied in terms of inhibitory effects on IL-6-stimulated CRP production (i.e. on classical signalling), free and total (both free IL-6R and receptor bound to satralizumab) soluble IL-6R concentration (i.e. on trans-signalling). Results confirmed similar potency to inhibit CRP production and to bind to soluble IL-6R for both products. However, given that CRP and free soluble IL-6R are both general inflammatory biomarkers

not specific for NMOSD and that satralizumab has not been studied in any disease model in vivo, additional clarification regarding the mechanism of action of satralizumab and the role of classical signalling and trans-signalling in NMO was required by the Applicant. The Applicant recognized that further results are needed to understand the impact on preventing IL-6 downstream signalling specifically on NMOSD. Nevertheless, NMOSD patients could benefit from the anti-inflammatory effects following a blockage of the pleiotropic actions of IL-6 as described in other immune-mediated conditions (e.g. RA). The CHMP acknowledged this argumentation and no further clarifications were required during the procedure on this aspect.

No specific secondary PD studies were provided. Taking into consideration data supporting the low potential for ADCC or CDC activities, the lack of high risk of CRS and lack of toxicological target organs or tissues identified in the toxicological studies in cynomolgus monkey, no secondary PD studies were considered necessary.

No dedicated safety pharmacology studies were conducted, but endpoints were included in the 26-weeks pivotal toxicity study in monkeys. No adverse functional or structural effects in cardiovascular, respiratory, and central nervous systems were observed.

Pharmacokinetics

The method used for analyses of satralizumab in plasma in non-clinical GLP studies was ELISA using human soluble IL-6R as the capture reagent, biotinylated rabbit anti-satralizumab antibody that recognizes the CDR of satralizumab, and streptavidin-peroxidase conjugate as detection reagents for spectrophotometrically quantification of immobilised biotinylated satralizumab. During the procedure, the Applicant clarified that although the method validation study for determination of satralizumab in monkey plasma was conducted under non-GLP conditions, it was performed in a manner largely consistent with GLP principles and the validation study was audited and accepted by the Quality Assurance Unit in the laboratory

Nonclinical PK studies with satralizumab were conducted in cynomolgus monkeys following single SC or IV administration repeated SC administration of 2, 10 and 50 mg/kg once weekly for 4 and 26-weeks. Results indicated a good absorption from SC tissues, limited tissue distribution and slow elimination. Overall, no obvious sex differences in PK were found.

The results of the ePPND study suggested that satralizumab passed the blood-placenta barrier and that the infants were exposed to satralizumab during their dams' pregnant period. Upon request, the Applicant agreed to include in SmPC section on breast-feeding the standard formulation for monoclonal antibodies as requested by the Safety Working Party.

Toxicology

The toxicity profile of satralizumab has been characterised in Cynomolgus monkey in studies up to 26 weeks duration. The doses chosen are considered appropriate to characterise the toxicity of satralizumab and to make proper risk assessments. During the procedure, the Applicant was asked to further discuss the relevance of testicular findings observed in monkeys. Based on the information and reasoning provided by the Applicant, these findings were not considered to be related to the treatment with satralizumab. No AE of treatment have been identified in the study programme suggesting that the treatment was well tolerated in monkeys.

No genotoxicity and carcinogenicity studies have been performed which can be agreed for the aforementioned reasons.

The ePPND study performed to evaluate potential developmental toxicity did not identify major causes for concern. This information has been included in section 5.3 of the SmPC. During the procedure, the Applicant further discussed the potential role of satralizumab on the death from multiple inflammations

of an infant from a dam exposed to the highest dose. While it could not be ruled out that the immune-modulatory effect of IL-6 could have an impact on the ability to mount an immune response to an infection leading to septicaemia in this case, it can be agreed that a causative relation between the effects on IL-6 levels and the infant death was not apparent. The clinical relevance of the effects on IL-6 remained elusive but will become apparent with further clinical development.

ADAs development was commonly seen in the studies in monkey (overall incidence of 12-22%), and some animals showed neutralization activity. However, the immunogenicity of a product in animals (including monkeys) is usually a poor predictor of the immunogenicity in humans.

An *in vitro* blood cytokine assay did not identify a high risk of CRS. This information has been included in section 5.3 of the SmPC.

Satralizumab was considered well tolerated in monkeys up to doses of 50mg/kg/week, as the toxicities seen in the programme are few and non-adverse.

Ecotoxicity/environmental risk assessment

The CHMP agrees on the justification for not performing ERA studies based on composition of naturally occurring amino acids.

2.3.6. Conclusion on the non-clinical aspects

Overall, non-clinical studies provided adequate evidence that satralizumab inhibits both classical IL-6 signalling and IL-6 trans-signalling preventing IL-6 downstream signalling through these two pathways. No NMOSD model has been established in cynomolgus monkey and therefore, efficacy in *in vivo* NMOSD models has not been investigated. Non-clinical PK studies conducted in cynomolgus monkeys indicated a good absorption from SC tissues, limited tissue distribution and slow elimination.

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and toxicity to reproduction and development. An *in vitro* blood cytokine assay did not identify a high risk of CRS. This information has been included in section 5.3 of the SmPC.

2.4. Clinical aspects

The clinical development program for satralizumab in patients with NMO and NMOSD includes two ongoing (at the clinical cut-off date) global Phase III pivotal studies: Study BN40898 in adult and adolescent patients with satralizumab in addition to background IST and Study BN40900 in adult patients with satralizumab as a monotherapy. In addition, two Phase I studies have been conducted in Japan, one in healthy volunteers (SA-001JG) and one in RA patients (SA-105JG).

GCP

The Applicant claimed that the Clinical trials were performed in accordance with GCP.

The Applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.4.1. Introduction

- **Tabular overview of clinical studies**

Table 2: Clinical Trials Contributing Clinical Pharmacology Data

Study # [Region]	Study Design	Population	No. of Patients	Route and Dosing Regimen	Study period	Analytes Measured		
						PK/ADA	PD	Others
Pivotal Phase III Studies								
BN40898 (SA-307JG) [Global]*	Phase III multiple doses, randomized placebo controlled, add on to baseline immunosuppressive treatment	NMO & NMOSD, adults and adolescents ≥ 12 years	SA: 41 Placebo: 42	SC: 120 mg Q2Wx3 (LD), then Q4W	Double Blind Period: until total PDRs = 26.	Yes (ADA II)	CRP, IL-6, sIL-6R, C3, C4, and CH50	AQP4Ab, plasmablasts
BN40900 (SA-309JG) [Global]*	Phase III multiple doses, randomized placebo controlled, monotherapy	NMO & NMOSD, adults	SA: 63 Placebo: 32	SC: 120 mg Q2Wx3 (LD), then Q4W	Double-Blind Period: 1.5 years after date of randomization of last patient enrolled.	Yes (ADA II)	CRP, IL-6, sIL-6R, C3, C4, and CH50	AQP4Ab, plasmablasts
Supportive Studies								
SA-001JP (JN41389) [Japan]	Phase I Parts A and B: placebo-controlled, randomized, double-blind, inter-individual, dose escalation study (single SC dose) Part C: open-label, (single IV dose)	Healthy subjects (Parts A and C Japanese, Part B Caucasians)	SA (SC): 60 SA (IV): 12 Placebo: 12	SC: 30, 60, 120, 240 mg IV: 60, 120 mg	10 weeks	Yes (ADA I), no NAb	CRP, IL-6, sIL-6R, C3, C4, CH50	
SA-105JP JN41391 [Japan]	Phase I, multiple doses, open-label	RA patients, adults	SA: 33	SC: 120 mg Q2Wx3 and then 30, 60, 120 mg Q4W until W16. Extension : 120 mg	64 weeks Primary evaluation period: up to 32 weeks; extension period: 32 weeks	Yes (ADA I), IgE	CRP, IL-6, sIL-6R	

AQP4: aquaporin 4; AQP4Ab; anti-AQP4 antibody C3: complement component 3; C4: complement component 4; CH50: total complement activity; CRP: C-reactive protein; IL6 : interleukin 6; LD : loading dose; Q2W : every 2 weeks; Q4W: every 4 weeks; SA: satralizumab; sIL6-R : soluble IL-6 receptor; RA: rheumatoid arthritis

2.4.2. Pharmacokinetics

Methods

Quantification of satralizumab

An ELISA was validated to measure satralizumab concentrations in serum. The assay, which detects target-binding competent drug, is based on soluble IL-6R (sIL-6R) to capture satralizumab and a polyclonal anti-satralizumab rabbit antibody, and a Horseradish peroxidase (HRP) conjugated goat anti-rabbit antibody conjugated for detection.

Detection of anti-drug antibodies (ADA)

The immunogenicity testing strategy for satralizumab followed a classical multitiered analytical approach, involving screening, confirmation for samples testing positive, titration assays and assays for detection of neutralising antibodies. A commercial assay to detect IgE was also employed (ImmunoCAP).

Two different validated electrochemiluminescence immunoassays (ECLIAs) were used in the clinical studies to screen for anti-satralizumab antibodies in human serum samples. The ADA I assay was used in studies SA-001JP and SA-105JP. The assay was also used in Studies BN40898 and BN40900 until ADA assay II became available. Data generated with ADA assay I in studies BN40898 and BN40900 were used in the submission only if the data were not generated with ADA assay II. Selection criteria for the re-assay using ADA assay II were such that each ADA negative subject had several samples reanalysed.

The ADA assay I consists of a sandwich-type bridging ECLIA with an additional competitive displacement step for the confirmation assay. Satralizumab is used for capture (biotinylated, capture on a streptavidin coated plate) and detection (ruthenylated), after pre-incubation with the sample. The presence of satralizumab in a sample considerably reduces the sensitivity of the method to levels that required the development of another assay for the NMO/NMOSD population.

The ADA assay II and multitiered immunogenicity strategy was identical to ADA Assay I, with an additional acid-dissociation step prior to sample incubation with biotinylated and ruthenylated satralizumab. The drug tolerance was improved with no interference up to 60 µg/mL satralizumab for ADA 100 ng/mL and up to 200 µg/mL satralizumab for ADA 500 ng/mL.

Neutralizing antibodies (NAb) to satralizumab in human serum were determined by a competitive ligand binding assay using an electrochemiluminescence (ECL) readout. The neutralizing antibody method is based on pre-incubating ADA samples with a fixed quantity of ruthenylated satralizumab before adding the solution to plates coated with human sIL-6R. Unbound ruthenylated satralizumab will bind to immobilized sIL-6R, whereas ruthenylated satralizumab complexed with neutralizing anti-satralizumab antibodies will not. The amount of ruthenylated satralizumab bound to sIL-6R is detected by ECL and evaluated against a pre-determined cut-point. Despite the implementation of an upfront acid dissociation step, satralizumab concentrations of > 1.0 µg/mL caused false negative assay results.

The IgE-antibodies assay is based on the commercially available ImmunoCAP assay system. Satralizumab is covalently bound to a cellulose carrier, which is contained in a reaction capsule (ImmunoCAP). The ImmunoCAPs react with any specific IgE antibody in the serum. After a wash step, detection occurs via binding of a β-D-galactosidase labelled human anti-humanIgE antibody and fluorometric measurement. Reduced assay response was observed in presence of satralizumab and sIL-6R.

Detection of PD markers: IL-6, sIL-6R and Anti-AQP4 Antibodies

A commercial sandwich ELISA assay (Quantikine® Human IL-6 Immunoassay) was used to measure serum concentrations of endogenous IL-6. An immobilized murine monoclonal antibody specific for human IL-6 was used for capture of IL-6 and detection occurred via an anti-IL-6 polyclonal antibody conjugated to peroxidase for reaction with a chromogenic substrate.

A commercial sandwich ELISA assay (Quantikine® Human sIL-6R Immunoassay) was used to measure serum concentrations of endogenous sIL-6R. An immobilized murine monoclonal antibody specific for

human sIL-6R was used for capture of sIL-6R and detection occurred via an anti-IL-6R polyclonal antibody conjugated to peroxidase for reaction with a chromogenic substrate.

Analysis of AQP4-IgG was done according to predefined procedures using a research assay kit which was qualified fit for-purpose. The AQP4AbELISA "Cosmic" II (Cosmic Corporation Co., Ltd., Japan) uses a bridging format with immobilized human recombinant AQP4 antigen for AQP4-IgGcapture and biotinylated human recombinant AQP4 antigen together with streptavidin peroxidase / tetramethyl-benzidine for photometric detection.

Pharmacokinetic data analysis

A non-compartmental model and a population PK analysis were used.

The population PK analysis was conducted via nonlinear mixed-effects modelling with the NONMEM (NONlinear Mixed Effects Modeling) software. Non-parametric bootstrap 95% confidence intervals (CIs) were obtained for the parameters of the final model by generating 200 datasets from the original dataset through random sampling with replacement using the individual as the sampling unit. Model-based simulations were performed by a combination of R and NONMEM software. The simulation R scripts created the simulation datasets and started NONMEM; NONMEM performed the simulations; the same R scripts read the NONMEM output and prepared the simulation plots and tables.

The satralizumab population PK analysis was conducted in two stages. In Stage 1 (Report No. 1093049), the data from study SA-001JP (healthy subjects) were combined with data from patients with NMO/NMOSD receiving satralizumab in addition to baseline IST (BN40898) (up to 06 June 2018). A covariate analysis was performed after removing data from RA patients. In Stage 2 (Report No. 1094498), the data from the second Phase III study (BN40900) in patients receiving satralizumab as monotherapy (up to 12 October 2018) were combined with the Stage 1 dataset with additional PK data from the OLE of BN40898. Estimated parameters from both models were very similar. The data from this final dataset/model is described here.

The final model was a 2-compartment model with a linear and a non-linear (Michaelis-Menten) clearance and first order absorption. The parameter estimates of the final model are presented in Table 3.

Bootstrap parameter estimates and CI on parameter estimates were consistent with the final model estimates and asymptotic CI. When intra-subject variability (18%) was included in the model, it only led to a small change in the inter-individual variability (from 30% to 27%) and residual error (from 17.5 to 14%), despite a drop of 600 in objective function (OFV). Analysis of the impact of co-medication on ADA was performed but no significant relationships were found.

Table 3: Parameter estimates of the final model

Fixed Effect Parameter		Estimate	RSE (%)	95%CI
CL (L/day)	θ1	0.0601	7.46	0.0513 - 0.0689
V_C (L)	θ2	3.46	6.04	3.05 - 3.87
Q (L/day)	θ3	0.336	12.6	0.253 - 0.419
V_P (L)	θ4	2.07	9.84	1.67 - 2.47
V_{max} (µg/mL/day)	θ5	0.455	3.67	0.422 - 0.488
K_m (µg/mL)	θ6	0.462	8.47	0.385 - 0.539
k_a (1/day)	θ7	0.251	6.99	0.216 - 0.285
FSC	θ8	0.854	6.09	0.752 - 0.956
σ_{IV}	θ9	0.417	30.7	0.166 - 0.668
σHV	θ10	0.84	10.2	0.672 - 1.01

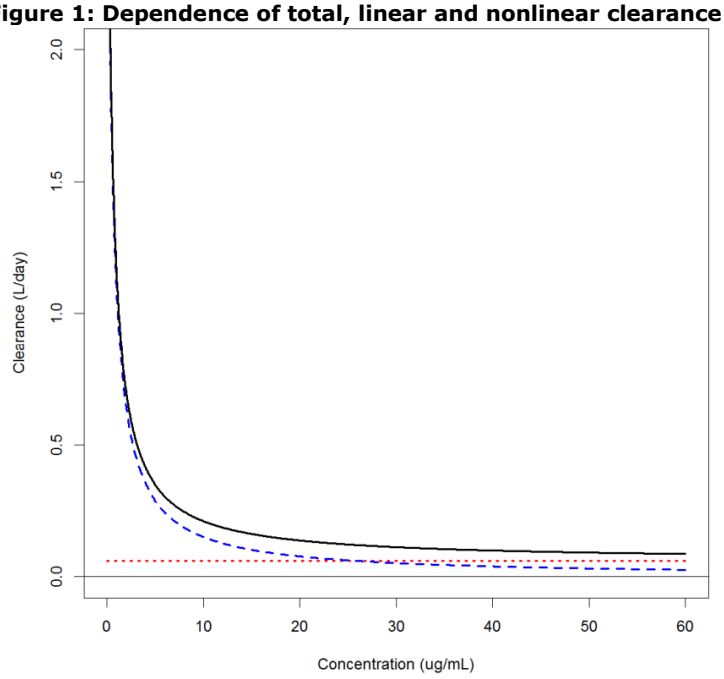
σST309	θ11	1.66	8.83	1.37 - 1.94
CL, Q ~ WT	θ12	0.75	Fixed	
CL ~ HV	θ13	1.96	7.37	1.67 - 2.24
CL ~ ADA_T	θ14	1.45	8.76	1.2 - 1.7
CL ~ FORM	θ15	1.09	1.04	1.06 - 1.11
V_C, V_P ~ WT	θ16	1	Fixed	
F_{SC} ~ ADA (NMO/NMOSD)	θ17	0.866	2.42	0.825 - 0.907

Variance Parameter		Estimate	RSE (%)	95%CI	Variability	Shrinkage
ω2CL	Ω(1,1)	0.0894	16.6	0.0603 - 0.118	CV=29.9%	21.2%
ω2Vc	Ω(2,2)	0.0296	19.5	0.0183 - 0.041	CV=17.2%	24.8%
ω2Q	Ω(3,3)	1.13	19.3	0.7 - 1.55	CV=106%	25.2%
ω2Vp	Ω(4,4)	0.28	16.2	0.191 - 0.369	CV=52.9%	15.8%
ω2KA	Ω(5,5)	0.329	21.7	0.189 - 0.47	CV=57.4%	29.3%
ω^2ADA_T	Ω(6,6)	0.284	23.3	0.154 - 0.414	CV=53.3%	11.3%
ω2σ	Ω(7,7)	0.212	11.2	0.165 - 0.258	CV=46.0%	-2.7%
σ2	Σ(1,1)	0.0307	15.4	0.0214 - 0.04	CV=17.5%	1.2%

σ_{IV}=residual error multiplication factor for IV administration; σ_{HV}=residual error multiplication factor for HV SC administration; σ_{ST309}=residual error multiplication factor for BN40900.
CL: Clearance, V_C: Central volume of distribution, Q: inter-compartmental clearance, V_P: peripheral volume of distribution, V_{max}: Maximum Michaelis-Menten elimination rate, K_m: Michaelis-Menten constant, K_a: First order absorption rate constant, F_{SC}: subcutaneous bioavailability, ADA: Anti-drug antibodies, NMO: Neuromyelitis Optica, NMOSD: Neuromyelitis Optica Spectrum Disorder, CV: Coefficient of Variation, CI: Coefficient Intervals, RSE: relative standard error.

At lower exposures, the non-linear clearance ($V_C \cdot V_{max}/(K_m+C)$), reflecting target mediated drug disposition (TMDD), predominated, accounting for a lesser proportion of the total clearance at higher exposures, see Figure 1. At a concentration of 25.7 µg/mL, equal to the mean satralizumab concentration (over time and between patients) at steady-state, the two components of total clearance contributed approximately equally to elimination of satralizumab. Consequently, the effect of ADA on total clearance was approximately 20% and the effect of formulation was approximately 4%.

Figure 1: Dependence of total, linear and nonlinear clearance on satralizumab serum concentrations



Solid black line: total clearance, dashed blue line: nonlinear clearance, dotted red line: linear clearance.

Based on the final model, individual concentration-time profiles and the corresponding PK parameters were simulated based on the individual subject parameters using the 120 mg every four weeks (Q4W) dosing regimen (Table 4). The time-independent effect of ADA on bioavailability was included while the time-dependent effect on linear clearance was not accounted for as it is not possible, using the model, to predict the appearance of ADAs.

Table 4: Predicted Steady-State Exposures and Receptor Occupancy by Study, Conditional Simulation in Children and Adults given satralizumab 120 mg SC Q4W

Parameter	Age <18 NMO/NMOSD Patients Study BN40898		Age ≥18 NMO/NMOSD Patients Studies BN40898 and BN40900	
	Mean (SD)	Median [Q05 - Q95]	Mean (SD)	Median [Q05 - Q95]
C_{trough} (μg/mL)	19.9 (16.1)	13.7 [3.29–44.5]	19.7 (12)	18.8 [2.88–40.2]
C_{max} (μg/mL)	31.9 (20.9)	23.4 [9.49–62.5]	31.5 (14.6)	29.5 [10.4–56.9]
$AUC_{0\text{-}28,\ ss}$ (μg/mL day)	746 (529)	527 [195–1540]	736 (379)	710 [202–1400]
RO (%) at C_{trough}	86.8 (29.5)	96.7 [42.5–99]	94.4 (11.8)	97.6 [86.2–98.9]
Fraction of dose eliminated by linear pathway	0.487 (0.198)	0.475 [0.201–0.694]	0.469 (0.153)	0.508 [0.191–0.668]

C_{trough}: trough Concentration, C_{max}: maximum concentration, $AUC_{0\text{-}28,\ SS}$: Area under the concentration-time curve from hour 0 to day 28 at steady state, RO: Receptor occupancy, NMO: Neuromyelitis Optica, NMOSD: Neuromyelitis Optica Spectrum Disorder, SD: Standard deviation

The summaries of exposures stratified by covariate groups for patients with NMO/NMOSD are presented in Table 5 (also for those covariates that were not retained in the final model). Since many covariates were correlated with body weight (BW), summaries of body weight by covariate levels are also provided. The results were consistent with the predicted decrease of exposure in patients with higher BW. Steady-state area under the concentration-time curve tau (AUC_T) for patients in the lowest BW category (39.3-57.3kg) were 40% higher than for patients in the middle BW category (57.3 - 75.0 kg). Patients in the highest BW category (75.0 - 151.0 kg) had 50% lower AUC_T compared to patients in the middle category.

Table 5: Median [Q05 - Q95] Predicted Steady-State Exposures by Covariates for All NMO/NMOSD Patients (Studies BN40898 and BN40900), Conditional Simulation for Final Model 224 following 120 mg SC Q4W Dosing

Covariate	Level	N	C_{trough} (μg/mL)	C_{max} (μg/mL)	AUC (μg/mL day)	BW (kg)
All NMO/NMOSD Patients		154	18.3 [2.79 - 41.2]	29.4 [10 - 57.3]	705 [199 -1410]	63.2 [47.3 - 111]
Pediatric Patient	Adult	146	18.8 [2.88 - 40.2]	29.5 [10.4 -56.9]	710 [202 -1400]	63 [47.8 - 108]
	Pediatric	8	13.7 [3.29 - 44.5]	23.4 [9.49 -62.5]	527 [195 -1540]	71.6 [44 - 123]

Body Weight Tertile	39.3 - 57.3 kg	52	29.5 [12.5 - 46.8]	44 [28.4 -61.8]	1070 [585 -1550]	51 [43.9 - 57]
	57.3 - 75.0 kg	52	20.1 [7.84 - 34.4]	31 [19.1 -48.2]	739 [376 -1190]	63.4 [58.2 -74.4]
	75.0 - 151.0 kg	50	8.98 [0.226 -19.9]	17 [5.43 -29.1]	379 [69.4 - 721]	89.8 [76.3 - 139]
Gender	Male	24	11.1 [0.378 -32.3]	21.9 [6.04 -45.8]	468 [81.8-1130]	85.6 [57.2 - 148]
	Female	130	19.7 [3.25 - 42.9]	32.3 [11.1 -57.7]	759 [214 -1440]	61.2 [46.4 - 105]
Race	Caucasian	88	16.4 [2.91 - 38.5]	29 [10.5 -53.9]	643 [205 -1340]	70 [47.9 - 107]
	Black	15	9.18 [0.916 -21.5]	18.1 [7.43 -33.8]	383 [120 - 768]	79.3 [62.7 - 129]
	Asian	45	26.5 [7.61 - 43]	40.1 [16.2 -61.3]	962 [347 -1480]	56.3 [42.7 -74.2]
	Other	6	15.8 [3.65 - 34.7]	28.8 [11.4 -46.2]	649 [218 -1160]	67.4 [55 - 122]
Renal Function	Normal Function	130	16.1 [2.76 - 38.5]	28.6 [9.85 -53.7]	639 [198 -1340]	67.1 [47.2 - 118]
	Mild Impairment	21	24.2 [9.77 - 43.1]	39.4 [18.1 -61.8]	887 [414 -1490]	55 [48 - 85.3]
	Moderate Impairment	3	33.6 [14.2 - 47.2]	45.5 [26 - 65.4]	1130 [577 -1600]	59 [48.9 - 68]
Azathioprine Baseline Treatment	No	127	16.4 [1.7 - 43]	28.7 [8.78 -57.7]	644 [161 -1450]	66 [47.6 - 119]
	Yes	27	24.6 [8.72 - 38.5]	38.6 [19.8 -55.3]	847 [435 -1350]	57.3 [47.3 -88.8]
Mycophenolate Mofetil Baseline Treatment	No	141	18.8 [2.97 - 40.3]	29.4 [10.3 -57.3]	708 [201 -1400]	63 [47 - 108]
	Yes	13	15.5 [1.74 - 40.1]	25.7 [8.6 - 55.7]	583 [146 -1380]	66 [50.2 - 116]
Oral Corticosteroids Baseline Treatment	No	115	16.3 [2.38 - 38.4]	28.6 [9.15 -53.3]	636 [180 -1340]	68 [47.9 - 118]
	Yes	39	25.3 [7.1 - 43.6]	41.3 [15.2 -61.8]	972 [334 -1500]	57 [41.9 -99.4]
Relapsed NMO/NMOSD Patients	No	94	19.9 [2.96 - 43.2]	31.8 [10.6 -58.5]	767 [207 -1450]	60.4 [45.9 - 107]
	Yes	60	15.4 [1.24 - 34]	27.7 [8.46 -45.8]	606 [145 -1150]	69.4 [48.5 - 118]
AQP4 Seropositive Status	Seronegative	51	19.8 [2.07 - 41.9]	33.4 [8.97 -58.7]	720 [171 -1440]	64 [47.8 - 108]
	Seropositive	103	16.6 [3.21 - 39.5]	29 [12.1 -55.3]	662 [227 -1390]	63.1 [47.1 - 115]
Confirmed Presence of ADA	ADA negative	61	29 [11.2 -45.3]	42.9 [21 -61.8]	1020 [466 -1520]	57 [45.7 -82.4]
	ADA positive	93	12 [0.485 -34.3]	22.7 [7.05 -46.2]	499 [109 –1160]	73 [48.9 –127]

C_{trough}: trough Concentration, C_{max}: maximum concentration, AUC: Area under the concentration-time curve, BW: body weight, NMO: Neuromyelitis Optica, NMOSD: Neuromyelitis Optica Spectrum Disorder, ADA: anti-drug antibodies.

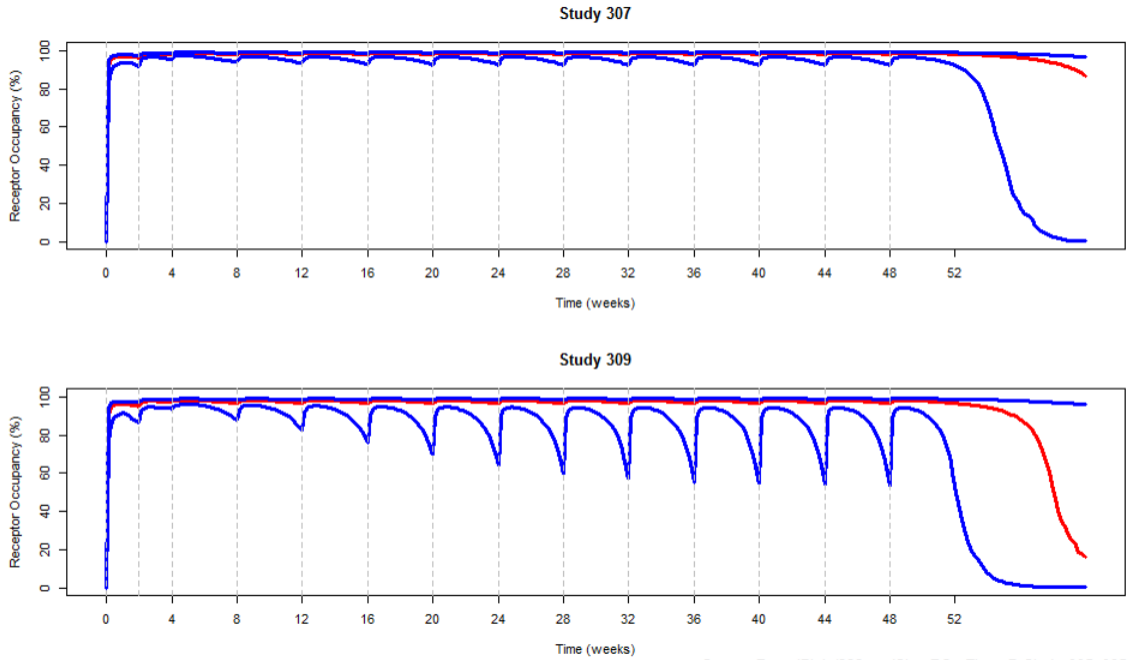
Based on the non-linear clearance parameters as estimated from the population pharmacokinetics (popPK) model, the unobserved IL-6 receptor occupancy (RO) can be calculated. Computed concentrations (C) were used to predict unobserved receptor occupancy and CL_{total} as follows:

$$RO=C/(K_m+C);\ CL_{total}=CL+V_C \cdot V_{max}/(C+K_m),$$

where K_M,V_C, and V_{max} are Michaelis-Menten constant, volume of the central compartment, and maximum Michaelis-Menten elimination rate, respectively.

Individual simulations of RO are shown graphically (median and 90% prediction interval) for the two Phase III trials (Figure 2). While the median RO remained high throughout the dose interval in both Phase III trials (>95%), the lower bound of the 90% CI was lower in study BN40900 relative to study BN40898, which is consistent with the lower exposure observed in this trial. RO was considered high in all subgroups, as defined by the Applicant.

Figure 2: Receptor Occupancy over Time: Individual Predictions.



Top: study BN40898; bottom: study BN40900. Median (red) and 5th/95th % prediction intervals (blue) of the simulated receptor occupancy following 120 mg SC Q4W regimen (with an additional dose at Week 2), by study. Values for each subject were simulated using individual predictions of PK parameters.

Absorption

In the pop PK analysis, satralizumab SC bioavailability was 85.4% (95% CI: 75.2-95.6%). The absorption rate constant was 0.251 /day (95% CI: 0.216 - 0.285).

No data is available regarding the impact of the injection site on PK. Ctrough following administration in the abdomen and in the thigh was similar (Table 6) when taking into account differences in BW.

Table 6: Serum Satralizumab Concentration (Mean ± SD) by Administration Site in Studies BN40898 and BN40900

		Abdomen			Thigh		
		N	Bodyweight (kg)	Serum conc. (µg/mL)	N	Bodyweight (kg)	Serum conc. (µg/mL)
Study BN40898	Week 8*	29	59.5 ±11.8	22.1 ± 8.98	6	66.4 ±19.9	20.5 ± 9.14
	Week 12**	25	60.5 ± 11.7	21.0 ± 8.94	8	63.0±18.4	22.7 ± 11.5
Study BN40900	Week 8*	45	78.5 ±25.9	15.2 ± 9.93	6	93.4 ±19.2	11.0 ± 8.23
	Week 12**	47	79.2 ± 24.5	14.6 ± 10.7	5	69.5±20.3	16.9 ± 14.0

Comparability of the G1 and G2.1 processes was demonstrated by a thorough comparability program comprising routine analytical and extended characterization of the physicochemical properties of the antibody as well as *in vitro* functional assays. As comparability was demonstrated, no clinical comparability studies were done.

No food effect is expected, given the SC administration.

Distribution

Satralizumab undergoes biphasic distribution. For a 60 kg NMO/NMOSD patient, the population PK predicts a V_C of 3.46 l (95% CI: 3.21 - 3.97), a V_P of 2.07 l (95% CI: 1.78 - 2.59) and a Q of 0.336 l/day (95% CI: 0.261 - 0.443).

Elimination

Satralizumab demonstrated target mediated drug disposition. The CL_{total} of satralizumab is concentration-dependent. Linear clearance is estimated to be 0.0601 l/day (95% CI: 0.0524 - 0.0695). At therapeutic exposure, the linear CL represents approximately 50% of the CL_{total}. The associated terminal $t_{1/2}$ is approximately 30 days (range 22-37 days) based on data pooled from the phase 3 studies.

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

Dose proportionality

Satralizumab PK was shown to be non-linear across the dose range of 30-240 mg SC. Faster elimination was observed at lower concentrations, consistent with target-mediated drug disposition.

Time dependency & immunogenicity

Time dependency in the PK has been evaluated in the popPK model and the results did not point towards a time dependency in the PK of satralizumab because the effect of ADAs generation on the bioavailability of the SC formulation were modelled as time independent.

Table 7: ADA status and persistence in studies with multiple dosing SA-105 JP, BN40898 and BN40900

Study		ADA positive (%)	Persistence of TIADA
SA-105 JP (RA)		2/33 (6%)	NA
BN40898	Double blind	17/ 41 (41%)	NA
	Open label extension	34/65 (52%)	25/32 (78%)
	Adolescents	5/8 (63%)	NA
BN40900	Double blind	45/63 (71%)	NA
	Open label extension	58/80 (73%)	45/58 (78%)

TIADA: treatment induced ADA, ADA: Anti-drug antibodies, NA: not available.

In the two Phase III trials, lower exposures were observed in patients who developed ADAs. Patients who went on to develop ADAs generally had higher BW, lower exposure and lower bioavailability prior to developing ADAs. Observed differences in exposure between patients with and without detected ADAs were the result of a combination of the observed BW differences between patients with and without detected ADAs, lower satralizumab bioavailability (by 13%) in patients with detected ADAs (prior to detection of ADA), and higher satralizumab linear clearance (by 45%) at times when ADA was detected. Given that linear and non-linear clearances were contributing approximately equally to CL_{total} at steady state, the effect of ADA on total clearance was approximately 20%. The combined effects of ADA on bioavailability and linear clearance may lead to the approximately two-fold lower steady-state exposure in patients with detected ADAs compared to ADA-negative patients of the same BW.

For patients with detected ADAs, median RO at the end of the dosing intervals (trough) was about 95%, while the lowest RO was below 30%.

Intra- and inter-individual variability

Inter-individual variability (%CV) was described in the pop PK model. On the linear clearance, it amounted to 30%, and on the V_C 17%. Intra-individual variability was not reported.

Pharmacokinetics in target population

PK in the target population is described by the pop PK model that also contains healthy subject data. PK parameters in NMO patients are summarized in Table 4.

Special populations

No dedicated intrinsic factors studies were conducted. However, factors, such as age, gender, BW, renal function, and ADA, were evaluated in the popPK analysis.

As anticipated based on the known mechanisms of clearance for satralizumab and confirmed by the popPK analysis, the PK was not impacted in patients with mild renal impairment, nor by age, race or gender.

Elimination of IgG antibodies such as satralizumab is thought to occur via proteolytic metabolism in endothelial cells (i.e., not cleared by hepatic metabolism). Therefore, no formal study on the effect of hepatic impairment on the PK of satralizumab has been conducted.

BW was shown to be a significant covariate. Satralizumab exposure in the tertile of patients with the highest BW (i.e. BW >75 kg) was approximately 50% lower compared to those in the 2nd tertile. The Applicant considers that treatment benefit was comparable in all BW groups and that no dose adjustment is required.

Satralizumab exposure (mean and range) and RO were similar in adolescents [13-17 years] and adults (Table 4) which is consistent with the observed similar BW of the adolescent patients and the adults, as well as the similar incidence of ADA in both populations. Once the BW effect is accounted for age has no significant effect on satralizumab PK.

Pharmacokinetic interaction studies

Inflammation that results in increased IL-6 levels has been shown to inhibit the expression of CYP450 isozymes and hence the metabolism of substrate concomitant medications. Satralizumab is designed to block IL-6R signalling (and hence normalize CYP levels), which has the potential to alter the metabolism of concomitant medications.

Based on literature data for tocilizumab, sarilumab and sirukumab, there is a risk of interaction at baseline levels of IL-6 in RA patients (50-80 pg/mL), with AUC ratio (AUCR) in the range of 0.43-0.61 for the CYP3A4 substrate simvastatin and similar data for CYP2C9 and 2C19 substrates.

Peripheral IL-6 values in NMOSD are lower than in systemic inflammatory diseases. Masuda et al (2018) report median values of 2.8 pg/mL based on 20 individuals with NMOSD. Uzawa et al (2010) report that even around the time of relapse, values in all but one of 31 NMOSD patients were found to be $\leq$ 4 pg/mL. In contrast, Barros et al, 2016 reported a median value in 20 NMOSD patients of 58.5 pg/mL at during remission, and a median $\leq$ 80 pg/mL during relapse. However, the Applicant noted that overall, caution is warranted when comparing absolute IL-6 values between studies given that different studies have used different platforms and matrices, and because clinical values fall in the low pg/mL range. The

NMOSD patients in the studies with satralizumab (and placebo) demonstrated lower IL-6 levels (1.57-37.2 pg/mL), suggesting the risk of interaction is low. Nevertheless, a warning for co-administration with narrow therapeutic index substrates of CYP450 3A4, 1A2, 2C9 or 2C19 has been included in section 4.5. of the SmPC.

Exposure relevant for safety evaluation

In NMO/NMOSD patients, median [5th and 95th percentile] PK parameters were as follows: C_{max} 29.4 [10-57.3] µg/mL , AUC 705 [199-1410] µg/mL/day, and C_{trough} 18.3 [2.79 – 41.2].

For the exposure safety analysis, concentrations at day 56 were used (C_{trough}, Ctr56) as a surrogate for C_{max} and AUC, as these were demonstrated to correlate.

2.4.3. Pharmacodynamics

Mechanism of action

Satralizumab binds specifically to membrane-bound and soluble IL-6R, but the PD data on it is relatively scarce. In comparison to tocilizumab, it was designed to have: (1) a longer plasma half-life; (2) a lower risk of immunogenicity, and (3) reduced effector mechanisms such as ADCC and CDC.

IL-6 induces differentiation of B cells into antibody-producing cells, is involved in inflammatory response, induction of differentiation and proliferation of various cells, regulation of immune response, and increased production of platelets. On the basis of *in vitro* studies, IL-6 promotes differentiation of inflammatory Th17 cells and plasmablasts, inducing the production of pathogenic antibodies and may also increase blood-brain barrier permeability.

In NMOSD, elevated IL-6 levels have been described in the patients' CSF and serum during relapses, and CSF IL-6 levels are correlated with disease severity of NMOSD patients. IL-6 promotes survival of plasmablasts and may enhance their AQP4-IgG production. IL-6R blockade has inhibited the survival of plasmablasts *in vitro*. A few small open-label studies using IL-6R blockade have suggested an effect on relapse risk reduction in patients with NMO, and overall, it appears reasonable that satralizumab could have a role in treating NMOSD.

Primary pharmacology

The functional inhibitory activity of satralizumab was demonstrated using human plasmablasts, human T cells, and human fibroblast-like synoviocytes, while human myeloma cells were used to test ADCC toxicity and CDC. Satralizumab decreased IL-6-induced IgG1 production by human plasmablasts, inhibited IL-6-induced proliferation of human peripheral T-cells and inhibit IL-6 induced production of monocyte chemoattractant protein-1 (MCP-1) and VEGF in human fibroblast-like synoviocytes. Using U266 cells, a human multiple myeloma cell line expressing hIL-6R and peripheral blood mononuclear cells from healthy human donors, satralizumab was shown not to induce ADCC or CDC.

The supporting Phase I studies, SA-001 JP in healthy subjects and SA-105JP in patients with RA provided the initial understanding of PK/PD/immunogenicity with a single ascending or multiple dosing. Results from the pivotal studies in patients with NMO/NMOSD represent the key data for the NMO/NMOSD indication, and they used a flat dosing regimen.

The main PD markers, soluble IL-6R (sIL-6R) and IL-6 concentrations were determined as a direct assessment of target engagement. Serum sIL-6R concentrations were measured by ELISA using a monoclonal mouse antibody against IL-6R for capture and a HRP labelled anti IL-6 polyclonal antibody

for detection. This assay measures the bound soluble receptor bound as well as the free receptor. CRP, C3, C4, and total complement activity (CH50) were quantified as inflammation biomarkers.

The PD markers IL-6 and sIL-6R have a direct link to the proposed mechanism, and CRP is synthesized by hepatocytes as a direct effect of IL-6 signalling in response to proinflammatory cytokines. IL-6 and sIL-6R levels show marked, consistent and dose-dependent elevation after administration of satralizumab in all studied populations. The levels do not seem to be elevated at baseline in NMO/NMOSD patients. The findings are not at variance with the basic hypothesis of IL levels rising as a result of receptor blockade by satralizumab, Also CRP levels show a marked and fairly consistent decrease after administration of satralizumab and is visible despite the high variability of the serum levels. This finding strongly suggests that the principal cause is the inhibitory effect on hepatocytes in producing acute-phase proteins such as CRP (or indeed fibrinogen) rather than the proposed reduction of inflammation.

Secondary pharmacology

The available secondary pharmacology data is limited. The data of the Phase I studies (healthy controls (Study SA-001JP) is incorporated in the above section.

Relationship between plasma concentration and effect

Individual predicted trough concentrations at Week 8 (Day 56) following actual dosing history (Ctr56) were used as a measure of exposure. The individual exposure was predicted using the popPK model from Stage 1 for the BN40898 study and from Stage 2 for the BN40900 study. The low and high exposure groups were defined by the exposure being below or equal to, and above median of the exposure distribution among patients administered satralizumab. The median exposure used for the exposure-response analyses was 22 µg/mL and 12.6 µg/ml for BN40898 and BN40900, respectively, and 16.8 µg/ml for the pooled analysis.

Exposure/safety

Graphical analyses were performed for the relationship between satralizumab concentrations and the occurrence of (severe) AE, moderate or severe AEs of infections and infestations, gastrointestinal AEs, neutropenia, thrombocytopenia, and main safety parameters ie neutrophil, WBC, and platelet counts, bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum albumin, total protein, total cholesterol, high density lipoprotein (HDL)-cholesterol, low density lipoprotein LDL-cholesterol, and triglycerides.

The results of the graphical analyses were the following:

- Minor decrease of WBC counts and neutrophil counts were observed in the high exposure group while remaining in the normal range.
- Platelet counts were stable in the placebo group and slightly declined in the active arm patients, with no difference between exposure groups.
- Total bilirubin slightly increased but then remained stable and within the normal range in the high exposure group.
- ALT, AST, serum albumin, total protein, triglycerides, and total, HDL, and LDL cholesterol did not show any consistent changes (either in absolute terms or change from baseline).

Logistic regression models were implemented to assess correlation of the probability of AE occurrence with exposure; the analysis was performed separately for Ctr56 and logarithm of Ctr56 as exposure measures. To define CI for the logistic regression function, 1000 bootstrap samples were drawn with replacement from the analysis population and the logistic regression were fitted to each of these samples.

For each Ctr56 value, 90% CI was defined as the 5th and 95th percentiles of the model predictions among 1000 bootstrap datasets. There were very few AEs of neutropenia and thrombocytopenia; therefore, comparisons of distributions of exposures for different grades of events could not be performed. Overall, residual error was high to very high for these models (86 to 8496%), thus strongly undermining the value of these analyses.

The summary of the occurrence of the AE for all patients from the BN40900 study, including placebo patients, is presented in Table 8. The logistic regression models (placebo excluded) indicated no significant relationships between exposure and probabilities of any AE.

Table 8: Summary of Adverse Events by Exposure Group, Study BN40900

	Placebo	Active Treatment	
		Low Exposure	High Exposure
Total Number of Patients	32	30	29
Adverse Event Type			
Serious Adverse Events	5 (15.6%)	6 (20%)	5 (17.2%)
Severe Adverse Events	2 (6.2%)	9 (30%)	7 (24.1%)
Moderate and severe Infections/ Infestations	8 (25%)	10 (33.3%)	8 (27.6%)
Severe Infections/Infestations	1 (3.1%)	2 (6.7%)	4 (13.8%)
Gastrointestinal Disorders	13 (40.6%)	12 (40%)	12 (41.4%)
Neutropenia	1 (3.1%)	1 (3.3%)	2 (6.9%)
Thrombocytopenia	1 (3.1%)	2 (6.7%)	1 (3.4%)

Exposure/QTcF

The predicted placebo-adjusted change from baseline in Corrected QT interval by Fredericia (ΔΔQTcF) concentration relationship and its upper one-sided 95% CI was constructed by simulation using a bootstrap procedure and was presented graphically together with the observed values. Specifically, 1000 datasets were created from an original dataset by random sampling with replacement using individual subject as a sample unit. The model was fitted to each of the created datasets, and estimated parameters were used to compute the predicted ΔΔQTcF for the range of concentrations spanning all observed concentrations. At each concentration value, 5th, 50th and 95th percentiles of the predictions were computed and presented graphically. The predicted mean and upper one-sided 95% CI for the mean ΔΔQTcF at satralizumab C_{max} were computed at the mean predicted steady-state satralizumab C_{max} following 120mg Q4W dosing. A correction for circadian variation was not feasible due to the variability in sampling timepoints.

In the monotherapy study BN40900, at mean predicted C_{max} value of 26.5 µg/mL, predicted ΔΔQTcF was estimated at 8.31 msec (90%CI: 6.35 - 10.89 msec), with the upper bound of the CI exceeded 10msec safety threshold used to evaluate QTc prolongation and risk of Torsades de Pointes.

For pooled data, at mean predicted C_{max} value of 31.5 µg/mL, predicted ΔΔQTcF was estimated at 6.32 msec (90%CI: 4.48 - 8.76 msec), with the upper bound of the CI below the 10 msec safety threshold.

Exposure/pharmacodynamics

Graphical analyses were performed for the relationship between satralizumab concentrations and CRP, fibrinogen, C3, C4, CH50, IL-6, sIL-6R, visual analogue scale (VAS) for pain score, Functional Assessment of Chronic Illness Therapy (FACIT) fatigue score and ADA status.

Following treatment start, median levels of CRP, fibrinogen, and complement components C3, C4, and CH50 declined quickly in the active treatment arm and then stayed approximately constant with no appreciable differences between median values in the two exposure groups. The variability was slightly lower in the high exposure group for all parameters. There were no changes in median values over time in the placebo group.

There were no consistent changes in FACIT fatigue score or VAS pain score in any of the 3 exposure groups.

There were no appreciable differences in the median values of CRP, fibrinogen, and complement components C3, C4, and CH50 between patients with and without detected ADAs but inter-subject variability was higher in patients with detected ADAs. The median levels of IL-6 and sIL-6R were approximately the same in patients with and without detected ADAs, but inter-subject variability was higher in patients with detected ADAs. There were no consistent changes in FACIT fatigue and VAS scale scores between the ADA groups.

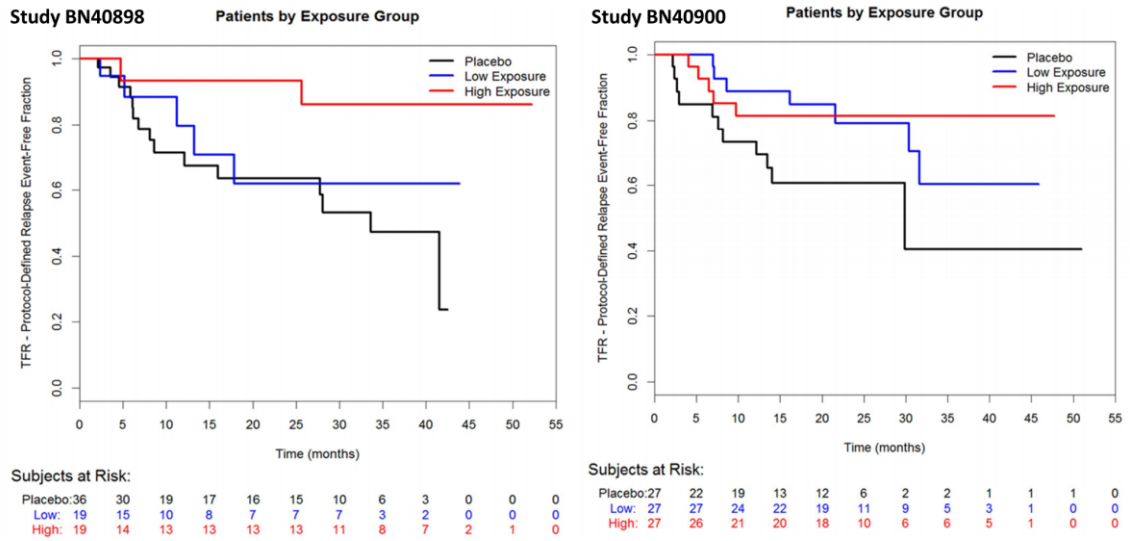
Exposure/efficacy analysis of time to first relapse (Cox proportional hazards model)

Exposure-efficacy analysis was performed for each of the two Phase III studies separately for all time to first relapse (TFR) measures. Protocol-defined relapse (PDR) (TFR1) was the primary measure. All other TFR measures in including clinical relapse (TFR2), treated clinical relapse (TFR3), treated clinical relapse optic neuritis (TFR4), protocol-defined relapse based on CEC adjudication (TFR5), protocol-defined relapse based on Expanded disability status scale (EDSS)/Functional System Score (FSS) increase (TFR6) were used for the sensitivity analysis.

The exposure-TFR relationship was investigated through semi-parametric Cox proportional hazard analysis (CPH). The analysis was performed in two ways: (i) including only patients in the active arm, and (ii) also including the placebo patients. Base CPH models were established first, followed by covariate CPH modelling aimed to assess the effects of covariates on the exposure-response relationship in order to remove confounding effects of the prognostic factors. No covariate was retained in the models. Exposure (day 56, individually predicted) and observed time to TFR1 (relapses occurring after day 56) in studies BN40898 and BN40900 are shown in Figure 3 for all NMOSD patients irrespectively of AQP4-IgG serostatus and in Figure 4 for only AQP4-IgG positive patients.

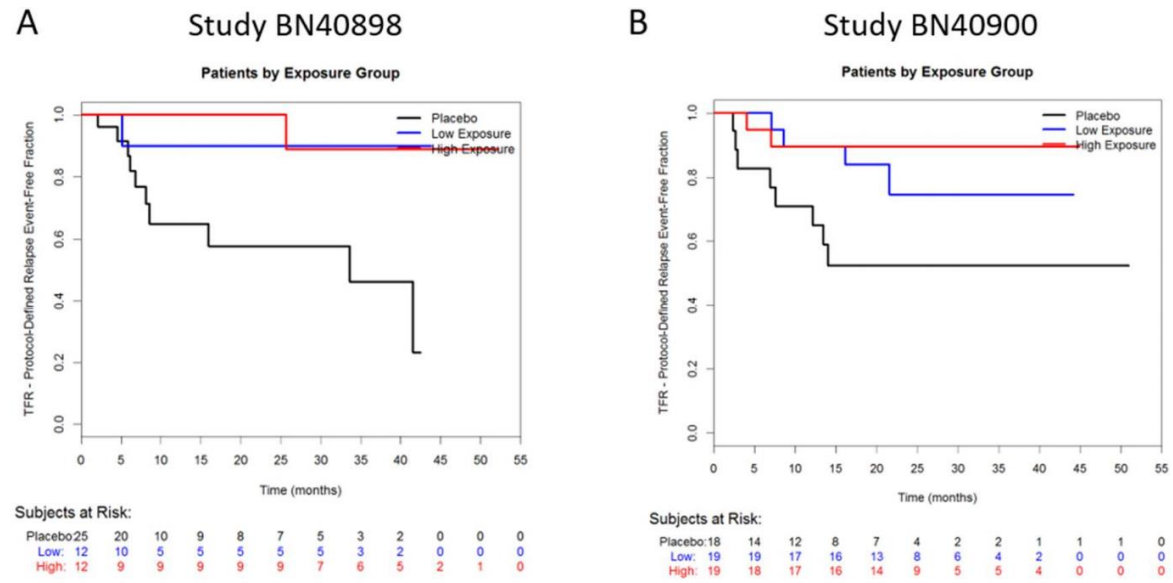
For all TFR measures (TFR1 -TFR6) time to relapse appeared to correlate with satralizumab exposure. Placebo patients and patients in the low exposure group had similar time to the first relapse, while patients in the high exposure group had longer relapse-free survival. Parameters were estimated with high uncertainty (>50%) in all models. The visual predictive check simulations using the CPH model show that there is an overlap between the predictions for the low and high exposure groups as well as between the predictions for the low exposure group and the placebo group. All the results in AQP4-IgG positive patients, by study and with the pooled dataset, indicate that placebo-treated patients have shorter time to first relapse when compared to satralizumab-treated patients.

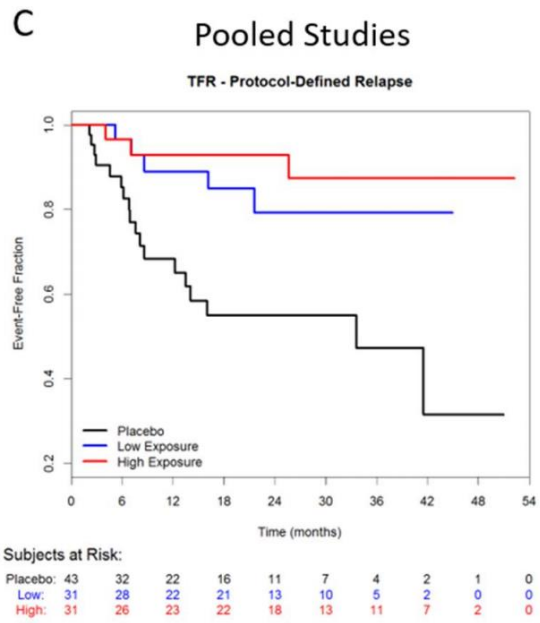
Figure 3: Kaplan-Meier plots: time to First Protocol-Defined Relapse (TFR1) by Exposure (irrespective of AQP4-IgG serostatus)



Ctr56, satralizumab trough concentration at Day 56, was used as an exposure measure. Low = exposure < median exposure; High= exposure ≥ median exposure. The median exposures used for the exposure-response analyses were 22 μg/mL and 12.6 μg/mL in BN40898 and BN40900 Studies, respectively

Figure 4: Kaplan-Meier plots: time to First Protocol-Defined Relapse (TFR1) by Exposure (AQP4-IgG positive patients)





Ctr56, satralizumab trough concentration at Day 56, was used as an exposure measure. Low = exposure < median exposure; High= exposure ≥ median exposure. The median exposures used for the exposure-response analyses were: A: 22 μg/mL, B: 12.6 μg/mL, C: 17.4 μg/Ml

2.4.4. Discussion on clinical pharmacology

Methods

Quantification of satralizumab

The assay quantified only target binding competent drug, which is also referred to as free drug. Interferences by non-neutralizing ADAs should in principle not lead to interferences. Against theoretical expectations, both IL-6 and IL-6R did not lead to significant interferences at physiologically relevant concentrations. Upon request, the Applicant provided analysis certificates for critical reagents and missing bioanalysis reports and parallelism was demonstrated in study samples from NMO patients.

Overall, the methods is adequately validated for the intended purpose.

Detection of anti-drug antibodies (ADA)

During the procedure, the Applicant clarified the process of analysis and re-analysis using ADA assay II. Even if not all samples were re-analysed, no significant differences in the ADA status were noted in a selection of each subjects samples analysed with ADA assay II. Therefore, the re-analysis strategy was considered acceptable.

Stability was only investigated in ADA assay I. Upon request, the Applicant clarified that stability data for ADA assay I was generated to support the use of quality control samples stored for up to one month under frozen condition in the ADA assay to monitor the assay performance. The assessment did not intend to evaluate the stability of real ADA samples. The stability of antibodies in low pH conditions for a short period of time is considered well accepted, being widely utilized in protein purification and production steps. These arguments were considered acceptable.

ADA I

In RA patients, false positive results may be obtained due to the presence of auto antibodies. The drug tolerance in these patients is unknown, leading to uncertainty about the net effect of false positive and false negative results. However, since the RA data is only supportive, the issue was not pursued.

Drug tolerance issues were identified, where essentially the 240 mg dose group (healthy subjects) would obtain false negative results, and all NMO patients. For them the development of ADA assay II was necessary (see below). For the remaining dose groups in healthy subjects, the assay is adequate for the detections of ADAs.

Report 1093535 refers to two different sets of reagents used in either the healthy subjects and RA patients or the NMO/NMOSD patients. It was unclear what the differences were between these sets of reagents and what implications this could have on the assay readout. It seemed that the same set that was used in the method validation 1093534 and for the healthy subjects and RA patients. Lot numbers of these reagents were however not the same in the provided reports, and analysis certificates or cross-validation reports for the change of critical reagents were not provided. Furthermore, reports of ADA analysis were referred to but were not provided for studies SA-001JP and SA-105JP (PRD12-023), therefore it was also unclear which of the different normalization factors and cutpoints were used, since the method for determining the disease specific normalization factor and cut point changed during the validation of the method. In their response, the Applicant provided the reports and acceptable explanations regarding the use of the different sets of reagents and cutpoints.

ADA II

The implementation of an acid dissociation step improved drug tolerance for the use in the NMO/NMOSD population with tolerance up to 20 µg/mL satralizumab for ADA 100 ng/mL and up to 200 µg/mL satralizumab for ADA 500 ng/mL. In those individuals with satralizumab concentrations above the median, false negative results may be measured for ADA levels below 500 ng/mL ($C_{max,ss}$ of 30 µg/mL and $C_{trough,ss}$ of 19 µg/mL at 120mg Q4W in adults; Q95 $C_{max,ss}$ of 63 µg/mL, < 18 years and Q95 $C_{trough,ss}$ of 45 µg/mL, < 18 years, similar Q95 in adults). The drug tolerance was further improved, so that the risk of false negative results was strongly reduced.

NAb

The neutralizing antibody assay suffers from drug tolerance issue from 1 µg/mL (despite the use of an acid dissociation step in VR 1093791), which represents most of the clinical samples. The impact of ADAs on PD is unknown due to the inadequacy of the NAb assay. As other assay formats were expected to have similar drug tolerance issues, a new assay was not requested. The Applicant considers that the impact of ADAs on the PD of satralizumab is low, as no consistent differences in PD parameters other than sIL-6R were observed. This is acceptable, however the lower target engagement in ADA positive patients should be treated as a sign of potential neutralisation.

IgE

The validation of the IgE ImmunoCAP assay is basic, but is sufficient for the intended purpose, as it was used in Study SA-105JP only and is not required per guideline.

Detection of PD markers: IL-6, sIL-6R and Anti-AQP4 Antibodies

IL-6

This assay provides a sensitive, and specific method to quantify human IL-6 levels and is adequate for the intended purpose. No significant interference with satralizumab or sIL-6R was observed at clinically relevant concentrations, therefore the measured concentration can be viewed as the total concentration.

sIL-6R

No significant interference with IL-6 at clinically relevant levels was observed. A significant interference by satralizumab was circumvented by adding an excess of satralizumab to all samples in the phase III studies. It is unclear whether the excess of satralizumab was used in the phase I studies as no analysis report was provided. No clarification was requested to the Applicant.

This assay provides a sensitive, and specific method to quantify human sIL-6R levels and is adequate for the intended purpose.

Anti-aquaporin 4 antibodies (AQP4Ab)

The assay is considered fit for purpose. No significant interferences were observed.

Pharmacokinetic data analysis

Although initially the PK of satralizumab was to be studied using data from four clinical trials (one in healthy volunteers (Study SA-001JP), another one in patients with RA (Study SA-015JP) , and two in the target population (Study BN40898 and Study BN40900) , i.e. patients with NMO or NMOSD) finally data from patients with RA were excluded because their data were different from the other two groups of participants and considering that these patients were out of the scope of the intended drug development. Data from study SA-105JP are therefore excluded from the final PopPK models but this data had not been excluded at the timepoint of the covariate analysis. The exclusion is acceptable, as target differences can be expected, and the Applicant clarified that the covariate analysis had been performed after the exclusion of the RA study data.

The final population PK model shows that the disposition of satralizumab can be described by a two-compartment model with parallel linear and Michaelis-Menten elimination, and that it depends on body weight, ADAs development, formulation (i.e. formulation for Phase I-III or market formulation) and disease status (Healthy volunteers vs patients with NMO/NMOSD). Considering that linear clearance and volume parameters increased with weight, it is anticipated that exposure of satralizumab in females should be higher than in males. The imbalances in favour of female population (>80% of the recruited patients) provide a sufficiently sized safety database for the characterisation of the female safety profile. In addition, the female population included individuals within a range of 39.4-151 kg. The increased exposure according BW does not seem to have relevant impact on the safety profile.

The Applicant was requested to investigate intra-individual variability before the covariate analysis. It is agreed that the estimate of inter-occasion variability (IOV) is small (18%), however with a significant drop in OFV, it should have been taken into the model. Goodness of fit graphs show that higher concentrations were better described when IOV was included in the model. Since goodness of fit is nevertheless acceptable with the old model, and the residual error is not very different, it could be accepted that the old model was used.

Covariate analysis was performed only for the formulation in the stage 2 model and the covariate analysis of the stage 1 model was performed when data from RA patients were still included. Since the PK in RA patients was shown to be different, this raises concerns regarding the adequacy of the covariate analysis in the target population. The Applicant performed a new covariate analysis for the following covariates on CL and/or F1: Study, co-medication at baseline (Azathioprine, Mycophenolate Mofetil and oral corticosteroids), oral corticosteroids rescue therapy, IV corticosteroids rescue therapy. None of the covariates had a significant effect, therefore the model was not updated. Mechanistically, an effect of the co-medication would have been expected on ADAs and thereby on CL, the data however did not show this. It is therefore acceptable not to update the model at this time.

The pop PK report containing the new analyses has been provided**.**

The Applicant considers that the difference in PK observed between healthy subjects and the target population is not due to co-medications. It is agreed that the different co-medications were not significant

covariates in this small dataset. A trend in ETA for ADA effect on CL might indicate that ADAs may have a smaller impact on CL in individuals who are treated with oral corticosteroids. This should be considered in future applications to other populations.

In order to cast light on which subgroups may show a lack of target engagement, the Applicant was asked to provide RO graphs for the following subgroups: BW in bins of 10 kg, ADA status, AQP4-IgG serology, co-medication and any other covariate that may be significant after the new covariate analysis. The requested RO graphs were provided. It was agreed that in the presented analysis, RO group in over/under the median is less informative than the exposure. The presented analysis was considered too undifferentiated to be useful. The Applicant considered all predicted RO levels high and it was therefore not possible to define a target RO on the basis of the available data. It was not agreed that RO can be considered as high in all subgroups. In the plots of exposure or RO by BW or BW and ADAs, patients over 100 kg seem at risk of low exposure and low RO both for their average and trough concentration and RO.

While no differences can be seen between the RO graphs for AQP4 antibody status, obvious differences are visible when the patients are stratified by ADA status, bodyweight and study. It is noted that the Applicant supplied RO graphs per study instead of the requested graphs per co-medication type. Since different co-medications were not significant covariates in the earlier analyses, this could be accepted.

While the median predicted RO was high in all subgroups, the 5th percentile was significantly lower in the third BW tertile (>75kg), in ADA positive patients, and in patients in study BN4090 (monotherapy). It would be expected that these lower levels of RO would be correlated with a lower efficacy.

The Applicant notes that BW is the strongest determinant of exposure (which is agreed with), however without suggesting a dose adjustment according to weight. The Applicant provided efficacy data in 5 weight bins and considered that a similar level of efficacy is seen in each bin, irrespective of the exposure and predicted RO level. A larger variability in response is seen in the BW group > 90 kg. Exposure and RO may still be acceptable at 90 kg, but not over 100 kg, which results in skewed data when binning > 90 kg. It is expected that the value of 1 for the hazard of PDR would not be included in the CI if only patients > 100 kg were looked at. The Applicant then individually reviewed the patients with low predicted RO, in order to better understand whether these patients were at a greater risk of protocol-defined relapse (PDR). The Applicant considers that no obvious difference was seen in these patients. It was noted that the calculated RO presented were significantly higher than the predicted RO at trough. The Applicant clarified the discrepancy between predicted and calculated RO, where one plot showed RO at trough of cycle 13, while the table presented average RO trough over the treatment period. RO values are found less reliable when close to Km (Michaelis constant), due to the steepness of the curve. Therefore, caution is warranted in drawing conclusions from the RO analysis, which is considered to only have a minor role in this application.

Overall, it seems that predicted RO has no obvious correlation with efficacy, which is surprising.

Absorption, Distribution and Elimination

SC bioavailability was high as determined in the popPK model. It is recommended to inject satralizumab in the abdomen or the thigh and rotate between injection sites (section 4.2 of the SmPC). C_{trough} concentrations stratified by injection site support the lack of influence of the injection site for the thigh and the abdomen. Since analytical comparability was demonstrated, it is acceptable that no clinical comparability studies were performed.

The distribution of satralizumab is in the expected range for a humanized monoclonal antibody.

The CL and $t_{1/2}$ are in the expected range for a humanized monoclonal antibody. The lack of excretion and biotransformation studies was acceptable given the nature of the test item.

Dose proportionality

Satralizumab PK was shown to be non-linear, which is consistent with target-mediated drug disposition.

Time dependency & immunogenicity

Over 50% of satralizumab subjects were ADA positive in the single ascending dose study, except in the SC 240 mg group with 17%. Given the selected timepoints, no interference by satralizumab on the ADA assay readout was expected, except for the 240 mg group, who may have false negative results.

The RA patients receiving multiple doses of satralizumab (and allowed concomitant immunotherapy) showed only 6% ADA positive results. As the ADA assay did not define a drug tolerance in this population, it is unclear whether the ADA positive rate may be underestimated. The concomitant immunotherapy may also decrease the ADA positive rate.

Considering the OLE periods in NMO/NMOSD studies, 52% patients had at least one ADA positive sample in study BN40898, with concomitant corticosteroid therapy. In the monotherapy study BN40900, 73% patients had at least one ADA positive sample.

The ADA positive patients are at risk of higher satralizumab linear clearance (by 45%) at times when ADA are positive; and at risk of a lack of target engagement with the lowest RO being below 30% in the ADA positive group.

Intra- and inter-individual variability

Inter- and intra-individual variability were relatively low.

Pharmacokinetics in target population

The description of PK in target population is based on the population PK model. Disease is a significant covariate on the CL, according to the covariate analysis.

Special populations

No dedicated intrinsic factors studies were conducted. The intrinsic factors were evaluated in the popPK analysis. This was considered adequate.

The PK was similar in patients with mild renal impairment and normal renal function, once BW was accounted for. The same was true for race or gender. Liver insufficiency is not expected to have an impact on the disposition of satralizumab, however it is excluded in the SmPC since no subject with reduced liver function were included in the clinical studies.

The highest BW tertile (> 75kg) shows a lower exposure and RO. This was however not correlated to lower efficacy in NMOSD patients (see above), therefore no dose adjustment is warranted based on the current dataset. If satralizumab was to be used in other indications, the patients > 100 kg may benefit from a dose adjustment.

The Applicant also considered BW to be a factor in the probability of developing ADAs, which was considered speculative and was removed from the SmPC. Following the Applicant's hypothesis that immune tolerance may be induced by high exposure, the insufficient dose in the patients with higher BW may be the cause of their higher incidence of ADAs, which in turn may affect the PK of satralizumab.

The PK of satralizumab in children (i.e. adolescents from 13 to 17 years) was evaluated during the popPK models development since in Study BN40898 patients from 13 to less than 18 years were included. The exposure predicted for children of this age range is similar to that predicted in adults. With the exception of age distribution, all other baseline characteristics were similar between adults and adolescent subjects. It was agreed that no specific dose adjustment is necessary for adolescent patients.

The studies cover a BW range 39.4-151 kg, which is higher than the median weight at age 12. A low BW 12 year old patient may therefore have an exposure that is higher than what is covered by the current safety dataset. The CHMP agrees on the Applicant´s proposal to the following information in section 4.2 of the SmPC "The posology in adolescent patients ≥12 years of age with body weight ≥ 40 kg and adult patients is the same (see sections 5.1 and 5.2). The safety and efficacy of satralizumab in children with body weight < 40 kg have not yet been established. No data are available." No dose adjustment is required for patients over 65 years of age, which is expected for antibodies that are degraded by proteolysis, which is age-independent.

Interactions

IL-6 mediated disease-drug interaction were studied using the SimCYP platform. However, the platform could not be considered qualified for the intended use and it was agreed that the preferred approach to describe IL-6 mediated interactions would be to base the SmPC text on available clinical data from blockade of IL-6 signalling. Additionally, mean baseline IL-6 levels were very modestly elevated in the clinical studies submitted and concerns were raised that the patient population in the study may not be representative for the population that may be treated clinically. Therefore, the Applicant was requested to justify which IL-6 concentration is representative for the NMO/NMOSD population that will be treated. In their response, the Applicant provided data on IL-6 levels and their effect on other medicinal products, as requested. The Applicant also presented literature data for the range of IL-6 concentrations that have been observed in NMOSD patients at different stages of their disease. The NMOSD patients in the studies with satralizumab (and placebo) demonstrated lower IL-6 levels than what was reported in certain literature sources. Nevertheless, the Applicant agreed to include a warning for co-administration with narrow therapeutic index substrates of CYP450 3A4, 1A2, 2C9 or 2C19 in section 4.5 of the SmPC, which was endorsed.

The overall PK interaction potential of satralizumab is considered low since satralizumab is an IgG.

Exposure relevant for safety evaluation

The use of day 56 concentrations is acceptable, since steady state is reached at that timepoint. Upon request, the Applicant justified the use of C_{trough} instead of C_{max} or AUC. The Applicant´s selection was considered acceptable since C_{trough} correlated with both C_{max} and AUC, in particular since sampling was not sufficient to determine C_{max} accurately.

Relationship between plasma concentration and effect

The study of the relationships between exposure and response (safety, efficacy or PD markers), patients were divided in two groups for the graphical analysis: low or high exposure depending on whether they had Concentration at day 56 lower or higher than the mean of the patients.

Exposure/safety

It was not possible to assess the performance of the exposure /safety model as no uncertainty estimates were available. Upon request, the Applicant presented RSE for the exposure/safety analyses. The RSE was very high in the logistic regression models, which may be due to the size of the dataset. The conclusions from the graphical analysis, which do not demonstrate significant exposure/safety relationships, are considered more reliable.

No significant relationships between exposure and probabilities of any adverse events (AEs) were observed, with the exception of the exposure QT analysis. Regarding the significance of this finding, see clinical safety.

Exposure/pharmacodynamics

The graphical exposure/pharmacodynamics analyses demonstrated a rapid response for CRP, fibrinogen, and complement components C3, C4, and CH50 with no appreciable differences between median values in the two exposure groups.

For markers of target engagement, sIL-6R and IL-6, the variability was considerably larger in the low exposure group than the high exposure group when looking at values over time and change from baseline for IL-6 and especially when looking at sIL-6R. This tendency increased in ADA positive patients. Overall, this indicated low target engagement at lower exposures. At some level and duration, this might increase the risk of a relapse, however data currently do not support this (see discussion on RO). The Applicant was requested to explain why there is more variability in sIL6-R and the other PD variables with the lower exposure and what impact this variability can be expected to have on OR and on time to first relapse. The Applicant clarified that sIL-6R is a marker of target engagement, and therefore reflects RO, rather than impacting it. This greater variability in the low exposure group may indicate lower RO in some individuals but high levels of RO were achieved in almost all patients. It is unlikely that the larger variability observed for PD markers in the low exposure group is indicative of a lack of overall clinical response in this group.

Exposure/efficacy analysis of time to first relapse (Cox proportional hazards model)

AQP4-IgG positive and negative patients

During the procedure, the Applicant justified that Day 56 was selected as the landmark time to limit the number of excluded events from the analysis while being able to use an exposure measure which is representative of the overall treatment period. The justification provided by the Applicant was agreed.

BIC (Bayesian information criterion) indicated that no covariate was significant. However, the BIC for TFR1 did not show differences between the treated and the placebo groups, indicating that CPH modelling may not be adequate to describe the data. The description of the time course is generally poor and other (hazard) functions should be considered. The Applicant did not update the exposure/response model. The Applicant claims that the hazard function was adequate, despite very large residual error. The Applicant did not discuss what alternative hazard functions were investigated. It is understood that continuous exposure was included in the model, however the Applicant did not present the results per exposure quartiles as requested, and instead presented two group (over and under the median), as previously. The requested covariates were looked at, however, as in other analyses, studies were used instead of separating per type of co-medication.

In line with the discussion on RO, since RO differences did not seem to correlate with efficacy, it was not expected to observe differences in the exposure/response relationship either. The Applicant did not discuss the impact of the co-medication on both the TRF1 and the exposure. The pooled analysis was considered exploratory, which was acceptable. It was therefore the individual analysis of each study that was considered relevant in terms of exposure response, considering that the population and treatment of both phase III studies were different. It should be noted that the provided graphs were not stratified for AQP4 serology, as requested.

The Applicant concludes that differences in efficacy could not be explained by the exposure. It was agreed that the population PK modelling approach and the exposure/response modelling could not help identifying which subgroups may suffer from a lack of efficacy in the NMOSD patient population. If satralizumab was to be used in other indications, the patients > 100 kg may benefit from a dose adjustment.

Since the model was not considered adequate (uncertainty > 50%), conclusions on the exposure/response relationship cannot be drawn from the predicted data. Observed data show that patients in the low exposure group had an intermediate relapse-free survival compared to the high exposure group and placebo group.

AQP4-IgG positive patients

The indication for satralizumab has been restricted to AQP4-IgG seropositive NMOSD patients, therefore a new exposure/efficacy analysis was provided for only AQP4-IgG seropositive patients. A new analysis with a new definition of event, as the sum of the previously defined event and the events of use of rescue medication was requested but not provided. This analysis was not requested again.

As previously, pooled analyses are considered only exploratory, as the co-medication study BN40898 may have an effect on the time to relapse and the population in the studies are not comparable. Therefore, the individual E/R analyses per study should be considered.

The dataset is small; thus a selection bias may confound the covariate analysis. Therefore a model without covariate as used here is appropriate. Overall, the number of events, and the number of patients is small, leading to high parameter uncertainty, thus preventing to reach conclusions on an exposure efficacy relationship, in particular since all patients were given the same dose. Any result should be interpreted with caution. The analysis however indicates that satralizumab seems to have an effect on TFR1 when compared to placebo.

The role of AQP4-IgG antibodies in the pathophysiology of NMOSD is still not definitely determined. As an extension to the exposure efficacy question, the Applicant was asked to evaluate associations between satralizumab concentrations, RO, and relapses with AQP-4 Ab titers. However, limitations from the analytical methods (ELISA limits of quantification and cell-based assay variability) prevent from providing the information required and this issue was not further pursued.

SmPC

The SmPC adequately describes the PK characteristics of satralizumab.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology was supported by two Phase III trials along with additional data from Phase I studies. The clinical pharmacology of satralizumab was considered sufficiently described.

2.5. Clinical efficacy

Table 9: Summary of Studies Contributing to Efficacy Evaluation of Satralizumab in NMO / NMOSD

Study No.	Study Design	Population	No. of Patients	Dose, Route, and Regimen
Pivotal Phase III Study BN40898 (SA-307JG)				
Double-Blind Period	Phase III, multi-center, randomized, add-on to baseline treatment, DB, placebo-controlled study End of DB period: After 26 PDRs	Patients with NMO and NMOSD Adults and adolescents (age ≥12 years)	Total: 83 Randomized 1:1 Satralizumab: 41 Placebo: 42 (UK [2], Italy [9], Germany [4], France [1], Poland [23], Ukraine [3], Spain [3], Hungary [2], Taiwan [12], Japan [22] and US [2])	SAT Group: satralizumab 120 mg SC injections at Week 0, 2, 4, and Q4W thereafter; added to baseline treatment PLB Group: placebo SC injections at Week 0, 2, 4, and Q4W thereafter; added to baseline treatment
Open-Label Extension Period	Open label period	Patients who experienced a PDR, completed the DB period, or experienced a clinical relapse and received rescue therapy	Entered: 42 Ongoing at CCOD: 33	All Patients: satralizumab 120 mg SC injections at Week 0, 2, 4, and Q4W thereafter; added to baseline treatment
Pivotal Phase III Study BN40900 (SA-309JG)				
Double-Blind Period	Phase III, multi-center, randomized, monotherapy, double-blind, placebo-controlled study End of DB period: 1.5 years after the date of randomization of the last patient enrolled	Patients with NMO and NMOSD Adults (≥18 years)	Total: 95 Randomized 2:1 Satralizumab: 63 Placebo: 32 (US [47], Canada [11], Italy [1], Poland [8], Bulgaria [4], Romania [1], Croatia [1], Ukraine [10], Georgia [1], Turkey [1], Malaysia [1], Taiwan [4], and South Korea [5])	SAT Group: satralizumab 120 mg SC injections at Week 0, 2, 4, and Q4W thereafter PLB Group: placebo SC injections at Week 0, 2, 4, and Q4W thereafter
Open-Label Extension Period	Open label period	Patients who experienced a PDR or completed the DB period	Entered: 35 Ongoing at CCOD: 29	All Patients: satralizumab 120 mg SC injections at Week 0, 2, 4, and Q4W thereafter

CCOD = clinical cut-off date, CSR = clinical study report; DB=Double-blind; OLE = open-label extension; SC = subcutaneous; PDR =protocol-defined relapse; Q4W= every four weeks.

2.5.1. Dose response studies

Satralizumab dose finding was performed in two studies, including one Phase 1 single ascending dose study in Caucasian and Japanese healthy volunteers (SA-001JP) and one Phase 1b multiple dose study in Japanese RA patients (SA-105JP). PD endpoints were used (membrane-bound-IL-6R and soluble IL-6R).

In healthy subjects (SA-001JP), placebo-controlled, randomized, double-blind (DB), inter-individual, SC dose escalation (up to 240 mg SC) as well as open label single IV administration (up to 120 mg IV) were studied. In total, 72 subjects were exposed to satralizumab and 12 to placebo (mean age: 23.3 to 25.3 years, mean BW 60.2 to 61.5 kg, mean body mass index (BMI) 20.8 to 21.3 kg/m^2).

Serum sIL-6R elevated in a dose dependent manner and dose levels at 120 and 240 mg showed comparable peak levels of sIL-6R. The duration for which sIL-6Rs saturation was observed, showed a dose-dependent prolongation. At dose levels of 120 and 240 mg, sIL-6R saturation was sustained for more than 28 days at peak level. Therefore, the dose levels over 120 mg/body were considered appropriate for a Q4W administration interval.

2.5.2. Main studies

Two pivotal Phase III studies BN40898 and BN40900 were conducted:

- Study BN40898 is a multicenter, DB, placebo-controlled study to assess the efficacy and safety of satralizumab as an add-on to baseline IST in adult and adolescent (12 to 17-year-old) patients.
- Study BN40900 is a multicenter, DB, placebo-controlled study to assess the efficacy and safety of satralizumab as monotherapy in adult patients.

Study BN40898 and study BN40900

Methods

Study BN40898 was an add-on study in which patients were required to be receiving baseline IST treatment at a stable dose as monotherapy for at least 8 weeks prior to baseline and during the DB period. Conversely, the monotherapy study BN40900 enrolled patients who had either discontinued or had not previously received treatment for NMOSD; these treatments were prohibited from baseline to the end of the study.

In both studies, patients who experienced a PDR during the DB period or completed the DB period could enter the OLE period. In Study BN40898, patients who experienced a clinical relapse that did not meet the definition of a PDR but was treated with rescue therapy could also enter the OLE; in Study BN40900 these patients had to remain in the DB period.

Patients who experienced a clinical relapse and did not enter the OLE were asked to continue in the study in the follow-up phase for 24 weeks from the last dose of study treatment.

The designs of the pivotal studies BN40898 and BN40900 are presented in Figure 5 and Figure 6.

Figure 5: Study BN40898 Design

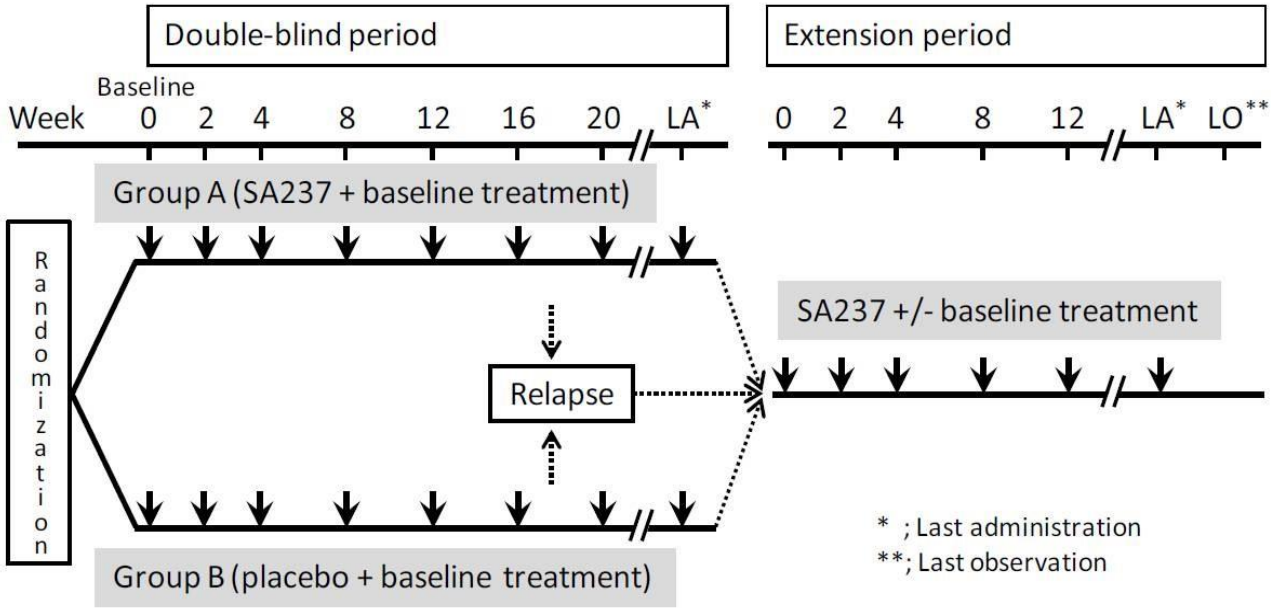
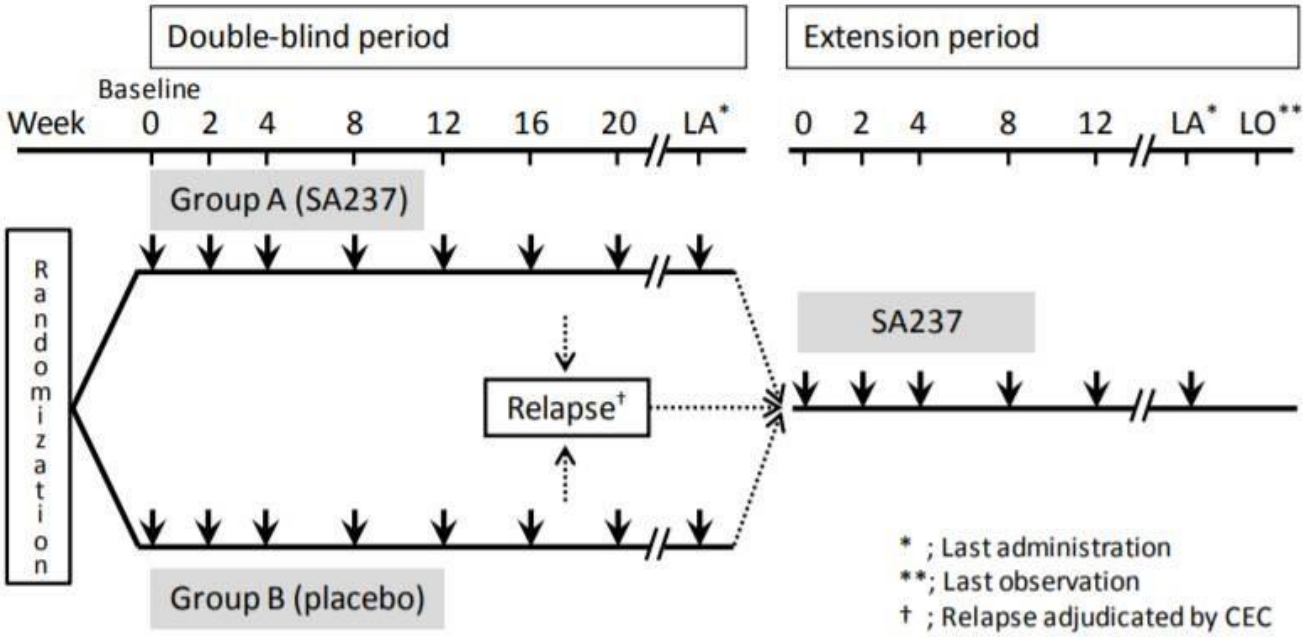


Figure 6: Study BN40900 Design



CEC: Clinical Endpoint Committee; SA237: satralizumab.

Study Participants

Inclusion criteria:

Patients had to meet all of the following criteria for study entry:

1. Patients diagnosed as having either:

   a. NMO as defined by Wingerchuk et al. 2006, which required the following: optic neuritis AND acute myelitis AND least two of three supportive criteria:
      - Contiguous spinal cord lesion identified on an MRI scan extending over 3 vertebral segments
      - Brain MRI not meeting diagnostic criteria for Multiple Sclerosis
      - NMO-immunoglobulin G (IgG) (AQP4-IgG) seropositive status.

   OR

   b. NMOSD as defined by EITHER of the following criteria with AQP4-IgG seropositive status at screening (Wingerchuk 2007):
      i. Idiopathic single or recurrent events of longitudinally extensive myelitis (≥3 vertebral segment spinal cord MRI lesion).
      ii. Optic neuritis: recurrent or simultaneous bilateral

2. BN40898: Clinical evidence of at least 2 documented relapses (including first attack) in the last 2 years prior to screening, at least one of which had occurred in the 12 months prior to screening.

   BN40900: Clinical evidence of at least 1 documented relapse (including first attack) in the last 12 months prior to screening.

3. EDSS score from 0 to 6.5 inclusive at screening.

4. Age at the time of informed consent: 12-74 years inclusive (BN40898), 18-74 years inclusive (BN40900).

5. BN40898: One of the following IST at stable dose as a monotherapy for 8 weeks prior to baseline:

- Adults: azathioprine (≤ 3 mg/kg/day), or mycophenolate mofetil (≤ 3000 mg/day), or oral corticosteroids (15 mg/day [prednisolone equivalent]).
- Adolescents: oral corticosteroids together with either azathioprine or mycophenolate mofetil.

6. Ability and willingness to provide written informed consent and to comply with the requirements of the protocol.

Exclusion criteria:

1. Any previous treatment with IL-6 inhibitory therapy (e.g. tocilizumab), alemtuzumab, total body irradiation or bone marrow transplantation at any time.
2. Any previous treatment with anti-CD20, eculizumab, belimumab, (anti-B-lymphocyte stimulator monoclonal antibody BN40900) any other treatment for prevention of multiple sclerosis relapse (e.g. interferon, natalizumab, glatiramer acetate, fingolimod, teriflunomide or dimethyl fumarate) within 6 months prior to baseline.
3. Any previous treatment with anti-CD4, cladribine, mitoxantrone (and cyclophosphamide BN40900) within 2 years prior to baseline
4. Treatment with any investigational agent within 3 months prior to baseline.

There were further 15 general safety exclusion criteria and 5 laboratory exclusion criteria.

Treatments

In the pivotal studies, the patients received an SC injection of satralizumab 120 mg or placebo at Weeks 0, 2 and 4, and Q4W thereafter during the double-blind period. In the OLE, all patients received open-label treatment with satralizumab at a dose of 120 mg SC at Weeks 0, 2 and 4 and Q4W thereafter. In Study BN40898, patients who experienced a clinical relapse that did not meet the definition of a PDR but was treated with rescue therapy could also enter the OLE; in Study BN40900 these patients had to remain in the DB period.

Rescue therapy for clinical relapse was given by the discretion of the investigator and included pulse IV corticosteroids, IV immunoglobulin (IVIG), and/or apheresis (including plasma exchange and plasmapheresis) in both studies while oral corticosteroids for tapering was also permitted in study BN40900.

Objectives

The objectives of studies BN40898 and BN40900 were

- To evaluate the efficacy of satralizumab (add-on therapy; BN40898) (monotherapy; BN40900) compared with placebo in patients with NMO and NMOSD.
- To evaluate the safety (add-on therapy; BN40898) (monotherapy; BN40900) compared with placebo in patients with NMO and NMOSD
- To examine the PD and PK of satralizumab.
- To examine the immunogenicity of satralizumab.

Outcomes/endpoints

The efficacy analyses were performed on the intent-to-treat (ITT) population for each individual study.

Primary efficacy endpoint

There are currently no validated endpoints to evaluate the efficacy of agents for the treatment of NMO or NMOSD. Because substantial disability can result from any given relapse and in order to reduce the potential risk associated with use of placebo, a time to-event outcome (i.e. TFR) instead of annualized relapse rate (ARR) was chosen as the primary efficacy measure in studies BN40898 and BN40900. TFR is defined as the time from the date of randomization until the first occurrence of relapse, where the time point of relapse onset is defined as the time at which the patient experiences any new or worsening neurological NMO/NMOSD symptoms representing clinical relapse.

The primary efficacy endpoint of TFR was based on PDRs to be adjudicated by an independent central Clinical Endpoint Committee (CEC) who reviewed all cases of relapse and evaluated each to see if it met the criteria for a PDR. Moreover, only those relapses with EDSS/FSS assessment conducted by the examining investigator within 7 days after the patient reported the event to the site were included in the primary analysis.

At the GCP inspection, critical issues were found concerning a weak process for segregation of examining and treating investigators at clinical sites and various steps related to the relapse assessment process.

In study BN40898, patients were censored if given with rescue treatment or if there was a change in background IST therapy.

Protocol defined relapse was defined as:

The occurrence of new or worsening neurological symptoms attributable to NMO or NMOSD persisting for >24 hours and not attributable to confounding clinical factors (e.g. fever, infection, injury, change in mood, adverse reactions to medications). The new or worsening neurologic symptoms must have met *either* of the following:

- An increase of at least 1.0 point on the EDSS score if the baseline score was 1.0 or higher or a 2.0-point increase on the EDSS if the baseline score was zero;
- An increase of at least 2.0 points on one of the appropriate FSS;
- An increase of at least 1.0 point on two or more of the appropriate FSS if the baseline score was one or more;
- An increase of at least 1.0 point in single eye FSS when the baseline score in that eye was one or more.

New or worsening neurological symptoms that occurred less than 31 days following the onset of a PDR will be considered part of the same relapse, and the onset date used in the analysis was the onset date of the first relapse.

The base for comparison of the increase was the score from the most recent EDSS/FSS assessment visit prior to the relapse. The appropriate FSS change must have affected at least one of the following functional systems: pyramidal, cerebellar, brainstem, sensory, bowel/bladder, or visual (single eye).

In order to assess the consistency of the effect of satralizumab on relapses in a real-world setting where there is no CEC adjudication and assessment of relapses is by the patient's treating clinician, the primary endpoint was assessed using sensitivity analyses based on clinical relapses. The time to first clinical relapse and time to first treated clinical relapse was included in the efficacy analysis of both studies BN40898 and BN40900. In study BN40898, patients were censored if given rescue treatment or if there was a change in IST.

Key secondary endpoints

Change from baseline in VAS score for pain and in FACIT fatigue scale at Week 24 were included in both studies BN40898 and BN40900 as key secondary endpoints. The objective of the key secondary endpoints was to evaluate the benefit of satralizumab on pre-existing residual pain (VAS) and fatigue (FACIT fatigue scale), independently of relapses, within the first 24 weeks of treatment.

The VAS is a subjective measure of pain and it consists of a 100 mm line with descriptors of 'no pain' and 'pain as bad as it could be' at either end. Patients are asked to rate their pain by placing a mark on the line corresponding to their current level of pain. The distance along the line from the 'no pain' marker is then measured with a ruler giving a pain score out of 100.

The FACIT fatigue scale includes 13 questions which measure fatigue/asthenia for patients with chronic, life-threatening illnesses. For each question, a patient rates their condition for the past week on a 5-point Likert scale ranging from 0 (not at all) to 4 (very much). For the change in FACIT fatigue, descriptive statistics were calculated for the change in FACIT fatigue by averaging the individual question scores.

Other secondary endpoints were designed to measure changes in pre-existing symptoms and, therefore, were assessed at pre-specified time points (every 24 weeks form baseline). The following were included as efficacy endpoints in both studies: Change in Short Form Health Survey 36 Version 2 (SF-36v2) Scores, Change in EuroQol-5D 3 Level Version (EQ-5D-3L), Change in Modified Rankin Scale (mRS) Score, Change in Zarit Burden Interview (ZBI) Score, Change in EDSS Score, Change in Visual Acuity (Snellen Chart), ARR, and Proportion of Relapse-free Patients. There were two additional efficacy assessments included in the BN40900 study only: Change in Low-contrast Sloan Letter Chart (LCSLC) and Change in Timed 25-Foot Walk (T25W).

Sample Size

Study BN40898

A two-sided log-rank test was used to determine the sample size between the two groups. The sample size of 70, randomized in a 1:1 ratio to the two treatment groups with 26 TFR events in total was predicted to provide 80% power, maintaining the type I error rate of 0.05, and assuming a 2-year drop-out rate of approximately 10%. The TFR hazard ratio 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 exponential distribution with annual hazard rate of 0.4184.

Study BN40900

The original plan for the sample size was based on the following:

A two-sided log-rank test was used to determine the sample size between the two groups. The sample size of 70, randomized in a 2:1 ratio to the two treatment groups with 19 TFR events in total was predicted to provide 80% power, maintaining the type I error rate of 0.05, and assuming a 2-year drop-out rate of approximately 10%. The TFR hazard ratio of satralizumab over placebo was assumed to be 0.25. The distribution of TFR in the placebo group was assumed to follow an exponential distribution with annual hazard rate of 0.4602.

In protocol version 6 (dated 01 Mar 2016) the following changes were made:

The sample size was increased from 70 to 90 patients and the total number of CEC confirmed PDRs needed for primary analysis was increased from 19 to 44. These changes were done due to modified assumptions about the hazard ratio in the sample size calculation. The hazard ratio of satralizumab over placebo was modified considering the mechanism of action of satralizumab. It was assumed, that the hazard ratio is 1.0 during the initial 2 months. Additionally, the estimated post-baseline ARR in the placebo group was updated from 0.4 to 1.35.

In protocol version 8 (dated 14 Jun 2018) the following changes were made:

The definition of the end of the double-blind period was changed to include a maximal duration completion of 1.5 years after the date of the last patient randomized, if the target number of CEC confirmed PDRs (44) has not been reached.

Randomisation

In Study BN40898, eligible patients were randomized to one of the two treatment groups: placebo (PCB) or satralizumab (SAT) in a 1:1 ratio via an interactive web/voice response system (IxRS) according to a pre-defined listing of randomization. The randomization was stratified by baseline ARR (ARR: 1, vs >1) and geographical region (Asia and Europe/Other). Administration of the study treatment occurred on the same day as randomization.

In Study BN40900, eligible patients were randomized in a 2:1 ratio to satralizumab and placebo groups via an lxRS according to a predefined listing of randomization. The randomization was stratified by baseline therapy for prevention of NMO or NMOSD relapse (B-cell depleting therapy or immunosuppressants/others) and the most recent relapse (first attack or relapse) in the last year prior to screening.

Blinding (masking)

To maintain the blind during the DB period, a placebo vial filled with a solution identical in composition, colour, appearance, and packaging to the satralizumab vial, but without the satralizumab active ingredient, was supplied. Patients, investigator staff, persons performing the assessments, data analysts, and the Sponsor remained blinded to the identity of the treatment throughout the DB period.

To further ensure blinding of the study, site staff, study monitors, the Sponsor, and the study team were blinded for some of the laboratory results that could reveal treatment allocation, such as serum satralizumab concentration, high-sensitivity CRP, IL-6, sIL-6R, ADA, AQP4-IgG (except at screening), plasmablasts, and complement (C3, C4, and CH50), until the primary analysis. Fibrinogen data was provided to the sites throughout the DB period for safety reasons; the possible bias introduced by the availability of fibrinogen data was discussed during SA (EMEA/H/SA/2571/2/FU/2/2018/PA/II) and further evaluated in a separate bias assessment report (see conduction study for further details).

To maintain blinding of the efficacy assessment, the Applicant specified two study features in the protocol: (1) the segregation of the treating and examining investigators at each study site and (2) the independent review of reported relapses by the CEC. The treating Investigator was responsible for patient care and the examining assessor was responsible for the administration of the EDSS and FSS. The examining assessor who filled in the EDSS/FSS data included in the relapse assessment form did not have access to laboratory data. Before adjudication, the CEC package including relapse data was checked staff at the CRO for completeness and adherence to the scoring conventions of the EDSS scale. Finally, the independent CEC reviewed the data and made a final assessment.

Statistical methods

Analysis populations

The ITT population was the primary analysis population for the efficacy analysis and included all patients randomized. Patients were analysed in the group to which they were randomized.

The Per-Protocol Set (PPS) population included all patients in the ITT population who received at least 3 doses of study drug, and without any major protocol deviations that were considered to have an impact on efficacy.

Efficacy analysis

All analyses were stratified using the same stratification variables as in the randomisation (see above).

Kaplan-Meier estimates and their 95% CIs at 6-month intervals were used to describe the TFR based on PDR distribution in addition to the hazard ratio (HR). For study BN40898, the TFR was censored at the earliest day of 1) the end of DB period, 2) switching or increasing the baseline treatment, or 3) receiving rescue therapy for clinical relapse. For study BN 40900 the TFR was censored at the end of DB period.

The key sensitivity analyses included in both studies BN40898 and BN40900 were those of time to first clinical relapse and time to first treated clinical relapse; these analyses allow for the assessment of the efficacy of satralizumab in the real-world setting, where relapse assessment is conducted by the patient's treating clinician rather than the CEC employed in the clinical study setting.

Both key secondary efficacy endpoints were analysed using Analysis of Covariance (ANCOVA). The ANCOVA analyses for change from baseline to Week 24 included treatment group as a fixed effect; and baseline measurements and stratification factors as covariates. The missing data was imputed by the baseline observation carried forward (BOCF) method. Exploratory analyses of the key secondary endpoints were performed using ANCOVA multiple imputation method (random hot deck; change from baseline to Week 24) and mixed-effect model repeated measures (MMRM) (change from baseline to every 24-week interval). The random hot deck imputation method using a regression-based approach was conducted. In this imputation method, missing values were replaced with values from a similar responding unit. The MMRM included treatment group, protocol-specified visit, treatment-by-visit interaction as fixed effects; the baseline measurements and stratification factors as a covariate; and visit as a repeated measure. The unstructured covariance matrix was assumed in the model. For all MMRM analyses, in case of normality assumption not being met, generalized estimating equations (GEE) or Generalized Linear Mixed-effect model analysis was used. The normality assumption was checked prior to unblinding.

For the FACIT fatigue questionnaire, if there were less than 7 responses recorded, then the total fatigue score was considered missing. If there were 7 or more responses recorded, then the total fatigue score for that questionnaire was calculated as the average of the non-missing scores multiplied by 13. This approach was taken in both studies BN40898 and BN40900.

Results

Participant flow

In study BN40898, the total of 83 enrolled patients were randomized in 1:1 ratio to receive either satralizumab (SAT) or matching placebo SC (PCB group) treatment at Weeks 0, 2, and 4, and Q4W thereafter, administered in combination with the baseline immunosuppressive treatment (Figure 7). For each patient, the DB period lasted until they received their first dose of treatment in the OLE, or until the withdrawal visit. For the study, the DB period included in the primary analysis ended once the total number of PDRs confirmed by the CEC reached 26.

In study BN40900, a total of 95 patients were randomized in a 2:1 ratio to receive either satralizumab (SAT) (N=63) or matching placebo SC (PCB group) (N=32) treatment at Weeks 0, 2, and 4, and Q4W thereafter (Figure 8). For each patient, the DB period lasted until the day before they received the first

dose of treatment in the OLE, or until the withdrawal visit. For the study, the DB period for the primary analysis ended when the last patient enrolled was treated for 1.5 years since the date of randomization. Patients who experienced a relapse that did not meet the definition of a PDR were treated with rescue therapy and continued to receive study treatment in the DB period at the discretion of the investigator.

Figure 7: Participant flow in study BN40898

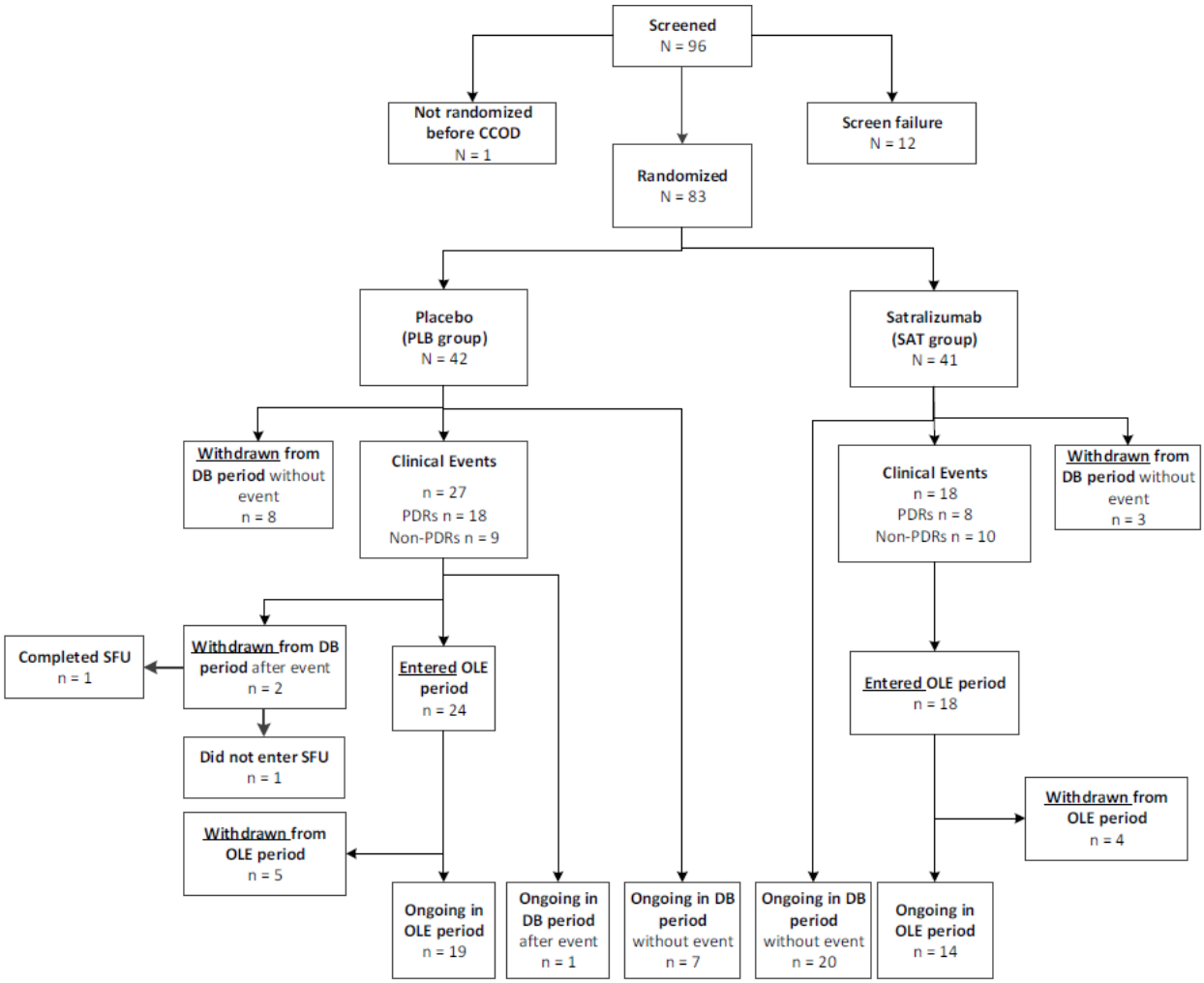
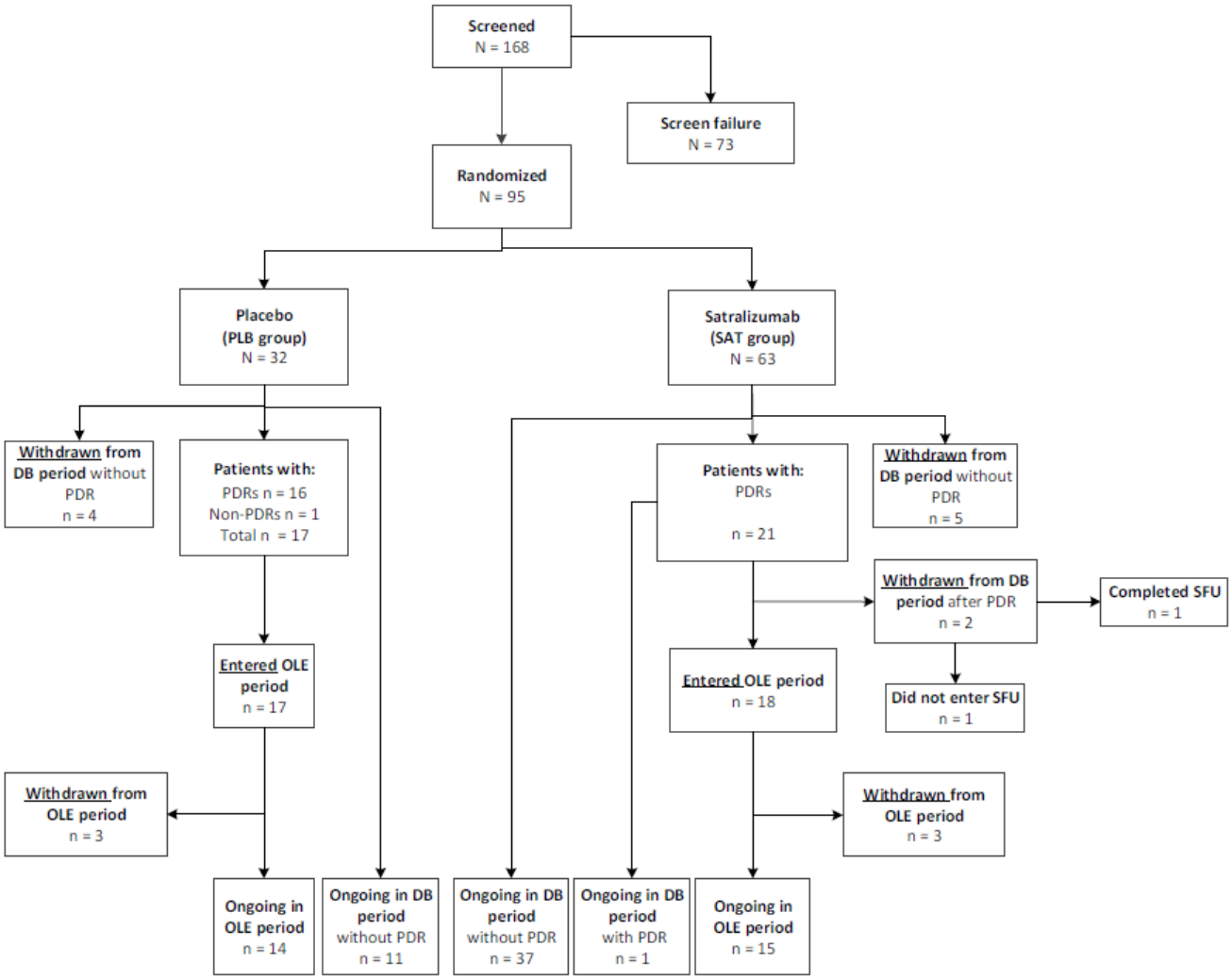


Figure 8: Participant flow in study BN40900



Recruitment

- Study 40900: first patient enrolled: 05-Aug-2014 and data cut-off: 12-Oct-2018
- Study 40898: first patient enrolled: 20-Feb-2014 and data cut-off: 06-Jun-2018

Conduct of the study

Fibrinogen levels-related GCP breach

On 2018, the Applicant requested a follow-up SA to discuss with EMA, a GCP breach in the conduction of the two studies. Fibrinogen concentration data had been utilised on 2 occasions (in November 2015 and May 2017) by the previous Sponsor in attempts to assume treatment assignment for both pivotal studies. HRs were calculated based on this assumed treatment assignment. A temporal association with protocol amendments first increasing size and the required number of primary endpoint events (Q1 2016 amend 6) and later revising the end of study as the maximum of 1.5 years after the date of randomization of the last patient and therefore, decreasing the number of events (Q2 2018 amend 8) were seen in study BN40900. No changes were made to Study BN40898.

Within the SA (EMEA/H/SA/2571/2/FU/2/2018/PA/II), the Applicant presented this GCP breach and seeked advice about the adequacy of the proposed mitigation actions including the implementation of

independent safety and efficacy medical reviewers, and limitation of efficacy reviewer access to laboratory parameters as well as the commitment to prepare a bias report analysing the potential biases on the clinical data to be submitted within this MAA. Overall, the CHMP agreed with the proposed mitigation actions for the further study conduct but it was concluded that scientific integrity of both studies should be fully investigated at the time of MAA.

During that SA, the CHMP specifically questioned whether information on fibrinogen concentrations may have impacted treatment decisions regarding clinical parameter assessments (e.g. EDSS, relapses) in both studies given that it seemed plausible that investigators were informed about the association between SAT exposure and fibrinogen concentrations which were available to the investigators for safety purposes. The Applicant presented the relapse assessment procedure as described in the blinding section above and noted that the examining assessor had not access to laboratory data.

Moreover, the CHMP requested the Applicant to clarify whether the calculations had an impact on the protocol amendment (number 6) to increase the required number of events in the protocol of study BN40900 in Q1 2016. The Applicant stated that the decision was based on the faster relapse accumulation and higher number of early relapses (i.e. relapses within the first 2 months after randomization) than assumed in the initial sample size calculation and was completely independent of the treatment assignment attempt.

Findings during GCP inspections

Four GCP inspections, including two clinical site-, a Sponsor-, and a CRO-inspection were performed.

The inspections resulted in critical findings relating to deficiencies in the documentation recording the segregation of treating and examining investigators and to the review of the CEC package performed by the Sponsor before sending it to the CEC. A total of 10 critical findings and 19 major findings were identified. According to the integrated inspection report, data from at least 33 (28%) of patients could have been negatively affected in terms of data integrity

The inspection team reported findings associated with the difficulty to effectively confirm the segregation of the examining and treating investigators. In particular, the following findings were found incomplete documentation, missing documents, documents filed out the trial master file (eTMF), changes made to forms not adhering to ALCOA (Attributable, Legible, Contemporaneous, Original, and Accurate) principles and missing or erroneous notes-to-file.

Moreover, the inspection team found that queries and answers shared between the Sponsor/CRO staff and the investigators as well as changes in the FSS and EDSS scores, were not recorded and stored in a clear and systematic way to reconstruct and trace all events in both trials from a chronological point of view (e.g. if the EDSS was adapted according to FSS or vice versa and if changes were done in agreement with the investigator or the way the CRO determined). Additionally, one potentially leading query was identified in the integrated inspection report. Finally, the inspector reported noted numerous accesses to the electronic system (VCAS) used for managing relapse assessment forms.

Baseline data

In study BN49898, the most common treatment at baseline (BN40898) was oral corticosteroids (44.6%), followed by azathioprine (34.9%) and mycophenolate (14.5%). The number of adolescents enrolled in the trial was 7: of them, 3 (1 Asian, 2 African American) were in the placebo (PCB) arm and 4 (white) in the satralizumab (SAT) arm, with mean ages 15.7 and 15.3 years, respectively (Table 10).

In study BN40900, there was a higher proportion of female patients in the PCB group (96.9%) compared to the SAT group (73.0%) and the higher proportion of black/African American patients in the SAT group

(20.6%) compared to the PCB group (9.4%). Patients were predominantly female (81.1%) and the majority of the patients were of white (62.1%) race. The mean age of patients was 44 years and the median age was 45 years. The majority of patients were <65 years of age (98.9%). Two-thirds (67.4%) of the patients were AQP4-IgG-seropositive at baseline (number of AQP4-IgG-seronegative patients was capped at approximately 30%). A total of 33 patients (34.7%) had not received IST or corticosteroid treatment for relapse prevention prior to baseline (SAT: PCB 23 [36.5%]: 10 [31.3%]). Four patients (6.3%) in the SAT group and 3 patients (9.4%) in the PCB group received treatment for relapse prevention prior to baseline with corticosteroids alone (Table 11).

Table 10: Baseline demographic, disease and treatment characteristics (BN40898)

	Placebo (N=42) n (%)	SA237 (N=41) n (%)	Total (N=83) n (%)
Age (years)			
n	42	41	83
Mean (SD)	43.4 (12.0)	40.8 (16.1)	42.1 (14.2)
Min - Max	14 - 65	13 - 73	13 - 73
Median	44.0	41.0	42.0
Age Group			
n	42	41	83
<18 years	3 (7.1%)	4 (9.8%)	7 (8.4%)
>=18 years	39 (92.9%)	37 (90.2%)	76 (91.6%)
Gender			
n	42	41	83
Male	2 (4.8%)	4 (9.8%)	6 (7.2%)
Female	40 (95.2%)	37 (90.2%)	77 (92.8%)
Race			
n	42	41	83
American Indian/Alaska Native	0	0	0
Asian [Japanese]	10 (23.8%)	11 (26.8%)	21 (25.3%)
Asian [Non-Japanese]	8 (19.0%)	6 (14.6%)	14 (16.9%)
Black/African American	2 (4.8%)	0	2 (2.4%)
Native Hawaiian/other Pacific Islander	0	0	0
White	21 (50.0%)	24 (58.5%)	45 (54.2%)
Other	1 (2.4%)	0	1 (1.2%)
Racial Subgroup			
n	42	41	83
Japanese	10 (23.8%)	11 (26.8%)	21 (25.3%)
Non-Japanese	32 (76.2%)	30 (73.2%)	62 (74.7%)
Geographic Region			
n	42	41	83
Asia	18 (42.9%)	16 (39.0%)	34 (41.0%)
Europe/Other	24 (57.1%)	25 (61.0%)	49 (59.0%)
Ethnicity			
n	42	41	83
Hispanic or Latino	0	0	0
Not Hispanic or Latino	40 (95.2%)	41 (100%)	81 (97.6%)
Not reported	2 (4.8%)	0	2 (2.4%)
Height (cm)			
n	42	41	83
Mean (SD)	163.63 (6.88)	162.00 (8.69)	162.83 (7.82)
Min - Max	150.0 - 185.5	146.5 - 179.0	146.5 - 185.5
Median	163.00	162.00	162.50
Body Weight (kg)			
n	42	41	83
Mean (SD)	64.41 (18.42)	61.76 (14.41)	63.10 (16.51)
Min - Max	39.4 - 140.4	45.3 - 99.0	39.4 - 140.4
25%-ile	54.00	52.00	52.50
Median	61.35	57.00	58.40
75%-ile	74.00	63.40	70.00

BMI (kg/m2)			
n	42	41	83
Mean (SD)	23.91 (5.90)	23.50 (4.91)	23.71 (5.40)
Min - Max	15.9 - 47.9	17.4 - 37.7	15.9 - 47.9
Median	22.84	21.67	22.64
BMI Category (kg/m2)			
n	42	41	83
<18.5	4 (9.5%)	2 (4.9%)	6 (7.2%)
18.5 to <25	27 (64.3%)	26 (63.4%)	53 (63.9%)
25 to <30	5 (11.9%)	8 (19.5%)	13 (15.7%)
>=30	6 (14.3%)	5 (12.2%)	11 (13.3%)
Weight Category			
n	42	41	83
< Median	19 (45.2%)	22 (53.7%)	41 (49.4%)
>= Median	23 (54.8%)	19 (46.3%)	42 (50.6%)

	Placebo (N=42) n (%)	SA237 (N=41) n (%)	Total (N=83) n (%)
Baseline ARR			
n	42	41	83
Mean (SD)	1.50 (0.60)	1.48 (0.63)	1.49 (0.61)
Min - Max	1.0 - 3.0	1.0 - 3.5	1.0 - 3.5
Median	1.50	1.50	1.50
Baseline ARR Category			
n	42	41	83
1	20 (47.6%)	20 (48.8%)	40 (48.2%)
>1	22 (52.4%)	21 (51.2%)	43 (51.8%)
Diagnosis			
n	42	41	83
NMO	28 (66.7%)	33 (80.5%)	61 (73.5%)
NMOSD	14 (33.3%)	8 (19.5%)	22 (26.5%)
Anti-AQP4 status			
n	42	41	83
Positive	28 (66.7%)	27 (65.9%)	55 (66.3%)
Negative	14 (33.3%)	14 (34.1%)	28 (33.7%)
Baseline Treatment			
n	42	41	83
Azathioprine	13 (31.0%)	16 (39.0%)	29 (34.9%)
Mycophenolate Mofetil	8 (19.0%)	4 (9.8%)	12 (14.5%)
Oral Corticosteroids	20 (47.6%)	17 (41.5%)	37 (44.6%)
Azathioprine + Oral Corticosteroids	0	3 (7.3%)	3 (3.6%)
Mycophenolate Mofetil + Oral Corticosteroids	1 (2.4%)	1 (2.4%)	2 (2.4%)
Baseline EDSS			
n	41	41	82
Mean (SD)	3.63 (1.32)	3.83 (1.57)	3.73 (1.45)
Min - Max	1.5 - 6.5	1.0 - 6.5	1.0 - 6.5
Median	3.50	3.50	3.50

Table 11: Baseline demographic, disease and treatment characteristics (BN40900)

	Placebo (N=32) n (%)	SA237 (N=63) n (%)	Total (N=95) n (%)
Age (years)			
n	32	63	95
Mean (SD)	40.5 (10.5)	45.3 (12.0)	43.7 (11.7)
Min - Max	20 - 56	21 - 70	20 - 70
Median	42.5	46.0	45.0
Age Group			
n	32	63	95
<65 years	32 (100%)	62 (98.4%)	94 (98.9%)
>=65 years	0	1 (1.6%)	1 (1.1%)
Gender			
n	32	63	95
Male	1 (3.1%)	17 (27.0%)	18 (18.9%)
Female	31 (96.9%)	46 (73.0%)	77 (81.1%)
Race			
n	32	63	95
American Indian/Alaska Native	0	2 (3.2%)	2 (2.1%)
Asian [Japanese]	0	0	0
Asian [Non-Japanese]	6 (18.8%)	8 (12.7%)	14 (14.7%)
Black/African American	3 (9.4%)	13 (20.6%)	16 (16.8%)
Native Hawaiian/other Pacific Islander	0	0	0
White	22 (68.8%)	37 (58.7%)	59 (62.1%)
Other	1 (3.1%)	3 (4.8%)	4 (4.2%)
Geographic Region1			
n	32	63	95
Asia	5 (15.6%)	5 (7.9%)	10 (10.5%)
Europe/US/Other	27 (84.4%)	58 (92.1%)	85 (89.5%)
Geographic Region2			
n	32	63	95
Asia	5 (15.6%)	5 (7.9%)	10 (10.5%)
Europe/Other	11 (34.4%)	16 (25.4%)	27 (28.4%)
North America	16 (50.0%)	42 (66.7%)	58 (61.1%)
Ethnicity			
n	32	63	95
Hispanic or Latino	3 (9.4%)	9 (14.3%)	12 (12.6%)
Not Hispanic or Latino	28 (87.5%)	50 (79.4%)	78 (82.1%)
Not reported	0	4 (6.3%)	4 (4.2%)
Unknown	1 (3.1%)	0	1 (1.1%)
Height (cm)			
n	32	62	94
Mean (SD)	163.82 (6.05)	166.13 (10.21)	165.34 (9.05)
Min - Max	154.9 - 182.0	151.0 - 193.0	151.0 - 193.0
Median	162.50	165.35	165.00
Body Weight (kg)			
n	32	63	95
Mean (SD)	70.48 (19.00)	78.89 (24.92)	76.06 (23.33)
Min - Max	42.1 - 117.3	45.7 - 151.0	42.1 - 151.0
25%-ile	56.50	60.00	58.50
Median	69.00	75.30	72.70
75%-ile	78.70	90.50	88.50
Weight Category			
n	32	63	95
< Median	18 (56.3%)	29 (46.0%)	47 (49.5%)
>= Median	14 (43.8%)	34 (54.0%)	48 (50.5%)
BMI (kg/m2)			
n	32	62	94
Mean (SD)	26.22 (7.00)	28.53 (8.62)	27.74 (8.14)
Min - Max	17.5 - 44.1	18.0 - 62.2	17.5 - 62.2
Median	24.58	26.91	25.64
BMI Category (kg/m2)			
n	32	62	94
<18.5	3 (9.4%)	1 (1.6%)	4 (4.3%)
18.5 to <25	14 (43.8%)	27 (43.5%)	41 (43.6%)
25 to <30	8 (25.0%)	13 (21.0%)	21 (22.3%)
>=30	7 (21.9%)	21 (33.9%)	28 (29.8%)

	Placebo (N=32) n (%)	SA237 (N=63) n (%)	Total (N=95) n (%)
Diagnosis			
n	32	63	95
NMO	24 (75.0%)	47 (74.6%)	71 (74.7%)
NMOSD	8 (25.0%)	16 (25.4%)	24 (25.3%)
Anti-AQP4 status			
n	32	63	95
Positive	23 (71.9%)	41 (65.1%)	64 (67.4%)
Negative	9 (28.1%)	22 (34.9%)	31 (32.6%)
Prior therapy			
n	32	63	95
B-cell depleting therapy	4 (12.5%)	8 (12.7%)	12 (12.6%)
Immunosuppresants/Others	28 (87.5%)	55 (87.3%)	83 (87.4%)
Most recent attack			
n	32	63	95
First attack	4 (12.5%)	7 (11.1%)	11 (11.6%)
Relapse	28 (87.5%)	56 (88.9%)	84 (88.4%)
Baseline EDSS			
n	32	63	95
Mean (SD)	3.66 (1.61)	3.92 (1.50)	3.83 (1.54)
Min - Max	1.0 - 6.5	1.5 - 6.5	1.0 - 6.5
Median	3.50	4.00	3.50

Numbers analysed

The efficacy analyses were performed on the ITT population for each study (Table 12).

Table 12: Numbers analysed in study BN40898 and BN40900

	Study BN40898			**Study BN40900**		
Population	**Placebo (N=42) n (%)**	**SA237 (N=41) n (%)**	**Total (N=83) n (%)**	**Placebo (N=32) n (%)**	**SA237 (N=63) n (%)**	**Total (N=95) n (%)**
ITT	42 (100%)	41 (100%)	83 (100%)	32 (100%)	63 (100%)	95 (100%)
PPS	39 (92.9 %)	35 (85.4%)	74 (89.2%)	30 (93.8%)	56 (88.9%)	86 (90.5%)
All SA237	24 (57.1%)	41 (100%)	65 (78.3%)	17 (53.1%)	63 (100%)	80 (84.2%)
Safety-evaluable	42 (100%)	41 (100%)	83 (100%)	32 (100%)	63 (100%)	95 (100%)
PK PP	24 (57.1%)	41 (100%)	65 (78.3%)	17 (53.1%)	63 (100%)	80 (84.2%)
Adolescent	3 (7.1%)	4 (9.8%)	7 (8.4%)	NA	NA	NA

ITT= Intention-to-treat; PPS = per protocol set; PK= pharmacokinetics; NA = Not applicable ITT population summarized according to randomized treatment group. Safety population and other populations summarized according to received treatment.
Tables derived from CSR BN40898 Nr. 1089823, p.75 and CSR BN40900 Nr. 1089825, p.73

Outcomes and estimation

The data presented are based on the primary analysis conducted on the basis of the DB primary evaluation period of 24 weeks in each pivotal study.

In study BN40898, an analysis using the stratified log-rank test showed that treatment with SAT led to a statistically significant 62% reduction in the HR of experiencing a protocol-defined relapse compared to PCB.

Figure 9: Time to first relapse (PDR) during the DB period (ITT population) in the study BN40898, all patients

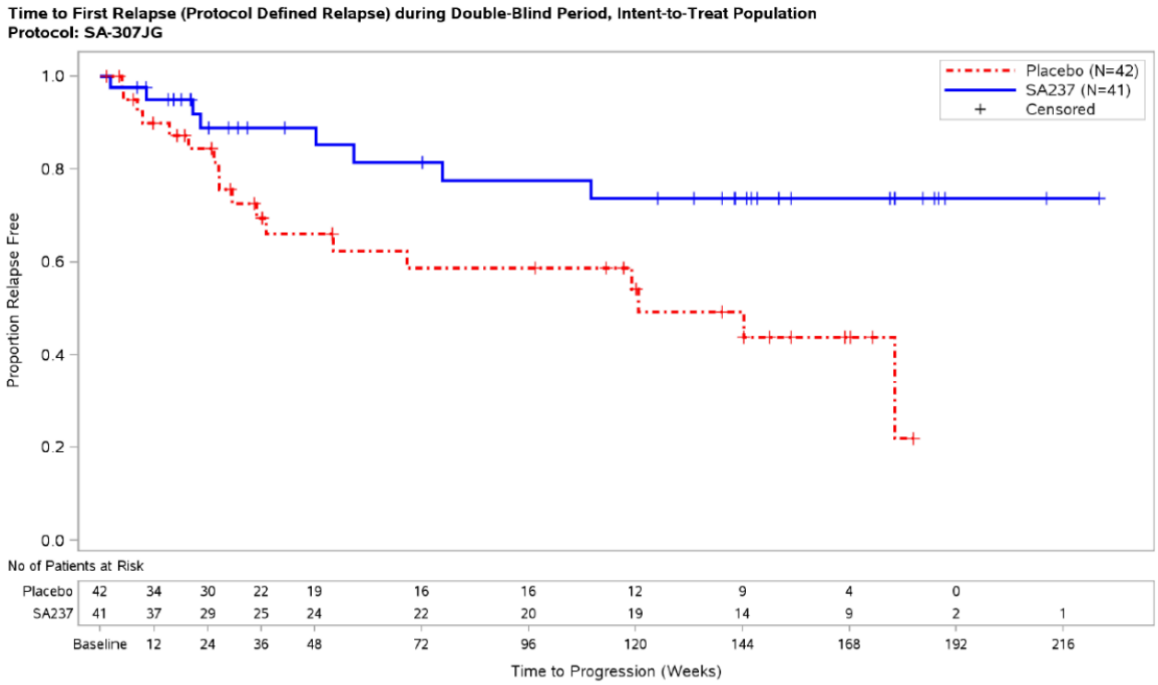


Table 1: Summary of primary efficacy endpoints of the study BN40898, all patients

Variable	Placebo N=42	Satralizumab N=41
Primary Endpoint		
Time to first PDR during DB period		
Hazard ratio (95% CI)		0.38 (0.16, 0.88)
p-value (Log-rank)		0.0184
Proportion of relapse-free patients at		
Week 48	66.02 %	88.86 %
Week 96	58.68 %	77.58 %

In study BN40890, an analysis using the stratified log-rank test showed that treatment with SAT led to a statistically significant 55% reduction in the HR of experiencing a protocol-defined relapse compared to PCB.

Figure 1: Time to first relapse (PDR) during the DB period (ITT population) in the study BN40900, all patients

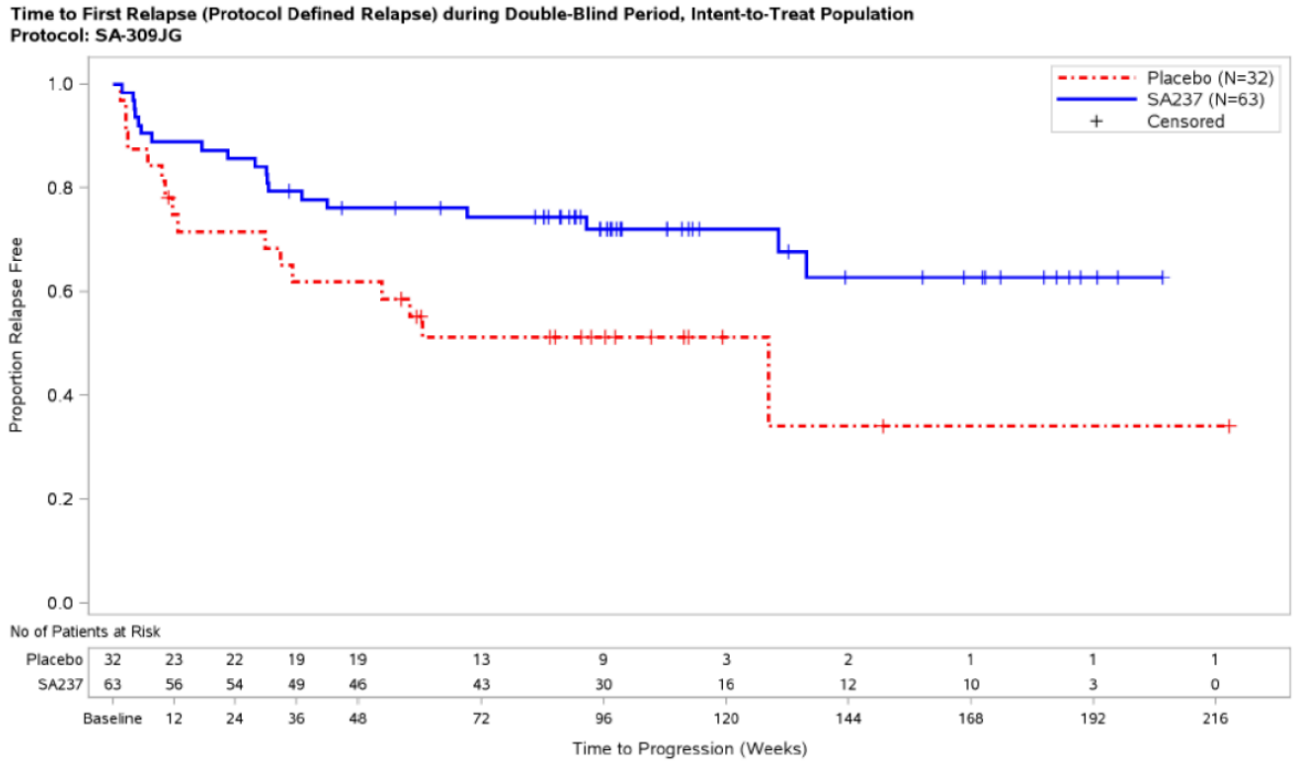


Table 2: Summary of primary efficacy endpoints of the study BN40900, all patients

Variable	Placebo N=32	Satralizumab N=63
Primary Endpoint		
Time to first PDR during DB period		
Hazard ratio (95% CI)		0.45 (0.23–0.89)
p-value (Log-rank)		0.0184
Proportion of relapse-free patients at		
Week 48	61.85 %	76.13 %
Week 96	51.21 %	72.14 %

In study BN40898 patients were censored if there was a change in baseline treatment or if they were treated with rescue treatment. Upon request, the Applicant presented a new analysis when time to first PDR, rescue medication and change in baseline medications were considered as events (Table 15

Table).

Table 3: Primary efficacy endpoint in study BN40989 when PDR, rescue medication and change in baseline therapy were considered as events, all patients

	Study BN40898 * (N=83)	
	Placebo (n=42)	Satralizumab (n=41)
Time to first PDR during DB period		
Patients with an event	28 (66.7%)	19 (46.3%)
Hazard ratio (95% CI)	0.60 (0.33, 1.08)	
p value (log-rank)	0.0847	
Proportion of relapse-free patients		
Week 48 (95% CI)	50.0% (33.68, 64.30)	66.5% (49.35, 79.04)
Week 96 (95% CI)	42.1% (26.60, 56.82)	58.1% (40.81, 71.93)

*Recue medication or increased dose of baseline treatment were considered as PDR Event

Sensitivity analyses were consistent with the primary analysis in the sense that the HR estimates were all below 1.00, in both studies. In study BN 40898, hardly any sensitivity analysis reached statistical significance (<0.05).

Table 16: Sensitivity analyses of primary efficacy endpoint of the study BN40898 during the DB period, all patients

Sensitivity Analysis	Patients with events (n)	Proportion of relapse free patients at Week 48 (%)	Hazard Ratio (95% CI)	p-value (Two sided log-rank test)
ITT Population (PLB: N=42, SAT: N=41)				
PDR based on EDSS/FSS Increase Relative to Baseline (summary and plot)	PLB: 19 SAT: 11	PLB: 61.83 SAT: 82.90	0.52 (0.25, 1.09)	0.0794
PDR Regardless of 7 Day Assessment Limit (summary and plot)	PLB: 19 SAT: 9	PLB: 64.02 SAT: 85.97	0.41 (0.19, 0.92)	0.0256
Clinical Relapse (summary and plot)	PLB: 27 SAT: 18	PLB: 50.57 SAT: 69.23	0.59 (0.33, 1.08)	0.0859
Treated Clinical Relapse (summary and plot)	PLB: 26 SAT: 18	PLB: 52.49 SAT:69.23	0.62 (0.34, 1.14)	0.1236
Treated Clinical Relapse: Optic Neuritis (summary and plot)	PLB: 11 SAT: 7	PLB: 75.47 SAT:81.34	0.59 (0.23, 1.52)	0.2665
Per-protocol population (PLB: N=39, SAT: N=35)				
PDR (summary and plot)	PLB: 18 SAT: 8	PLB: 63.69 SAT: 86.87	0.40 (0.17, 0.93)	0.0286

EDSS=Expanded Disability Status Scale; FSS=Functional System Score; DPR=Protocol Defined Relapse; TFR=Time to first relapse

Table 17: Sensitivity analyses of primary efficacy endpoint of the study BN40900 during the DB period, all patients

Sensitivity Analysis	Patients with events (n)	Proportion of relapse free patients at Week 48 (%)	Hazard Ratio (95% CI)	p-value (Two sided log-rank test)
ITT Population (PLB: N=32, SAT: N=63)				
PDR censored by affecting medications* (summary and plot)	PLB: 16 SAT: 19	PLB: 61.57 SAT: 75.72	0.45 (0.23, 0.89)	0.0194
PDR Regardless of 7 Day EDSS Assessment Limit (summary and plot)	PLB: 16 SAT: 21	PLB: 61.85 SAT: 76.13	0.49 (0.25, 0.95)	0.0301
Clinical Relapse (summary and plot)	PLB: 17 SAT: 31	PLB: 56.25 SAT: 64.94	0.74 (0.41, 1.35)	0.3212
Treated Clinical Relapse (summary and plot)	PLB: 17 SAT: 21	PLB: 56.25 SAT:74.24	0.46 (0.24, 0.88)	0.0158
Treated Clinical Relapse: Optic Neuritis (summary and plot)	PLB: 7 SAT: 8	PLB: 74.65 SAT: 91.70	0.43 (0.15, 1.20)	0.0975
TFR based on PDR during DB period using weighted log-rank test (summary)	PLB: 16 SAT: 19	-	-	0.0252
Per-protocol population (PLB: N=30, SAT: N=56)				
PDR (summary and plot)	PLB: 16 SAT: 16	PLB: 59.24 SAT: 76.79	0.40 (0.20, 0.81)	0.0082

Censored at the first start date of the following medication: 1. Relapse prevention therapy, 2 Rescue therapy, 3 Systemic administration of steroid for other indication form more than 5 days. EDSS=Expanded Disability Status Scale; FSS=Functional System Score; DPR=Protocol Defined Relapse; TFR=Time to first relapse

Key secondary efficacy endpoints

The key secondary endpoints for the change in pain and fatigue are not met in any of the two pivotal trials.

Table 18: Summary of key secondary endpoints of the study BN40898 and BN40900, all patients

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

Other secondary efficacy endpoints

ARR using the first relapses for PDRs in study BN40898 was 0.11 (95% CI 0.05-0.21) unadjusted in the verum arm vs. 0.32 (95% CI 0.19-0.51) in the placebo arm, giving a 74% reduction in adjusted ARR (adjusted ARR ratio 0.261; 95% CI 0.087,0.787; p=0.0175).

ARR using the first relapses for PDRs in study BN40900 was 0.17 (95% CI 0.10-0.26) unadjusted in the verum arm vs. 0.41 (95% CI 0.19-0.51) in the placebo arm, giving a 73% reduction in adjusted ARR (adjusted ARR ratio 0.275; p=0.0668).

Ancillary analyses

To identify potential prognostic factors, a Cox regression for time to PDR in patients treated with PCB (N=74) was conducted. BW ≥ median (vs. below median) (HR=1.58 95% CI(0.79, 3.16) p=0.1950) and AQP4-IgG seronegative (versus seropositive) (HR=0.60 95% CI(0.28, 1.31) p=0.1984) were identified as possible negative prognostic factors.

Results by Aquaporin-4-Immunoglobulin G Serostatus

Patients who were AQP4-IgG-seropositive at baseline had a higher risk of relapses and a lower HR than those who were AQP4-IgG-seronegative. Therefore, AQP4-IgG serostatus appears to be both prognostic and predictive. Further subgroup analyses for time to PDR were performed.

Figure 2: Time to First PDR during the DB Period in AQP4-seropositive Patients in Study BN40898

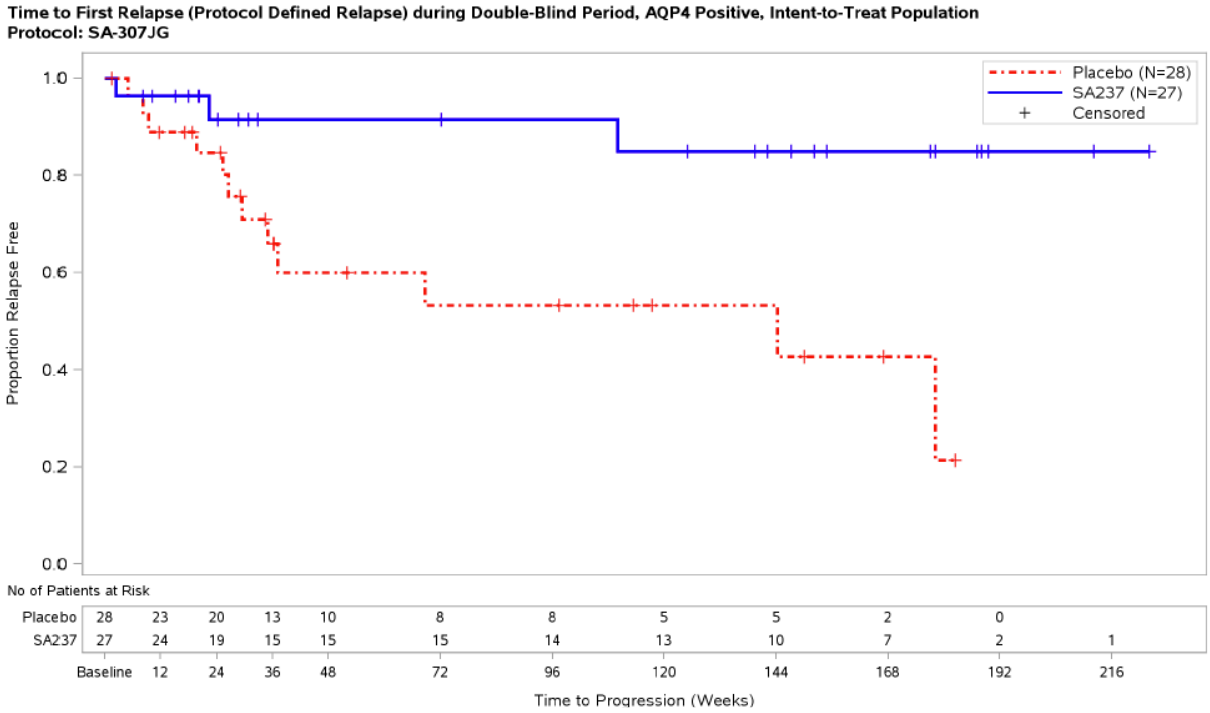


Figure 3: Time to First PDR during the DB Period in AQP4-seronegative Patients in Study BN40898

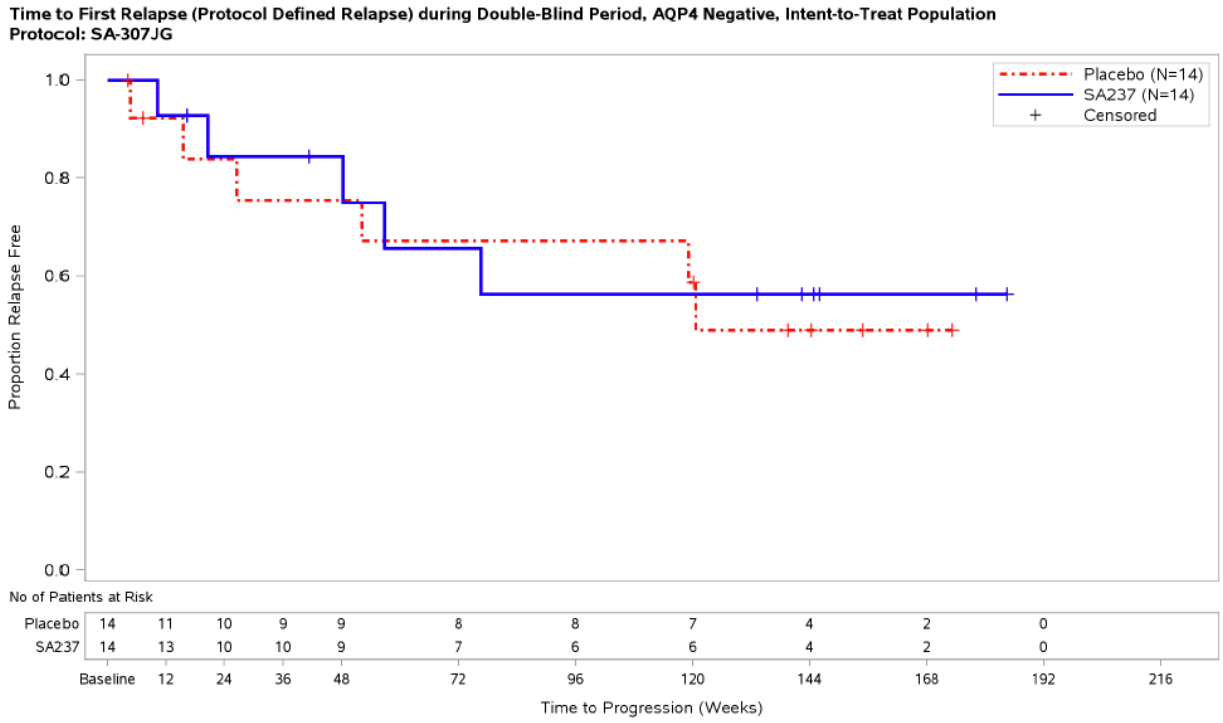


Figure 4: Time to First PDR during the DB Period in AQP4-seropositive Patients in Study BN40900

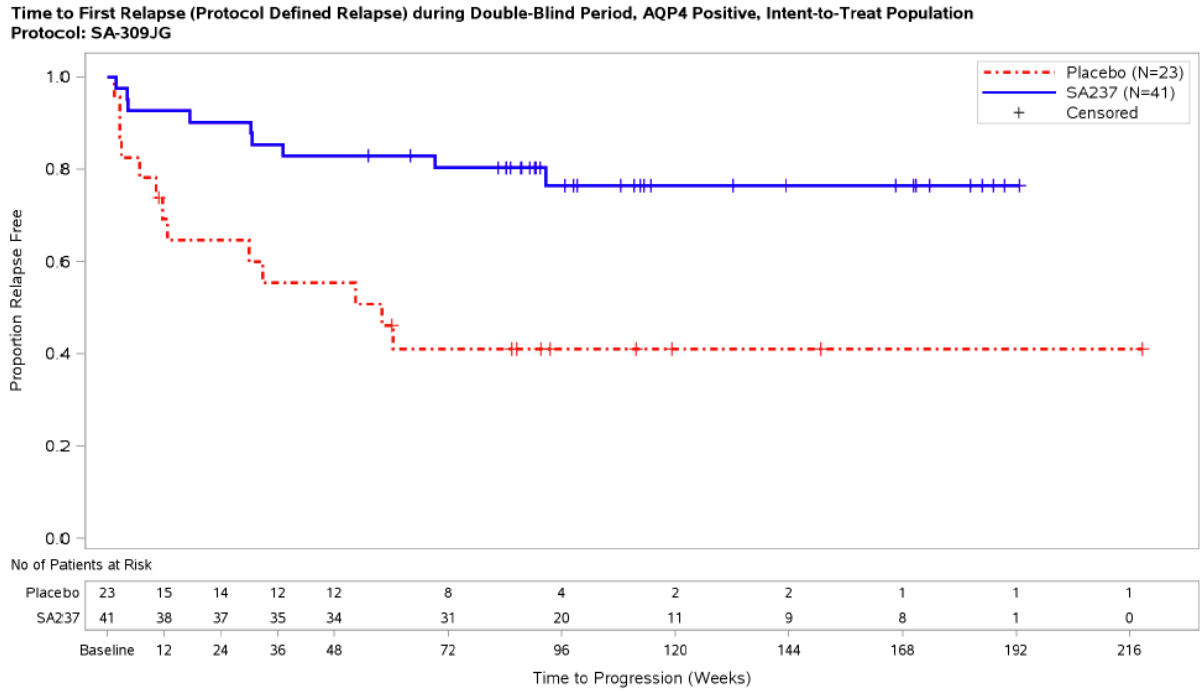
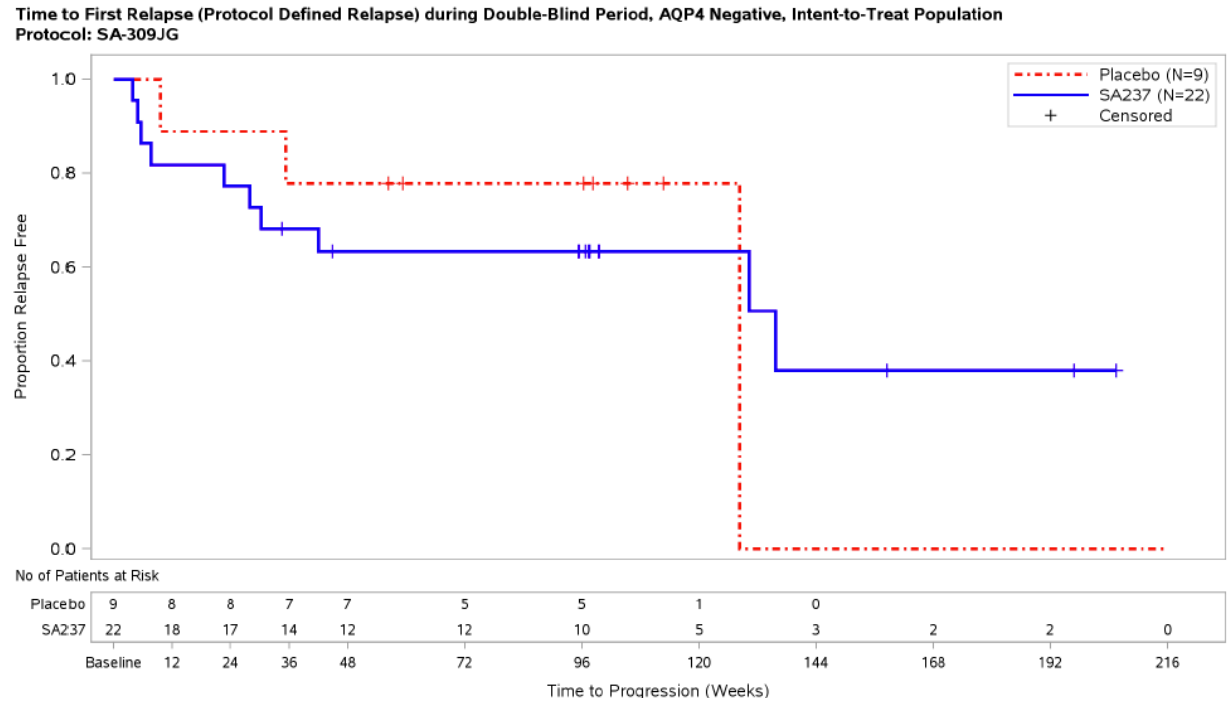


Figure 5: Time to First PDR during the DP Period in AQP4-seronegative Patients in Study BN40900



When data across studies BN40898 and BN40900 were pooled, treatment with satralizumab led to an overall HR of 0.25 [95% CI]; (0.12-0.50]) in AQP4-IgG-seropositive patients. Differences in the time to first PDR in AQP4-IgG seronegative patients between those patients receiving satralizumab and those receiving placebo were not significant (Table 19).

Table 19: Time to First PDR during the DB Period by Aquaporin-4 Status in Studies BN40898 and BN40900

	Study BN40898 (N=83)		Study BN40900 (N=95)		Studies BN40898 and BN40900 Pooled (N=178)	
	Placebo (n=42)	Satralizumab (n=41)	Placebo (n=32)	Satralizumab (n=63)	Placebo (n=74)	Satralizumab (n=104)
AQP4-IgG-seropositive						
	n=28	n=27	n=23	n=41	n=51	n=68
Patients with an event	12 (42.9%)	3 (11.1%)	13 (56.5%)	9 (22.0%)	25 (49.0%)	12 (17.6%)
Hazard ratio (95% CI)	0.21 (0.06, 0.75)		0.26 (0.11, 0.63)		0.25 (0.12, 0.50)	
p-value (log-rank)	0.0086		0.0014		<0.0001	
AQP4-IgG-seronegative						
	n=14	n=14	n=9	n=22	n=23	n=36
Patients with an event	6 (42.9%)	5 (35.7%)	3 (33.3%)	10 (45.5%)	9 (39.1%)	15 (41.7%)
Hazard ratio (95% CI)	0.66 (0.20, 2.23)		1.19 (0.30, 4.78)		0.97 (0.41, 2.33)	
p-value (log-rank)	0.5047		0.8036		0.9540	

Upon request, the Applicant provided sensitivity analysis for efficacy endpoints for AQP4-IgG seropositive patients (Figure 15 and

Figure 16). For AQP4-IgG seropositive patients in Study BN40898, the Applicant has been requested to provide two additional analyses (i) counting time to first PDR, rescue medication and change in baseline medications as events and (ii) when only time to first PDR and rescue treatment were considered events. The corresponding analyses yielded (i) a HR of 0.55 (CI 0.26, 1.14) and (ii) a HR of 0.51 (CI 0.24, 1.10).

Figure 6: Time to first relapse during the double-blind period, study BN40898 AQP4-IgG positive patients

Time to Relapse	Total	Placebo (N=28)		SA237 (N=27)					Plot Hazard Ratio + 95% CI
	n	n	Events	n	Events	Hazard Ratio	95% CI	p-value (Log-rank)	
PDR (Primary)	55	28	12	27	3	0.208	(0.058, 0.750)	0.0086	
PDR (Regardless of EDSS/FSS Assessment Limit of 7 Days)	55	28	13	27	4	0.266	(0.085, 0.831)	0.0151	
PDR (As per Investigator Assessment captured on CRF)	55	28	14	27	6	0.371	(0.140, 0.983)	0.0387	
Treated Clinical Relapse	55	28	18	27	11	0.573	(0.267, 1.229)	0.1477	
Clinical Relapse	55	28	19	27	11	0.528	(0.248, 1.124)	0.0924	

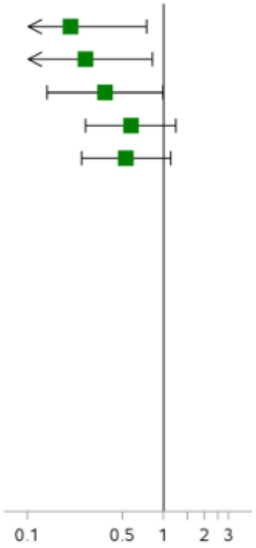
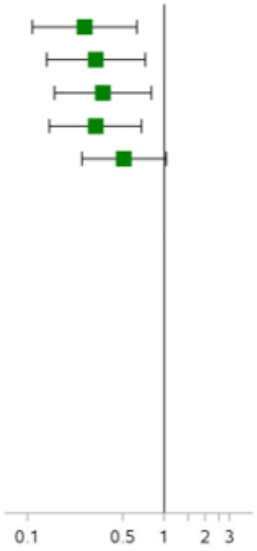


Figure 7: Time to first relapse during the double-blind period, study BN40900 AQP4-IgG positive patients

Time to Relapse	Total	Placebo (N=23)		SA237 (N=41)		Hazard Ratio	95% CI	p-value (Log-rank)	Plot Hazard Ratio + 95% CI
	n	n	Events	n	Events				
PDR (Primary)	64	23	13	41	9	0.261	(0.108, 0.627)	0.0014	
PDR (Regardless of EDSS/FSS Assessment Limit of 7 Days)	64	23	13	41	11	0.315	(0.137, 0.724)	0.0044	
PDR (As per Investigator Assessment captured on CRF)	64	23	13	41	12	0.356	(0.158, 0.802)	0.0098	
Treated Clinical Relapse	64	23	14	41	13	0.313	(0.144, 0.680)	0.0021	
Clinical Relapse	64	23	14	41	19	0.506	(0.248, 1.031)	0.0561	



Results by Region

When data across studies BN40898 and BN40900 were pooled, treatment with satralizumab led to a HR of 0.09 (95% CI): (0.01, 0.70) in patients from Asia, HR 0.42 (95% CI): 0.42 (0.19, 0.93) in Europe/Other, and a HR of 0.70 (95% CI): (0.28, 1.70) for patients from North America.

Some imbalances could be confounding factors that could have contributed to a lower efficacy in the overall population in North America, for example, differences in the proportion of black patients, BW differences and AQP4-IgG serostatus.

Results by Race

When data across the two studies were pooled, treatment with satralizumab led to a HR of 0.14 (95% CI): (0.03, 0.62) in Asian patients and a HR of 0.38 (95% CI): (0.20, 0.74) in white patients. The number of black patients included in the studies was small and, therefore, a HR for this subgroup could not be determined. Of the 13 black patients receiving satralizumab, 7 (53.8%) experienced a PDR, and in the 5 receiving placebo, 1 (20.0%) experienced a PDR.

Results by body weight

In study BN40898, results for the different BW quartiles were variable showing no evident trend. In study BN40900, results were consistent across all BW quartiles. Thus, while BW was shown to possibly be a negative prognostic factor, it did not seem to be predictive of treatment effect.

Results by Anti-drug Antibody Status

In Study BN40898, ADAs were detected in 17 out of 41 patients (41.5%) treated with satralizumab during the DB period. In Study BN40900, ADAs were detected in 45 out of 63 patients (71.4%) treated with satralizumab during the DB period (Table 20).

Table 4: Time to First PDR during the DB Period by ADA Status for the Pooled Patient Population of Study BN40898 and BN40900, all patients

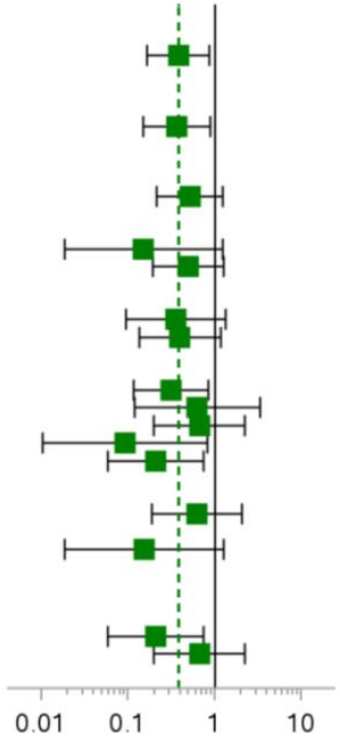
	Study BN40898 (N=83)			Study BN40900 (N=95)		
	Placebo (n=42)	Satralizumab (n=41)		Placebo (n=32)	Satralizumab (n=63)	
		ADA Negative (n=24)	**ADA Positive (n=17)**		**ADA Negative (n=18)**	**ADA Positive (n=45)**
Patients with an event	18 (42.9%)	3 (12.5%)	5 (29.4%)	16 (50.0%)	5 (27.8%)	14 (31.1%)
Hazard ratio (95% CI)		0.22 (0.06, 0.75)	0.68 (0.24, 1.86)		0.50 (0.18, 1.40)	0.43 (0.20, 0.91)
p value (log-rank)		0.0082	0.1200		0.0584	0.0242

Other Subgroup Analyses

There was a directionally consistent treatment effect with HR<1 in most subgroups (HR <1) (Table 21 Table 22).

Table 5: Time to first PDR during the DB Period by Subgroup, study BN40898, all patients

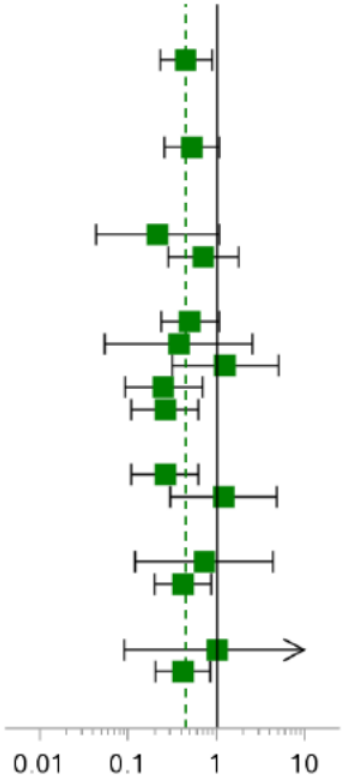
Baseline Risk Factors	Total	Placebo (N=42)		SA237 (N=41)						Plot Hazard Ratio + 95% CI
	n	n	Events	n	Events	Hazard Ratio	95% CI	p-value (Log-rank)	Interaction p-value	
All Patients	83	42	18	41	8	0.378	(0.164, 0.875)	0.0184		
Age Category									0.9374	
<18	7	3	1	4	1	0.000	(0.000, NE)	0.1573		
>=18	76	39	17	37	7	0.362	(0.149, 0.878)	0.0192		
Race Category									0.0965	
Japanese	21	10	3	11		0.000	(0.000, NE)	0.0499		
Non-Japanese	62	32	15	30	8	0.514	(0.213, 1.244)	0.1337		
Region*									0.2688	
ASIA	34	18	7	16	1	0.150	(0.018, 1.231)	0.0419		
EUROPE/OTHER	49	24	11	25	7	0.495	(0.191, 1.283)	0.1400		
Baseline ARR**									0.8994	
1	40	20	8	20	3	0.354	(0.094, 1.341)	0.1105		
>1	43	22	10	21	5	0.396	(0.134, 1.167)	0.0823		
NMO/NMOSD and AQP4 Status									0.4069***	
NMO	61	28	12	33	6	0.314	(0.115, 0.852)	0.0169		
NMOSD	22	14	6	8	2	0.628	(0.118, 3.329)	0.5813		
NMO and AQP4 Negative	28	14	6	14	5	0.663	(0.197, 2.235)	0.5047		
NMO and AQP4 Positive	33	14	6	19	1	0.092	(0.010, 0.827)	0.0110		
NMO/NMOSD and AQP4 Positive	55	28	12	27	3	0.208	(0.058, 0.750)	0.0086		
Baseline Treatment									0.4773	
AZATHIOPRINE	29	13	7	16	5	0.621	(0.188, 2.051)	0.4307		
MYCOPHENOLATE MOFETIL	12	8	2	4	1	0.000	(0.000, NE)	0.1025		
ORAL CSs	37	20	8	17	1	0.152	(0.018, 1.253)	0.0462		
AZATHIOPRINE+ORAL CSs	3			3	1	NE	(NE , NE)	NE		
MYCOPHENOLATE MOFETIL+ORAL CSs	2	1	1	1		0.000	(0.000, NE)	0.3173		
AQP4 Status - ELISA									0.1469	
Positive	55	28	12	27	3	0.208	(0.058, 0.750)	0.0086		
Negative	28	14	6	14	5	0.663	(0.197, 2.235)	0.5047		



AQP4: Aquaporin-4, ARR: Annualised Relapse Rate. ELISA: Enzyme-Linked Immunosorbent Assay. NMO= Neuromyelitis Optica; NMOSD= Neuromyelitis Optica Spectrum Disorders; ORAL CSs= Oral Corticosteorids.
Protocol Defined Relapse: Adjudicated by the Clinical Endpoint Committee, EDSS assessment performed within 7 days of relapse reporting.
Model is stratified by baseline ARR (1, >1) and geographical region (Asia, Europe/other).
*Stratified by baseline ARR only ** Stratified by geographic region only. *** Interaction p-value only for NMO vs. NMOSD subgroups.

Table 6: Time to first PDR during the DB Period by Subgroup, study BN40900, all patients

Baseline Risk Factors	Total	Placebo (N=32)		SA237 (N=63)		Hazard Ratio	95% CI	p-value (Log-rank)	Interaction p-value	Plot Hazard Ratio + 95% CI
	n	n	Events	n	Events					
All Patients	95	32	16	63	19	0.450	(0.228, 0.889)	0.0184		
Geographic Region1									0.0709	
ASIA	10	5	3	5		0.000	(0.000, NE)	0.0101		
EUROPE/US/OTHER	85	27	13	58	19	0.519	(0.252, 1.068)	0.0701		
Geographic Region2									0.1068	
ASIA	10	5	3	5		0.000	(0.000, NE)	0.0101		
EUROPE/OTHER	27	11	6	16	3	0.212	(0.043, 1.056)	0.0371		
NORTH AMERICA	58	16	7	42	16	0.706	(0.285, 1.749)	0.4502		
NMO/NMOSD and AQP4 Status									0.6013***	
NMO	71	24	13	47	17	0.496	(0.234, 1.048)	0.0611		
NMOSD	24	8	3	16	2	0.369	(0.054, 2.539)	0.2986		
NMO and AQP4 Negative	30	9	3	21	10	1.250	(0.312, 5.005)	0.7525		
NMO and AQP4 Positive	41	15	10	26	7	0.251	(0.091, 0.689)	0.0043		
NMO/NMOSD and AQP4 Positive	64	23	13	41	9	0.261	(0.108, 0.627)	0.0014		
Anti-AQP4 Status									0.0223	
POSITIVE	64	23	13	41	9	0.261	(0.108, 0.627)	0.0014		
NEGATIVE	31	9	3	22	10	1.192	(0.298, 4.775)	0.8036		
Prior therapy*									0.5790	
B-CELL DEPLETING THERAPY	12	4	2	8	3	0.715	(0.119, 4.296)	0.7130		
IMMUNOSUPPRESANTS/OTHERS	83	28	14	55	16	0.415	(0.199, 0.868)	0.0159		
Most recent attack**									0.4842	
FIRST ATTACK	11	4	1	7	3	0.995	(0.090, 11.018)	0.9970		
RELAPSE	84	28	15	56	16	0.417	(0.205, 0.851)	0.0132		



AQP4: Aquaporin-4, ARR: NMO= Neuromyelitis Optica; NMOSD= Neuromyelitis Optica Spectrum Disorders.
Protocol Defined Relapse: Adjudicated by the Clinical Endpoint Committee, EDSS assessment performed within 7 days of relapse reporting.
Model is stratified by prior therapy (B-cell depletting therapy or immunosuppressants/Others) and most recent attack (first attack or relapse).
*Stratified by most recent attack only ** Stratified by prior therapy only. *** Interaction p-value only for NMO vs. NMOSD subgroups.

Persistence of efficacy and/or tolerance effects

Maintenance of efficacy was analysed based on data from the DB period and the OLE and includes only patients initially randomized to satralizumab. Thus, data over a period of up to 4 years are available for the evaluation of long-term efficacy. The ARR by year for treated clinical relapses over the combined DB and OLE period for patients originally assigned to satralizumab was assessed (Table 23). No patients receiving satralizumab withdrew from the OLE due to a clinical relapse.

Table 23: ARR (Treated Clinical Relapse) by Year in those Randomized to Satralizumab in the Pooled ITT Population of Studies BN40898 and BN40900

	SA237 (N=104)
Overall	
Number of patients at risk	104
Number of patients with relapse	39
Number of relapses	65
Total patient-years followed	255.8
Unadjusted annualized relapse rate *	0.254
Adjusted annualized relapse rate **	0.2522
95% CI of adjusted annualized relapse rate	(0.1918, 0.3316)
Year 1	
Number of patients at risk	104
Number of patients with relapse	29
Number of relapses	39
Total patient-years followed	99.9
Unadjusted annualized relapse rate *	0.390
Adjusted annualized relapse rate **	0.3989
95% CI of adjusted annualized relapse rate	(0.2818, 0.5647)
Year 2	
Number of patients at risk	95
Number of patients with relapse	12
Number of relapses	15
Total patient-years followed	84.6
Unadjusted annualized relapse rate *	0.177
Adjusted annualized relapse rate **	0.2032
95% CI of adjusted annualized relapse rate	(0.1219, 0.3387)
Year 3	
Number of patients at risk	64
Number of patients with relapse	6
Number of relapses	9
Total patient-years followed	51.6
Unadjusted annualized relapse rate *	0.174
Adjusted annualized relapse rate **	0.1485
95% CI of adjusted annualized relapse rate	(0.0630, 0.3500)
Year 4	
Number of patients at risk	38
Number of patients with relapse	2
Number of relapses	2
Total patient-years followed	19.6
Unadjusted annualized relapse rate *	0.102
Adjusted annualized relapse rate **	0.0819
95% CI of adjusted annualized relapse rate	(0.0200, 0.3360)

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as

well as the benefit risk assessment (see later sections).

Table 24: Summary of efficacy for trial BN40898 (AQP4 seronegative and seropositive patients)

Title: A Multicenter, Randomized, Addition to Baseline Treatment, Double-Blind, Placebo-Controlled, Phase III Study to Evaluate the Efficacy and Safety of Satralizumab in Patients with Neuromyelitis Optica (NMO) and NMO Spectrum Disorder (NMOSD)				
Study identifier	BN40898			
Design	Multicenter, randomized, double-blind, placebo-controlled, parallel-group, add-on study (AQP4 seronegative and seropositive patients)			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Time to event study (time to first relapse) Not applicable At least 48 weeks	
Hypothesis	Superiority			
Treatment groups	Satralizumab (+baseline treatment)		Satralizumab 120 mg SC at Week 0, 2, and 4 and thereafter every 4 weeks. N = 41 patients (4 adolescents)	
	Placebo (+baseline treatment)		Matching treatment N= 42 patients (3 adolescents)	
Endpoints and definitions	Primary endpoint	Time to first relapse based on PDR	Time to First Relapse (TFR) based on Clinical Endpoint Committee (CEC) confirmed Protocol-Defined Relapse (PDR) during DB period	
	Secondary endpoint	Change in VAS for pain score	Change in VAS for pain score from baseline to Week 24	
	Secondary endpoint	Change in FACIT fatigue scale score	Change in FACIT fatigue scale score from baseline to Week 24	
Database lock	06 June 2018			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat (AQP4 seronegative and seropositive patients)			
Descriptive statistics and estimate variability	Treatment group		Placebo	Satralizumab
	Number of subjects		42	41
	Time to first PDR during DB period (weeks)		120.6 (median) (37.0, NE) 18 (42.9%) event	NE NE 8 (19.5%) event
	Proportion relapse-free patients Week 48 Week 96		 66.0% 58.7%	 88.9% 77.6%
Effect estimate per comparison	Primary endpoint		Comparison groups	
			Hazard ratio	0.38
			95%CI	0.16, 0.88
			P-value (Log-rank)	0.0184
Analysis description	**Sensitivity analysis (all relapses reported by investigators=clinical relapse)**			
Analysis population and time point description	Intent to treat (AQP4 seronegative and seropositive patients)			
Descriptive statistics and estimate variability	Treatment group		Placebo	Satralizumab
	Number of subjects		42	41

	Time to first clinical relapse (weeks)	52.1 (median) (26.4, 144.3) 27 (64.3%) event	NE (median) (22.3 -NE) 18 (43.9%) event
	Proportion relapse-free patients Week 48 Week 96	 50.6% 45.0%	 69.2% 60.4%
Effect estimate per comparison	Primary endpoint	Comparison groups	
		Hazard ratio	0.59
		95% CI	0.33, 1.08
		P-value (Log-rank)	0.0859
Analysis description	**Secondary analysis**		
Analysis population and time point description	Intent to treat (AQP4 seronegative and seropositive patients)		
Descriptive statistics and estimate variability	Treatment group	Placebo	Satralizumab
	Number of subjects	42	41
	Change in VAS pain baseline to Week 24 (BOCF)	-3.505 (2.357) Adjusted mean (SE)	2.871 (2.391) Adjusted mean (SE)
	95% CI	-8.198, 1.188	-1.890, 7.632
Effect estimate per comparison	Treatment effect (ANCOVA)	Comparison groups	
		Δ adjusted mean (SE)	6.376 (3.344)
		95% CI	-0.280, 13.033
		P-value	0.0602
Descriptive statistics and estimate variability	Treatment group	Placebo	Satralizumab
	Number of subjects	42	41
	Change in FACIT Fatigue baseline to Week 24 (BOCF)	2.234 (0.943) Adjusted mean (SE)	0.145 (0.963) Adjusted mean (SE)
	95% CI	0.356, 4.112	-1.772, 2.061
Effect estimate per comparison	Treatment effect (ANCOVA)	Comparison groups	
		Δ adjusted mean (SE)	-2.089 (1.338)
		95% CI	-4.752, 0.574
		P-value	0.1224
Notes			

Table 7: Summary of efficacy for trial BN40900 (AQP4 seronegative and seropositive patients)

Title: A Multicenter, Randomized, Double-Blind, Placebo-controlled, Phase III Study to Evaluate the Efficacy and Safety of Satralizumab as Monotherapy in Patients with Neuromyelitis Optica (NMO) and Neuromyelitis Optica Spectrum Disorder (NMOSD)		
Study identifier	BN40900	
Design	Multicenter, randomized, double-blind, placebo-controlled, parallel-group study (AQP4 seronegative and seropositive patients)	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Time to event study (time to first relapse) Not applicable At least 96 weeks
Hypothesis	Superiority	
Treatment groups	Satralizumab	Satralizumab 120 mg SC at Week 0, 2, and 4 and thereafter every 4 weeks. N = 63 patients
	Placebo	Matching treatment N= 32 patients

Endpoints and definitions	Primary endpoint	Time to first relapse based on PDR	Time to First Relapse (TFR) based on Clinical Endpoint Committee (CEC) confirmed Protocol-Defined Relapse (PDR) during DB period	
	Secondary endpoint	Change in VAS for pain score	Change in VAS for pain score from baseline to Week 24	
	Secondary endpoint	Change in FACIT fatigue scale score	Change in FACIT fatigue scale score from baseline to Week 24	
Database lock	12 October 2018			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat (AQP4 seronegative and seropositive patients)			
Descriptive statistics and estimate variability	Treatment group		Placebo	Satralizumab
	Number of subjects		32	63
	Time to first PDR during DB period (weeks)		128.3 (median) (29.9, NE) 16 (50.0%) event	NE (135.7, NE) 19 (30.2%) event
	Proportion relapse-free patients Week 48 Week 96		 61.9% 51.2%	 76.1% 72.1%
Effect estimate per comparison	Primary endpoint		Comparison groups	
			Hazard ratio	0.45
			95%CI	0.23, 0.89
			P-value (Log-rank)	0.0184
Analysis description	**Sensitivity analysis (all relapses reported by investigators=clinical relapse)**			
Analysis population and time point description	Intent to treat (AQP4 seronegative and seropositive patients)			
Descriptive statistics and estimate variability	Treatment group		Placebo	Satralizumab
	Number of subjects		32	63
	Time to first clinical relapse (weeks)		60.4 (median) (11.7, NE) 17 (53.1%) event	135.7 (median) (56.1 -NE) 31 (49.2%) event
	Proportion relapse-free patients Week 48 Week 96		 56.3% 49.3%	 64.9% 54.6%
Effect estimate per comparison	Primary endpoint		Comparison groups	
			Hazard ratio	0.74
			95% CI	0.41, 1.35
			P-value (Log-rank)	0.3212
Analysis description	**Secondary analysis** (AQP4 seronegative and seropositive patients)			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group		Placebo	Satralizumab
	Number of subjects		32	63
	Change in VAS pain baseline to Week 24 (BOCF)		-5.949 (4.832) Adjusted mean (SE)	-2.735 (4.260) Adjusted mean (SE)
	95% CI		-15.550, 3.652	-11.199, 5.730

Effect estimate per comparison	Treatment effect (ANCOVA)	Comparison groups	
		Δ adjusted mean (SE)	3.215 (4.178)
		95% CI	-5.086, 11.515)
		P-value	0.4436
Descriptive statistics and estimate variability	Treatment group	Placebo	Satralizumab
	Number of subjects	32	63
	Change in FACIT Fatigue baseline to Week 24 (BOCF)	3.602 (1.820) Adjusted mean (SE)	5.709 (1.610) Adjusted mean (SE)
	95% CI	-0.013, 7.218	2.510, 8.907
Effect estimate per comparison	Treatment effect (ANCOVA)	Comparison groups	
		Δ adjusted mean (SE)	2.107 (1.567)
		95% CI	-1.008, 5.221
		P-value	0.1824
Notes			

Table 26: Summary of efficacy for trial BN40898 (AQP4 seropositive patients)

Title: A Multicenter, Randomized, Addition to Baseline Treatment, Double-Blind, Placebo-Controlled, Phase III Study to Evaluate the Efficacy and Safety of Satralizumab in Patients with Neuromyelitis Optica (NMO) and NMO Spectrum Disorder (NMOSD)			
Study identifier	BN40898		
Design	Multicenter, randomized, double-blind, placebo-controlled, parallel-group, add-on study (AQP4 seropositive patients)		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Time to event study (time to first relapse) Not applicable At least 48 weeks
Hypothesis	Superiority		
Treatment groups	Satralizumab (+baseline treatment)		Satralizumab 120 mg SC at Week 0, 2, and 4 and thereafter every 4 weeks. N = 27 patients (1 adolescent)
	Placebo (+baseline treatment)		Matching treatment N= 28 patients (2 adolescents)
Endpoints and definitions	Primary endpoint	Time to first relapse based on PDR	Time to First Relapse (TFR) based on Clinical Endpoint Committee (CEC) confirmed Protocol-Defined Relapse (PDR) during DB period
	Secondary endpoint	Change in VAS for pain score	Change in VAS for pain score from baseline to Week 24
	Secondary endpoint	Change in FACIT fatigue scale score	Change in FACIT fatigue scale score from baseline to Week 24
Database lock	06 June 2018		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (AQP4 seropositive patients)		
Descriptive statistics and estimate variability	Treatment group	Placebo	Satralizumab
	Number of subjects	28	27
	Time to first PDR during DB period (weeks)		

	Proportion relapse-free patients	57,1%	88.9%
Effect estimate per comparison	Primary endpoint	Comparison groups	
		Hazard ratio	0.21
		95%CI	0.058, 0.75
		P-value (Log-rank)	0.0086
Analysis description	**Sensitivity analysis (all relapses reported by investigators=clinical relapse)**		
Analysis population and time point description	Intent to treat (AQP4 seropositive patients)		
Descriptive statistics and estimate variability	Treatment group	Placebo	Satralizumab
	Number of subjects	28	27
	Time to first clinical relapse (weeks)		
	Proportion relapse-free patients		
Effect estimate per comparison	Primary endpoint	Comparison groups	
		Hazard ratio	0.53
		95% CI	0.25, 1.12
		P-value (Log-rank)	0.092
Analysis description	**Secondary analysis**		
Analysis population and time point description	Intent to treat (AQP4 seropositive patients)		
Descriptive statistics and estimate variability	Treatment group	Placebo	Satralizumab
	Number of subjects	28	27
	Change in VAS pain baseline to Week 24 (BOCF)		
	95% CI		
Effect estimate per comparison	Treatment effect (ANCOVA)	Comparison groups	
		Δ adjusted mean (SE)	
		95% CI	
		P-value	
Descriptive statistics and estimate variability	Treatment group	Placebo	Satralizumab
	Number of subjects	28	27
	Change in FACIT Fatigue baseline to Week 24 (BOCF)		
	95% CI		
Effect estimate per comparison	Treatment effect (ANCOVA)	Comparison groups	
		Δ adjusted mean (SE)	
		95% CI	
		P-value	
Notes			

Table 27: Summary of efficacy for trial BN40900 (AQP4 seropositive patients)

Title: A Multicenter, Randomized, Double-Blind, Placebo-controlled, Phase III Study to Evaluate the Efficacy and Safety of Satralizumab as Monotherapy in Patients with Neuromyelitis Optica (NMO) and Neuromyelitis Optica Spectrum Disorder (NMOSD)	
Study identifier	BN40900

Design	Multicenter, randomized, double-blind, placebo-controlled, parallel-group study (AQP4 seropositive patients)		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Time to event study (time to first relapse) Not applicable At least 96 weeks
Hypothesis	Superiority		
Treatment groups	Satralizumab		Satralizumab 120 mg SC at Week 0, 2, and 4 and thereafter every 4 weeks. N = 41 patients
	Placebo		Matching treatment N= 23 patients
Endpoints and definitions	Primary endpoint	Time to first relapse based on PDR	Time to First Relapse (TFR) based on Clinical Endpoint Committee (CEC) confirmed Protocol-Defined Relapse (PDR) during DB period
	Secondary endpoint	Change in VAS for pain score	Change in VAS for pain score from baseline to Week 24
	Secondary endpoint	Change in FACIT fatigue scale score	Change in FACIT fatigue scale score from baseline to Week 24
Database lock	12 October 2018		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (AQP4 seropositive patients)		
Descriptive statistics and estimate variability	Treatment group	Placebo	Satralizumab
	Number of subjects	23	41
	Time to first PDR during DB period (weeks)		
	Proportion relapse-free patients	43.5%	78.0%
Effect estimate per comparison	Primary endpoint	Comparison groups	
		Hazard ratio	0.26
		95%CI	0.11, 0.63
		P-value (Log-rank)	0.0014
Analysis description	**Sensitivity analysis (all relapses reported by investigators=clinical relapse)**		
Analysis population and time point description	Intent to treat (AQP4 seropositive patients)		
Descriptive statistics and estimate variability	Treatment group	Placebo	Satralizumab
	Number of subjects	23	41
	Time to first clinical relapse (weeks)		
	Proportion relapse-free patients		
Effect estimate per comparison	Primary endpoint	Comparison groups	
		Hazard ratio	0.51
		95% CI	0.25, 1.03
		P-value (Log-rank)	0.056
Analysis description	**Secondary analysis** (AQP4 seropositive patients)		

Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Placebo	Satralizumab
	Number of subjects	23	41
	Change in VAS pain baseline to Week 24 (BOCF)		
	95% CI		
Effect estimate per comparison	Treatment effect (ANCOVA)	Comparison groups	
		Δ adjusted mean (SE)	
		95% CI	
		P-value	
Descriptive statistics and estimate variability	Treatment group	Placebo	Satralizumab
	Number of subjects	23	41
	Change in FACIT Fatigue baseline to Week 24 (BOCF)		
	95% CI		
Effect estimate per comparison	Treatment effect (ANCOVA)	Comparison groups	
		Δ adjusted mean (SE)	
		95% CI	
		P-value	
Notes			

Analysis performed across trials (pooled analyses and meta-analysis)

Pooling of studies

An analysis plan was made to pooling of the datasets from each pivotal phase III trial for safety and the primary and key secondary efficacy analyses. Both event-driven studies were regarded as conducted in the same target group of patients, the visit schedules as well as the same primary and key secondary endpoints (i.e., time to first protocol-defined relapse, change in VAS for pain to Week 24, change in FACIT fatigue score to Week 24), were uniform. Target numbers of PDR of 26 for Study BN40898 and of 44 for Study BN40900. One important difference between the two pivotal studies though, was that patients in Study BN40898 patients were censored when experiencing a relapse requiring rescue treatment or if there was a change in baseline medication.

The consistency of the satralizumab treatment effect was tested by analyses of the relapse-related endpoints in subgroups including region, race, BW, AQP4-IgG serostatus, and ADA status across the two studies BN40898 and BN40900. Pooling of data from studies BN40898 and BN40900 was used for these subgroup analyses to help overcome the problem of limited patient numbers.

Pooled results have been presented in most of the previous sections in parallel with the results of single studies.

Table 28: Time to first PDR during the DB period in individual studies and in the pooled data

	Study BN40898 (N=83)		Study BN40900 (N=95)		Studies BN40898 and BN40900 Pooled (N=178)	
	Placebo (n=42)	Satralizumab (n=41)	Placebo (n=32)	Satralizumab (n=63)	Placebo (n=74)	Satralizumab (n=104)
Time to First PDR during DB Period						
Patients with an event	18 (42.9%)	8 (19.5%)	16 (50.0%)	19 (30.2%)	34 (45.9%)	27 (26.0%)
Hazard ratio (95% CI)		0.38 (0.16, 0.88)		0.45 (0.23, 0.89)		0.42 (0.25, 0.71)
p value (log-rank)		0.0184		0.0184		0.0008
Proportion of Relapse-free Patients						
Week 48 (95% CI)	66.0% (47.65, 79.25)	88.9% (72.81, 95.70)	61.9% (42.66, 76.26)	76.1% (63.55, 84.86)	64.4% (51.65, 74.63)	80.5% (71.12, 87.14)
Week 96 (95% CI)	58.7% (39.85, 73.43)	77.6% (58.08, 88.82)	51.2% (32.36, 67.23)	72.1% (58.91, 81.75)	55.3% (42.18, 66.66)	74.2% (63.89, 82.02)

The similarity of the pivotal trial designs has reasonably enabled the scrutiny of them in parallel and by pooling of the datasets. The consistency of the results despite many differences between the trial populations may be considered positive. On the other hand, the pooling of data for efficacy analyses brings about a significant additional element of heterogeneity albeit that the primary and secondary endpoints as well as visit schedules of the trials were uniform, not taking into account that patients with relapses needing rescue treatment were censored in study BN40898.

The pooled analysis was obviously not pre-planned, as evidenced by the varying stratifications and censoring rules, which makes extra demands on the comparability and poolability, as well as e.g. sensitivity analyses, and limits the extent of subgroup analyses, which partly remain study-specific and very restricted. Considering the sample size, the heterogeneity and breaking down into various subsets leaves an uncertainty as to whether useful information can finally be gathered through the many numbers of subgroup analyses. Moreover, pooling is not necessarily straightforward in that the GCP violation and the succeeding protocol amendments result in loss of control of type 1 error in the study BN40900.

Clinical studies in special populations

Special subpopulations within the pivotal studies were age-based.

Subpopulation of the elderly

The inclusion was restricted to patients under 75 years of age in each pivotal study. The study BN40898 included a minimum quota of adolescent patients. PK aspects in these special subpopulations have been commented on previously. The subpopulation of the elderly (65-74 years) was limited: in the study BN40898 the age grouping is mainly given as adolescents vs. adults (≥18 years, and in the study BN40900 only one patient≥65 years was enrolled.

There were only four patients 65 years or older when entering the two pivotal studies. Six additional patients reached the age of 65 years during the study period. No data are presented for these additional patients. To enable some analyses, the Applicant used all patients age > 55 years at screening. This yielded 29 patients pooled from the two pivotal studies, and 24 of these were AQP4-IgG positive. In these 24 patients, there were 4 PDRs (1 SAT) and 6 rescue treated relapses (all in SAT). Due to few patients and events any conclusion is difficult to draw, but this pattern with fewer PDRs but more slightly milder relapses in the SAT treated patients. EDSS change in the six rescue treated relapses show that

these probably were mild. Of patients censored, most (10 of 18) stayed in the study until study end and 6 had a relapse treated with rescue as discussed above.

In total, with the available sparse data including reduced number of patients and events does not allow reaching conclusions. However, a similar trend is observed in patients aged over 55 years as in younger patients.

Subpopulation of adolescents

The spectrum of disease in children appears to be similar to that in adults but the incidence is considerably lower (approximately 0.02:100 000 but variable by race). The study BN40898 included a minimum quota of adolescent patients (n=8; at least four were to be AQP4-IgG-positive), based on the hypothesis that from a PK point of view it would be acceptable to apply the flat dosing to this age cohort. Specific modifications were made to inclusion criterion 2 (they had to have clinical evidence of at least 2 documented relapses including the first attack prior to screening) and laboratory inclusion criterion (in case of retest, the last retest value before randomization must meet the study criteria), and as the baseline IST, azathioprine or mycophenolate mofetil combined with corticosteroids were allowed. The following endpoints were specified for the adolescent population in listings by the protocol: TFR (protocol-defined relapse), EDSS scores. Visual acuity (Snellen chart) scores, SF-36 domain scores, SF-36 summary score (physical and mental), VAS for pain score, FACIT fatigue scale score, EQ-5D scores, mRS scores, and ZBI scores.

The majority of the adolescent patients (n=6) were females. Four patients were white, 2 patients were black/African American, and 1 patient was Asian (non-Japanese). The mean age was 15 years, age range 13-17 years. 5 patients were diagnosed with NMO and 2 patients with NMOSD. Three patients (2 in the PCB group and 1 in the SAT group) tested positive for AQP4-IgG at screening. Three patients had a baseline ARR of 1 and four patients had a baseline ARR >1. During the DB period, a clinical relapse was experienced by 3 of 3 adolescents in the PCB group (1 PDR) and 1 of 4 adolescents in the SAT group (1 PDR). Consequently, the HR for the primary endpoint of time to first PDR in this subgroup could not be correctly calculated and was inconclusive, due to the small sample size.

The available, albeit limited, efficacy data in adolescent patients enrolled in Study BN40898 do not lend arguments to doubting extrapolation.

Supportive studies

The supportive studies Phase I studies with healthy controls and RA patients do not provide data for assessment of efficacy.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical development program designed with satralizumab on NMO/NMOSD patients enrolled 178 patients in the two Phase III studies. These data provided the study population for the initial efficacy assessment. Since efficacy was not shown in patients lacking AQP4-IgG, the Applicant suggested a restriction in the indication to only include patients with AQP4-IgG. Thus, the pooled study population for further analyses comprise of 119 patients. Both studies are randomized and placebo-controlled by design, with the difference that the study BN40898 (55 patients) investigated the study drug or placebo as an add-on treatment to stable baseline IST, whereas the study BN40900 (64 patients) compared satralizumab to placebo as monotherapy in treatment of NMO/NMOSD. At the time, there was no

approved treatment for the disease, and consequently, a placebo-controlled design (with 2:1 randomization scheme) was acceptable and justified. Both studies were designed to have OLE phases, which are on-going. The patient population is stringently defined by the inclusion and exclusion criteria, and although the diagnostic criteria have been revised during the course of the study, it is considered that the study population is essentially representative of the NMO/NMOSD spectrum. The study BN40898 had a small quota for adolescents which is too limited for assessment of efficacy. However, kinetic and bibliographic data support extrapolation of efficacy from adults to this subgroup. The number of elderly patients was very limited, only 4 patients were 65 years or older at randomisation. In a subgroup analysis performed on patients aged over 55 years, the available data are still limited with respect to number of patients (5 treated with placebo, 19 with satralizumab) and events (4 PDRs, 6 TCRs) and do not allow reaching conclusions. However, a similar trend with respect to efficacy is observed in patients aged over 55 years as in younger patients.

Both global Phase III studies BN40898 and BN40900 were event driven studies with a primary endpoint of time to first PDR during the DB period, the duration of which was determined by the target number of PDRs. As the disability associated with NMO/NMOSD accumulates predominantly through relapses, the choice of the primary endpoint is acceptable. The definition for the criteria of the clinical endpoint is detailed by the protocol, and the events were adjudicated centrally by an independent CEC.

The selected key secondary endpoints were clinically determined: pain, measured with VAS score, and fatigue measured with FACIT score at 24 weeks. The choices are in principle adequate, as both overall pain and fatigue are regarded as the most common and disabling symptoms of NMO/NMOSD. The other secondary endpoints were also based on clinical assessment (change in EDSS score as a measure of disability, mRS as an overall outcome score, visual acuity scores), or self-assessment (SF-36 Generic Health Survey summary scores for Physical and Mental domains and domain wise scores for quality-of-life assessment, as well as EQ-5D scores). Time-to-event dimension yielded ARR and the proportion of relapse-free patients. The caregiver burden was attempted to assess with Zarit burden interview scores. On the whole, the selection of secondary endpoints is pertinent. However, the timepoints used for measurements of secondary efficacy endpoints were inappropriate and yielded data only from patients without relapses.

The statistical methodology is principally acceptable. However, unblinding, as an overshadowing breach of GCP conduct, was disclosed: the changes in fibrinogen levels indicative of treatment assignment were available during the studies, and the primary efficacy endpoint was calculated based on this. A temporal association with protocol amendments first increasing the number of events aimed at, at later decreasing the number of events aimed at, was seen in study BN40900. According to Scientific Advice procedure (EMEA/H/SA/2571/2/FU/2/2018/PA/II), a separate bias assessment report was submitted by the Applicant in which no introduction of bias could be detected. However, as with pre-planned interim analyses, these calculations lead to spending of alpha in both studies, and the main issue, the loss of control over the type I error, has been further discussed, but this cannot be controlled in retrospect. The efficacy data estimated using fibrinogen data may, or may not, have been used in the decisions for protocol amendments.

The pivotal studies have a similar design with equal dosage, primary endpoint (except differences in censoring patients in of rescue therapy) and most of the secondary endpoints, and this intrinsic similarity with some harmonizing measures have enabled pooling of the datasets and assessment of the pooled data for additional statistical power. Nevertheless, the populations have many differences arising from the geographical, racial and demographical variability. While adding strength to the side of 'benefit despite variability', the ensuing heterogeneity also obscures the role of individual predictors (weight, race, geography, ADA status) and detracts from the possibility to perform reasonable subgroup analyses, which dimension is essentially curtailed by the limited sample size at the outset.

GCP inspections

Four GCP inspections, including two clinical site-, a Sponsor-, and a CRO-inspection were performed during the assessment period.

The inspections identified critical findings associated with the difficulty to effectively confirm the segregation of the examining and treating investigators. In response to a request from the inspection team, the Applicant reviewed the totality of these issues and, in collaboration with the CRO and site staff, provided confirmation for the separation of the roles for all but 6 out of 86 total findings which could not be resolved due to site closure or change in site staff. The CHMP concluded that even if the documentation intended to ensure that the examining and treating investigators were separated in some cases was not optimal, there were no evidence that unblinding of the examining assessor had occurred.

Additional critical findings concerned the review of the CEC package by the Sponsor, a process that included queries to the investigators and changes of the relapse assessment forms. One potentially leading query was identified in the integrated inspection report. Finally, numerous accesses to the electronic system (VCAS) used for managing relapse assessment forms were noted. In response to a request from the inspection team, the Applicant acknowledged the numerous changes to the CEC package forms as well as limitations to evaluate the temporal sequence of events: (1) the use of a paper-based process instead of an electronic data capture system and (2) the incomplete corrective action of filing the relapse packages with queries together in the eTMF because the text was truncated in some of the queries due to technical limitations. As part of the responses, the Applicant performed a post database-lock internal review to identify and assess the impact of query-related corrections to relapse documentation. According to the report, queries were triggered as appropriate and resulted in corrections to the forms when necessary. Further, an evaluation of the validity of all changes made in response to queries, using the clinical data available in the complete relapse assessment dossier, could identify the rationale for each change. During the oral explanation, the Applicant confirmed that all documentation had been completed and filed in date order as requested, and the corrective action had been resolved. The final Applicant position was that these changes were required to ensure complete and accurate forms. Finally, even if there were numerous accesses to VCAS, the Applicant reviewed the complete access listing and confirmed the access rights were given appropriately.

Efficacy data and additional analyses

The primary clinical effect size in the pivotal studies (AQP4-IgG seropositive patients) were of the same magnitude, HR 0.21 and 0.26 respectively (in the pooled analysis HR was 0.25), which is not only statistically significant but are also considered clinically meaningful and relevant. Since the efficacy cannot be considered demonstrated in the AQP-IgG negative subpopulation, the indication has been restricted to patients who have AQP4-IgG.

A reduced effect was observed in both studies when relapses were analysed according the treating investigators (sensitivity analysis for AQP4-IgG seropositive patients), with respect to the relapses adjudicated by the CEC Study BN40898: HR 0.53; 95% CI: 0.25-1.12, p-value: 0.092; Study BN40900: HR 0.51; 95% CI: 0.25-1.03, p-value: 0.056). The difference in effect size between physician diagnosed and protocol-defined relapses has not changed for either study, why the effect size of the medicinal product in real life may be less pronounced.

The support that the sensitivity analyses give to the main result is not substantial although they are largely consistent. To correct for the lack of sensitivity analysis challenging the censoring rules in study BN40898 (censoring at a relapse not fulfilling PDR criteria but needing pre-defined rescue treatment), a supplementary analysis in which the rescue therapy and increase in background IST were accounted as

events, yielded a HR of 0.60 with 95% CI [0.33, 1.08] and a p-value of 0.0847 and a HR of 0.55 (CI 0.26, 1.14) in the AQP4-IgG seropositive NMOSD group.

The clinical secondary endpoints were not met, which was a consistent finding in both studies and repeated when only AQP4-IgG positive patients were included in the analyses. The reasons for this may be low scores at baseline and because assessment at week 24 was performed in patients still remaining in the study, i e those without a relapse.

Another issue is dose-exposure-response relationship. On the basis of PK studies, it is apparent that there is variability in exposure, which depends on factors such as BW and the potential presence of ADAs, which lead to lower exposure levels. It was expected this would have a bearing on efficacy. Lower exposure and RO were however not demonstrated to correlate with lower efficacy based on the full patient population. There may be neutralising ADAs, but there is no assay for detection and their clinical impact seems minor. Since the exposure/efficacy analysis has been performed in a biased dataset containing AQP4-IgG seronegative patients and repeated in AQP4-IgG seropositive patients. The AQP4-IgG seropositive patients analysis suggested that the satralizumab effect on TFR1 was not dependant on the exposure, when compared to placebo. There is thus no indication that the dose is not adequate.

Potential predictors in light of statistics could also be race, in that Asian population had a clearer effect whereas black patients did not respond as expected, but these associations may be confounded by asymmetries in the distribution of BW and AQP4-IgG seropositivity between races, as well as the very limited size of e.g. the subgroup of black people. In the literature, probable differences in clinical phenotype in patients with African ancestry are described, but the major pathophysiology is likely similar in AQP4-IgG seropositive patients with African ancestry comparted to other AQP4-IgG seropositive patients. The baseline BW and anti-AQP4-IgG status were comparable between the placebo and satralizumab groups in black patients and the results obtained in these patients (high relapse rate in the satralizumab group) are likely a chance findings.

2.5.4. Conclusions on the clinical efficacy

The primary clinical effect size in the pivotal studies for AQP4-IgG seropositive patients were statistically significant and clinically meaningful and relevant. Even if the effect size was reduced when relapses were analysed according the treating investigators, there was still nearly a 50% reduction on the rate relapse for the intended population of AQP4-IgG seropositive patients, an effect size that can be still considered clinically relevant.

The complete lack of effect for the key secondary outcome endpoints left the primary efficacy endpoint without support. On the other hand, this may not undermine the effect on the primary outcome assessing the effect on prevention of relapses, the key determinant of permanent neurological impairment in NMOSD.

Nevertheless, both the Fibrinogen levels-related GCP breach and the aforementioned findings recorded in the GCP inspections affecting both trials raised concerns over the reliability and robustness of the efficacy findings. The importance of these GCP issues are further discuss in the B/R assessment (section 3).

2.6. Clinical safety

Patient exposure

The safety data for satralizumab is based on the primary analysis of the two pivotal Phase III studies BN40898 and BN40900 in patients with NMO and NMOSD, from a total of 145 satralizumab-treated patients with 328 patient-years of exposure (mean duration: 114 weeks; including data from 63 patients who switched to administration via PFS), in which 90 patients followed for more than 96 weeks. In addition, supportive safety data are provided from 72 healthy volunteers (Study SA-001JP) and 33 RA patients (Study SA-105JP).

During the DB period, a total of 104 patients were exposed to at least one dose of satralizumab, and a total of 74 patients were exposed to at least one dose of placebo (Table 29). The pooled patient population with respect to background IST during the DB period is rather unbalanced since more patients in the placebo group are coming from the study BN40898 with a background IST (42 out of 74 patients), while the majority of satralizumab treatment patients are coming from the study BN40900 (63 out of 104 patients).

The patients age stretches from 13 to 73 years old in the pooled dataset from 2 phase III studies. Overall, 7 patients at age 12 to <18 years old were treated with satralizumab. Seven patients <18 years of age were included into the study BN40898 (placebo n=3, satralizumab n=4) during the DB period (Table 30). The mean duration of observation in the DB period was 33.2 weeks (median: 31.7 weeks, range: 13.0-72.1 weeks) and the mean duration of observation on satralizumab including the OLE phase was 55.3 weeks (median: 44.1 weeks, range: 16.3-99.3 weeks). The Applicant reported 4 patients above 65 years in satralizumab treatment group in the pooled dataset (Table 30). However, it is not clear if there were elderly patients in the placebo group. Among patients treated with satralizumab there were 20.2% of males while in placebo group there were only 4.1% of males. Regarding BW and BMI both treatment groups in the pooled dataset were relatively-well balanced, but it should be noted that patients BW and BMI were higher in the BN40900 study (monotherapy) compared to study BN40898 (add-on treatment). Median BW in placebo group was 61 kg and 69 kg, satralizumab group 57 kg and 75 kg in studies BN40898 and BN40900, respectively. Similar differences were noted also for the BMI: BMI ≥30 in placebo group – 14% and 22%; satralizumab 12% and 34% in studies BN40898 and BN40900, respectively.

The baseline disease characteristics regarding proportion of NMO and NMOSD patients, number of relapses, EDSS as well as proportion of patients positive for AQP4-IgG were balanced between treatment groups in pooled safety dataset as well as individual studies. Mean number of relapses in the two years prior to randomization was 1.18, and approximately equal proportions of patients in each group had ARR >1 (in total, 37.6%).

Table 29: Duration of DB Period for Safety Analysis (DB Period; Pooled Studies BN40898 and BN40900)

	Placebo (N=74)	SA237 (N=104)
Total Patient Years	100.10	193.74
Duration (Weeks)		
0 - 23	21 (28.4%)	14 (13.5%)
24 - 47	15 (20.3%)	18 (17.3%)
48 - 71	8 (10.8%)	5 (4.8%)
72 - 95	5 (6.8%)	15 (14.4%)
96 - 119	9 (12.2%)	16 (15.4%)
120 - 143	5 (6.8%)	8 (7.7%)
144 - 167	6 (8.1%)	9 (8.7%)
168 - 191	4 (5.4%)	14 (13.5%)
192 - 215	0	4 (3.8%)
216 - 239	1 (1.4%)	1 (1.0%)
Mean (SD)	70.6 (55.8)	97.2 (61.2)
Median	54.6	96.1
Min - Max	7 - 219	8 - 224

DB period starts on the day of first dose. The DB period ends on the earliest day of 1) clinical cutoff date, 2) the day before the first treatment in the extension period, 3) the end of the study, or 4) last contact for patients lost to follow up.

Table 30: Extent of Exposure to satralizumab by Age Group and Gender (Safety-evaluable Population; DB Period; Pooled Studies BN40898 and BN40900)

	Patients			Person time*		
Age group (years)	Male (N=21)	Female (N=83)	Total (N=104)	Male (N=21)	Female (N=83)	Total (N=104)
12-17	1 (4.8%)	3 (3.6%)	4 (3.8%)	113	843	956
18-64	20 (95.2%)	76 (91.6%)	96 (92.3%)	13766	50611	64377
65-74	0	4 (4.8%)	4 (3.8%)	NE	1849	1849
Total patients numbers/person time	21 (100%)	83 (100%)	104 (100%)	13879	53303	67182

N= number of patients exposed to SA237. * Person time is the sum of exposure across all patients in unit: days. Person time in days may be divided by 365.25 to obtain person time in years

Adverse events

In general, in both Phase III studies, the overall rates of AEs and serious AEs (SAEs) were comparable between treatment groups. The frequency of severe AEs was high with 17 patients (27%, 32 events/100PY) in Satralizumab group in the study BN40898, which is higher than that in the PCB groups (6.3% 9.85 events /100PY). In study BN40900, the rate was lower in both the SAT group (12%, 6.37events/100PY) and the PCB group (12%, 11.67 events/100PY).

Table 31: Overview of Adverse Events (Pooled Phase III studies; DB Period BN40898 and BN40900)

	Placebo (N=74) n (%)	E	SA237 (N=104) n (%)	E
Total Number of Events	64 (86.5%)	507	95 (91.3%)	927
Total Number of Patients Withdrawn from Study due to an AE	6 (8.1%)	6	4 (3.8%)	5
Total Number of Patients with at Least One :				
AE with Fatal Outcome	0		0	
Serious AE	14 (18.9%)	18	19 (18.3%)	29
Serious AE Leading to Treatment Discontinuation	4 (5.4%)	4	1 (1.0%)	1
Serious AE Leading to Dose Interruption	4 (5.4%)	5	8 (7.7%)	10
Serious Adverse Drug Reaction	5 (6.8%)	8	3 (2.9%)	3
AE Leading to Dose Interruption	13 (17.6%)	17	23 (22.1%)	41
AE Leading to Treatment Discontinuation	5 (6.8%)	5	4 (3.8%)	5
Adverse Drug Reaction	31 (41.9%)	127	39 (37.5%)	161
Adverse Drug Reaction Leading to Treatment Discontinuation	3 (4.1%)	3	3 (2.9%)	4
Severe AE	7 (9.5%)	11	22 (21.2%)	42
Infection AE	40 (54.1%)	155	62 (59.6%)	219
Serious Infections AE	6 (8.1%)	7	8 (7.7%)	8
Potential Opportunistic Infections	10 (13.5%)	28	7 (6.7%)	11
Injection Related Reactions	7 (9.5%)	9	13 (12.5%)	33

N=number of patients with event, E=Number of events

In general, the AE rates were comparable between SAT and PCB treatment arms in individual studies BN40898 and BN40900 as well as in pooled safety dataset during DB period for AEs leading to discontinuation or dose interruption, infections, serious infections and potential opportunistic infections (Table 31). More injection related reactions (IRR) were reported in SAT-treated compared to PCB patients in pooled safety dataset from the DB period (Table 31). This difference was driven primarily by data of the study BN40898 (SAT - 21.65 AEs/100PY, PCB – 3.36 AEs/100PY). It is unclear if it could be related to background IST.

Nasopharyngitis, upper respiratory tract infection and urinary tract infection were the most frequently reported AEs observed in both studies, the higher frequencies of these events were in the SAT than PCB group except for urinary tract infection. The most frequently reported AEs (≥10%) for SAT versus PCB in the study BN40898 were nasopharyngitis (24.4% vas 16.7%), upper respiratory tract infection (24.4% vs 14.3%), urinary tract infection (17.1% vas 16.7%). The most frequently reported AEs (≥10%) for SAT versus PCB in study BN40900 were nasopharyngitis (14.3% vas 3.1%), upper respiratory tract infection (15.9% vs 18.8%), and urinary tract infection (17.5% vas 25.5%).

The lower rate of AEs/100PY in the SAT group was also observed in the System Organ Class (SOC) Blood and Lymphatic System Disorders based on event/100 PY (58.94% vs 28.39% events/100Py). In fact, more patients (n=31, 29.8%) in the SAT group than PCB (n=13, 17.6%) reported these AEs. The higher rate of AEs in the PCB group was mainly driven by multiple events reported by 3 patients; 2 patients in the study BN40898 (1 patient reported 20 events and a second patient reported 14 events) and 1 patient in the study BN40900 (9 events of neutropenia). For AEs presented by 100PY, multiple occurrences of the same AE in one patient are counted multiple times. In addition, 2 patients reporting multiple events are coming from the study BN40898 with concomitant IST.

The frequency of neutropenia, leukopenia and decreased white blood cell count were higher in the SAT group vs PCB (5.8% vs 4.1%, 7.7% vs 5.4% and 5.8% vs 0, respectively). In the study BN40898, the frequency of leukopenia report was more frequent in SAT vs PCB (14.6% vs 9.5%).

AEs by SOC gastrointestinal were reported in 37% of patients, an only nausea was reported in the SAT group with a higher frequency than in PCB (13.5 % vs 6.8%).

A higher frequency of AEs in the SOC Musculoskeletal and Connective Tissue Disorders was observed in the SAT group than in PCB (43.3% vs 21.6%), including arthralgia (13.5% vs 1.4% pooled data).

The majority of AEs were of mild or moderate intensity. There is no clear trend concerning severe AEs since the severe AEs were widely distributed with only 1 or 2 patients per each AE Preferred Term (PT).

According to the Applicant, severe AEs were reported more frequently in the SAT group compared with the PCB group (PCB: 10.99 events/100PY; SAT: 21.68 events/100PY) in the pooled phase III studies in the DB period. Among severe AEs, psychiatric AEs were reported only in treatment arm, one suicide attempt (study BN40898) and 3 patients with AEs under SOC of psychiatric disorders including 2 cases with depression and 2 with changed mental status (study BN40900).

The overall incidence of severe AEs (17.69 events/100PY) and rates of severe AEs by PT for all patients treated with satralizumab during the Overall SA237 period remained similar to the rates reported in the DB period.

Table 32: AEs Reported in ≥25% of Patients in Either Treatment Group by SOC (Pooled Phase III Studies, DB Period)

System Organ Class	Placebo (N=74) (PY=100.10)			Satralizumab (N=104) (PY=193.74)		
	No. of events	Events/100PY (95% CI)	No. of patients (%)	No. of events	Events/100PY (95% CI)	No. of patients (%)
Infections and Infestations	155	154.85 (131.43, 181.24)	40 (54.1)	219	113.04 (98.56, 129.04)	62 (59.6)
Gastrointestinal Disorders	47	46.96 (34.50, 62.44)	28 (37.8)	89	45.94 (36.89, 56.53)	39 (37.5)
Musculoskeletal and Connective Tissue Disorders	31	30.97 (21.04, 43.96)	16 (21.6)	84	43.36 (34.58, 53.68)	45 (43.3)
Nervous System Disorders	31	30.97 (21.04, 43.96)	21 (28.4)	66	34.07 (26.35, 43.34)	32 (30.8)
Injury, Poisoning and Procedural Complications	28	27.97 (18.59, 40.43)	20 (27.0)	69	35.62 (27.71, 45.07)	32 (30.8)
Investigations	37	36.96 (26.03, 50.95)	21 (28.4)	65	33.55 (25.89, 42.76)	30 (28.8)
Blood and lymphatic system disorders	59	58.94 (44.87, 76.03)	13 (17.6)	55	28.39 (21.39, 36.95)	31 (29.8)
Skin and subcutaneous tissue disorders	15	14.99 (8.39, 24.72)	10 (13.5)	49	25.29 (18.71, 33.44)	30 (28.8)

No=number; PY=patient-years

Table 33: AEs Reported in ≥ 5% of Patients in Either Treatment Group by PT (Pooled Phase III Studies, DB Period)

Preferred Term	Placebo (N=74) (PY=100.10)			Satralizumab (N=104) (PY=193.74)		
	No. of events	Events/100PY (95% CI)	No. of patients (%)	No. of events	Events/100PY (95% CI)	No. of patients (%)
Urinary tract infection	32	31.97 (21.87, 45.13)	15 (20.3%)	44	22.71 (16.50, 30.49)	18 (17.3%)
Upper respiratory tract infection	26	25.98 (16.97, 38.06)	12 (16.2%)	46	23.74 (17.38, 31.67)	20 (19.2%)
Headache	11	10.99 (5.49, 19.66)	8 (10.8%)	35	18.07 (12.58, 25.13)	20 (19.2%)
Nasopharyngitis	14	13.99 (7.65, 23.47)	8 (10.8%)	33	17.03 (7.65, 23.47)	19 (18.3%)
Injection-Related Reactions	9	8.99 (4.11, 17.07)	7 (9.5%)	33	17.03 (11.73, 23.92)	13 (12.5%)
Nausea	9	8.99 (4.11, 17.07)	5 (6.8%)	17	8.77 (5.11, 14.05)	14 (13.5%)
Back Pain	12	11.99 (6.19, 20.94)	8 (10.8%)	9	4.65 (2.12, 8.82)	8 (7.7%)
Pain in extremity	6	5.99 (2.20, 13.05)	6 (8.1%)	13	6.71 (3.57, 11.47)	10 (9.6%)
Arthralgia	1	1.00 (0.03, 5.57	1 (1.4%)	14	7.23 (3.95, 12.12)	14 (13.5%)
Constipation	10	9.99 (4.79, 18.37	9 (12.2%)	5	2.58 (0.84, 6.02)	5 (4.8%)
Fatigue	4	4.00 (1.09, 10.23)	3 (4.1%)	11	5.68 (2.83, 10.16)	9 (8.7%)
Leukopenia	13	12.99 (6.92, 22.21)	4 (5.4%)	12	6.19 (3.20, 10.82)	8 (7.7%)
Rash	4	4.00 (1.09, 10.23)	3 (4.1%)	14	7.23 (3.95, 12.12)	9 (8.7%)

Preferred Term	Placebo (N=74) (PY=100.10)			Satralizumab (N=104) (PY=193.74)		
	No. of events	Events/100PY (95% CI)	No. of patients (%)	No. of events	Events/100PY (95% CI)	No. of patients (%)
Depression	2	2.00 (0.24, 7.22)	2 (2.7%)	9	4.65 (2.12, 8.82)	7 (6.7%)
Lymphopenia	10	9.99 (4.79, 18.37)	4 (5.4%)	9	4.65 (2.12, 8.82)	5 (4.8%)
Neutropenia	12	11.99 (6.19, 20.94)	3 (4.1%)	8	4.13 (1.78, 8.14)	6 (5.8%)
Fall	4	4.00 (1.09, 10.23)	4 (5.4%)	4	2.06 (0.56, 5.29)	4 (3.8%)
Insomnia	1	1.00 (0.03, 5.57)	1 (1.4%)	6	3.10 (1.14, 6.74)	6 (5.8%)
Oral herpes	20	19.98 (12.20, 30.86)	4 (5.4%)	7	3.61 (1.45, 7.44)	3 (2.9%)
Pruritus	1	1.00 (0.03, 5.57)	1 (1.4%)	8	4.13 (1.78, 8.14)	6 (5.8%)
Hypoaesthesia	0	0.00 (NE, 3.69)	0	7	3.61 (1.45, 7.44)	6 (5.8%)
Pyrexia	7	6.99 (2.81, 14.41)	5 (6.8%)	1	0.52 (0.01, 2.88)	1 (1.0%)
White blood cell count decreased	0	0.00 (NE, 3.69)	0	10	5.16 (2.48, 9.49)	6 (5.8%)

Table 8: Severe AE by SOC (Study BN40900, DB Period)

System Organ Class	Placebo (N = 32) (PY = 40.59)			Satralizumab (N = 63) PY = (115.21)			Preferred Term (Number of events)	
							Placebo	Satralizumab
	No. of events	Events/ 100PY (95% CI)	No. of patients (%)	No. of events	Events/ 100PY (95% CI)	No. of patients (%)		
All Events	4	9.85 (2.68, 25.23)	2 (6.3%)	37	32.11 (22.61, 44.27)	17 (27.0%)		
Infections and Infestations	1	2.46 (0.06, 13.73)	1 (3.1%)	7	6.08 (2.44, 12.52)	6 (9.5%)	Tooth abscess (1)	Urinary tract infection (1); Influenza (1); Cellulitis (1); Pneumonia (1); Gastrointestinal viral infection (1); Pulmonary sepsis (1); Pyelonephritis (1)
Gastrointestinal Disorders	1	2.46 (0.06, 13.73)	1 (3.1%)	4	3.47 (0.95, 8.89)	3 (4.8%)	Constipation (1)	Nausea (1); Diarrhoea (1); Constipation (1); Enterocolitis (1)
Musculoskeletal and Connective Tissue Disorders	0	0.00 (NE, 9.09)	0	4	3.47 (0.95, 8.89)	3 (4.8%)		Pain in extremity (1); Arthralgia (1); Back pain (1); Spinal pain (1)
Injury, Poisoning and Procedural Complications	0	0.00 (NE, 9.09)	0	5	4.34 (1.41, 10.13)	4 (6.3%)		Injection-related reaction (2); Thermal burn (1); Injury (1); Radius fracture (1)
Nervous System Disorders	1	2.46 (0.06, 13.73)	1 (3.1%)	0	0.00 (NE, 3.20)	0	Cervical radiculopathy (1)	
Skin and Subcutaneous	0	0.00 (NE, 9.09)	0	1	0.87	1 (1.6%)		Dermatitis (1)
General Disorders and Administration Site Conditions	1	2.46 (0.06, 13.73)	1 (3.1%)	5	4.34 (1.41, 10.13)	5 (7.9%)	Pain (1)	Fatigue (1); Pain (1); Chest pain (1); Hypothermia (1); Pyrexia (1)
Respiratory, Thoracic and Mediastinal Disorders	0	0.00 (NE, 9.09)	0	2	1.74 (0.21, 6.27)	2 (3.2%)		Apnoea (1); Pulmonary oedema (1);
Psychiatric Disorders	0	0.00 (NE, 9.09)	0	5	4.34 (1.41, 10.13)	3 (4.8%)		Depression (2); Insomnia (1); Mental status changes (2)
Eye Disorders	0	0.00 (NE, 9.09)	0	2	1.74 (0.21, 6.27)	2 (3.2%)		Eye pain (1); Keratoconus (1)
Cardiac Disorders	0	0.00 (NE, 9.09)	0	2	1.74 (0.21, 6.27)	2 (3.2%)		Bradycardia (1); Acute myocardial infarction (1)

No=number; NE=non evaluable; PY=patient-years

Adverse events of special interest

Infection

The incidence rates of infectious AEs were higher in both treatment arms, with a slightly higher incidence in the SAT treated group than PCB (BN40898: 68.3% vs 61.9% and BN40900 54% vs 43.8%). A higher proportion of patients reported severe infectious AEs in SAT treatment arm (9.5%, 6.08 events/100PY) compared to PCB (3.1%, 2.46 events/100PY) in the BN40900 study.

The incidence of serious infection AEs under the basket of lower respiratory tract infections were numerically higher in SAT treated group vs PCB (5.68 AE/100PY vs 4 AE /100 patient years) including bronchitis (3.61AE/100PY vs 3 AE/100PY), pneumonia (1.55 AE/100PY vs 0 AE/100PY) and pulmonary sepsis (0.52AE/100PY vs 0 AE/100PY).

Table 35: Overview of Infections Coded according to the SOC Infections and Infestations (Studies BN40898 and BN40900, DB Period)

	BN40898						BN40900					
	Placebo (N = 42) (PY = 59.50)			Satralizumab (N = 41) PY = (78.52)			Placebo (N = 32) (PY = 40.59)			Satralizumab (N = 63) PY = (115.21)		
	No. of events	Events/ 100PY (95% CI)	No. of patients (%)	No. of events	Events/ 100PY (95% CI)	No. of patients (%)	No. of events	Events/ 100PY (95% CI)	No. of patients (%)	No. of events	Events/ 100PY (95% CI)	No. of patients (%)
Infection AE	89	149.57 (120.12,184.06)	26 (61.9)	104	132.45 (108.22, 160.48)	28 (68.3)	66	162.60 (125.75, 206.86)	14 (43.8)	115	99.81 (82.41, 119.81)	34 (54)
Serious Infections AE	3	5.04 (1.04, 14.73)	3 (7.1)	2	2.55 (0.31, 9.20)	2 (4.9)	4	9.85 (2.68, 25.23)	3 (9.4)	6	5.21 (1.91, 11.33)	6 (9.5)
Severe Infections AE	2	3.36 (0.41, 12.14)	2 (4.8%)	0	0.00 (NE, 4.70)	0	1	2.46 (0.06, 13.73)	1 (3.1%)	7	6.08 (2.44, 12.52)	6 (9.5%)
Potential Opportunistic Infections	21	35.29 (21.85, 53.95)	5 (11.9)	8	10.19 (4.40, 20.07)	4 (9.8)	7	17.25 (6.93, 35.53)	5 (15.6)	3	2.60 (0.54, 7.61)	3 (4.8)

Table 36: Rates of Infections per 100 Patient Years by Predefined Basket (Studies BN40898 and BN40900, DB Period)

	BN40898				BN40900			
	Placebo (N = 42) (PY = 59.50)		Satralizumab (N = 41) PY = (78.52)		Placebo (N = 42) (PY = 59.50)		Satralizumab (N = 41) PY = (78.52)	
	No. of events	Events/ 100PY (95% CI)	No. of events	Events/ 100PY (95% CI)	No. of events	Events/ 100PY (95% CI)	No. of events	Events/ 100PY (95% CI)
Upper respiratory tract infections	43	72.26 (52.30, 97.34)	66	84.05 (65.01, 106.94)	20	49.27 (30.10, 76.10)	41	35.59 (25.54, 48.28)
Urinary tract infections	14	23.53 (12.86, 39.48)	13	16.56 (8.82, 28.31)	25	61.59 (39.86, 90.92)	39	33.85 (24.07, 46.27)
Skin infections	7	11.76 (4.73, 24.24)	3	3.82 (0.79, 11.17)	2	4.93 (0.60, 17.80)	8	6.94 (3.00, 13.68)
Lower respiratory tract infections	2	3.36 (0.41, 12.14)	6	7.64 (2.80, 16.63)	2	4.93 (0.60, 17.80)	5	4.34 (1.41, 10.13)
Gastrointestinal infections	2	3.36 (0.41, 12.14)	3	3.82 (0.79, 11.17)	3	7.39 (1.52, 21.60)	5	4.34 (1.41, 10.13)
Sepsis	1	1.68 (0.04, 9.36)	0	0.00 (0.00, 4.70)	0	0.00 (0.00, 9.09)	2	1.74 (0.21, 6.27)

No=number; PY=patient-years. Investigator text for AEs encoded using MedDRA version MedDRA 16.1

Table 37: Most Common Infections (≥5% in either Treatment Group) by PT (Pooled Phase III Studies; DB Period)

Preferred Term	Placebo (N=74) (PY=100.10)			Satralizumab (N=104) (PY=193.74)		
	No. of events	Events/100PY (95% CI)	No. of patients (%)	No. of events	Events/100PY (95% CI)	No. of patients (%)
Urinary tract infection	32	31.97 (21.87, 45.13)	15 (20.3%)	44	22.71 (16.50, 30.49)	18 (17.3%)
Upper respiratory tract infection	26	25.98 (16.97, 38.06)	12 (16.2%)	46	23.74 (17.38, 31.67)	20 (19.2%)
Nasopharyngitis	14	13.99 (7.65, 23.47)	8 (10.8%)	33	17.03 (11.73, 23.92)	19 (18.3%)
Influenza	8	7.99 (3.45, 15.75)	6 (8.1%)	5	2.58 (0.84, 6.02)	5 (4.8%)
Cystitis	7	6.99 (2.81, 14.41)	5 (6.8%)	6	3.10 (1.14, 6.74)	5 (4.8%)
Oral herpes	20	19.98 (12.20, 30.86)	4 (5.4%)	7	3.61 (1.45, 7.44)	3 (2.9%)

No=number; PY=patient-years.

Injection-related reactions

In the pooled DB Period, 7 patients (9.5%) in the PCB group reported 9 IRRs (8.99 events/100PY) and 14 patients (13.5%) in the SAT group reported 36 IRR events (18.58 events/100PY).

Local IRRs: 6 events in 5 patients in the PCB group and 18 events in 8 patients in the SAT group, no IRRs were serious, and none led to discontinuation of study drug or withdrawal.

Systemic IRRs: 3 events in 3 patients in the PCB group and 17 events in 6 patients in the SAT group. Symptoms associated with systemic IRRs were headache (6 events in 2 patients), nausea (3 events in 1 patient), diarrhoea (3 events in 2 patients), vertigo (2 events in 1 patient), and single event of chills, hypertension, pyrexia, micturition urgency, vision blurred, and diastolic hypotension.

All systemic IRR were of mild intensity except for one case of hypertension in the SAT group in study BN40898 and 2 events of vertigo reported as severe in Study BN40900. All events resolved, except 1 mild systemic IRR of blurred vision assessed by the investigator as unrelated to satralizumab.

Anaphylaxis

No anaphylactic reactions to satralizumab identified by the Standard MedDRA Query Anaphylactic reactions were reported. The potential cases suspected by using Sampson's criteria were not considered anaphylactic reactions.

Depression and Suicidality

At baseline, a greater proportion of patients in the SAT group compared to the PCB group reported suicidal ideation or behaviour (PCB: 6.8%, SAT: 20.2%). Post-baseline, the proportion of patients reporting any suicidal ideation was similar between the treatment groups (PCB: 4.1%, SAT: 4.8%) during the DB period. No self-injurious behaviours without suicidal intent were reported post-baseline (at baseline, PCB: 0, SAT: 2 patients [1.9%]).

No additional post-baseline suicidal ideation, behaviour or self-injurious behaviour without intent was captured on Columbia Suicide Severity Rating Scale in the Overall SA237 period up to clinical cut-off date (CCOD).

The incidences rates of depression reported in the phase III studies during the DB period is higher in SAT than in PCB (6.7% vs 2.7%).

Gastrointestinal disorders

AEs reported in 37% of patients in group by SOC gastrointestinal. A higher frequency of nausea was reported in the SAT group than PCB (13.5 % vs 6.8%, Table 33).

Gastritis was reported in 4 patients (3.8%) in SAT group but none in the PCB.

Malignancies

Three different types of malignancies were reported in 3 patients. Two were in the PCB, one event of squamous cell carcinoma in the SAT group was judged as not related to the study drug.

Serious adverse event/deaths/other significant events

No deaths were reported.

Study BN40898: In the DB period, 9 patients (21.4%) in the PCB group and 7 patients (17.1%) in the SAT group experienced at least one SAE (Table 38).

Study BN40900: In the DB period, 5 patients (15.6%) in the PCB group and 12 patients (19.0%) in the SAT group experienced at least one SAE (Table 39).

The most commonly reported SAEs in the SAT group were under the SOC Infections and Infestations (in both phase III studies), Injury and Poisoning and Procedural Complications (in the study BN 40898) and Psychiatric disorders (in the study BN 40900). In other SOCs, SAEs were reported in 1-2 patients in the SAT group (Table 38 and Table 39).

Table 38: SAEs by SOC (Study BN40898, DB Period)

System Organ Class	Placebo (N = 42) (PY = 59.50)			Satralizumab (N = 41) PY = (78.52)		
	No. of events	Events/ 100PY (95% CI)	No. of patients (%)	No. of events	Events/ 100PY (95% CI)	No. of patients (%)
All Events	12	20.17 (10.42, 35.23)	9 (21.4%)	9	11.46 (5.24, 21.76)	7 (17.1%)
Infections and infestations	3	5.04 (1.04, 14.73)	3 (7.1%)	2	2.55 (0.31, 9.20)	2 (4.9%)
Blood and lymphatic system disorders	3	5.04 (1.04, 14.73)	3 (7.1%)	1	1.27 (0.03, 7.10)	1 (2.4%)
Injury, poisoning and procedural complications	0	0.00 (NE, 6.20)	0	3	3.82 (0.79, 11.17)	2 (4.9%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	3.36 (0.41, 12.14)	2 (4.8%)	0	0.00 (NE, 4.70)	0
Reproductive system and breast disorders	1	1.68 (0.04, 9.36)	1 (2.4%)	1	1.27 (0.03, 7.10)	1 (2.4%)
Eye disorders	1	1.68 (0.04, 9.36)	1 (2.4%)	0	0.00 (NE, 4.70)	0
Gastrointestinal disorders	1	1.68 (0.04, 9.36)	1 (2.4%)	0	0.00 (NE , 4.70)	0
Nervous system disorders	0	0.00 (NE, 6.20)	0	1	1.27 (0.03, 7.10)	1 (2.4%)
Psychiatric disorders	0	0.00 (NE, 6.20)	0	1	1.27 (0.03, 7.10)	1 (2.4%)
Renal and urinary disorders	1	1.68 (0.04, 9.36)	1 (2.4%)	0	0.00 (NE , 4.70)	0

No=number; PY=patient-years. Investigator text for AEs encoded using MedDRA version MedDRA 16.1
For AEs presented by 100PY, multiple occurrences of the same AE in one patient are counted multiple times.

Table 39: SAEs by SOC (Study BN40900, DB Period)

System Organ Class	Placebo (N = 32) (PY = 40.59)			Satralizumab (N = 63) PY = (115.21)		
	No. of events	Events/ 100PY (95% CI)	No. of patients (%)	No. of events	Events/ 100PY (95% CI)	No. of patients (%)
All Events	6	14.78 (5.42, 32.17)	5 (15.6%)	20	17.36 (10.60, 26.81)	12 (19.0%)
Infections and infestations	4	9.85 (2.68, 25.23)	3 (9.4%)	6	5.21 (1.91, 11.33)	6 (9.5%)
Psychiatric disorders	0	0.00 (NE, 9.09)	0	3	2.60 (0.54, 7.61)	2 (3.2%)
Cardiac disorders	0	0.00 (NE, 9.09)	0	2	1.74 (0.21, 6.27)	2 (3.2%)
Gastrointestinal disorders	0	0.00 (NE, 9.09)	0	2	1.74 (0.21, 6.27)	2 (3.2%)
General disorders and administration site conditions	0	0.00 (NE, 9.09)	0	2	1.74 (0.21, 6.27)	2 (3.2%)
Injury, poisoning and procedural complications	0	0.00 (NE, 9.09)	0	2	1.74 (0.21, 6.27)	2 (3.2%)
Nervous system disorders	2	4.93 (0.60, 17.80)	2 (6.3%)	0	0.00 (NE , 3.20)	0
Respiratory, thoracic and mediastinal disorders	0	0.00 (NE, 9.09)	0	2	1.74 (0.21, 6.27)	2 (3.2%)
Eye disorders	0	0.00 (NE, 9.09)	0	1	0.87 (0.02, 4.84)	1 (1.6%)

No=number; NE=non evaluable; PY=patient-years

Laboratory findings

Neutrophils, leukocytes and white blood cell count

In the pooled data during the DB period, a higher proportion of patients in the SAT group had at least one post-baseline neutrophil count decrease resulting in a shift from baseline to a higher (worse) grade, compared to the patients in the PCB group (SAT vs PCB: 31.7% vs 21.6%). The proportion of patients who had a post-baseline shift to grade 3 or 4 decrease in neutrophil counts was also higher in the SAT group than in the PCB group (10 of 104 patients, 9.6% vs 4 of 74, 5.4%). The trend was similar in the overall SA237 period and the individual studies.

In the pooled phase III studies during the DB period, a higher proportion of patients in the SAT group had at least one post-baseline leukocyte count decrease resulting in a shift from baseline to a higher (worse) grade, compared to the patients with shifts in the PCB group (SAT vs PCB: 54.8% vs 28.4%). The proportion of patients who had a post-baseline shift to not low to grade 3 decrease in leukocyte counts was also higher in the SAT group than in the placebo group (5 of 104 patients, 5.6 % vs 0).

The trend was similar in the overall SA237 period and the individual phase III studies.

Platelets

In the pooled data, during the DB period, a higher proportion of patients in the SAT group had at least one post-baseline platelet count decrease resulting in a shift from baseline to a higher (worse) grade, compared to the patients with shifts in the PCB group (SAT vs PCB: 24% vs 9.5%). Most of the patients had platelet count decreases with shifts to grade 1, with 2 of 104 patients (1.9%) in SAT group with levels shifting to a decreased count of grade 2.

No patient had grade 3 or grade 4 decrease in platelet counts.

Liver enzymes and total bilirubin

In the pooled data during the DB period, there was a higher proportion of patients in the SAT group that had post-baseline ALT increases (29 of 104 patients [27.9%]) or AST increases (19 of 104 patients [18.3%]) resulting in a shift from baseline to higher (worse) grade, compared with the patients with shifts in grades in the PCB group (ALT: 9 of 74 patients [12.2%]; AST: 10 of 74 patients [13.5%]).

Most ALT or AST increases were transient and grade 1-2, resolving with ongoing satralizumab treatment. Post-baseline transaminase increases above grade 1 (>3 x upper limit of normal [ULN]) occurred in 5 (4.8%) in the SAT group. The highest Common Terminology Criteria for Adverse Events (CTCAE) grade ALT elevation was a grade 3 event (5.3 x ULN) in one patient treated with satralizumab during the DB period in Study BN40898, leading to withdrawal at week 4. One additional patient in the study had a post-baseline shift to grade 3 AST increase (8.8 x ULN) and a post-baseline shift to grade 3 ALT increase (11.7x ULN) in the OLE period and withdrew from the study due to lack of effect. Elevated ALT and AST returned back to baseline levels in both patients after discontinuation of satralizumab. None of the patients with grade 3 elevations in transaminases had elevated bilirubin during the study.

During the DB period, 3 patients in the SAT group had a post-baseline shift to grade 2 increase in bilirubin, and one additional patient in the overall SA237 period, but none with a post-baseline grade 3-4 increase.

Lipid

During the DB period, the patients in the SAT group had at least one post-baseline increase in cholesterol resulting in a shift from baseline to a higher (worse) grade in 44 of 104 patients [42.3%] whereas in 25 of 74 patients [33.8%] in the PCB group. None had a post-baseline grade 3-4 increase in cholesterol. A higher proportion of patients in the SAT group had a post-baseline increase in cholesterol resulting in a shift above Grade 1 (> 7.75 mmol/L) compared with patients in the PCB group (11 of 104 patients [10.6% vs 1 of 74 patients [1.4%]).

During the DB period, 66 of 104 patients [63.5%] in the SAT group had a post-baseline triglyceride increase resulting in a shift from baseline to higher (worse) grades in comparison with 36 of 74 patients [48.6%] in the PCB group.

Fibrinogen

In the pooled analysis, there was a higher incidence of patients in the SAT group with a post-baseline fibrinogen level decreases resulting in a shift from baseline to a higher (worse) grade (total 74 of 104 patients, 71.2%; shift from not low to grade 2 in 46.6%) compared with patients with in the PCB group (total, 15 of 74 patients, 20.3%; shift from not low to grade 2 in 4.2%). The trend in fibrinogen levels appeared uniform in the overall SAT treatment period.

Complement

A decline in mean C3, C4, and CH50 values was observed as early as the first post-baseline assessment at week 2 in the SAT group during the DB period in each study, and thereafter the mean values remained stable.

In pooled data, during the DB period, the proportion of patients with 'not low' baseline values shifting to low post-baseline C3, C4 and CH50 values was higher in the SAT group compared to the PCB group as early as at week 2 (C3: 7.9% PCB vs 36.2% SAT; C4: 1.4% PCB vs 32.0% SAT; and CH50: 1.8% PCB vs 33.3% SAT). This trend was apparent throughout the DB period and uniform in the overall SA237 period.

Vital Signs

During the DB period, more patients in the SAT group (41.3%) compared to the PCB group (18.9%) had post-baseline value(s) of systolic blood pressure (SBP)> 140 mmHg. There was also an imbalance at baseline (12.5% of patients in the SAT group and 2.7% of patients in PCB group had baseline SBP > 140 mmHg). There was an unexpected increased incidence of bradycardia in association with vital sign check (post-baseline pulse rate <60 in 32.7% in SAT group vs 20.3% in PCB group).

ECG

Abnormal ECG findings were more frequently reported in the SAT treated group than PCB in study BN40898 (46.9% vs 17.9%), with no baseline imbalance, particularly those of RR and QTcF intervals. Of these, abnormal QTcF interval has appeared more common in patients on satralizumab than in those on PCB group during the DB phase (17.8 vs. 7.3 %) in the pool data, albeit that the major difference is in the mildest prolongation (450-480) and the differences have not been considered clinically significant. The two cases described as clinically significant, one case of bradycardia and one of nodal rhythm, resolved without changes in the treatment regimen.

Safety in special populations

In the Phase III studies, the proportion of APQ4-IgG seronegative patients was approximately the intended 30% (AQP4-IgG seropositive: 119 patients; AQP4-IgG seronegative: 59 patients). A higher incidence of infections in the SAT group in AQP4-IgG seronegative patients (135.70 AEs/100PY) compared with the PCB groups (125.94 AEs/100Py) was not consistently observed across studies. The incidence of infections in the SAT group (102.62 AEs /100PY) was lower than the PCB group (173.24 AEs/100PY) in AQP4-IgG seropositive patients.

A total of 7 adolescent patients (defined as 12-17 years of age, N=4 in SAT group), representing 3.9% of the total number of patients in the pooled population, were enrolled in the study BN40898 prior to the CCOD. Five adolescent patients reported 28 AEs during the DB period. All AEs were mild or moderate and resolved, and none led to discontinued treatment. Five events experienced by one patient were considered related to study treatment by the investigator.

The Applicant reported 4 patients above 65 years of age in SAT group in the pooled dataset. Additional 6 patients reached the age of 65 during the study by CCOD. There were 29 patients aged >55 years at entry (SAT:23, PCB:6). The rate of AEs in the overall SA237 period in both age subgroups were comparable to the rates reported in the SAT and PCB groups in the DB period; however, the rates of SAEs, SAEs leading to dose interruption, and serious infections were numerically higher in patients aged >55 years compared with patients aged ≤55 years (SAE: 20.47 events/100PY vs. 10.71 events/100PY; SAE leading to dose interruption: 7.22 events/100PY vs. 2.54 events/100PY; serious infection AE: 7.22 events/100PY vs. 3.10 events/100PY).

Baseline BW: In the study BN40898, the median baseline BW of patients across groups was 58.40 kg (range: 39.4-140.4 kg), whereas in the study BN40900, it was 72.70 kg (range: 42.1-151.0 kg). The AE profile was comparable across subgroups stratified by baseline BW (median split). However, in the study BN40900 the patients in the SAT arm with the lowest BW (<50 kg) had a higher incidence of all AEs as well as serious and severe AEs compared to PCB arm (converted to events/100PY, all SAEs:

1035.22 vs. 444.49; serious AEs 36.54 vs. 0; severe AEs 170.51 vs. 0). This AE profile was not observed in the study BN40898, and the subgroups are small.

There are no data on the use of satralizumab in pregnant and breastfeeding women.

Immunological events

The incidence rates of ADA were higher in the study BN40900 than in the study BN40898 (71-72% vs 41-52%).

In the pooled studies during the DB period, a higher incidences of IRR were observed in ADA-positive patients (7 patients, 11.3% with 19.78 events per 100PY) compared with ADA-negative (6 patients, 14.3% with 13.33 events per 100PY) and in the PCB group (8.99 events per 100PY).

During the Overall SA237 period, no difference was evident in the IRR rate between ADA-positive and ADA-negative subgroups.

A higher incidence of AE leading to dose interruption were also observed in ADA-positive patients (13 patients, 21.0% with 24.28 events per 100PY) compared with ADA-negative (10 patients, 23.8% with 16.96 events per 100PY), most commonly due to infections

Arthralgia was reported equally in the pooled data between the ADA-positive and ADA-negative subgroups.

Safety related to drug-drug interactions and other interactions

No formal drug-drug interaction (DDI) studies have been performed with satralizumab.

Physiologically-based pharmacokinetic (PBPK) modelling has been applied to explore the potential impact of a reduction in IL-6 levels on the expression of CYP450 enzymes. The risk of drug interaction through increased expression of CYP450 enzymes resulting from reduced IL-6 levels is addressed in the SmPC.

See PK and PD Section.

Safety of Satralizumab Prefilled Syringes

Overall, 63 patients with NMO or NMOSD switched from the vial formulation to the PFS with Needle Safety Device (NSD) during the OLE period of the studies. The majority of the patients were female (87.3%, n = 55) and 4 of them were adolescents (< 18 years).

All 63 patients were exposed to at least one dose of satralizumab supplied in PFS. with a median duration of exposure of 33.6 weeks. Of these, 43 patients (68.3%) reported at least one AE, the most frequently reported AEs being nasopharyngitis (11.1%) and upper respiratory tract infection (9.5%). No new safety concerns of satralizumab prefilled syringes were identified.

Discontinuation due to AES

AEs leading to discontinuation from treatment were described for 8 cases in 7 patients. Discontinuations in the DB period were in the study BN40898 SAT group increased transaminases, decreased neutrophil count and urticaria, and in PCB group breast and hepatic cancer, thrombocytopenia, lymphopenia, and neutropenia. In the study BN40900, one SAT patient discontinued treatment due to serious pneumonia, and one PCB patient due to systemic lupus erythematosus.

AEs leading to discontinuation from treatment in the OLE were in the BN40898 cases of endocarditis (serious), vasculitis, and infectious enterocolitis (serious). None were reported in the study BN40900. The case of vasculitis was deemed mild but it has recurred and led to withdrawal.

Post marketing experience

There is no post-marketing experience with satralizumab.

2.6.1. Discussion on clinical safety

The safety assessment of satralizumab is based on data from two phase III studies (BN40898 and BN40898). In addition, data from healthy controls in phase I study (SA-001JP) and phase II study in patients with RA (SA-105JP) were presented.

Even though phase III studies had different designs, patients recruited into both studies covered a broad spectrum of NMO and NMOSD patients in terms of presence and absence of AQP4-IgG, including patients treated as add-on to background IST and on monotherapy with satralizumab. Patients in Study BN40898 had to be on a stable dose of one of the following: azathioprine, mycophenolate mofetil or oral corticosteroids alone (for adolescents, the combination of azathioprine plus oral corticosteroids or mycophenolate mofetil plus oral corticosteroids was allowed) for 8 weeks prior to baseline. Patients in Study BN40900 did not receive background IST. Both phase III studies were followed by OLE studies, which are still on-going and only limited number of patients were included in the Summary of Clinical Safety. The Applicant's safety presentation and pooling strategy are considered acceptable despite differences in terms of some features of study design, patient population, eligibility for entering the OLE etc.

Safety population

The total exposure of 104 patients treated with satralizumab during the DB period (41 in the Study BN40898 and 63 in the Study BN40900) was 193.74 patient years. During the DB study period in the pooled data set 90 patients treated with satralizumab were exposed up to 23 weeks, 72 patients at least 48 weeks and 48 patients at least 95 weeks. In general, the exposure to satralizumab during DB period in the pooled data set is longer (median 93.7 weeks) compared to placebo exposure (median 42.6 weeks). In the overall pool, 145 patients were treated with satralizumab for a total exposure of 327.93 PY with 134 patients for at least 1 year, 90 patients for at least 2 years and 9 patients for at least 4 years. Six patients (8.1%) in placebo group and 4 (3.8%) patients in satralizumab group withdrew from treatment due to AEs during DB period.

The pooled patient population with respect to background IST during the DB period is unbalanced with more patients in the placebo group from the study BN40898 with concomitant IST (42 out of 74 patients), while the majority of satralizumab patients are from the monotherapy study BN40900 (63 out of 104 patients), which needs to be taken into account when interpreting the reported AEs frequencies between treatment arms.

Given the low prevalence of NMOSD, the drug exposure can be considered acceptable for the short-term safety assessment of satralizumab. As for the long-term safety profile, the safety database is too limited for drawing conclusions for less frequent or delayed events. The OLE Studies are ongoing until product registration, and the percentage of patients continuing in the OLE part is high in both studies, which thus may be expected to provide additional safety data.

The limited exposure of adolescents and elderly patients precludes full safety assessment. Analysis of AEs in the small adolescent subpopulation does not give rise to specific safety concerns related to young

age. The number of elderly patients (>65) at baseline is minute, and their AE profile may not appear conspicuous.

Scrutiny of subcategories by gender, BW, and BMI inevitably leads to a few very small subgroups in the limited safety database.

As the majority of the NMOSD patients are females and the half of the patient population was under 39 years of age, the population of women of childbearing age remained sizable in the target population. The Applicant agrees to include use in pregnant and breastfeeding women as missing information in the Satralizumab risk management plan (RMP). The Applicant proposal of conducting a global single-arm pregnancy safety study to collect information for 10 years on pregnancy complications and birth outcomes in women exposed to satralizumab during pregnancy in patients with NMOSD is agreed.

Safety profile and specific AEs of interest

As a humanized monoclonal antibody, satralizumab is expected to manifest class effects such as immune responses: post-infusion responses, antibody formation, as well as increased susceptibility to infections due to its mechanism of action; the production of IL-6 and sIL-6R is stimulated by pathogenic bacterial lipoproteins and lipopolysaccharides with an activating effect on the innate immunological response, and consequently, satralizumab is expected to have an immunosuppressive effect on the immunity to bacterial and viral infections. Upon request, the Applicant accepted to include serious infection as an important identified risk in the RMP.

Most patients included in the DB period of phase 3 studies reported AEs: in the SAT group (91.3%) and in the placebo group (86.5%), the majority of mild or moderate intensity. Severe AEs were reported more frequently in the SAT group compared to the PCB group.

In general, the AE rate was largely similar between SAT and PCB arms in individual studies as well as in the pooled safety dataset during DB period for severe AEs, AEs leading to discontinuation or dose interruption or reduction. The safety profile, in light of the available data, may be considered expected.

ADA were detected in over half of patients in the SAT group during the DB period and in almost 2/3 of patients during the OLE period. Though incidence of IRRs in ADA-positive population (11.3%, 19.79 events per 100PY) was slightly higher than the ADA-negative population (14.3%, 13.33 events per 100PY), when comparing the rate of IRRs by ADA status around the time of IRRs (i.e. before, after and at the same time of an IRR), they were comparable: 15.26 events per 100 PY during ADA-positive periods compared with 17.50 events per 100 PY during ADA-negative periods), which suggested a lack of correlation between the ADA presence and IRRs

The Applicant has provided an account of the complement factors (C3, C4, CH50) in relation to infections, confirming that lowering of complement levels with a potential effect does occur but has in most cases remained reasonably modest, i.e. mild or moderate. The low number of patients with considerably lowered complement components leads to an analysis with very small numbers which calls for caution in the interpretations, which may also be hampered by an unexpectedly high incidences in the placebo groups. Several cases of expected severe infections such as pneumonia and sepsis have been associated with only mildly decreased or even normal complement values. The Applicant did not consider C3 levels monitoring based on the justification that monitoring of the C3 levels will cause additional burden to patients without prediction of appearance of infection. This position is considered acceptable.

The laboratory abnormalities have been discussed during the procedure, and the Applicant has agreed to list neutropenia, leukopenia, thrombocytopenia, increase of liver enzymes, hyperbilirubinemia and hyperlipidaemia as ADR. Data-driven dose modification in case of thrombocytopenia suggested by the Applicant - if the platelet count is below 75 $x10^9$/L and confirmed by repeat testing, dose should be interrupted until platelet count ≥ 75 $x10^9$/L, - is considered acceptable.

It is notable that gastritis is reported as an AE practically solely on-treatment (up to 10.8% in the study BN40898). Thus, addition of gastritis as an ADR is endorsed.

Vital signs, ECG, and other concerns

The somewhat unexpected finding of more frequent cardiac abnormalities seems to involve some lengthening of QTcF and RR intervals. Also, in association with the vital sign check, bradycardia was observed in the SAT group; together with the two cases of bradyarrhythmia deemed clinically significant, incorporation of bradycardia as an ADR is acceptable.

The Applicant has corrected an erroneous double entry of subjects with systolic hypertensive values, making a point of the potentially beneficial impact that an anti-inflammatory treatment could have in terms of hypertension through effectors of endothelial dysfunction and arterial stiffness, whereas noting that no support to a possible causal link with a hypertensive effect is given by a literature review. However, especially the study BN40900 and the pooled data indicate that abnormal systolic blood pressure is overrepresented in the SAT group post-baseline, not explained by the slight imbalance at baseline. This warrants inclusion of hypertension as an ADR.

Additionally, recognition of the major cardiovascular event risk as a potential risk in susceptible patient population is supported not only by the hyperlipidaemic and hypertensive effect but also by the preliminary finding on the proarrhythmic properties. The Applicant accepts to include major cardiovascular event as an important potential risk in the Satralizumab RMP.

The primarily noted apparent discrepancy in lifetime suicidal ideation was elicited by the used form of The Columbia Suicide Severity Rating Scale. Nevertheless, all recruited patients have fulfilled the inclusion and exclusion criteria including the required absence of active suicidal ideation within 6 months prior to screening or attempted suicide within the last three years before screening, according to the Applicant, and consequently the finding is accepted as chance variation.

2.6.2. Conclusions on the clinical safety

The safety database of satralizumab is expectedly limited both in terms of numbers and duration of the exposure. The challenge of identifying AEs is obvious, especially concerning special subpopulations. Consequently, specific weight should be given to ADRs that may be interpreted as class effects of anti-IL6R antibodies on the basis of available, larger safety databases, even if the evidence produced during the clinical development program of satralizumab may not appear quite as solid or compelling. The surfaced safety aspects have not given rise to major objections, and most relevant ADRs are observed in the SmPC.

The OLE studies are ongoing with a relatively high percentage of patients continuing, so that some additional longer-term safety data may be expected to be submitted by the Applicant within due time.

2.7. Risk Management Plan

Safety concerns

Table 40: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Serious infections
Important potential risks	Serious hypersensitivity Hepatotoxicity Major cardiovascular events
Missing information	Use in pregnant and breastfeeding women

Pharmacovigilance plan

Table 41: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Date(s)
Category 1—Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorization				
Not applicable				
Category 2—Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3—Required additional pharmacovigilance activities (by a competent authority such as CHMP/PRAC or NCA)—i.e., studies that investigate a safety concern or evaluate the effectiveness of risk minimization activities				
Study WN42349: A multicentre, single-arm, open-label study (Planned)	To evaluate the long-term safety and efficacy of satralizumab in patients with NMOSD	Risk of serious infections Risk of hepatotoxicity	Final report submission	Q2 2025
Study WN42856: a global observational 10-year single-arm prospective study (Planned)	To assess the frequency of maternal, fetal, and infant adverse outcomes among women with NMOSD exposed to satralizumab during the 6 months prior to the last menstrual period or at any time during pregnancy.	Use in pregnant and breastfeeding women	Protocol submission	Q4 2021
			Final report submission	Q4 2033

CHMP= Committee for Medicinal Products for Human Use; NCA=National Competent Authority; NMOSD=Neuromyelitis optica spectrum disorder; PRAC=Pharmacovigilance Risk Assessment Committee

Risk minimisation measures

Table 42: Summary Table of Pharmacovigilance Activities and Risk-Minimization Activities by Safety Concern

Safety Concern	Risk-Minimization Measure(s)	Pharmacovigilance Activities
Serious infection	**Routine risk-minimization measures:** **Routine risk communication** • SmPC Section 4.2 – Posology and method of administration, dose modification advice for neutropenia • SmPC Section 4.4 - Special warnings and precautions for use: Infections, neutrophil count	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None

Safety Concern	Risk-Minimization Measure(s)	Pharmacovigilance Activities
	• PL Section 2 – What you need to know before you use Enspryng: warnings and precautions - infections **Routine risk-minimization activities recommending specific clinical measures to address the risk:** • SmPC Sections 4.2 and 4.4 provide monitoring and dose modification/treatment management recommendations for neutropenia • PL Section 2 provides Instructions on recognition of signs and symptoms of infections, laboratory tests and treatment interruption/delay **Other risk minimization measures beyond the Product Information:** • Medicine's legal status: The medicinal product is subject to restricted medical prescription **Additional risk-minimization measures:** • Patient alert card	**Additional pharmacovigilance activities:** • Study WN42349
Serious hypersensitivity	**Routine risk-minimization measures:** **Routine risk communication:** • SmPC Section 4.2 - Posology and method of administration, administration by the patient and/or caregiver • SmPC Section 4.3 – Contraindications • PL Section 2 - What you need to know before you use Enspryng: Do not use Enspryng, warnings and precautions • PL Section 4 – Possible side effects **Routine risk-minimization activities recommending specific clinical measures to address the risk:** • SmPC Section 4.2 provide management guidelines (initial administration of satralizumab under HCP's supervision and instructions in case of symptoms of serious allergic reactions) • SmPC Section 4.3 includes a contraindication to satralizumab for hypersensitivity to the active substance or any of the excipients • PL Section 4 provides instructions on recognition of signs and symptoms of hypersensitivity reactions and on the need to access emergency care in case of such reactions, as well as treatment interruption/discontinuation **Other risk minimization measures beyond the Product Information**: • Medicine's legal status: The medicinal product is subject to restricted medical prescription. **Additional risk-minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Evaluation and presentation of cumulative data collected in postmarketing setting in PSURs/PBRERs **Additional pharmacovigilance activities:** • None

Safety Concern	Risk-Minimization Measure(s)	Pharmacovigilance Activities
Hepatotoxicity	**Routine risk-minimization measures:** **Routine risk communication:** • SmPC Section 4.2 - Posology and method of administration, dose modification advice for liver enzyme abnormalities, special populations: hepatic impairment • SmPC Section 4.4 - Special warnings and precautions for use: Liver enzymes • SmPC Section 4.8 – Undesirable effects • PL Section 2 - What you need to know before you use Enspryng: Do not use Enspryng, warnings and precautions – liver enzymes • PL Section 4 – Possible side effects **Routine risk-minimization activities recommending specific clinical measures to address the risk:** • SmPC Sections 4.2 and 4.4 provide monitoring and dose modification/treatment management recommendations for liver enzyme abnormalities • PL Section 2 provides Instructions on recognition of relevant signs and symptoms and laboratory tests, on the need to seek immediate medical attention **Other risk minimization measures beyond the Product Information:** • Medicine's legal status: The medicinal product is subject to restricted medical prescription **Additional risk-minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Evaluation and presentation of cumulative data collected in postmarketing setting in PSURs/PBRERs **Additional pharmacovigilance activities:** • Study WN42349

Safety Concern	Risk-Minimization Measure(s)	Pharmacovigilance Activities
Major cardiovascular events	**Routine risk-minimization measures:** **Routine risk communication:** • SmPC Section 4.8 - Undesirable effects • PL Section 4 – Possible side effects **Routine risk-minimization activities recommending specific clinical measures to address the risk:** • None **Other risk minimization measures beyond the Product Information:** • Medicine's legal status: The medicinal product is subject to restricted medical prescription **Additional risk-minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Evaluation and presentation of cumulative data collected in postmarketing setting in PSURs/PBRERs **Additional pharmacovigilance activities:** • None
Use in pregnant and breastfeeding women	**Routine risk-minimization measures:** **Routine risk communication:** • SmPC Section 4.6 Fertility, pregnancy and lactation: Pregnancy, breastfeeding • SmPC section 5.3 Preclinical safety data: Reproductive toxicity • PL Section 2 - What you need to know before you use Enspryng: pregnancy and breastfeeding **Routine risk-minimization activities recommending specific clinical measures to address the risk:** • None **Other risk minimization measures beyond the Product Information:** • Medicine's legal status: The medicinal product is subject to restricted medical prescription **Additional risk-minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Evaluation and presentation of cumulative data collected in postmarketing setting in PSURs/PBRERs **Additional pharmacovigilance activities:** • WN42856

PL = Package leaflet: SmPC = Summary of product characteristics

Conclusion

The CHMP and PRAC considered that the risk management plan version 2.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the Applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The Applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 01.06.2020. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The Applicant declared that satralizumab has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers satralizumab to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the Applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Enspryng (satralizumab) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

NMO and NMOSD are autoimmune inflammatory disorders of the CNS, predominantly targeting the spinal cord and optic nerve but also the brain. They often lead to substantial neurological disability, mainly through relapses, and an increased mortality. The reported incidence rates range is 0.07-0.079: 100 000 and the prevalence 1.04-1.09: 100 000.

Serum AQP4-IgG, a highly disease-specific feature, are present in 70-80% of patients. IL-6 seems to have a central mediating role in the immunopathogenesis of NMO/NMOSD. After the first attack, patients with NMOSD experience unpredictable relapses that may lead to permanent and accumulating neurological damage and disability. The clinical symptoms include visual and mobility impairment,

(including blindness), impaired mobility, sensory disturbances and, neuropathic pain, and bowel and bladder dysfunction. Accordingly, relapse prevention remains the primary therapeutic goal in patients with NMO and NMOSD, and the key endpoints would thus be time to relapses or relapse rate over time as well as measures of clinical disability.

3.1.2. Available therapies and unmet medical need

The treatment of NMO/NMOSD consists of treatment of acute relapses (usually corticosteroids or plasma exchange), prevention of relapses, symptom management, and rehabilitation. Prevention is of primary importance, and immunosuppressants are a rational treatment option. Consensus treatment regimens have been published and are widely used throughout the world with apparent clinical benefit, but the evidence has been scanty to support the long used treatment options (e.g. retrospective case series for azathioprine and prednisone, and methotrexate, as well as small prospective series for mitoxantrone and rituximab), so there has been an unmet medical need for therapy over the years.

The first approved treatment for adults with AQP4-IgG antibody-positive NMO/NMOSD appeared on the market in 2019 (eculizumab).

3.1.3. Main clinical studies

The key design features of the submitted two pivotal phase III studies are presented in Table 43.

Table 43: The key design features of the submitted two pivotal Phase III studies

	Study BN40898 (SA-307JG)	Study BN40900 (SA-309JG)
Phase	III	
Study Design	Multi-center, randomized, double-blind, parallel-group, add-on to baseline therapy, placebo controlled, event-driven study with an open-label extension period	Multi-center, randomized, double-blind, parallel-group, monotherapy, placebo controlled, event-driven study with an open-label extension period
Patient Population	Adolescent (age 12- <18 years) and adult patients (age ≥18 years) with NMO and NMOSD	Adult patients (age ≥18 years) with NMO and NMOSD
Randomized Patients at CCOD	83	95
Regions	Asia (including Japan) (41.0%) Europe (56.6%) North America (2.4%)	North America (61.1%) Europe/Other (28.4%) Asia (10.5%)
Satralizumab Dose	120 mg SC at Weeks 0, 2 and 4 Q4W thereafter	
Comparator	Placebo	
Primary Endpoint	Time to First Relapse based on PDR (with EDSS/FSS assessment performed within 7 days of patient reporting relapse symptoms to site) during the DB period. Time to first clinical relapse and time to first treated clinical relapse were included as sensitivity analyses of the primary endpoint.	
Key Secondary Endpoints	Change from baseline in VAS score for pain at Week 24 Change from baseline in FACIT fatigue score at Week 24	

CCOD=clinical cut-off date; DB=Double-blind; EDSS=Expanded Disability Status Scale; FACIT=Functional Assessment of Chronic Illness Therapy; FSS=Functional Systems Score; NMO=Neuromyelitis Optica; NMOSD=Neuromyelitis Optica Spectrum Disorders; PDR=Protocol-defined relapse; Q4W=every 4 weeks; SC=Subcutaneous; VAS=Visual Analogue Scale.

3.2. Favourable effects

Pivotal study BN40898

Primary efficacy endpoint: time to protocol-defined relapse through the DB period

An analysis using the stratified log-rank test showed that treatment with satralizumab in in the original ITT population led to a statistically significant reduction in the HR of experiencing a protocol-defined relapse compared to placebo HR: 0.38, 95% CI: 0.16, 0.88, p=0.0184. The corresponding result in the subgroup of AQP4-IgG seropositive patients was HR: 0.21, 95% CI: 0.06-0.75, p=0.0086).

Consistently with this finding, the number of patients given rescue therapy was higher in the PCB arm (64%) in comparison to the SAT arm (41%).

Sensitivity analyses (treated clinical relapse and clinical relapse) did not reach statistical significance but showed a consistent trend of lower HRs 0.57 and 053 respectively. Similar results were yielded in analyses only including AQP4-IgG seropositive patients, HR 0.55 and 0.51 respectively. Additional sensitivity analyses of the primary efficacy endpoint included relapses treated with rescue treatment with the PDRs as well as rescue treated relapses and increase in baseline medication with the PDRs. These yielded HRs and 95% CIs of 0.51 (0.24, 1.10) and 0.55 (0.26, 1.14) respectively.

Key secondary efficacy endpoints

Key secondary endpoints did not show a statistically significant effect.

Secondary efficacy endpoints

Secondary endpoints did not show a statistically significant effect

Pivotal study BN40900

Primary efficacy endpoint: time to protocol-defined relapse through the DB period

An analysis using the stratified log-rank test showed that treatment with satralizumab led to a statistically significant 62% reduction in the risk of experiencing a protocol-defined relapse compared to placebo, HR: 0.38, 95% CI 0.16, 0.88 in the original ITT population. Re-analysing the primary efficacy endpoint only including AQP4-IgG seropositive patents yielded HR: 0.26, 95% CI: 0.11-0.63, p-value 0.0014.

Consistently with this finding, the number of patients given rescue therapy was higher in the PCB arm (62%) in comparison to the SAT arm (32%).

Sensitivity analyses (treated clinical relapse and clinical relapse) showed HRs 0.31 and 0.51 respectively. Additional sensitivity analyses of the primary efficacy endpoint performed in the AQP4-IgG seropositive patients included relapses treated with rescue treatment with the PDRs as well as rescue treated relapses and increase in baseline medication with the PDRs. These yielded HRs and 95% CIs of 0.37 (0.18, 0,79) for both analyses (in this study patients were not censored if in need of rescue treatment or increase in baseline treatment).

Key secondary efficacy endpoints

Key secondary endpoints did not show a statistically significant effect.

Secondary efficacy endpoints

Secondary endpoints did not show a statistically significant effect.

3.3. Uncertainties and limitations about favourable effects

A key consideration for the possibility to evaluate the efficacy are the concerns regarding the conduct of the trials and thereby the reliability of the data. It is difficult to firmly conclude that the performed calculations on primary efficacy endpoint using fibrinogen data would not have resulted in loss of control of type 1 error which questions the robustness of the results as well as trial integrity of study BN40900. Further, for both studies, the GCP inspections raised concerns about the effective the segregation of treating and examining investigators and in the implementation of the review of the CEC package (including queries sent to the investigators) performed by the Sponsor before sending it to the CEC.

The positive primary efficacy outcome is supported by the finding of a similar effect size in each pivotal trial, even despite the differences between the study populations (add-on vs. monotherapy; demographical, geographical and racial variability). The sensitivity analyses are sufficiently consistent not to overshadow the main result but provide some additional support despite not often reaching statistical significance. However, the disparity between physician diagnosed and protocol-defined relapses casts some doubt on the effect size of the medicinal product in real life. Whereas the definition of relapse is endorsed as "true relapses" and they are more likely to be detected, clinical relapses may arguably be considered more relevant events. Further, when relapses needing rescue therapy or change in baseline medication were accounted as events instead of leading to censoring in study BN40898, efficacy was no longer significant.

The complete lack of effect for the key secondary outcome endpoints may be due to low baseline values and improper timepoints fore measurement, resulting in data collected only from relapse free patients. Nevertheless, this leaves the primary efficacy endpoint without support from secondary efficacy endpoints.

Albeit that the heterogeneity of the study populations may increase the representativeness of the whole cohort by including more of the real-life variability of the NMOSD spectrum, it also creates additional subgrouping, which leads to comparisons for which the studies are not statistically powered. There were only four patients 65 years or older when entering the pivotal studies. Six additional patients reached the age of 65 years during the study period. To enable some analyses, the Applicant used all patients age > 55 years at screening. In the two pivotal trials 24 AQP4 seropositive patients (5 treated with placebo, 19 with satralizumab) aged > 55 years were included. In these, there were 4 PDRs (1 in satralizumab) and 6 rescue treated relapses (all in satralizumab). Due to few patients and events any firm conclusion is difficult to draw, but a similar trend is observed in patients aged over 55 years as in younger patients. The seeming lack of efficacy in patients with African/African American ancestry may be explained by small samples and chance variation.

Exposure-efficacy analyses, efficacy and PK data together initially suggested that the variability of exposure in different groups may have a bearing on effect, leaving a possibility of a low-exposure group. This issue has been properly addressed by the Applicant, alas, no specific subgroup has been identified. Since the exposure/efficacy analysis has been performed in a biased dataset containing AQP4-IgG seronegative patients, no conclusions on the adequacy of the dose could be drawn initially. A new exposure/efficacy analysis in AQP4-IgG seropositive patients only indicates that satralizumab seems to have an effect on TFR1 when compared to placebo. There was however no significant difference between satralizumab exposure groups.

3.4. Unfavourable effects

The following most frequently reported AEs were identified as ADRs in patients treated with satralizumab in the pooled data of the two phase 3 trials: arthralgia (13.5%); headache (19.2%); migraine (3.8%); musculoskeletal stiffness (4.8%); insomnia (5.8%); IRR (12.5%); peripheral oedema (4.8%); pruritus

(5.8%); rash (8.7%); allergic rhinitis (3.8%); hypofibrinogenaemia (2.9%). All these ADRs has been reported in drugs of the same pharmacological class.

According to the IRR listing presented by the Applicant, the IRR events per 100 patient years were higher in in the SAT group (36 events, 18.58%) than PCB (9 events, 8.99%), in both systemic IRRs (SAT vs PCB: 9.29% vs 3%) and Local IRRs (SAT vs PCB: 9.81% vs 5.99%).

In addition, based on the assessment safety data, ADRs reported in the same drug class and mechanical plausibility, the following adverse events are also considered as unfavourable effects associated with satralizumab treatment:

- Infections, reported by 59.6% of patients on SAT vs 54.1% of patients on PCB. Upper respiratory tract infection (19.2%vs 16.2%), nasopharyngitis (18.3% vs 10.8%) and urinary tract infection (17.3% vs 20.3%) were the most frequently reported infections. There is some indications that serious infections, which were few, may be more common in patients treated with satralizumab as well as in patients with lower complement levels, suggesting a higher risk.
- Leukopenia and neutropenia: A higher proportion of patients in the SAT group had at least one post-baseline leukocyte count decrease (SAT vs PCB: 54.8% vs 28.4%) or neutrophil count decrease (SAT vs PCB: 31.7% vs 21.6%). The proportion of patients who had a post-baseline shift to Grade 3 or 4 decrease in neutrophil counts was also higher in the SAT group (SAT: 9.6% vs. PCB: 5.4%).
- Thrombocytopenia: A higher proportion of patients in the SAT group had at least one post-baseline platelet count decrease resulting in a shift from baseline to a worse grade (SAT vs PCB: 24% vs 9.5%).
- Elevation of transaminases: A higher incidence of patients in the SAT group that had post-baseline ALT and AST increases (27.9% and 18.3%, respectively) than in PCB (12.2% and 13.5%, respectively). One case of very high increase (8.8-11.7 x ULN) with positive de-challenge with SAT suggesting a possible causal relationship.
- Elevated lipids levels: A higher incidence of patients in the SAT group had a post-baseline increase in cholesterol levels resulting in grade shift (SAT: 20.2% vs PCB:10.8%); a similar increase triglyceride levels (SAT:63.5% vs PCB: 48.6%).
- Hypofibrinogenemia: A higher incidence of patients in the SAT groups who had a post-baseline fibrinogen level decreases resulting in a shift from baseline to a worse grade (SAT: 71.2% vs. PCB:20.3%).
- Bradyarrhythmic effect: post-baseline pulse rate <60 in 32.7% in SAT group vs 20.3% in PCB group.
- Formation of ADA: ADA were detected in 59.6% patients in SAT group during DB period and in 63.45% (of 145 patients) treated with satralizumab during the OLE period.

3.5. Uncertainties and limitations about unfavourable effects

The major expected unfavourable effects, serious infections and hypersensitivity, have not been given very substantial support by the collected data; however, this is to large extent due to the very restricted safety database and the limited duration of exposure. Even more so, the cardiovascular effects, apart from the potential bradyarrhythmic effect, are not directly supported by ADR observations. However, the convergent findings of laboratory parameters and the observations together with the knowledge of the pharmacological mechanism and similar pharmacological agents point out the risk of major unfavourable

effects that need to be taken into consideration in clinical practice as well as in measures of pharmacovigilance.

The haematological effects, leuko-, neutro- and thrombocytopenia and hypofibrinogenemia, as well as the potential risk of hepatotoxicity are evident, although the most serious manifestations were not encountered, and so appears the effect on cholesterol and triglycerides, although their long-term course, and effects are not known.

The exposure of pregnant women is an obvious risk with missing data, which must not be overlooked in this patient population but deserves further discussion on the options of data collection; as well, the potential risk of malignancy has not received support by data but obviously requires sizable long-term data to be assessable.

A definite source of uncertainty in the assessment of risks is the variability of the study population. To be representative, the inclusion needs to be broad-based, and the downside is the subdivision into variable and often very small subgroups. This is exemplified by this study population, which does not allow in-depth subgroup analyses. Consequently, all inferences as to the unfavourable effects characteristic of special subpopulations such as adolescents or the elderly remain very preliminary, and the risk of not uncovering these problems at all is substantial and makes a very pedantic scrutiny necessary.

The significance of ADA is not definitely known. In this dataset, their safety profiles appeared largely comparable. Though incidence of IRRs in ADA-positive population was slightly higher than the ADA-negative population, when comparing the rate of IRRs by ADA status around the time of IRRs (i.e. before, after and at the same time of an IRR), they were comparable.

3.6. Effects Table

Table 44: Effects Table for satralizumab, 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. (CCOD October 12, 2018)

Effect	Short Description	Unit	Treatment	Result	Uncertainties/ Strength of evidence	References
Favourable Effects						
HR (95% CI)	Time to first protocol-defined relapse, from randomization to end of study	weeks	SAT 120 mg Placebo	0.38 (0.16, 0.88)	GCP violation P=0.0184	Study BN40898
HR (95% CI)	Time to first protocol-defined relapse, from randomization to end of study	weeks	SAT 120 mg Placebo	0.21 (0.058, 0.75)	GCP violation P=0086	Study BN40898 AQP4-IgG seropositive only
HR (95% CI)	Time to first protocol-defined relapse, from randomization to end of study	weeks	SAT 120 mg Placebo	0.38 (0.16, 0.88)	GCP violation P=0.0184	Study BN40900
HR (95% CI)	Time to first protocol-defined relapse, from randomization to end of study	weeks	SAT 120 mg Placebo	0.26 (0.11, 0.63	GCP violation P=0.0014	Study BN40900 AQP4-IgG seropositive only
HR (95% CI)	Time to treated clinical relapse, from randomization to end of study	weeks	SAT 120 mg Placebo	0.62 (0.34, 1.14)	GCP violation p=0.1236	Study BN40898

Effect	Short Description	Unit	Treatment	Result	Uncertainties/ Strength of evidence	References
HR (95% CI)	Time to treated clinical relapse, from randomization to end of study	weeks	SAT 120 mg Placebo	0.57 (0.27, 1.23)	GCP violation p=0.15	Study BN40898 AQP4-IgG seropositive only
HR (95% CI)	Time to treated clinical relapse, from randomization to end of study	weeks	SAT 120 mg Placebo	0.46 (0.24, 0.88)	GCP violation, integrity of study questioned, loss of type 1 error control p=0.0158	Study BN40900
HR (95% CI)	Time to treated clinical relapse, from randomization to end of study	weeks	SAT 120 mg Placebo	0.31 (0.14, 0.68)	GCP violation, integrity of study questioned, loss of type 1 error control p=0.0021	Study BN40900 AQP4-IgG seropositive only
Difference in mean change from baseline (95% CI)	VAS (0-100) difference in mean change from baseline to week 24	mm	SAT 120 mg Placebo	6.376 (0.280, 13.03)	p=0.0602, Numerically worse result for SAT treated patients. Placebo treated patients received more pain medication at baseline and during the study Patients with PDR left DB phase of study why a limited number of patients had week 24 assessment.	Study BN40898
Difference in mean change from baseline (95% CI)	VAS (0-100) difference in mean change from baseline to week 24	mm	SAT 120 mg Placebo	10.799 (2,356, 19.242)	Numerically worse result for SAT treated patients. Placebo treated patients received more pain medication at baseline and during the study Patients with PDR left DB phase of study why a limited number of patients had week 24 assessment.	Study BN40898 AQP4-IgG seropositive only
Difference in mean change from baseline (95% CI)	VAS (0-100) difference in mean change from baseline to week 24	mm	SAT 120 mg Placebo	3.215 (-5.086, 11.515)	p=0.44 Patients with PDR left DB phase of study why a limited number of patients had week 24 assessment.	Study BN40900
Difference in mean change from baseline (95% CI)	VAS (0-100) difference in mean change from baseline to week 24	mm	SAT 120 mg Placebo	7.052 (-3.999, 18.102)	Patients with PDR left DB phase of study why a limited number of patients had week 24 assessment.	Study BN40900 AQP4-IgG seropositive only

Effect	Short Description	Unit	Treatment	Result	Uncertainties/ Strength of evidence	References
Difference in mean change from baseline (95% CI)	Difference in FACIT fatigue score (0-52 points) mean change from baseline to week 24	points	SAT 120 mg Placebo	-2.089 (-4.752, 0.574)	p=0.1224 Changes from baseline were small in both groups. Patients with PDR left DB phase of study why a limited number of patients had week 24 assessment.	Study BN40898
Difference in mean change from baseline (95% CI)	Difference in FACIT fatigue score (0-52 points) mean change from baseline to week 24	points	SAT 120 mg Placebo	-2.944 (-6.004, 0.117)	Changes from baseline were small in both groups. Patients with PDR left DB phase of study why a limited number of patients had week 24 assessment.	Study BN40898 AQP4-IgG seropositive only
Difference in mean change from baseline (95% CI)	Difference in FACIT fatigue score (0-52 points) mean change from baseline to week 24	points	SAT 120 mg Placebo	2.107 (-1.008, 5.221)	p=0.1824 Changes from baseline were small in both groups. Patients with PDR left DB phase of study why a limited number of patients had week 24 assessment.	Study BN40900
Difference in mean change from baseline (95% CI)	Difference in FACIT fatigue score (0-52 points) mean change from baseline to week 24	points	SAT 120 mg Placebo	2.127 (-1.648, 5.903)	Changes from baseline were small in both groups. Patients with PDR left DB phase of study why a limited number of patients had week 24 assessment.	Study BN40900 AQP4-IgG seropositive only

Unfavourable Effects

Serious infections	Events/100 PY (95% CI)	SAT 120mg Placebo	4.13 (1.8-8.1) 6.99 (2.8-14.4)	Few events	Pooled Phase III
Infections	Events/100 PY (95% CI)	SAT 120mg Placebo	113 (99-129) 155 (131-181)		Pooled Phase III
Arthralgia	%	SAT 120mg Placebo	13.5% 1.4%		Pooled Phase III DB
IRR	%	SAT 120mg Placebo	12.5% 9.5%		Pooled Phase III DB
Fibrinogen level decrease[1]	%	SAT 120mg Placebo	71.2% 20.3%		Pooled Phase III DB
Neutropenia Neutrophil count decrease[1]	%	SAT 120mg Placebo SAT 120mg Placebo	5.8% 4.1% 31.7% 21.6%		Pooled Phase III DB
Leukopenia Leukocyte count decrease[1] White blood cell count decreased. [1]	%	SAT 120mg Placebo SAT 120mg Placebo SAT Placebo:	7.7% 5.4% 54.8% 28.4% 5.8% 0	See above	Pooled Phase III DB

Effect	Short Description	Unit	Treatment	Result	Uncertainties/ Strength of evidence	References
Liver Enzyme ALT[1] Liver Enzyme AST[1]	%		SAT 120mg Placebo SAT 120mg Placebo	27.9% 12.2% 18.3% 13.5%	See above	Pooled Phase III DB

Note: [1] Laboratory abnormalities

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The considerable disability associated with NMO/NMOSD spectrum diseases is known to accumulate predominantly through relapses, and in consequence, the primary aim of therapy is their prevention. The chosen primary endpoint of time-to-event type does not catch all aspects of disease but is widely accepted and acceptable (EMA/CHMP/SAWP/712652/2014), and the studied population is considered to be essentially representative of the target population. The acquired primary effect (HR 0.21-026) in prevention of clinical relapses is considered clinically relevant and meaningful in the target population. However, the disparity between physician-diagnosed and protocol-defined relapses casts some doubt on the effect size of the medicinal product in real life. Whereas the definition of relapse is endorsed as "true relapses" and they are more likely to be detected, the clinical relapses may arguably be considered more relevant events.

There is a lack of support of efficacy by the key secondary endpoints associated with clinical symptoms and well-being, albeit that the time period of 24 weeks may not be long for an effect in symptoms such as pain and fatigue, which may be slower-evolving and have many determinants. The timepoints used for measurement of secondary endpoints resulted in data only from relapse free patients. Further, scores were low at randomisation, leaving little opportunity for further reductions in these endpoints. The lack of observed effect in secondary endpoints may not undermine the primary outcome, but still do not lend any support to it.

Efficacy data derived from adolescents included in the pivotal trials are too scarce to draw any conclusion on efficacy in this subpopulation. However, bibliographic data points to essential similarity between paediatric and adult disease. The currently accepted view is that immunopathological mechanisms underlying lesion formation are comparable across all ages, particularly in AQP4-IgG seropositive patients (Branwell et al, 2008) which is currently the relevant NMOSD subpopulation in question for marketing authorisation. PK data are similar in adolescents and adults. Thus, extrapolation of efficacy from adults to adolescents seems reasonable. Data in elderly people are very sparse. However, a similar trend with respect to efficacy is observed in patients aged over 55 years as in younger patients.

A key consideration for the possibility to evaluate the benefit-risk balance are the concerns regarding the conduct of the trials and thereby the reliability of the data.

Even if it cannot be completely rule out that that the calculations of HR early during the conduct of the study using fibrinogen level were not considered when deciding the protocol amendments number 6 and 8, it is acknowledged that no introduction of bias could be detected in the separate bias assessment report submitted by the Applicant. This is a remaining uncertainty, but it is not considered to have had a major impact on the overall results of the pivotal studies. With respect to the inspection findings associated with the difficulty to effectively confirm the segregation of the examining and treating investigators, although retrospectively collected data does not have the same quality assuring value as prospectively collected information, the separation of the roles has been confirmed in writing by site staff

in all but six findings (out of 86 total findings). The CHMP concluded that even if the documentation intended to ensure that the examining and treating investigators were separated in some cases was not optimal, there were no evidence that unblinding of the examining assessor had occurred. Finally, the GCP inspection team reported deficiencies in the implementation of the intermediate review of the CEC package by the Sponsor including queries, answers, and changes in the forms not recorded in a systematic way to trace all events from a chronological point of view, a potentially directive query and numerous access to the electronic system (VCAS) used for managing relapse assessment forms. During the evaluation, the Applicant has acknowledged the findings and provided clarifications in writing and during an oral explanation. As part of the responses, the Applicant performed a post database-lock internal review to identify and assess the impact of query-related corrections to relapse documentation. According to the report, queries were triggered as appropriate and resulted in corrections to the forms when necessary. During the oral explanation, the Applicant acknowledged the incomplete corrective action of filing the relapse packages with queries submitted as part of the responses due to technical limitations but confirmed that all documentation has been completed and filed in date order as requested, and therefore, the corrective action has been resolved. Finally, even if there were numerous accesses to VCAS, the Applicant reviewed the complete access listing and confirmed the access rights were given appropriately

Satralizumab was generally well tolerated by NMO and NMOSD patients in the two phase III studies. However, the available safety data is considered very limited with no more than 145 patients with NMO and NMOSD having been exposed to satralizumab; furthermore, the limited duration of exposure precludes the assessment of any long-term risks.

The heterogeneity of the limited database challenges the evaluation of safety in the special subpopulations, such as the safety profile in adolescents (n=4, SAT group during DB period and n=7 during OLE period) or the elderly above 65 years of age (n=4, SAT group), and no firm conclusions can be drawn.

The most notable ADR were considered class effects. Serious infections, serious hypersensitivity, risk of liver toxicity, risk of major cardiovascular events, and exposure in pregnant and breastfeeding women are identified as safety concerns.

3.7.2. Balance of benefits and risks

A clinically relevant effect of satralizumab in treatment of NMO/NMOSD spectrum disease with AQP4-IgG has been demonstrated in the pivotal studies. The limitations and uncertainties posed by the fibrinogen levels-related GCP breach as well as the findings in the GCP inspection were considered in the decision on the B/R but in the absence of evidence of an intentional attempt of research misconduct or factual unblinding, efficacy on the prevention of relapses is considered demonstrated.

The observed safety profile of satralizumab per se does not raise any severe or unmanageable concerns; it is noted, however, that the conclusions are based on a very limited safety database.

3.7.3. Additional considerations on the benefit-risk balance

Not Applicable

3.8. Conclusions

The overall B/R of Enspryng is positive

Divergent position(s) are appended to this report.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Enspryng is not similar to Soliris within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 2.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the benefit-risk balance of Enspryng is favourable in the following indication:

> Enspryng is indicated as a monotherapy or in combination with immunosuppressive therapy (IST) for the treatment of neuromyelitis optica spectrum disorders (NMOSD) in adult and adolescent patients from 12 years of age who are anti-aquaporin-4 IgG (AQP4-IgG) seropositive (see section 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

A patient alert card to address the risk(s) of serious infections:

- The card informs the patient that satralizumab may increase the risk of infection
- Patents/carers are instructed to recognise signs or symptoms of infections and seek medical care from a healthcare professional
- The card provides a warning message for healthcare professionals treating the patient at any time, including in conditions of emergency, that the patient is using satralizumab
- Contact details of the patient's satralizumab prescriber

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that satralizumab is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0220/2019 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Appendices

1. CHMP AR on similarity dated 22 April 2021.
2. Divergent positions to the majority recommendation.

APPENDIX

DIVERGENT POSITION DATED 22 April 2021

DIVERGENT POSITION DATED 22 April 2021

Enspryng EMEA/H/C/004788/0000

The undersigned member(s) of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation of Enspryng indicated as a monotherapy or in combination with immunosuppressive therapy (IST) for the treatment of neuromyelitis optica spectrum disorders (NMOSD) in adult and adolescent patients from 12 years of age who are anti-aquaporin-4 IgG (AQP4-IgG) seropositive.

The reasons for divergent opinion were the following:

Both the fibrinogen levels-related GCP breach and the findings recorded in the GCP inspections affecting both trials raise concerns over the reliability and robustness of the efficacy findings.

1. The efficacy data estimated using fibrinogen data may have been used in the decisions. There are serious concerns about the maintenance of the blinding and the effect on both studies by the calculation of HR based on unblinded fibrinogen levels. It is difficult to conclude that the performed calculations would not have resulted in loss of control of type 1 error which questions the robustness of the results as well as trial integrity of this study.

2. The integrated inspection report (including inspection finding from the initial sponsor (Chugai), the CRO (Parexel), sites in Spain and Poland) resulted in 10 critical and 19 major findings. Such critical issues were found in both studies and severely question the integrity of the trial data, such as issues concerning
    a. a weak process for segregation of examining and treating investigators at clinical sites,
    b. interference in relapse assessment as there was an intermediate step of review of the relapse assessment forms by Sponsor and CRO staff raising directive queries to investigator before the CEC members assessed the forms,
    c. innumerable, untraceable changes done on relapse assessment forms and 4) numerous accesses to the electronic system (VCAS) used for managing relapse assessment form.
    d. at least 33 (28%) of patients were negatively affected in terms of data integrity. This seriously questions the reliability and the quality of the remaining data can be questioned as well.
    e. the post database-lock internal review performed by the Applicant to correct the deficiencies may be considered limited and does not give reassurance that the results may be reliable.

Overall, it is questioned if the data from the pivotal studies can be used for a B/R assessment and therefore, we consider the B/R balance as negative.

Andrea Laslop (Austria)

Christian Gartner (Co-opted)

Dana Gabriela Marin (Romania)

Maria Concepcion Prieto Yerro (Spain)